Clinical Handbook of Psychotropic Drugs for Children and Adolescents

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HOW TO USE THIS BOOK

The *Clinical Handbook of Psychotropic Drugs for Children and Adolescents* uses color coding and icons for intuitive navigation:

- Blue sections contain general information on drugs / treatments and their availability.
- Green sections cover drug action and dosing.
- Red sections outline warnings and precautions.
- Orange sections detail patient- and care-related information, such as nursing considerations and patient advice.

Below is a summary of the colors and icons used.

General Information / Availability


Classification, Definition


Product Availability


Indications


General Comments

Pharmacology / Mechanisms of Action


Pharmacology


Pharmacological & Psychiatric Effects


Dosing


Pharmacokinetics


Onset and Duration of Action


Switching, Augmentation Strategies

Warnings and Precautions


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Contraindications

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Toxicity


Food Interactions


Drug Interactions

Patient-Related Issues


Lab Tests / Monitoring


Use in Pregnancy


Nursing Implications, Treatment


Patient Instructions

Additional useful sources of information are listed as


Further Reading

Clinical Handbook of Psychotropic Drugs for Children and Adolescents

5th edition

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The authors and publisher have made every effort to ensure that drug selections and dosages suggested in this text are in accord with current recommendations and practice at the time of publication. However, due to changing government regulations, continuing research, and changing information concerning drug therapy and reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage, or for added precautions. The authors and publisher disclaim any responsibility for any consequences which may follow from the use of information presented in this book.

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INTRODUCTION

The *Clinical Handbook of Psychotropic Drugs for Children and Adolescents* is intended to be a user-friendly and practical resource guide for those who prescribe, dispense, and administer psychotropic drugs to children and adolescents. Its content is derived from various forms of published literature (including randomized controlled trials (RCTs), meta-analyses, scientific data such as pharmacokinetic trials, cohort trials, case series, and case reports) as well as from leading clinical experts. We endeavor to continually update this handbook as the psychiatric literature evolves so we can continue to provide evidence-based clinically relevant information that is easily accessed and utilized to aid with patient care decisions. New sections, periodically added, reflect changes in therapy and in current practice.

The purpose of this handbook is to provide quick access to relevant, practical, and important information clinicians should be aware of when considering pharmacological options available in the treatment of childhood and adolescent psychiatric disorders. It provides an overview of the plausible alternatives, dosing guidelines, as well as information on drug interactions and potential side effects. It is meant to be a resource to both those in training and experienced clinicians.

For this 5th edition, we have once more revised and updated the handbook throughout. Three new chapters have been added covering (1) prescribing safely to children and adolescents, (2) pharmacogenetic information for common psychiatric drugs, and (3) aggression management in children and adolescents. Among the new treatments and formulations added is viloxazine, approved by the FDA for the treatment of ADHD in children and adolescents in 2021, the first new drug to be approved for this indication in over a decade and a non-stimulant medication with quick onset of action. Furthermore, we have added the neuroscience-based nomenclature system that focuses on pharmacology and mode of action to product availability tables within individual chapters.

Most children and adolescents with a diagnosable psychiatric disorder require multimodal interventions to address the symptoms of the disorder, the comorbid conditions, and the psychological, social, and developmental sequelae. Individual and family psychoeducation are essential, and psychosocial interventions should be considered for most psychiatric disorders before, or concurrently with pharmacotherapy.

While initially, many classes of psychotropic drugs were used to treat childhood and adolescent mental illness on the basis of efficacy in adults, much more published evidence has become available in this age group in recent years. The lack of regulatory approval in a country does not necessarily reflect lack of safety or efficacy or controlled studies in these age groups. While many product monographs include a statement that a drug has not been adequately studied in children and/or the safety of the drug has not been established under a specific age, published RCT evidence supporting safety and efficacy may be available.

In the Product Availability section of each chapter, the *Clinical Handbook* includes monograph statements regarding the recommendations for the use of each drug in children and adolescents. Approved indications for children are stated, as are those for adults; also included are unapproved (also called off-label) indications for these drugs. Each chapter includes data from open and double-blind studies, where available, regarding dosing, adverse effects, monitoring, and other important considerations in children and adolescents.

Given that changes may occur in a medication's indications over time, and differences are seen among countries, specific "indications" listed in this text as "approved" should be viewed in conjunction with prescribing information/product monographs approved in your jurisdiction of interest.

Because of a lack of comparative data in children and adolescents for most drug classes, Adverse Reaction tables and Drug Interaction charts reflect information that pertains to heterogeneous age groups (youth and adults).

Until systematic double-blind studies of various psychotropic drugs have been conducted to determine the efficacy, the pharmacokinetics, as well as the relative and absolute risks of each drug in this population, prescribers who choose to use specific psychotropic drugs in children and adolescents should review all available studies and monitor their patients on a regular basis. Informed consent should be obtained from the caregiver or youth (depending on the patient's age) for medication use in both approved and unapproved indications (see p. 2).

Dose comparisons and plasma levels are based on scientific data. However, it is important to note that some patients will respond to doses outside the reported ranges. Age, sex, and the medical condition of the child or adolescent must always be taken into consideration when prescribing any psychotropic agent.

Patient and Caregiver Information Sheets for most drug categories are provided as printable pdf files to facilitate education/counselling of patients receiving these medications and their caregivers. For details, please see p. 429.

For those who like the convenience of electronic resources, the *Clinical Handbook of Psychotropic Drugs for Children and Adolescents* is also available as an online version that provides even quicker access to all the information in the handbook, with added extras that include: (1) An autocompletion-powered search function, (2) full-text search, (3) browse features for generic names, trade names, indications, and interacting agents, (4) an enhanced responsive design that includes list view options as an alternative to table display, and (5) hundreds of additional references. Further details on this can be found at https://chpd.hogrefe.com/

Over the years, readers have asked many interesting questions and provided useful comments and suggestions regarding the content and format of the handbook. This input is critical to keeping this handbook current, accurate, and relevant to the readership. We appreciate readers' feedback, so we invite you to send e-mail to the address below with your comments and questions.

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Clinical Handbook of Psychotropic Drugs for Children and Adolescents Online

The *Clinical Handbook of Psychotropic Drugs for Children and Adolescents Online* is the full-text online version of the popular *Clinical Handbook of Psychotropic Drugs*. It retains all the practical features for which the Clinical Handbook is renowned and makes the information even more easily accessible.

As in the print edition, instantly recognizable icons and color coding allow you to find at a glance the information you seek. But the *CHPD for for Children and Adolescents Online* version offers much more. Unique features that allow even quicker access to the wealth of information include:

- **New:** Drug monographs that summarize the information on a single drug, with the option to display information on other drugs in the same class
- **New:** Side-by-side drug comparisons to see at a glance differences and similarities between them
- Auto-completion powered search function
- Full-text search
- Browse features for Generic Names, Trade Names, Indications, and Interacting Agents
- Enhanced responsive design, including list view option as alternative to table display
- Hundreds of additional references
- Literature hot links for quick access to further reading

Access to the *Clinical Handbook of Psychotropic Drugs for Children and Adolescents Online* is available by subscription. For details see **https://chpd.hogrefe.com**

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PRESCRIBING SAFELY AND ETHICALLY TO CHILDREN AND ADOLESCENTS

There are many factors to consider before prescribing a treatment to a young person. Appropriate treatments for psychiatric problems are evidence based and their use is justified. The ethics and principles behind safe prescribing practices are important in every prescription, and this section describes them broadly. It is important to note that there are expectations and guidelines for prescribers in every jurisdiction, so the first thing a prescriber should do is consult with the local regulatory bodies and guidance from their jurisdiction. These recommendations cannot supercede any regulations. For any prescription, the following would constitute the latest standards of safety and ethics

Consent

- Prescription medications require consent from an appropriate person (patient, caregiver, or legal representative)

Who can provide consent for children and adolescents?

- Most jurisdictions have specific laws and regulations regarding age of full treatment consent, but the following principles generally apply:
  - **For children under the age of consent**, the child's guardian (in the case of parent guardians, **both** parents) provides consent
  - **Children and adolescents under the age of consent but assessed to be able to understand treatment advice and make an appropriate decision** may be a "medical minor" or "competent minor" and be able to consent to medications without their parents' approval. Consult local regulations
  - **For adolescents at or over the age of the consent**, the adolescent themselves is able to provide full consent
  - **For children in involuntary medical settings**, the consent giver must be a legally appointed person following the laws of the jurisdiction

Obtaining Informed Consent

- Once the appropriate consent giver is identified, a process of explaining the treatment is undertaken, called "obtaining informed consent." Aspects of obtaining informed consent are as follows[1], and may be remembered by the acronym **BRAINS ED**:

Aspect	Definition	Example in obtaining informed consent for risperidone treatment for schizophrenia
Benefits	The expected positive outcomes	"The purpose of taking risperidone is to decrease the psychotic symptoms that you are having, and when risperidone works you should expect to be able to feel and function much better."
Regulatory (on-label/off-label use) discussion	A brief description of the status of the treatment and its implications	(Specific to Canada) "Risperidone has not been approved by Health Canada for use in children or adolescents but it has been studied extensively in this population and has been shown to be effective. This is "off-label" use and it is common for pediatric medications."
Alternatives	Possibilities that could also be chosen	"There are other antipsychotic medications that could be used. For example, aripiprazole is a medication that is associated with less weight gain and fewer blood sugar and fat abnormalities in some studies. While some psychotherapies may benefit people with schizophrenia, they are not primary treatment options and are unlikely to work as well."
Informed dissent (right to refuse and still receive care)	The rights to refuse treatment and implications for care	"I'm recommending this medication for you, but if you don't want to take it you are not required to, and this would not stop me from being your treatment provider."
Non-treatment scenarios	Implications of not choosing the treatment	"Without treatment schizophrenia often deteriorates and a larger impact on your function, including more of the disturbing symptoms and their effects on you, could happen."
Severe/important harms	Regardless of likelihood, severe harms that are possible	"Weight gain and appetite changes can result in increased blood glucose and lipids which can increase risk for heart and blood vessel problems and diabetes. People taking risperidone need to do blood tests to make sure that isn't developing. Sudden fever, confusion, or stiffness are medical emergencies and I'll explain what to do if those occur."
Expected/likely harms	Common or likely side effects	"Many people who take risperidone can report feeling very sleepy or fatigued, and weight gain is common. Dry mouth and headaches are also commonly reported. Many people experience nausea or problems with their digestive system. Restlessness (what we call "akathisia," a word for being unable to sit still) and tremor are also commonly seen." Contextual side effects can be ethically used to reduce the nocebo effect (expectation of negative effects). Nuisance or less dangerous side effects that occur commonly with most medications (e.g., headaches, nausea), could be summarized with statements like "if you notice any symptoms that bother you, please contact me or your health provider."[2] Provide written patient/caregiver medication information from a reliable source (see, e.g., Patient Information Sheets p. 429
Dependence discussion, starting and stopping	Tolerance, withdrawal, addiction potentials, and how to stop safely	"Though risperidone does not have habit-forming potential, withdrawal symptoms can happen. If you wish to stop the medication it would be best to do so with medical support."

Prescribing Safely

- Ensure you have the information necessary to understand the safety risk and be able to follow up on safety:
  - Establish important pre-treatment measurements (height, weight, waist circumference)
  - Baseline and periodic laboratory testing for certain medications is recommended for certain medications (e.g., lipid and glucose testing with antipsychotic treatment)
  - All individuals who could be pregnant should have a urine pregnancy test prior to starting medication
  - Complete a medication reconciliation, accounting for all currently taken prescription medications, non-prescription medications, nutritional, and complementary and alternative medications
  - Confirm any known allergies or previous adverse reactions
- Follow safe prescription practices to reduce error:
  - Avoid unsafe, unclear or unnecessary abbreviations (e.g., write “fluoxetine 20 milligrams taken once daily in the morning” not “flx 20 mg OD”)
  - Avoid trailing null digits (e.g., write “2 milligrams” not “2.0 milligrams”) and always include one digit to the left of any decimal (e.g., write “0.5 milligrams” not “.5 milligrams”)
  - Use printed/typed/electronic prescriptions when possible; use block capitals or legible writing with hand-written prescriptions
  - (In many jurisdictions) use the generic name of the drug on the prescription; indicate trade name specifically only when necessary (e.g. methylphenidate (Concerta))
- It is important to know the local regulations and laws for prescribing to children and adolescents. Be aware of jurisdiction-specific instructions for the following situations:
  - One parent consents to treatment, the other does not
  - The child/adolescent has a custodial caregiver
  - The child/adolescent wants treatment and does not want their parents to know
  - The proposed treatment is both off-label and experimental

Further Reading

References

1 Katz AL, Webb SA, Committee on Bioethics, et al. Informed consent in decision-making in pediatric practice. Pediatrics. 2016;138(2):e20161485. doi:10.1542/peds.2016-1485

2 Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: The problem of the nocebo effect for informed consent. Am J Bioeth. 2012;12(3):22–29. doi:10.1080/15265161.2011.652798

PSYCHIATRIC DISORDERS IN CHILDREN AND ADOLESCENTS

Significant psychiatric illnesses affect approximately 10–15% of North American children and adolescents.[1] These consist of conditions such as mood and anxiety disorders, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, Tourette's disorder, and autism spectrum disorder. Symptoms of these disorders are often serious and have an enormous impact on the lives of the patients and their families. Many factors complicate the recognition, management, and treatment of psychiatric disorders in children and adolescents. These include a high variance in symptom presentation and interpretation, diagnostic difficulties, scarcity of resources, research limitations, environmental influences, societal attitudes, and medication issues. In a significant change, DSM-5 (released 2013)[2] removed the category of disorders usually first diagnosed in infancy, childhood, or adolescence. Where applicable, diagnostic considerations specific to presentation of a disorder in infancy, childhood, or adolescence are included with each disorder.

This chapter covers the following diagnoses:

- Neurodevelopmental disorders
  - Autism spectrum disorder (ASD) (p. 5)
  - Attention-deficit/hyperactivity disorder (ADHD) (p. 6)
  - Tourette's disorder (p. 7)
- Schizophrenia (p. 8)
- Bipolar disorder (BD) (p. 10)
- Depressive disorders
  - Disruptive mood dysregulation disorder (DMDD) (p. 11)
  - Major depressive disorder (MDD) (p. 12)
- Anxiety disorders
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  - Specific phobia (p. 14)
  - Social anxiety disorder (p. 15)
  - Panic disorder (p. 16)
  - Generalized anxiety disorder (GAD) (p. 17)
- Obsessive-compulsive disorder (OCD) (p. 18)
- Posttraumatic stress disorder (PTSD) (p. 19)
- Disruptive, impulse-control, and conduct disorders
  - Oppositional defiant disorder (ODD) (p. 20)
  - Conduct disorder (CD) (p. 20)

This chapter also covers a clinically relevant syndrome that is frequently missed and has specific pharmacological treatment:

- Catatonia

NEURODEVELOPMENTAL DISORDERS

Autism Spectrum Disorder (ASD)

Autism spectrum disorder is a group of neurodevelopmental disorders that are characterized by persistent difficulties in social interactions and restricted/repetitive interests or behaviors

Neurodevelopmental disorders usually affect children before age 5; the majority of patients do not have intellectual disability

Autism spectrum disorder is best thought of as a neurodiversity (a different type of brain) requiring adaptations and accommodations to succeed in a neurotypical environment rather than as an illness to be treated

Behaviors within autism spectrum disorder that cause significant challenges may be the target of pharmacological therapy, however, it is important for prescribers to ensure these targets are narrow and that they are not attempting to treat the autism spectrum disorder itself

A major change in DSM-5 was to no longer differentiate between types of autism spectrum disorders to reflect a scientific consensus that four previously separate disorders are actually a single condition with different levels of symptom severity in two core domains: (1) deficits in social communication and social interaction and (2) restricted repetitive behaviors, interests, and activities

Prevalence

- 1.7%[3]
- 38% of patients with ASD involve significant intellectual disability (IQ below 70)
- 4–5 times higher incidence in males than females

Onset

- Symptoms may be recognized in the first year of life, but it is difficult to make a reliable diagnosis in children younger than age 2
- In some children, early development in language and cognition appears normal, then child begins to pursue unusual interests with intensity and social deficits become prominent when interacting with peers

Risk Factors

- Unknown; may be genetic or related to a viral infection or inherited enzyme deficiency; concordance in identical twins is 36–100% and less than 24% in fraternal twins
- Alterations observed in several brain regions, specifically medial prefrontal cortex and amygdala
- Evenly distributed among socioeconomic classes and ethnic groups
- There is no evidence to support a link between vaccinations and autism; previous evidence regarding this was fraudulent and retracted[4]

Comorbidity

- Intellectual disability (38%), ADHD
- High incidence of EEG abnormalities and seizure disorders[5]
- Depression may first appear in adolescence
- Gastrointestinal disorders are very common (46–84%) in children with autism spectrum disorder[6]
- Blindness, deafness, tuberous sclerosis, cerebral palsy, congenital rubella, neurofibromatosis

Presentation & Symptoms

- Symptoms are diverse across and within individuals and may change over course of development
- Qualitative impairment in social interactions and communication, and presence of repetitive and stereotypic activities or behavior

Autism Spectrum Disorder (ASD) (cont.)

Diagnosis

- Maladaptive behaviors include hyperactivity, anxiety, anger, as well as stereotypies and other repetitive behaviors; about 20–30% of children exhibit serious behavior problems such as temper tantrums, aggression, and self-injury (particularly those with severe intellectual disability). As the person ages, depression, obsessive-compulsive symptoms, inappropriate social interactions, and occasionally psychotic symptoms may become more prominent

Course of Illness

- Onset in first years of life may disrupt diverse developmental processes
- Tends to be a lifelong condition that may impact academic, cognitive, and social functioning
- Early diagnosis and treatment can improve long-term outcomes
- Epilepsy may develop during early adolescence
- Life expectancy is reduced in those with severe symptoms

Treatment

- Family, psychiatric, and medical history as well as occupational and psychological assessment important to determine treatment – including audiological, visual, neurological examinations, and laboratory screening
- Goals: to improve social response and communication and reduce unusual and maladaptive behaviors
- Multimodal treatment approach recommended: primarily educational and behavioral interventions; pharmacotherapy reserved for severe cases
- Pharmacological treatment may be effective for irritability (aggression, temper tantrums, self-injurious behavior, and repetitive and impulsive behaviors) but is generally not beneficial for core features. See chapters on antipsychotics (pp. 152–241), antidepressants (pp. 52–144), and anticonvulsants (pp. 305–330)
- This population appears to be at higher risk of experiencing adverse metabolic effects of second/third-generation antipsychotics
- 8 double-blind studies suggest naltrexone has minor benefit for self-injurious behavior
- Psychostimulants (pp. 25–36) and α_2 agonists (pp. 46–49) may be beneficial with comorbid ADHD – data contradictory

Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a heterogeneous behavioral disorder first evident in children before the age of 12

Prevalence

- There is no evidence to suggest that ADHD prevalence is increasing when standardized diagnostic procedures are followed[1]
- 3–7% (4–12% in the USA)

Onset

- Symptoms begin as early as age 3; several inattentive or hyperactive-impulsive symptoms must be present by age 12
- 3–6 times more common in male than female children (but may be underreported in females); some individuals with inattentive presentation may mask symptoms by being quiet

Risk Factors

- Genetic link suggested
- Complications during pregnancy or delivery
- Adverse family environment

Comorbidity

- Mood and anxiety disorders, bipolar disorder, Tourette's disorder, conduct disorder, oppositional defiant disorder, learning disorders, substance-related disorders
- Rule out vision and learning deficits, developmental delays, neurological abnormalities, endocrine disorders, sleep disorders, anxiety disorders

Presentation & Symptoms

- Presentations include: (1) predominantly inattentive (2) predominantly hyperactive-impulsive (3) combined presentation – most common; presentation may change over time
- Inattentive symptoms: poor attention to detail, trouble holding attention, trouble listening, trouble following instructions, trouble organizing tasks, avoids tasks requiring mental effort, often loses necessary items, easily distracted, often forgetful
- Hyperactive-impulsive symptoms: fidgets, trouble staying seated, runs or climbs inappropriately, unable to participate quietly, always "on the go," talks excessively, blurts out answers, trouble waiting his/her turn, often intrudes on others

Diagnosis

- Up to age 16: six or more inattentive or hyperactive-impulsive symptoms
- Age 17 and up: five or more inattentive or hyperactive-impulsive symptoms
- Symptoms must cause impairment in social, academic, or occupational functioning

Course of Illness

- Hyperactive-impulsive behaviors tend to diminish as the person ages; inattention and restlessness often continue
- About 70% of children who are diagnosed with ADHD continue to have some symptoms in mid-adolescence and for about 40% this continues into adulthood

Consequences of ADHD

- Can result in poor academic performance, self-esteem, social and interpersonal relationships
- High risk of injuries (4 times that of non-affected individuals) and 50% more likely to have a motor vehicle accident than non-affected individuals[7]
- If inadequately treated, these children and adolescents are at increased risk for abusing substances (50% vs. 30% in non-affected individuals) and developing antisocial personality disorder
- Educational and employment difficulties, problems with driving and with sexual relationships
- Risk of teen pregnancy is 50% (vs. 4% in non-affected individuals)
- 20% risk of incarceration (vs. 1% in non-affected individuals)
- Minor involuntary movements (tics) occur in 8–11% of school-age children with ADHD

Treatment

- One study found treatment did not affect prognosis in a large longitudinal study (MTA)[8], while another large longitudinal study (MGA)[9] found significant improvements in comorbid diagnoses in adults, academic achievements, and risk of substance use with pharmacological treatment, so collaborative, multimodal approaches, including psychoeducation, pharmacotherapy (stimulants, atomoxetine, α_2 agonists, selected antidepressants), and behavioral interventions are recommended and ongoing monitoring is necessary
- See chapters on Drugs for ADHD (pp. 25–50) and Antidepressants (pp. 52–144)

Tourette's Disorder

Prevalence

- Males: 0.1%, females: 0.01%

Onset

- One or more transient symptoms appear insidiously between ages 2 and 15 and are followed by more persistent motor and vocal tics
- Average age of onset: motor tics: age 7; vocal tics: age 11

Risk Factors

- Considered a hereditary disorder with an autosomal dominant pattern of inheritance; thought to be related to an abnormality in the dopamine system
- May develop secondary to idiopathic or hereditary disorders, e.g., Huntington's disease, infections, developmental disorders, or drugs

Comorbidity

- Most frequently obsessive-compulsive disorder (50–74%) and ADHD (50%); also oppositional defiant disorder, major depressive disorder, anxiety disorders, and disruptive behavior disorders

Tourette's Disorder (cont.)

Presentation & Symptoms

- Simple motor tics seen in about 90%
- Vocal tics and grunts seen in about 98%
- Coprolalia (foul language) occurs in 10–30%

Diagnosis

- Diagnosed when multiple motor tics and at least one vocal tic occur frequently over a period of at least one year

Course of Illness

- Tics show a fluctuating course and tend to decline by adulthood. Patients are able to suppress tics for short periods of time, but experience urges to perform tics and a sense of relief when they do occur
- Frequency and severity of tics can increase with stress, excitement, or caffeine use; mental or physical activities, alcohol, nicotine, and cannabinoids appear to decrease the incidence of tics
- May cause social embarrassment and decrease self-esteem, which can impair academic, social, or occupational functioning
- Repetitive or violent movements may result in self-injury (e.g., falls, fractures) or pain to muscles and joints. Vocal tics can affect breathing, speech, and swallowing

Treatment

- Pharmacotherapy: see chapters on antipsychotics (pp. 152–241) and α_2 agonists (pp. 46–49)
- Minor benefit seen with benzodiazepines (clonazepam) and botulinum toxin injection
- Behavioral approaches (minor benefit)

SCHIZOPHRENIA

Schizophrenia is a disorder characterized by psychotic ("positive") symptoms, deficit ("negative") symptoms, and cognitive symptoms

Psychotic symptoms can occur in children with a number of diagnoses, including schizophrenia, complex developmental disorders, and autism spectrum disorder

In adolescents, symptoms must be distinguished from those of bipolar disorder (BD) (e.g., mania), personality disorders (e.g., schizoid/schizotypal and borderline personality traits/disorders) and those resulting from substance use disorders or other medical conditions

Prevalence

- Rare in children; incidence below 0.2% under age 13
- Occurs twice as often in males as in females

Onset

- Onset typically occurs in late adolescence or early adulthood (ages 15–30), lifetime prevalence of 1%
- Mean age of onset in childhood-onset schizophrenia is 8.6 years and mean age of diagnosis is 10.6 years

Risk Factors

- Increased risk if first-degree relative has a diagnosis of schizophrenia (48% for identical twins, 13% for fraternal twins, 13% for offspring, and 9% for siblings)
- Substance use disorder

Comorbidity

- Mood disorders, obsessive-compulsive disorder (OCD), ADHD, oppositional defiant disorder (ODD), conduct disorder, substance use disorders
- Rule out schizoid/schizotypal personality disorders, developmental disorders, nonpsychotic behavioral disorders, as well as medical causes of psychotic symptoms including CNS lesions, tumors or infections, autoimmune disorders (e.g., anti-NMDA receptor encephalitis), metabolic disorders, and seizure disorders

Presentation & Symptoms

- Children
  - Onset of psychotic symptoms before age 12 is considered a severe form of schizophrenia. Prodromal signs seen before age 7 include: development delays, learning disabilities, behavioral problems, solitary play, excessive anxiety, neurological problems, speech and language difficulties, and social withdrawal
  - Symptoms occur insidiously rather than acutely; auditory hallucinations and delusions are the most common presenting symptoms
  - Children show three characteristic communication deficits: (1) loose associations, (2) illogical thinking, and (3) impaired language skills
  - There appears to be a high rate of genetic abnormalities in childhood-onset schizophrenia and progressive changes in brain morphology (ventricular enlargement and reduced total brain volume)
- Adolescents
  - The onset may occur insidiously after months of prodromal symptoms
  - Some patients may experience negative symptoms that overshadow the presence of positive symptoms or the onset may appear suddenly with an acute psychotic episode (e.g., precipitated by drug abuse)
- Both positive and negative symptoms can occur:
  - Positive symptoms include delusions, hallucinations, paranoia, speech and thought disruptions (e.g., word salad, thought broadcasting, and loose associations), disorganized or catatonic behaviors (e.g., waxy or stuporous posture; see p. 21), echolalia, or echopraxia
  - Negative symptoms include affective flattening or blunting, alogia, avolition, anhedonia, inattention, amotivation, anergia, and poor grooming and hygiene
  - Cognitive symptoms include poor executive function, concentration impairment, and working memory deficits

Diagnosis

- Symptoms must impair functioning (in one or more areas: work or academic performance, interpersonal relations, self-care) for a significant portion of the time
- Continuous signs of the disorder must be present for a period of six months (includes time periods of prodromal or residual symptoms) for diagnosis of schizophrenia (if symptoms present for more than one month but less than six months, this is diagnosed as schizophreniform disorder)

Course of Illness

- Childhood and adolescent-onset schizophrenia is generally more severe and treatment refractory, and has a poorer prognosis than adult-onset illness
- The earlier the diagnosis and treatment, the better the prognosis; early treatment may delay or prevent the onset of psychosis[10] and may have benefits on cognition

Consequences of Schizophrenia

- Variable, with some individuals experiencing multiple exacerbations and remissions, while others (about 50%) remain chronically ill with minimal improvement
- Can impair age-dependent social and cognitive skills and result in social dysfunction and academic underachievement
- Associated with cognitive and neurobiological deficits that produce long-term functional impairment
- Lifetime risk of suicide completion is estimated at 5% in this population.[11] Suicide risk is highest closest to the onset of symptoms

Treatment

- Multimodal treatment approach recommended, including psychoeducation, pharmacotherapy, and psychosocial interventions. Hospitalization may also be needed
- See chapter on antipsychotics (pp. 152–241)

BIPOLAR DISORDER (BD)

Bipolar disorder is an episodic mood disorder that is generally lifelong and consists of fluctuations of mood episodes between mania and depression

Prevalence

- Adolescents: about 1–2%
- Rarely can occur in young children; children may have atypical presentations (non-episodic presentations are better described by new DSM-5 diagnosis of disruptive mood dysregulation disorder (DMDD) – see p. 11)

Onset

- Median age of onset is approximately age 18, however, in retrospect, some parents report symptoms beginning during preschool years
- Onset prior to pubescence is rare; but a pediatric/adolescent presentation indicates a more severe pathology

Risk Factors

- Family history of mood disorder (concordance rate of 50–70% in identical twins vs. 13–30% in fraternal twins)
- Substance use disorder

Comorbidity

- Concurrent ADHD seen in 73–98% of prepubescent patients with BD, vs. 54–74% of adolescents
- High rates of conduct disorder, oppositional defiant disorder (ODD), tic disorders, anxiety disorders, substance use disorders
- High risk of suicidality

Presentation & Symptoms

- BD is often not recognized until late adolescence
- Overall, there is an even distribution when the genders are pooled; 1/3 of children first experience depression, 1/3 first experience mania, and 1/3 first present with mixed features
- Mania is often misdiagnosed in children and young adolescents because of an atypical presentation. Presentations characterized by short periods of mood lability with irritability, impulsivity, recklessness, aggressiveness, self-injury, or hypersexuality may be better described by DMDD
- Mania is frequently misdiagnosed as schizophrenia (severe cases) or ADHD, a behavior disorder (e.g., ODD or conduct disorder) or personality disorder (e.g., borderline personality disorder)

Diagnosis

- Consider age of onset, symptom duration, and whether symptoms represent an ongoing cyclical pattern of mood changes (classical BD) or a pattern of chronic irritability, mood lability, and impulsivity, which is better accounted for by diagnosis of DMDD
- Family history of BD often an important finding (in 40–50% of children)
- Bipolar disorder is the most common cause of catatonia (see p. 21)
- Children may have greater mood lability, persistent mood, behavioral, and possibly cognitive difficulties, which can hamper diagnosis – e.g., rage episode followed by lassitude, remorse, or depression (consider DMDD diagnosis)
- The clinician may not be able to ask complicated questions of young children, which makes it difficult to assess symptoms; multiple informants often needed to corroborate diagnosis

Course of Illness

- Chronic, remitting-relapsing
- Early onset BD patients have a more severe course of illness
- Childhood BD (as conceptualized by some in DSM-IV-TR) does not necessarily evolve into adult BD – the reason the DMDD diagnosis was created in DSM-5

Consequences of BD

- Approximately 10-fold increase of completed suicide compared to non-affected individuals

Treatment

- Long-term multimodal treatment approach recommended, including psychoeducation, pharmacotherapy, and psychosocial interventions
- Comorbid conditions (e.g., ADHD, anxiety disorders) should be treated once BD is stabilized
- Children may experience a worsening of their clinical picture if treated with psychostimulants or antidepressants without concurrent effective mood stabilizer treatment
- Lifestyle modification strategies include: stress reduction, regular sleep habits, accommodation at school, and avoidance of caffeine, alcohol, and illicit drugs
- Guidelines recommend initial therapy include mood stabilizer (lithium or valproate) and/or second/third-generation antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone) for manic presentations, or with mixed features
- Family psychoeducation plus skill building is important for treating bipolar disorder in youth
- See chapters on mood stabilizers (pp. 296–330), second-generation antipsychotics (pp. 175–205), third-generation antipsychotics (pp. 206–216) and antidepressants (pp. 52–144)
- Electroconvulsive therapy may be useful in patients with severe manic and/or catatonic symptoms unresponsive to standard treatment approaches (see pp. 145)[12]

DEPRESSIVE DISORDERS

Disruptive Mood Dysregulation Disorder (DMDD)

Frequent, severe, and recurrent non-episodic temper outbursts that are grossly out of proportion to the situation in terms of intensity or duration

Prevalence

- 0.8–3.3%

Onset

- Not diagnosable before age 6, or after age 18; symptoms must begin before age 10

Comorbidity

- Major depressive disorder (MDD), oppositional defiant disorder (ODD)
- Some patients with DMDD were previously diagnosed with pediatric bipolar disorder

Presentation & Symptoms

- Severe and recurrent temper outbursts that are grossly out of proportion to the situation in terms of intensity or duration
- These occur, on average, three or more times each week for one year or more

Diagnosis

- Persistently irritable or angry mood, most of the day and nearly every day, that is observable by parents, teachers, or peers
- Symptoms must be present in at least two settings (at home, at school, or with peers) for 12 or more months
- Symptoms must be severe in at least one of these settings
- During this period, the child must not have gone three or more consecutive months without symptoms

Course of Illness

- Children with DMDD are at risk for MDD or generalized anxiety disorder (GAD) later in life, but not lifelong bipolar disorder

Disruptive Mood Dysregulation Disorder (DMDD) (cont.)

Treatment

- Individual, family, or school-based therapy
- Pharmacotherapy: traditional mood stabilizers and second/third-generation antipsychotics (new diagnosis, limited RCT data at present)
- See chapters on mood stabilizers (lithium and anticonvulsants) (pp. 296–330), second-generation antipsychotics (pp. 175–205), and third-generation antipsychotics (pp. 206–216)

Major Depressive Disorder (MDD)

Major depressive disorder is a mood disorder with significant physical and mental symptoms that causes significant impairment in a child's functioning

Prevalence

- Preschoolers: rare
- Children and adolescents: 2–3%; younger patients are more likely 1:1 male to female, as adolescence develops, the ratio skews toward females 3:1
- Most recent studies establish that approximately 12% of adolescents (1 in 8) will experience a major depressive disorder; twice as frequent in females than males

Onset

- Most often starts in adolescence
- There is evidence that depression is becoming more prevalent in children under age 10

Risk Factors

- First-degree relatives with mood disorder (bipolar or major depressive disorder)
- Previous depressive episodes
- Anxiety disorders, chronic medical illness, substance abuse
- Strong association of childhood trauma and abuse with depression and suicidality in adulthood

Comorbidity

- Seen in about 40% of children and adolescents
- Common comorbidities in children: separation anxiety, ADHD
- Common comorbidities in adolescents: generalized anxiety disorder, social anxiety disorder, ADHD, conduct disorder, substance-related disorders
- Depression common in persons with intellectual disability (may be manifested by aggressive behavior)

Presentation & Symptoms

- Vary with age or equivalent developmental level. Children may not be able to localize their symptoms.
- Ages 3–4: disruptive behaviors (acting out, aggression, temper tantrums, hyperactivity, and oppositional behaviors), somatic symptoms (e.g., headache, stomach pains), enuresis and encopresis, social withdrawal, eating or sleeping difficulties, separation problems
- Ages 5–8: sadness, social withdrawal, low self-esteem, excessive guilt, self-blame, unexplainable somatic symptoms, enuresis and encopresis, being accident prone, carelessness, lying, oppositional and aggressive behaviors
- Ages 9–12: sadness, somatic complaints, difficulty concentrating, school problems, separation anxiety, isolation, apathy, anhedonia, hopelessness, irritability, suicidal ideation
- Adolescents: symptoms are similar to those seen in adults: mnemonic "MSIGECAPS" – Mood low, Sleep changes, Interests decline, Guilty/negative thoughts, Energy low, Concentration low, Appetite/weight change, Psychomotor change, Suicidal thinking
- 15% of adolescents present with the subtype "with atypical features," which includes mood reactivity and one of: hypersomnia, hyperphagia, leaden paralysis, or sensitivity to criticism
- Suicidal ideation can occur at any age. Suicide risk generally starts at age 10 and increases with each year until age 24.

Diagnosis	• Children may have greater mood lability, which can hamper diagnosis • The clinician may not be able to ask complicated questions of young children, which makes it difficult to assess depressive symptoms • Collateral history is often required to corroborate diagnosis
Course of Illness	• Variable with some individuals experiencing multiple exacerbations and remissions • 20% of adolescents will have a chronic (more than 2 years) episode of depression • Recurrence rates are up to 25% within 1 year, and 70% within 5 years • MDD in youth may be the index case of bipolar disorder (BD) – the rate of developing BD is 1–6% per year.[13] Risks for developing BD include psychotic symptoms, early age of onset, family history of BD
Consequences of Depression	• Lifetime risk of suicide completion in MDD is approximately 2.2% (4 x that of the general population)[14] • In adolescence, the relative risk of suicide completion is approximately 3.5 for patients with MDD vs. those without MDD • Can impair age-dependent social and cognitive skill development and result in social dysfunction and academic underachievement, tobacco use, substance/alcohol abuse, and teen pregnancy • Childhood depression strongly increases the risk for future mood disorders (4-fold increase in the risk of depression in adulthood for those who have experienced significant depressed mood as a child or adolescent) • A depressive episode in childhood may represent an early stage of classical bipolar disorder
Treatment	• Consider nonpharmacological treatment strategies for mild depression. Extensive evidence supports the use of cognitive-behavioral therapy (CBT) in children and adolescents or interpersonal therapy (IPT) • Nonpharmacological and pharmacological treatments have equivalent relapse rates • For moderate to severe, chronic or refractory depression, a multimodal treatment approach is recommended including psychoeducation, pharmacotherapy, and psychosocial interventions • Electroconvulsive therapy may be indicated for severe suicidal thinking, refractory depression, and multiple failed treatments • See chapter on antidepressants (pp. 52–144) • There is a high placebo response rate (up to 50%) in multicenter randomized controlled pharmacotherapy and psychotherapy trials in children and adolescents, which makes it more difficult to detect a therapeutic effect of the treatment

ANXIETY DISORDERS

Anxiety disorders are cognitive disorders characterized by excessive rumination, worrying, and fear

Anxiety disorders are the most common mental health disorder in children and adolescents: 3–10% prevalence in children under age 12[15] and 10–24% in adolescents[16]

There is a relatively strong relationship between anxiety disorders in children and their parents (risk is 2- to 4-fold if a parent has an anxiety disorder; risk for anxiety also high if a parent has a depressive disorder). Traumatic events during childhood reported to markedly increase risk for anxiety disorders later in life

It is important to rule out medical conditions that could contribute to or aggravate the anxiety disorder (e.g., asthma). 30–50% of children with anxiety disorders also have a mood disorder. Importantly, children, in general, are not required to have awareness or insight into the unreasonableness of or dysfunction caused by the anxiety disorder to qualify for the diagnosis

Children often cannot identify their emotional state as worried or anxious, and may display behaviors that are avoidant, aggressive, or regressive; clinical investigation with as many collateral sources of information as possible is required

Anxiety disorders in general add significantly to suicide risk as an independent risk factor: estimates range from 2- to 6-fold.

Separation Anxiety Disorder

Separation anxiety disorder is an anxiety disorder characterized by excessive fear or upset caused by separation from an attachment figure

Prevalence
- 3–5% in childhood; 0.7% in adolescence
- May be slightly more common in females than males

Onset
- Age 5–12. Typically, a diagnosis may not be made until age 8–9, as separation anxiety is considered a developmentally appropriate early sign of adjustment in those aged 6 months to 4 years

Risk Factors
- May be associated with parental anxiety or depressive disorders
- 50–75% of children with separation anxiety disorder are from homes associated with low socioeconomic status
- Reported to occur in up to 80% of children with school refusal

Comorbidity
- Major depressive disorder (MDD), posttraumatic stress disorder (PTSD), autism spectrum disorder (ASD)

Presentation & Symptoms
- Characterized by developmentally inappropriate and excessive anxiety or recurrent fear of separation from home or a loved one, e.g., may manifest as refusal to attend school (75% of cases) or repeated complaints of physical symptoms (e.g., headaches, stomach aches) or nightmares when separation occurs or is anticipated; some children develop signs of a panic attack
- Similar symptoms in males and females
- Children aged 5–8 most commonly manifest unrealistic worry about harm to parents or attachment figures and school refusal
- Children aged 9–12 usually manifest excessive distress at times of separation
- Adolescents manifest somatic complaints and school refusal
- May require parental assistance to complete simple tasks (e.g., getting dressed, brushing teeth)

Diagnosis
- Symptoms are persistent and must last at least 4 weeks in children and adolescents
- The disorder causes clinically significant distress in social, academic, or occupational functioning

Course of Illness
- The duration of the disorder reflects its severity
- Longitudinal studies suggest that childhood separation anxiety disorder may be a risk factor for other anxiety disorders

Treatment
- The majority of mild cases are treated with behavior therapy or other forms of psychotherapy
- Pharmacological therapy is generally reserved for severe cases or in the presence of serious psychiatric complications such as depression or suicidality
- See chapters on antidepressants (pp. 52–144) and benzodiazepines (pp. 263–276)

Specific Phobia

Prevalence
- The most common anxiety disorder in childhood and adolescence
- Approximately 10% of youths (large variance in studies)

Onset	• Generally in middle childhood; may occur after exposure to a particular occurrence or may develop as a fear of that occurrence happening • Peak onset is age 10–14 • May vary by type of specific phobia (for example, animal phobia peak incidence at age 7, thunderstorms peak at age 12)
Comorbidity	• High comorbidity with other anxiety disorders, major depressive disorder • Substance misuse often occurs as a coping strategy
Presentation & Symptoms	• Characterized by excessive and problematic fear or avoidance of specific objects or situations, as expressed verbally (openly worrying) or through behavior (clinging, freezing, crying, running) • The object or situation almost always causes an intense reaction • Avoidance or anxiety around potential exposure to the object or situation occurs regularly • Major subgroups include animal (dogs, spiders, snakes), natural environment (heights, water), blood-injection-injury (needles, dentistry), situational (enclosed areas, flying), and other (in children, commonly fear of vomiting/choking, loud sounds, costumed characters)
Diagnosis	• Must be persistent and last for more than 6 months, or be of sufficient clinical impairment to warrant immediate action • Major impairment in school, academic, family, or occupational functioning is required
Course of Illness	• Approximately 50% of cases are chronic (defined as lasting longer than 1 year) • Generally seen as a benign disorder, as specific phobia triggers can often be avoided. However, significant negative effects occur with avoidance (avoiding medical treatment, impaired hydration/nutritional status, reduced quality of life, depression, panic attacks)
Treatment	• The best treatment strategies are generally *in vivo* exposure-based therapies, particularly cognitive behavioral therapies centered around "systematic desensitization." This involves gradually increasing exposure to the phobic object or situation and learning to tolerate the anxiety, until practical *in vivo* exposure occurs • Short-term benzodiazepine treatment can be used for rare events (e.g., flying), but should be cautioned due to the risk for misuse

Social Anxiety Disorder

Social anxiety disorder is an anxiety disorder characterized by intense fear in social situations, resulting in significant functional difficulty

Prevalence	• 1–2%
Onset	• Seen in preschool- and school-aged children, but usually begins between ages 13 and 20; more than 50% of patients are affected before adolescence
Risk Factors	• Family history of social anxiety disorder • Early childhood trauma or abuse (up to 50%) • May be influenced by parental modeling of childhood social fears
Comorbidity	• Depressive disorders, panic disorder, and generalized anxiety disorder (GAD)

Social Anxiety Disorder (cont.)

Presentation & Symptoms

- Intense anxiety upon exposure to situations in which the individual may be scrutinized and possibly embarrassed; may involve specific fears related to a situation or close social contact

Diagnosis

- Presence of persistent (more than 6 months duration) marked fear or anxiety symptoms almost always occurring in social situations when exposed to possible scrutiny by others
- Symptoms are out of proportion to the situation and situations are avoided, or are endured with intense symptoms
- In children, anxiety symptoms (may be expressed by crying, freezing, tantrums, clinging, shrinking, or failing to speak) must occur with peer interactions (not just with adults)

Treatment

- The majority of mild cases are treated with behavior therapy or other forms of psychotherapy (e.g., CBT or IPT)
- There are limited data on effective pharmacological treatments in children
- Pharmacological therapy is generally reserved for moderate to severe cases
- See chapters on antidepressants (pp. 52–144) and anxiolytics (pp. 263–281)

Panic Disorder

Panic disorder is an anxiety disorder characterized by multiple, severe panic attacks

Prevalence

- 2–3.3%

Onset

- Often begins during adolescence; although it may start during childhood, it is often difficult to diagnose at an early age

Risk Factors

- Tends to run in families; risk high if both parents have an anxiety disorder (especially social anxiety disorder) or bipolar disorder
- Exposure to childhood sexual or physical abuse

Comorbidity

- Major depressive disorder, bipolar disorder, persistent depressive disorder, hypomania, other anxiety disorder (especially generalized anxiety disorder, social anxiety disorder, separation anxiety), or conduct disorder
- Asthma (6.5–24% in adults)

Presentation & Symptoms

- Panic attacks refer to unexpected and repeated periods of intense fear or discomfort, along with symptoms (below) which can last minutes to hours. Panic attacks frequently develop without warning
- Symptoms: racing or pounding heartbeat or palpitations, chest pain, intense fearfulness (a sense that something terrible is happening), dizziness or lightheadedness, faintness, shortness of breath or a feeling of being smothered, trembling or shaking, sweating, paresthesias, chills or heat sensations, fear of dying, losing control or losing one's mind, a sense of derealization or depersonalization

Diagnosis

- Four or more of the above symptoms occurring together
- At least one of the attacks followed by a 1 month or longer period of persistent concern or worry about future attacks and a maladaptive change in behavior related to the attacks

Course of Illness

- Panic attacks can interfere with relationships, schoolwork, and normal development. Children and adolescents with panic disorder may begin to feel anxious most of the time, even when they are not having panic attacks. Some begin to avoid situations where they fear a panic attack may occur, or situations where help may not be available; e.g., a child may be reluctant to go to school or be separated from his/her parents. In severe cases, the child or adolescent may be afraid to leave home (agoraphobia)
- Some children and adolescents with panic disorder can develop severe depression and may be at risk of suicidal behavior
- As an attempt to decrease anxiety, some adolescents with panic disorder will use alcohol or drugs
- Panic attacks during adolescence are associated with an increased risk of development of personality disorders during young adulthood

Treatment

- Many children and adolescents with panic disorder respond well to the combination of pharmacotherapy and psychotherapy. With treatment, the panic attacks can usually be stopped. Early treatment can prevent the complications of panic disorder such as agoraphobia, depression, and substance-related disorders
- Psychotherapy may also help the child and family learn ways to reduce stress or conflict that could otherwise cause a panic attack. With CBT techniques, the child may also learn new ways to control anxiety or panic attacks when they occur
- See chapters on antidepressants (pp. 52–144) and anxiolytics (pp. 263–281)

Generalized Anxiety Disorder (GAD)

Generalized anxiety disorder is an anxiety disorder characterized by worries and fears in a number of areas, with physical and psychological consequences

Prevalence

- 2.2% in patients 12–17 years of age

Onset

- Often begins in childhood or adolescence

Risk Factors

- Family history of anxiety or depression

Comorbidity

- Depressive disorders, social anxiety disorder, ADHD, substance use disorders

Presentation & Symptoms

- Excessive anxiety and worry incongruent with the circumstances or developmental age
- At least one of the following somatic complaints: feelings of restlessness, fatigue, irritability, difficulty concentrating, muscle tension, or sleep disturbance
- May include refusal to attend school

Diagnosis

- Symptoms present on more days than not for at least 6 months
- Symptoms cause clinically significant impairment in social, academic, or occupational functioning

Course of Illness

- Fluctuates, worsening at times (especially during times of stress), and persists for many years

Generalized Anxiety Disorder (GAD) (cont.)

Treatment

- The majority of mild cases are treated with behavior therapy or other forms of psychotherapy (e.g., CBT or IPT)
- Pharmacotherapy is generally reserved for moderate to severe cases
- See chapters on antidepressants (pp. 52–144) and anxiolytics (pp. 263–281)

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Obsessive-compulsive disorder is characterized by obsessions (excessive thoughts and worries about a particular topic) and compulsions (behaviors designed to decrease obsessions, whether realistic or not)

Prevalence

- Up to 3%

Onset

- In children, may be difficult to distinguish from mild rituals that are normal in early childhood
- Can begin as early as age 3

Comorbidity

- Major depressive disorder, bipolar disorder, ADHD, anxiety disorders (panic disorder, social anxiety disorder), schizophrenia, disruptive behavior disorders, Tourette's disorder

Presentation & Symptoms

- Similar to those seen in adults
- Obsessions: recurrent and persistent ideas, thoughts, impulses, or images that are experienced as intrusive, unwanted, and cause marked anxiety or distress
- Compulsions: repetitive behaviors (e.g., handwashing, checking) or mental acts (e.g., counting, repeating) performed to prevent or reduce anxiety or distress in response to an obsession or according to rigidly applied rules
- Children can be secretive about their symptoms fearing what others may think
- Young children may not be able to articulate the aims of the behaviors or mental acts

Diagnosis

- Obsessions and compulsions are time consuming (more than 1 h per day) or cause clinically significant impairment in social, academic, or occupational functioning

Course of Illness

- Can severely impact functioning and academic performance
- Untreated OCD can become chronic and incapacitating to the individual

Treatment

- Psychological treatments are the cornerstone of OCD management, specifically cognitive-behavioral therapy (CBT) utilizing exposure and response prevention (ERP)
- Pharmacotherapy may be necessary as an adjunct to behavioral treatments
- Electroconvulsive therapy and surgery have case-study-level evidence in severe and refractory cases
- See chapter on antidepressants (pp. 52–144)

POSTTRAUMATIC STRESS DISORDER (PTSD)

Posttraumatic stress disorder is a severe disorder characterized by specific psychological and physical symptoms that are related to an experienced traumatic event

Prevalence

- 14–43% of children and adolescents have experienced at least one traumatic event in their lifetime. Of those children and adolescents who have experienced a trauma, 3–15% of girls and 1–6% of boys meet criteria for PTSD

Onset

- Traumatic symptoms change depending on the developmental age of the individual and may occur immediately or as a delayed response to any significant trauma

Risk Factors

- Severity or repetition of the trauma
- Premorbid anxiety
- Females may be at higher risk than males
- For intentional abuse, risk is highest for sexual abuse, next is physical abuse, emotional abuse, and verbal abuse. The additive risk by types of intentional abuse are cumulative

Comorbidity

- Major depressive disorder
- Other disorders include other anxiety disorders such as separation anxiety, panic disorder, and generalized anxiety disorder, ADHD, oppositional defiant disorder, conduct disorder, and substance use disorders

Presentation & Symptoms

- The four symptom clusters of PTSD include:
  - Intrusion symptoms (memories, dreams, re-enactments, reaction to representations of the trauma)
  - Avoidance symptoms (efforts to avoid memories, reminders, or associations to the trauma)
  - Deficit, cognitive, and mood symptoms (amnesia to aspects of the trauma, exaggerated negative beliefs, distorted beliefs about the cause of the trauma, loss of interests, disconnection from others, emotional numbness)
  - Arousal symptoms (irritability, hypervigilance, self-destructive behavior, easy to startle, concentration problems, sleep problems)
- Children have different responses to trauma than adults. Children may not recognize the content of nightmares, or may re-enact the trauma in play situations. Under age 6, children do not need as many criteria to qualify for the diagnosis

Diagnosis

- Symptoms present for at least 1 month
- Symptoms cause clinically significant impairment in social, academic, or occupational functioning

Course of Illness

- Although some children show a natural remission in PTSD symptoms over a period of a few months, a significant number may exhibit symptoms for years if untreated
- Frequency, duration, and intensity of trauma is directly related to suicide risk; severity of trauma is correlated to severity of self-injurious behaviors, suicide attempts, and completed suicide

Treatment

- Once the trauma has occurred, early intervention is essential. Education and support from parents, the school, and peers is important. Emphasis needs to be placed upon establishing a feeling of safety
- Multimodal treatment usually required:
  - Cognitive-behavioral therapy is most effective and generally includes directly discussing the traumatic event (exposure), anxiety management techniques such as relaxation and assertiveness training, and correction of inaccurate or distorted trauma-related thoughts. Psychotherapy (individual, group, or family) that allows the child to speak, draw, play, or write about the event is helpful
  - Pharmacotherapy may be useful in dealing with agitation, anxiety, hyperarousal, impulsivity, self-injurious behavior, aggression, or with comorbid conditions such as MDD, ADHD or psychosis – see chapters on antidepressants (pp. 52–144), antipsychotics (pp. 152–241), α_2 agonists (pp. 46–49), anxiolytics (pp. 263–281), and anticonvulsants (pp. 305–330)

DISRUPTIVE, IMPULSE-CONTROL, AND CONDUCT DISORDERS

Oppositional Defiant Disorder (ODD)

Oppositional defiant disorder is a behavioral disorder characterized by inappropriate and repeated acts of hostility and disobedience in multiple situations

Prevalence	• 4–7%
Onset	• Recognized at an early age
Risk Factors	• Genetics • Dysfunctional family
Comorbidity	• ADHD, bipolar disorder, learning disorders, communication disorders, motor disorders
Presentation & Symptoms	• Persistent angry or irritable mood, argumentative or defiant behavior, vindictiveness • Frequent loss of temper, defiance, tendency to be argumentative, easily annoyed by others and deliberately trying to annoy others, spiteful, blaming others for own mistakes
Diagnosis	• For children under age 5: behaviors occur on most days for a period of 6 months • For children age 5 and above: behaviors occur at least once weekly for a period of 6 months • Behaviors are associated with distress in the individual or another in his/her social context, or cause clinically significant impairment in social, academic, or occupational functioning
Course of Illness	• 57% of patients with ODD and ADHD continue to have ODD symptoms after 4 years
Treatment	• Behavioral, including parent management training (response rate 40–50%) • Pharmacotherapy – see chapters on antipsychotics (pp. 152–241), antidepressants (pp. 52–144), stimulants (pp. 25–36), and mood stabilizers (pp. 296–330)

Conduct Disorder (CD)

Conduct disorder is a behavioral disorder characterized by significant intrusion into the basic rights of others and the consistent intentional violation of appropriate norms

Prevalence	• 1–10%

Onset	• Usually in early adolescence, but impairments can be seen by age 5 in early-onset conduct disorder
Risk Factors	• Dysfunctional family • Oppositional defiant disorder (2.7–40% of children develop conduct disorder)
Comorbidity	• ADHD, bipolar disorder, learning disorders, communication disorders, motor disorders
Presentation & Symptoms	• Childhood onset: signs of impulsivity, aggression, and hyperactivity by age 10 • Adolescent onset: no signs of impulsivity, aggression, and hyperactivity before age 10 • Symptoms include: repetitive and persistent pattern of disruptive behavior and violation of rights of others or of societal norms, aggression towards people and animals, theft, destruction of property, deceitfulness, serious violation of rules • Course specifiers include: limited prosocial emotions, lack of remorse or guilt, lack of empathy, unconcerned about performance, shallow or deficient affect
Diagnosis	• Three symptoms must be present within the past 12 months, and at least one symptom in the past 6 months • Causes clinically significant impairment in social, academic, or occupational functioning
Course of Illness	• Childhood onset: delinquent behavior and violent crimes often begin at an early age and increase in seriousness; continues into adulthood • Adolescent onset: only 25% continue delinquent behavior into adulthood; precursor to adult antisocial personality disorder
Treatment	• Behavioral therapies (including individual therapy, parent management training, and group therapy), interventions at school and with peer group • Pharmacotherapy – in conduct disorder with ADHD, treatment of ADHD is crucial to improve outcomes; in conduct disorder without ADHD, risperidone has moderate evidence for improving outcomes.[17] See chapters on antipsychotics (pp. 152–241), antidepressants (pp. 52–144), mood stabilizers (pp. 296–330), stimulants (pp. 25–36), and anxiolytics (pp. 263–281)

SYNDROME: Catatonia

Catatonia is an **often unrecognized** syndrome characterized by hypo-/hyper-activity, automatic behaviors and speech, abnormal vital signs, decreased output, and/or decreased oral intake. It should be considered to be a psychiatric emergency due to its high association with morbidity and mortality.[18]

Prevalence	• Estimated prevalence in inpatient psychiatric units is approximately 10%
Onset	• Occurs at any age • Usually acute onset, significant change from baseline behavior. However, many symptoms may be missed and a longstanding illness is possible
Risk Factors	• Most common underlying cause is bipolar disorder (approximately 50% of recognized cases), followed by schizophrenia (15%) • In child populations, emerging evidence that autism has a high prevalence of catatonia (12–20%), as does intellectual disability.[19] For these cases, the autism itself can be a cause of the catatonia

SYNDROME: Catatonia (cont.)

Comorbidity

- As catatonia is a syndrome caused by another underlying disorder (medical or psychiatric), comorbidity with an illness is 100%
- Malignant catatonia may develop, which is the presence of rigidity, autonomic instability, and altered mental status, and is associated with a high morbidity and mortality (without treatment, most patients will die)[20]
- Neuroleptic malignant syndrome (NMS, see p. 183) and serotonin syndrome (see p. 59) can be considered an iatrogenic type of malignant catatonia secondary to the use of psychiatric medications (in NMS, many antipsychotic medications; in serotonin syndrome, many antidepressants)

Presentation & Symptoms

- For any significantly compromised psychiatric patient, or a patient who has an abrupt change in presentation, clinical screening with a reliable scale (Bush-Francis Catatonia Rating Scale, Northoff Catatonia Rating Scale, Rogers Catatonia Scale, etc.) is strongly recommended
- Symptoms are generally hallmarked by a perceived automaticity and lack of control over the symptoms, rather than willful changes
- Motor symptoms include: hypo-/hyper-activity, unusual movements (freezing, staring, posturing, grimacing, mannerisms, stereotypies), *mitgehen* (an exaggerated response to touch), *gegenhalten* (involuntary resistance to passive movement), waxy flexibility, posturing, and ambitendency
- Speech disturbances include: mutism, verbal stereotypies, perseveration, and verbigeration
- Malignant catatonia: autonomic/thermoregulatory dysfunction, rigidity, altered sensorium/delirum

Diagnosis

- Each rating scale has its own guidelines for cut-offs, in general the presence of 2–4 screening criteria define the diagnosis

Course of Illness

- Response to treatment has not been well studied but decades of clinical experience show robust response to electroconvulsive therapy (ECT) or benzodiazepines
- If left untreated (4+ days), risk of permanent disability increases
- Very few controlled trials exist for the treatment of catatonia, but there has been a significant reduction in mortality since the introduction of ECT for catatonia and neuroleptic malignant syndrome

Treatment

- Benzodiazepines (e.g., lorazepam 1–2 mg immediately and q 3–6 h until underlying disorder can be treated). Higher doses may be necessary (as high as 24 mg/day of lorazepam[21] reported in the literature). Classically, response is robust (response rate 70%+), and few of the expected side effects from benzodiazepines (dizziness, drowsiness) are seen
- ECT (see pp. 145–151) has significant evidence and should be used in all patients with catatonia unresponsive to benzodiazepines or if a life-threatening syndrome occurs; if catatonia is seen in a major depressive disorder, ECT has first-line treatment recommendations in many guidelines
- Treatment (either benzodiazepines or ECT) must continue until the underlying cause is treated. Removal of catatonia treatment prior to this results in rapid recurrence. If catatonia is due to autism or intellectual disability, regular long-acting benzodiazepine or maintenance ECT should be strongly considered
- Zolpidem, glutamate antagonists, bromocriptine, valproate, and lithium all have case report evidence
- Pharmacotherapy – see chapters on anxiolytics (pp. 263–281) and hypnotics (pp. 282–295)

Further Reading

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DRUGS FOR ADHD

Classification

- Drugs for ADHD can be classified as follows:

Chemical Class	Agent	Page
Psychostimulant	Amphetamine and related drugs (e.g., lisdexamfetamine) Methylphenidate, dexmethylphenidate[B]	See p. 25
Selective norepinephrine reuptake inhibitor	Atomoxetine Viloxazine[B]	See p. 36 See p. 36
α_2 agonist	Clonidine Guanfacine	See p. 46
Antidepressant	Bupropion Venlafaxine, desvenlafaxine Tricyclic agents	See p. 67 See p. 73 See p. 102
Dopaminergic agent	Modafinil Armodafinil[B]	See p. 401

[B] Not marketed in Canada

Psychostimulants

Product Availability*

Generic Name	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Methylphenidate	Dopamine, norepinephrine/Multimodal	Ritalin	Tablets: 5 mg, 10 mg, 20 mg	Not recommended for children under age 6
		Methylin[B]	Oral solution: 5 mg/5 mL, 10 mg/5 mL	
		Ritalin SR, Methylin ER[B]	Sustained-release tablets: 10 mg[B], 20 mg	
		Metadate ER[B],	Sustained-release tablets: 20 mg	
		Metadate CD[B]	Extended-release capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg	
		Ritalin LA[B]	Extended-release capsules: 10 mg, 20 mg, 30 mg, 40 mg, 60 mg	
		Concerta	Extended-release tablets: 18 mg, 27 mg, 36 mg, 54 mg	

Psychostimulants (cont.)

Generic Name	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
		ACT Methylphenidate ER, Apo-Methylphenidate ER[C], PMS-Methylphenidate ER[B][C], Teva-Methylphenidate ER-C[B],[C]	Extended-release tablets: 18 mg, 27 mg, 36 mg, 54 mg	
		Aptensio XR[B]	Extended-release capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg	
		Biphentin[C]	Controlled-release capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg	
		Foquest[C]	Controlled-release capsules: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, 100 mg	
		Cotempla XR-ODT[B]	Extended-release orally disintegrating tablets: 8.6 mg, 17.3 mg, 25.9 mg	
		Quillichew ER[B]	Extended-release chewable tablets: 20 mg, 30 mg, 40 mg	
		Quillivant XR[B]	Extended-release suspension: 5 mg/mL (after reconstitution)	
		Jornay PM[B]	Delayed-release/Extended-release capsules: 20 mg, 40 mg, 60 mg, 80 mg, 100 mg	
Methylphenidate transdermal patch[B]	Dopamine, norepinephrine/Multimodal	Daytrana	Transdermal system: 10 mg/9 h, 15 mg/9 h, 20 mg/9 h, 30 mg/9 h	Safety and efficacy not established in children under age 6
Dexmethylphenidate[B]	Dopamine, norepinephrine/Multimodal	Focalin	Tablets: 2.5 mg, 5 mg, 10 mg	Safety and efficacy not established in children under age 6
		Focalin XR	Extended-release capsules 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg	
Amphetamine[B]	Dopamine, norepinephrine/Multimodal	Adzenys ER	Extended-release suspension: 1.25 mg/mL	Not recommended for children under age 6
		Adzenys XR-ODT	Extended-release orally disintegrating tablets: 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg	Not recommended for children under age 6
		Dyanavel XR	Suspension: 2.5 mg/mL	Not recommended for children under age 6
		Evekeo	Tablets: 5 mg, 10 mg	Not recommended for children under age 3
		Evekeo ODT	Orally disintegrating tablets: 5 mg, 10 mg, 15 mg, 20 mg	

Generic Name	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Dextroamphetamine/Amphetamine salts (mixed amphetamine salts)	Dopamine, norepinephrine/Multimodal	Adderall[B]	Tablets[B]: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg	Not recommended for children under age 3
		Adderall XR	Extended-release capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg	USA: Not recommended for children under age 3 Canada: Not recommended for children under age 6
		Mydayis[B]	Extended-release capsules: 12.5 mg, 25 mg, 37.5 mg, 50 mg	Not recommended for children under age 13
Dextroamphetamine	Dopamine, norepinephrine/Multimodal	Dexedrine	Tablets: 5 mg, 10 mg[B] Elixir: 5 mg/5 mL[B]	USA: Not recommended for children under age 3 Canada: Not recommended for children under age 6
		Dexedrine Spansules	Extended-release capsules: 5 mg[B], 10 mg, 15 mg	Not recommended for children under age 3
		Xelstrym[B]	Transdermal system: 4.5 mg/9 h, 9 mg/9 h, 13.5 mg/9 h, 18 mg/9 h	Safety and efficacy not established in children under age 6
		Zenzedi[B]	Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg	Not recommended for children under age 3
Lisdexamfetamine	Dopamine, norepinephrine/Multimodal	Vyvanse	Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg[B]	Not recommended for children under age 6
			Chewable tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg	
Methamphetamine[B] (desoxyephedrine)	Not listed	Desoxyn	Tablets: 5 mg	Not recommended for children under age 6

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- 👍 Attention-deficit/hyperactivity disorder (ADHD)
- Narcolepsy
- Decreasing anger, irritability, and aggression in brain-injured patients, oppositional defiant disorder, conduct disorder, and ADHD – positive results with methylphenidate
- Inattention and hyperactivity in autism and intellectual disability (paradoxical overactivity and agitation can occur) – controlled studies suggest methylphenidate has modest efficacy, contradictory data regarding benefit in autism; adverse effects may be more problematic in this population

In adults:

- 👍 ADHD
- 👍 Parkinson's disease
- 👍 Narcolepsy

‡ Indications listed here do not necessarily apply to all psychostimulants or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Psychostimulants (cont.)

- Obesity (amphetamine, dextroamphetamine – USA only)
- Binge-eating disorder (lisdexamfetamine)
- Decreasing anger, irritability, and aggression in brain-injured patients, oppositional defiant disorder, conduct disorder, and ADHD – positive results with methylphenidate
- Augmentation of cyclic antidepressants, SSRIs and RIMA
- Chronic fatigue syndrome; neurasthenia
- Schizophrenia: Negative symptoms; some improvement noted in cognitive deficits, mood, and concentration with low doses of dextroamphetamine

General Comments

- All psychostimulants, when dosed adequately, are considered to be equally effective at reducing symptoms of inattention, hyperactivity, and impulsivity
- Select trials have demonstrated decreases in interrupting, impulsive responses, fidgeting, finger-tapping, physical and verbal aggression, and negative or antisocial interactions
- Increase attention, focus, short-term memory, reaction time, and problem solving; improve interpersonal interactions
- Stimulants do not improve children's ratings of anxiety or measures of academic achievement
- Generally, response occurs within the first week; response seen in approximately 75% of children; effect not as robust in adolescents or very young children
- In preschoolers, clinical effects are variable and adverse effects more common – reserve for serious cases not responding to behavioral intervention
- An untreated comorbid mood or anxiety disorder may diminish response to stimulants or decrease the ability to tolerate the medication – data contradictory
- The effect of long-term stimulants on standardized exams, school completion, or quality of life outcomes is unknown
- Psychostimulants can be abused or diverted for street purposes; use with caution and careful monitoring. Choose formulations with lower risk for abuse and diversion (e.g., lisdexamfetamine) in patients with current substance use. Children with ADHD being effectively treated with stimulants may be less likely to abuse substances than those with untreated ADHD
- Lisdexamfetamine is a prodrug considered to have less potential for abuse and diversion than short-acting stimulants[1]
- See Precautions (p. 33) and Contraindications (p. 34) regarding patient risks

Pharmacology

- Mechanism of action in treating ADHD is not well understood
- Methylphenidate blocks the reuptake of norepinephrine (NE) and dopamine (DA) into presynaptic nerve endings. In addition to blocking NE and DA reuptake, amphetamines also promote the release of NE and DA from presynaptic neurons. Increases in DA are suggested to improve attention, decrease distractibility, and modulate motivation, thus improving performance
- Release of DA and NE in subcortical limbic areas (e.g., nucleus accumbens) has been proposed as the mechanism responsible for the abuse potential of these drugs
- See chart p. 41

Dosing

- See chart p. 41
- Treatment is often started at low doses in school-aged children and gradually increased over several days or weekly; initial improvement noted may plateau after 2–3 weeks of continuous use (e.g., a decreased "energizing" feeling) – this does not imply tolerance; patients should compare the plateau to their baseline, not to the peak effect seen in the first week
- The effect of stimulants is not always associated with the dose; doses above 1 mg/kg/day of methylphenidate may not result in an increased response, however, adverse effects can increase. Doses above 1 mg/kg/day may be tried in those tolerating the stimulant and who have had a moderate response. Some patients may be short-duration responders or high-dose responders[2]
- To minimize appetite-reducing effects, give drug with or after meals; food can affect T_{max} and/or C_{max} (see table p. 43)
- Patients who have problems swallowing pills may use one of several medications formulated as beads (Adderall XR, Foquest, Aptensio XR/Biphentin, Dexedrine Spansules, Jornay PM, Metadate CD, Mydayis, or Ritalin LA), by opening the capsule, sprinkling the beads in apple sauce or other soft food, and swallowing the mixture without chewing. Lisdexamfetamine capsules may be opened and the contents dispersed in a glass of plain

water, orange juice or yogurt. This has the advantage that it not only allows for medication of children who cannot swallow the whole capsule, but also enables fine tuning of the dose, and allows parents to reduce the dose if necessary prior to seeing the physician. Lisdexamfetamine chewable tablets provide similar dextroamphetamine exposure to the capsule formulation

- The orally disintegrating formulation of amphetamine (Evekeo ODT), amphetamine salts (Adzenys XR-ODT) or methylphenidate (Cotempla XR-ODT) may be dissolved on the tongue and swallowed
- Amphetamine extended-release liquid suspension (Dyanavel XR) available; also methylphenidate extended-release formulations as liquid suspension (Quillivant XR) and chewable tablet formulation of methylphenidate (Quillichew ER), and lisdexamfetamine (Vyvanse)
- Divided doses required with immediate-release (IR) formulations of methylphenidate (dose approximately every 4 h). Important to document "wear-off" times (changes in behavior/attention) and adjust dosing interval accordingly
- Problems falling asleep occur most frequently when the medication is wearing off and the patient experiences rebound irritability or return of symptoms. A small dose of methylphenidate at this time can minimize this effect. There is a group of children and adults who find it easier to go to bed, and easier to fall asleep when given a low dose of stimulant before bedtime
- Methylphenidate SR has an erratic release in slightly less than half of patients and has been shown to be somewhat less effective. However, for patients who are methylphenidate SR responders, the duration of 5 h can carry them through transitions such as lunch or the bus ride home such that they get their next dose before they experience rebound. Methylphenidate IR in adequate doses usually lasts less than 3.5 h and so, if given after breakfast, may wear off before the next dose at lunchtime and, if given after lunch, may wear off before the child returns home after school
- The extended-release formulations may decrease dysphoria between doses and/or rebound hyperactivity. Supplementation with short-acting formulations may be needed in the morning (to speed up onset) or in the afternoon (to extend duration of action)
- Jornay PM is a delayed-release/extended-release methylphenidate formulation intended for evening administration, resulting in onset of stimulant action (approximately 10 h after administration) in the morning upon waking
- Methylphenidate transdermal patch (Daytrana): Total dose delivered is dependent on patch size and wear time. Dose delivered over 9 h: 10 mg for 27.5 mg patch, 15 mg for 41.3 mg patch, 20 mg for 55 mg patch, and 30 mg for 82.5 mg patch. Dose titration recommended on a weekly basis (9 h wear period/day), as required. Patch can be removed earlier than 9 h for shorter duration of effect or if late-day adverse effects are problematic
- Dextroamphetamine transdermal patch (Xelstrym): Total dose delivered is dependent on patch size and wear time. Dose delivered over 9 h: 4.05 mg for 4.5 mg patch, 8.1 mg for 9 mg patch, 12.2 mg for 13.5 mg patch, and 16.2 mg for 18 mg patch. Dose titration recommended on a weekly basis (9 h wear period/day), as required. Patch can be removed earlier than 9 h for shorter duration of effect or if late-day adverse effects are problematic
- Methylphenidate extended-release suspension (Quillivant XR): Reconstitution required prior to dispensing. Shake bottle vigorously for 10 sec prior to dose administration
- Amphetamine extended-release suspension (Dyanavel XR): Shake bottle well prior to dispensing and prior to each use

Long-Acting Formulations

Drug	Drug[1]	Formulation	Duration of Effect	Usual Dosing[2]
Methylphenidate biphasic release	Aptensio XR, Biphentin	40% immediate-release beads + 60% delayed-release beads in a capsule	10–12 h	Once daily; can open and sprinkle on food
	Concerta	22% immediate-release coating + 78% delayed-release osmotic mechanism	10–12 h	Once daily
	Cotempla XR-ODT	25% immediate release + 75% delayed release formulated as an orally disintegrating tablet	12 h	Once daily; allow to disintegrate on tongue
	Foquest	20% immediate-release beads + 80% delayed-release beads in a capsule	16 h	Once daily; can open and sprinkle on food
	Metadate CD	30% immediate-release beads + 70% delayed-release beads in a capsule	8 h	Once daily
	Ritalin LA	50% immediate-release beads + 50% delayed-release beads in a capsule	6–8 h	Once daily; can open and sprinkle on food
Methylphenidate delayed release/extended release	Jornay PM	Beads coated with an extended-release layer and a delayed-release layer	10–14 h (onset delayed by 10 h)	Once daily in the evening; can open and sprinkle on food

Psychostimulants (cont.)

Drug	Drug[1]	Formulation	Duration of Effect	Usual Dosing[2]
Methylphenidate sustained/slow release	Ritalin SR	Provides a slow continual release of drug from a wax matrix	4–6 h	Multiple daily dosing
	ACT Methylphenidate ER, Apo-Methylphenidate ER, PMS-Methylphenidate ER[(B)]	Provides a slow continual release of drug from a polymer-coated tablet (though appearance and dosing similar to Concerta, these products do not deliver drug via an osmotic controlled release mechanism)	10–12 h	Once daily
	Methylin ER	Provides a slow continual release of drug due to diffusion and erosion from a hydrophilic polymer	4–8 h	Multiple daily dosing
	Metadate ER	Provides a slow continual release of drug from a wax matrix	4–8 h	Multiple daily dosing
	Quillichew ER	30% immediate release + 70% delayed release formulated as a chewable tablet	8 h	Once daily
	Quillivant XR	20% immediate release + 80% delayed release formulated as an oral suspension for reconstitution	12 h	Once daily
Methylphenidate transdermal patch	Daytrana	Drug dispersed in an acrylic adhesive which is dispersed in a silicone adhesive. Total dose delivered is dependent on patch size and wear time (see Dosing p. 41)	Depends on length of time patch applied	Apply in a.m., remove after 9 h
Dexmethylphenidate extended-release	Focalin XR	50% immediate-release beads + 50% enteric-coated delayed-release beads in a capsule	10–12 h	Once daily; can open and sprinkle on food
Amphetamine	Adzenys XR-ODT	50% immediate release + 50% delayed release formulated as an orally disintegrating tablet	10–12 h	Once daily; allow to disintegrate on tongue
	Dyanavel XR	Extended-release oral suspension	10–13 h	Once daily
Dextroamphetamine/ amphetamine salts	Adderall XR	50% immediate-release beads + 50% delayed-release beads in a capsule	10–12 h	Once daily; can open and sprinkle on food
	Mydayis	33.3% immediate-release beads + 33.3% each of two types of delayed-release beads (pH 5.5 release and pH 7 release) in a capsule	16 h	Once daily; can open and sprinkle on food
Dextroamphetamine	Dexedrine Spansules	50% immediate-release beads and 50% sustained-release beads in a capsule	4–9 h	Multiple daily dosing; can open and sprinkle on food
Dextroamphetamine transdermal patch	Xelstrym	Drug dispersed in an acrylic adhesive which is dispersed in a silicone adhesive. Total dose delivered is dependent on patch size and wear time (see Dosing p. 29)	Depends on length of time patch applied	Apply in a.m., remove after 9 h
Lisdexamfetamine	Vyvanse	Lisdexamfetamine is an inactive prodrug of dextroamphetamine and L-lysine. The drug is converted to active dextroamphetamine as the prodrug molecule is hydrolyzed (cleaving off the lysine amino acid portion)	10–13 h	Once daily (can open capsule and disperse contents in plain water, orange juice or yogurt). Chewable tablet should be chewed thoroughly before swallowing. The prolonged duration of lisdexamfetamine action is from its properties as a prodrug and not due to a physical delayed-release formulation

[1] See available dosage forms in product availability table p. 25; [2] "Usual" dosing implies: Most common dosing frequency. Note, occasionally "once daily" stimulants are given twice daily in some patients (e.g., adolescents requiring 16–18 h/day coverage) and some shorter-acting agents may be used once daily in some situations where a shorter daily duration of coverage is needed; [(B)] Not marketed in Canada

Switching Formulations

- It is generally recommended to start treatment with a low dose of a long-acting formulation and titrate the dose slowly to a therapeutic level
- Conversions between dosage formulations are approximations and are dependent on a number of factors:
  - the pharmacokinetics of each formulation, including the duration of action of each product
  - the patient's age and weight (dosing recommendations are often based on weight)
  - the patient's response may vary between different preparations of the same drug
- Check specific product labeling prior to attempting conversion between products/formulations. Due to differences in formulation and in drug base concentrations, many products are considered non-interchangeable, with many manufacturers recommending re-titration from starting dosages
- It is always important to monitor both response and adverse effects at each dosage level

Dosage Conversion

Immediate-Release Formulation	Extended-Release Formulation (Daily Dose)
Methylphenidate	
5 mg bid-tid	Metadate/Methylin ER, Biphentin, or Ritalin LA 10–20 mg, or Metadate CD 10–20 mg, or Concerta 18 mg
10 mg bid-tid	Metadate/Methylin ER, Biphentin, or Ritalin LA 20–30 mg, or Ritalin SR 20 mg, or Metadate CD 30 mg, or Concerta 27–36 mg
15 mg bid-tid	Metadate/Methylin ER, Biphentin, or Ritalin LA 30–40 mg, or Ritalin SR 40 mg, or Metadate CD 30–40 mg, or Concerta 36–54 mg
20 mg bid-tid	Metadate/Methylin ER, Biphentin, or Ritalin LA 40–50 mg, or Ritalin SR 40–60 mg, or Concerta 54–72 mg*
30 mg bid	Metadate/Methylin ER, Biphentin, or Ritalin LA 50–60 mg, or Ritalin SR 60 mg, or Concerta 72 mg*
Dexmethylphenidate	
Focalin 2.5 mg bid	Focalin XR 5 mg daily
Dextroamphetamine-amphetamine salts	
Adderall 5 mg bid	Adderall XR 10 mg daily
Dextroamphetamine	
5 mg bid	Dexedrine Spansules 10 mg daily (large inter-patient variance noted (from 1:1 to about 1:1.5 conversion)

* This amount comes from taking 2 × 36 mg tablets and roughly equates to 15 mg a.m. and 45 mg after lunch of methylphenidate IR

Notes: Conversion to methylphenidate transdermal patch or dextroamphetamine transdermal patch from other formulations is currently unknown; titration recommended (see Dosing p. 29)
Conversion to lisdexamfetamine not recommended; start at 20–30 mg daily and re-titrate to effective dose
Conversion to methylphenidate extended-release suspension (Quillivant XR) and chewable tablets (Quillichew ER) not recommended; start patients 6 years of age or older at 20 mg daily and titrate in 10 mg increments to effective dose
Conversion to methylphenidate extended-release orally disintegrating tablets (Cotempla XR-ODT) is not recommended; start patients 6 years of age or older at 17.3 mg daily and titrate to effective dose
Conversion to methylphenidate extended-release capsules (Aptensio XR/Biphentin or Foquest) not recommended. Start patients 6 years of age or older at the smallest available dosage (10 mg daily for Aptensio XR/Biphentin or 25 mg daily for Foquest) and titrate to effective dose
Conversion to Jornay PM not recommended; start patients 6 years of age or older at 20 mg daily administered in the evening at approximately 8 p.m. (range between 6:30 p.m. and 9:30 p.m. based on individual response) and titrate to effective dose, adjust administration based on response to achieve desired time of onset of action
Conversion to amphetamine tablets (Evekeo), suspension (Dyanavel XR) or amphetamine orally disintegrating tablets (Adzenys XR-ODT) or mixed amphetamine salts extended-release capsules (Mydayis) is not recommended. To avoid substitution errors and overdosage, do not substitute for other amphetamine products on a milligram-per-milligram basis because of different amphetamine base compositions and differing pharmacokinetic profiles

Pharmacokinetics

- See chart p. 42
- Large interindividual variation in absorption and bioavailability; food may affect T_{max} and C_{max} for some formulations (see table p. 43)
- Extended-release and osmotic-controlled release methylphenidate tablets are formulated with different cores which release active drug at different times (see Long-Acting Formulations p. 29)
- Transdermal patches release drug at a steady rate per hour, related to dose. Absorption and C_{max} may increase with chronic dosing; rate and extent of absorption increase if patch is applied to inflamed skin or if heat is applied over patch
- Lisdexamfetamine is converted to d-amphetamine and L-lysine by enzymatic hydrolysis; peak plasma concentration of d-amphetamine after 50 mg dose of lisdexamfetamine is approximately equivalent to 15–30 mg of immediate-release d-amphetamine. Lisdexamfetamine exposure is approx-

Psychostimulants (cont.)

imately 15% less with the chewable tablet formulation compared to the capsule, but overall dextroamphetamine exposure is similar between formulations
- ACT Methylphenidate ER, Apo-Methylphenidate ER, and PMS-Methylphenidate ER (Canada: removed from market) are similar in appearance and available dosage strengths to Concerta, and are marketed as generics of Concerta in Canada; however, these products are extended-release polymer-coated tablets and do not deliver drug via an osmotic-controlled release pump. While these products meet Health Canada bioequivalence standards, in single dose studies, peak methylphenidate blood level occurs up to 3 h sooner than with Concerta, and there is noticeable variability in the drug concentration time curve with some formulations when compared to Concerta
- With methylphenidate transdermal patch, it takes about 8 h after patch application for blood concentrations to reach maximum level. Substantial amounts of drug remain in body for about 6 h after patch removal
- With dextroamphetamine transdermal patch, it takes about 6 h after patch application for blood concentrations to reach maximum level. Substantial amounts of drug remain in body for about 24 h after patch removal, with evidence of accumulation (104% increase AUC) after repeated daily application compared to following a single patch application

Onset & Duration of Action

- See chart p. 42

Adverse Effects

- See chart p. 44
- Common adverse effects include restlessness, irritability, anxiety, insomnia or anorexia; worsening of aggressive behavior or hostility at start of therapy. Paradoxical psychiatric effects such as rebound, restlessness, irritability, anxiety, and increased aggression may be observed. Somatic effects such as insomnia, decreased appetite, tics, stomach ache, and headache are common, especially at the beginning of therapy. The slower the rate of titration, the less severe the initial side effects. Many of these psychiatric and somatic side effects may endure throughout treatment, making drug holidays useful to assess impact of relative risk vs. benefit, and necessitating the regular monitoring of growth
- Heart rate and blood pressure should be monitored at baseline and again when the dose has been optimized, or after every dose increase in patients with cardiac risk factors (e.g., hypertension, heart failure, myocardial infarction, or ventricular arrhythmia)
- For children, dose reduction should be considered if BP increases and pulse increases exceed the 75% percentile based on tables (BP percentiles in children require reference to gender and height as documented in pediatric tables)
- Controlled studies suggest that adverse effects in preschoolers (aged 3–7) are comparable to those seen in school-age children (dose dependent)
- While still potentially beneficial overall, adverse effects of stimulants may be more frequent or severe in children and adolescents with autism
- Effects on growth and weight appear to be small and related to dose and duration of drug use [drug holidays are sometimes used to mitigate this effect (evidence is contradictory)]
- Reports of exacerbation of OCD symptoms in children on high doses
- Drug-induced insomnia can be managed by changing the timing of the stimulant dose or using a shorter-acting formulation; addition of melatonin (data contradictory), clonidine (50–200 micrograms) or antihistamines at bedtime may be useful. In some patients, rebound ADHD symptoms and irritability may lead to insomnia as effects of stimulant wear off
- Reduced appetite, GI distress, and weight loss are common [can be minimized by taking medication after meals, eating smaller meals more frequently or drinking high-calorie fluids (e.g., Boost, Ensure) when thirsty, and eating before bedtime]
- Measure height and weight at baseline and repeat at least annually; if weight loss is evident (in patients who are not obese) despite attempts to increase caloric intake and compromises the child's health or growth, consider switching to a shorter-acting agent that allows for return of appetite late in the day, or use of non-stimulants such as atomoxetine, clonidine or guanfacine (methylphenidate-based forms may have less impact on appetite compared to amphetamine-based forms)
- Headache most common 2–3 h after a dose (tension-like or "achy"); tends to decrease over time [acetaminophen may be used as required]
- Hyperactive rebound can occur in the afternoon or evening [an earlier second dose of IR formulations, more frequent dosing or the use of long-acting formulations can be tried]
- Dysphoria or sadness has been noted to occur in patients taking stimulants, both during the day and when they are wearing off; more common with amphetamine-based products. Trial of a long-acting formulation or non-stimulant may be helpful. Rarely, use of a noradrenergic antidepressant may be helpful

- May exacerbate psychotic symptoms in children with a genetic predisposition or prior history of psychosis
- Risk of inducing mania or hypomania in patients with bipolar disorder who are not taking mood-stabilizing agents
- Recent FDA and Health Canada warning re priapism with methylphenidate dose increase or discontinuation; case reports of priapism in patients taking amphetamine-based stimulants (though patients were also taking other medications and causality could not be established)
- Chemical leukoderma (permanent loss of skin color) with methylphenidate patch (Daytrana)
- Single case report of eosinophilic hepatitis with lisdexamfetamine
- Case report of hyperhidrosis, excessive thirst, polydipsia, hyponatremia, and status epilepticus following methylphenidate overdose (single 1.5 mg/kg dose) in an 8-year-old boy[3, 4]
- Two cases of alopecia areata associated with Concerta which resolved with dechallenge, and did not recur with switch to an alternate extended-release methylphenidate formulation[5]
- Case report of awake bruxism following the second daily dose of Concerta 18 mg in a 9-year-old boy (confirmed by rechallenge)[6]
- Single case report of sudden, irreversible hearing loss following first dose of methylphenidate in a child[7]

D/C Discontinuation Syndrome

- Abrupt withdrawal after prolonged use may result in dysphoria, irritability or a rebound in symptoms of ADHD; increase in sleep and appetite reported
- If stimulant is taken in conjunction with an antipsychotic agent, sudden discontinuation of the stimulant may result in the emergence of extra-pyramidal side effects previously masked by the stimulant's anticholinergic properties and competition for D_2 receptors
- Case of priapism reported in 16-year-old each time he forgot to take his dose of extended-release methylphenidate (Concerta) 54 mg

Precautions

- Patients should be screened for cardiovascular risks by history[8] (early cardiac death in the family, family cardiac history, syncope, chest pain on exertion, etc.) and given a physical exam. An ECG or cardiology consult should be considered[9] but should not necessarily impede therapy if no evidence of cardiac concerns is present. If cardiac risk factors are present, the patient and/or parents should be informed of the relative risk and benefit of their treatment options, and treatment should only proceed with the consent of a cardiologist
- Health Canada warning: ADHD drugs may increase risk of suicidal thoughts and behaviors in some people; benefits still outweigh risks. Suicidal thinking should be assessed at baseline prior to starting and periodically while on treatment[10]
- Use cautiously in patients with anxiety, tension, agitation, restlessness, untreated mood or psychotic disorder
- May precipitate manic or hypomanic symptoms in patients with undiagnosed bipolar disorder, and exacerbate psychotic symptoms, thought disorder, and behavior disturbances in patients with psychosis
- May lower the seizure threshold (contradictory data); when starting stimulants in children with ADHD and seizures, careful monitoring pre and post stimulant treatment is required for each individual. In studies, most children with a seizure disorder and adequate control of seizures by anticonvulsant therapy were able to safely take methylphenidate
- Some manufacturers advise periodic CBC monitoring in patients on long-term therapy due to rare reports of leukopenia and anemia secondary to nutritional deficiency
- Chronic abuse in patients can lead to tolerance and psychic dependence. Drug dependence in children is rare; drug abuse or diversion is a risk, especially in adolescents with comorbid conduct or substance use disorders. Stimulants can be abused orally, intravenously or nasally and may be combined or adulterated with other drugs/substances
- Tic disorders; research investigating increased risk of tics with the use of stimulants has yielded contradictory results. Tics tend to wax and wane, often independent of therapy, though clinicians have commented that stimulants can unmask tics. In a patient where stimulants are associated with onset of tics, this may not be predictive of recurrence of tics at another time [addition of clonidine, guanfacine, or a high-potency antipsychotic may be effective at reducing tic severity and frequency]
- Some patients become tolerant to stimulant effects over time; may require an increased dosage or a drug holiday
- Application of external heat (e.g., heating pad, sauna, etc.) over Daytrana or Xelstrym patch results in temperature-dependent increase in drug release of (Daytrana: 2.5-fold increase; Xelstrym: 50% increase)
- Caution when switching from Concerta to ACT Methylphenidate ER, Apo-Methylphenidate ER, PMS-Methylphenidate ER or Teva-Methylphenidate ER-C (Canada: both removed from market) as medication delivery system and pharmacokinetics are not the same; while meeting Health Canada bioequivalence standards, these preparations have a pharmacokinetic profile that differs from Concerta, with a peak serum level (T_{max}) that occurs several hours earlier compared to Concerta; Health Canada has received numerous reports of loss of symptom control following switch from Concerta to one of the generic formulations

Psychostimulants (cont.)

Contraindications‡

- Structural cardiac abnormalities or cardiovascular disease, tachyarrhythmias, severe angina pectoris, moderate to severe hypertension
- Marked anxiety, tension, and agitation
- MAOI therapy (concurrent or within previous 14 days)
- Use cautiously and with careful monitoring in patients with a recent history of alcohol and/or drug abuse
- Anorexia nervosa
- Family history or diagnosis of Tourette's disorder or tics (excluding Concerta – Canada)
- Hyperthyroidism, thyrotoxicosis, pheochromocytoma, narrow-angle glaucoma
- Hereditary sucrose intolerance

Toxicity

- See p. 45

Lab Tests/Monitoring

- Baseline: Height, weight, blood pressure, and pulse and repeat regularly throughout treatment. Patients with a prior or family history of cardiac disease should be further evaluated via ECG and cardiology consult, including echocardiogram as necessary. Cardiac evaluation recommended if patient experiences excessive increase in blood pressure or pulse, exertional chest pain, or unexplained syncope

Use in Pregnancy◊

- See p. 45

Nursing Implications

- While medications have demonstrated superiority to behavior therapy alone, a multimodal approach to treatment of ADHD increases the probability of a positive outcome; some nonpharmacological approaches include parent training in behavioral modification strategies, individual and family psychotherapy as well as special educational accommodation for the child
- Ensure that extended-release or controlled-release formulations are taken appropriately according to product-specific directions
- For patients who have difficulty swallowing pills, Adderall XR, Aptensio XR, Biphentin, Dexedrine Spansules, Foquest, Jornay PM, Metadate CD, Mydayis or Ritalin LA can be prescribed; capsule can be opened and the beads sprinkled on apple sauce or other soft food and swallowed without chewing. Lisdexamfetamine (Vyvanse) capsules can be opened and the contents dispersed in a glass of plain water, orange juice or yogurt. Other alternatives include orally disintegrating tablets (Adzenys XR-ODT, Evekeo ODT or Cotempla XR-ODT), liquid suspension (Quillivant XR, Dyanavel XR), chewable tablets (Quillichew ER or Vyvanse) or transdermal patch (Daytrana or Xelstrym)
- Monitor therapy by watching for adverse effects and changes in concentration, mood, and activity level; report any changes in behavior or in sleeping or eating habits
- Monitor height and weight in children; consider drug-free periods (e.g., drug holidays during holiday periods or summer months) if inadvertent weight loss of more than 5% has occurred
- To minimize appetite-suppressant effects, give drug with or after meals and educate the family to provide adequate encouragement to their child to eat a full meal even if they are not hungry at dinner or late in the day when medication has worn off
- In patients with ADHD who drive, improvements in driving have been observed while on medication. Patients with a history of involvement in motor vehicle accidents should be cautioned about driving without first having taken medication or after medication effects have worn off (e.g., in the evening and night time)
- Patients should be informed that abrupt discontinuation of medication could lead to exacerbation of symptoms
- Doses of psychostimulants taken in latter part of day (e.g., after 4 p.m.) may cause or worsen insomnia (exception: Jornay PM is intended for evening administration between 6:30 and 9:30 p.m.; drug release is delayed until the next morning)
- Monitor heart rate and blood pressure prior to starting treatment and after initiation or dose increases
- Patients should be advised that the Concerta tablet shell does not dissolve and may be seen in the stool after a bowel movement

‡ Contraindications listed here do not necessarily apply to all products or all countries. Please refer to your country's specific product insert/product monograph for the most current details ◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

- Daytrana patch should be applied (immediately following removal from protective pouch) to clean, dry skin on the hip, 2 h before desired effect and removed 9 h after application; advise patient not to apply patch to inflamed skin and to avoid exposing area of application to external heat (e.g., electric heating pads). Rotate application sites. Dispose of patch by folding together the adhesive side – used patch can be disposed of in lidded container or flushed down the toilet (do not flush in areas with septic tank service)
- Several reports describing difficulties in removing the protective lining to expose the adhesive surface of Daytrana
- Xelstrym patch should be applied (immediately following removal from protective pouch) to clean, dry skin on hip, upper arm, chest, upper back or flank, 2 h before desired effect and removed 9 h after application. Rotate application sites. Dispose of patch by folding together the adhesive side – used patch should be disposed of in a lidded container. Do not flush down the toilet

Patient Instructions

- For detailed patient instructions on psychostimulants, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

DRUGS INTERACTING WITH METHYLPHENIDATE AND DEXMETHYLPHENIDATE

Class of Drug	Example	Interaction Effects
Alcohol		*In vitro* studies show altered drug release characteristics (84–98% of total methylphenidate dose released within the first 30–60 min) when taken with alcohol (40% concentration). Interactions are formulation specific
α_2 agonist	Clonidine, guanfacine	Additive effect on sleep, hyperactivity, and aggression associated with ADHD – use caution due to published case reports of sudden death with combination clonidine and methylphenidate use. However, Kapvay (clonidine XR) is FDA approved and Intuniv/Intuniv XR (guanfacine extended release) is FDA/Health Canada approved for combination use with long-acting stimulants
Antibacterial	Linezolid	Linezolid inhibits MAO enzymes – AVOID combination (discontinue stimulant while linezolid used)
Anticoagulant	Warfarin	Decreased metabolism of anticoagulant Increased INR response
Anticonvulsant	Carbamazepine Phenobarbital, phenytoin, primidone	Decreased plasma level of methylphenidate/dexmethylphenidate and metabolites due to increased metabolism Increased level of phenytoin and phenobarbital due to inhibited metabolism by methylphenidate
Antidepressant		
SSRI	Fluoxetine, sertraline, etc.	Additive effects in depression, persistent depressive disorder, and OCD in patients with ADHD; may improve response in refractory paraphilias and paraphilia-related disorders
SNRI	Venlafaxine	Case of serotonin syndrome with methylphenidate after one dose of venlafaxine given
NaSSA	Mirtazapine	May increase agitation and risk of mania, especially in patients with bipolar disorder
Tricyclic	Amitriptyline, desipramine	Used together to augment antidepressant effect Plasma level of tricyclic antidepressant may be increased Cardiovascular effects increased, with combination, in children; monitor blood pressure and ECG Case reports of neurotoxic effects with imipramine, but considered rare; monitor
RIMA	Moclobemide	Increased blood pressure and enhanced effect if used over prolonged period or in high doses
MAOI (Irreversible)	Phenelzine, tranylcypromine	Hypertensive crisis due to increased norepinephrine release while ability to metabolize monoamines is blocked by MAOI – AVOID; combination used very RARELY to augment antidepressant therapy with strict monitoring
Antihistamine	Diphenhydramine	Antagonism of sedative effects
Antipsychotic	General	Antipsychotics can counteract many signs of stimulant toxicity (e.g., anxiety, aggression, visual or auditory hallucinations, psychosis), may impair the stimulatory effect of amphetamines, and have additive adverse effects (e.g., insomnia, restlessness, tremor) Methylphenidate may exacerbate or prolong withdrawal dyskinesia following antipsychotic discontinuation; conversely, following stimulant discontinuation, antipsychotic-related extrapyramidal side effects may emerge (due to removal of anticholinergic activity of stimulant, reduced competition for post-synaptic D_2 receptor binding)

Psychostimulants (cont.)

Class of Drug	Example	Interaction Effects
Herbal preparation	Ephedra, St. John's wort, yohimbine	May cause hypertension, arrhythmias, and/or CNS stimulation
	Ginkgo biloba	Seizure threshold may be lowered with combination
Theophylline		Reports of increased tachycardia, palpitations, dizziness, weakness, and agitation

DRUGS INTERACTING WITH DEXTROAMPHETAMINE AND LISDEXAMFETAMINE

Class of Drug	Example	Interaction Effects
α_2 agonist	Clonidine, guanfacine	Additive effect on sleep, hyperactivity, and aggression associated with ADHD – use caution due to published case reports of sudden death with combination clonidine and methylphenidate use. However, Kapvay (clonidine XR) is FDA approved and Intuniv/Intuniv XR (guanfacine extended release) is FDA/Health Canada approved for combination use with long-acting stimulants
Acidifying agent	Ammonium chloride, fruit juices, ascorbic acid	Decreased absorption, increased elimination, and decreased plasma level of dextroamphetamine
Alkalinizing agent	Potassium citrate, sodium bicarbonate	Increased absorption, prolonged half-life, decreased elimination, and increased plasma level of dextroamphetamine
Antidepressant		
SSRI	Fluoxetine, sertraline, etc.	Additive effects in depression, persistent depressive disorder, and OCD in patients with ADHD
NaSSA	Mirtazapine	May increase agitation and risk of mania, especially in patients with bipolar disorder
Tricyclic	Amitriptyline, etc.	May enhance the stimulatory effect of amphetamines. Tricyclics may also potentiate the cardiovascular effects of amphetamines
RIMA	Moclobemide	Increased blood pressure and enhanced effect if used over prolonged period or in high doses
MAOI (Irreversible)	Phenelzine, tranylcypromine	Hypertensive crisis due to increased norepinephrine release while ability to metabolize monoamines is blocked by MAOI; AVOID
β-blocker	Propranolol	Increased blood pressure and tachycardia due to unopposed α stimulation

Selective Norepinephrine Reuptake Inhibitors

Product Availability*

Generic Name	Neuroscience-based Nomenclature*	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Atomoxetine	Norepinephrine/Reuptake inhibitor	Strattera	Capsules: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg	Safety and efficacy not established in children under age 6
Viloxazine[B]	Norepinephrine/Reuptake inhibitor	Qelbree	Extended-release capsules: 100 mg, 150 mg, 200 mg	Safety and efficacy not established in children under age 6

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. * Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada

Indications‡ (👍 approved)

- 👍 ADHD in children, adolescents, and adults
- Comorbid anxiety disorder: May reduce anxiety symptoms

General Comments

- Second-line ADHD treatments. May be effective for some patients who have not responded to stimulant treatment, who have comorbid anxiety, or individuals who have an active comorbid substance use disorder. Potential benefits include: low abuse potential (not controlled substances), lack of euphoria, lower risk of rebound, lower risk of tic or psychosis induction, around the clock ADHD symptom treatment, and less sleep disturbance
- Available evidence indicates that atomoxetine and viloxazine are superior to placebo for reducing the severity of ADHD symptoms over the short term
- Atomoxetine has a slow onset of action and response may take up to 4 weeks – titrate dose gradually to help mitigate adverse effects (especially in patients who may be poor CYP2D6 metabolizers: ~10% of the population). Response is first seen at 4 weeks of full dose and full optimization of drug response may require at least 3 months
- Viloxazine response is first seen after 1 week of treatment. No dose adjustment required in CYP2D6 poor metabolizers
- Ultrarapid metabolizers of CYP2D6 (28% of North Africans, Ethiopians, and Arabs; up to 10% of Caucasians; 3% of African Americans, and up to 1% of Hispanics, Chinese, and Japanese) would be expected to have reduced efficacy of atomoxetine
- Selective NRIs reduce both the inattentive and hyperactive/impulsive symptom clusters of ADHD
- Head-to-head studies show reduced response rates and effect sizes with atomoxetine in comparison to stimulants. There are currently no published studies comparing viloxazine to other ADHD treatments
- A large head-to-head trial of OROS methylphenidate (Concerta) vs. atomoxetine in over 600 children demonstrated that 40% of children who do not respond to one drug are responders to the other, indicating selective response

Pharmacology

- Selectively blocks the reuptake of norepinephrine; increases dopamine and norepinephrine in the frontal cortex (without increasing dopamine in subcortical areas) – leads to cognitive enhancement without abuse liability; suggested to be important in regulating attention, impulsivity, and activity levels
- No stimulant or euphoriant activity – may be advantageous in patients with comorbid substance use disorder

Dosing

Atomoxetine

- Dosing is based on body weight
- Children and adolescents up to 70 kg: See table p. 41; do not exceed 1.4 mg/kg or 100 mg/day, whichever is less
- Over 70 kg: See table p. 41; maximum of 100 mg/day. Doses above 100 mg/day have not been found to result in additional therapeutic benefit
- In patients with moderate hepatic dysfunction, reduce dose by 50%; in severe hepatic dysfunction, reduce dose to 25% of the usual therapeutic range
- No dose adjustment required in renal insufficiency; may exacerbate hypertension in patients with end-stage renal disease
- Lower doses required for those who are poor CYP2D6 metabolizers or receiving another drug that is a strong 2D6 inhibitor, such as paroxetine or fluoxetine
- If atomoxetine added to a regimen in combination with drugs that inhibit CYP2D6 (see Drug Interactions p. 40): Initiate atomoxetine dose as per table p. 41 but do not increase to the usual target dose unless symptoms fail to improve *after 4 weeks* and the initial dose is well tolerated
- If a strong CYP2D6 inhibitor such as fluoxetine, paroxetine or bupropion is added to a regimen containing atomoxetine, dosage reduction of atomoxetine should be considered
- For ultrarapid CYP2D6 metabolizers, be alert to reduced efficacy of atomoxetine - insufficient data available to allow calculation of an adjusted dose, therefore an alternative drug may need to be prescribed

Viloxazine

- Children: 100 mg daily for 1 week, then may increase in 100 mg increments weekly to maximum of 400 mg/day depending on response and tolerability
- Adolescents: 200 mg daily for 1 week, then may increase to 400 mg/day depending on response and tolerability

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Selective Norepinephrine Reuptake Inhibitors (cont.)

- No dose adjustment required with mild or moderate renal insufficiency. In patients with severe renal dysfunction, starting dose of 100 mg/day, then may increase in 50–100 mg increments weekly to maximum of 200 mg/day depending on response and tolerability
- Avoid use with hepatic dysfunction
- Do not cut, crush, or chew capsule. May open capsule and sprinkle contents on soft food (e.g., applesauce) prior to administration (consume within 2 h)

Pharmacokinetics

Atomoxetine

- Rapidly absorbed; may be taken with or without food – high-fat meal decreases rate but not extent of absorption (C_{max} delayed by 3 h and is 37% lower)
- Bioavailability: 63%; 94% in CYP2D6 poor metabolizers
- Protein binding: 98% for atomoxetine and 69% for hydroxyatomoxetine metabolite
- Volume of Distribution (V_D): 0.85 L/kg. Distributes primarily into total body water. In children and adolescents, V_D is similar across the patient weight range after normalizing for body weight, and increased nearly proportionally to increases in body weight
- Peak plasma level reached in 1–2 h; 3–4 h in CYP2D6 poor metabolizers
- Half-life = 5 h for atomoxetine and 6–8 h for hydroxyatomoxetine; in CYP2D6 poor metabolizers the values are 21.6 h and 34–40 h, respectively; metabolized primarily by CYP2D6, also by CYP2C19
- Hepatic dysfunction: 2-fold increase in AUC in moderate hepatic insufficiency and 4-fold increase in AUC in severe hepatic dysfunction (see Dosing above)

Viloxazine

- May be taken with or without food – high-fat meal decreases rate of absorption and slightly decreases extent of absorption (C_{max} delayed by 2 h and 9% lower, AUC 8% lower)
- Bioavailability: 88% (compared to (unmarketed) immediate-release formulation)
- Protein binding: 76–82%
- Peak plasma level reached in 5 h
- Half-life: 7 h

Adverse Effects

- See table p. 44

Atomoxetine

- Common: Rhinitis, upper abdominal pain, nausea, vomiting, decreased appetite, weight loss (seen initially, especially if dose titrated too rapidly, but levels off with time), dizziness, headache, fatigue, emotional lability, insomnia is more common in adults, somnolence in children
- Less frequent: Irritability, aggression, sedation, depression, dry mouth, constipation, mydriasis, tremor, pruritus, urinary retention, sexual dysfunction
- Small increases in blood pressure and pulse can occur at start of treatment; usually plateau with time. No effect on QTc interval reported at therapeutic doses
- Sexual dysfunction (2%) including erectile disturbance, impotence, and abnormal orgasm, reports of priapism
- Rare cases of elevated hepatic enzymes and bilirubin; severe hepatic injury reported in at least 6 individuals (out of 3.4 million) after several months of treatment; injury reversed when atomoxetine withdrawn in 5 patients (none required liver transplant); one adult died from hepatic and renal failure (the nature of the hepatic injury is considered to be idiosyncratic so that routine LFTs are of little benefit)
- Increased risk of suicidal ideation in children and adolescents (see Precautionsp. 39)
- Case report of atomoxetine-induced hypothermia in an 11-year-old boy[12]

Viloxazine

- Common: Somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, irritability, increased blood pressure and pulse rate
- Less frequent: Fever, abdominal pain, weight loss, upper respiratory tract infection
- Increased risk of suicidal ideation in children and adolescents (see Precautionsp. 39)

D/C Discontinuation Syndrome

- Evidence that no drug discontinuation or withdrawal syndrome exists for atomoxetine.[13] Manufacturer recommends that atomoxetine may be discontinued without tapering of the dose. ADHD symptoms will return gradually following discontinuation. No information available with viloxazine

Precautions

Atomoxetine

- Increased risk of suicidal ideation in children and adolescents. Suicidal thinking should be assessed at baseline prior to starting and periodically while on treatment
- Use with caution in patients with cardiovascular disease, including hypertension, arteriosclerosis, and tachyarrhythmias. Do a cardiac history and physical assessment prior to prescribing atomoxetine and evaluate symptoms suggestive of cardiac disease that develop during treatment. DO NOT USE in adults or children with structural cardiac abnormalities – myocardial infarction, stroke, and deaths reported
- Due to risk of hypertension, use cautiously in any condition that may predispose patients to hypertension
- Use caution in patients with liver dysfunction – see Dosing above
- Cases of liver injury reported (rare); discontinue drug in patients with jaundice or laboratory evidence of liver injury – rechallenge not advised
- Atomoxetine has been associated with adverse psychiatric effects such as anger, hostility, irritability or suicidal ideation. If these occur the dose should be lowered or the drug discontinued. May exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder

Viloxazine

- Use with caution in patients with personal/family history of suicide, bipolar disorder or depression. Suicidal thinking should be assessed at baseline prior to starting and periodically while on treatment

Contraindications

Atomoxetine

- Patients with structural cardiac abnormalities or cardiovascular disease, tachyarrhythmias, severe hypertension or severe angina, current or past history of pheochromocytoma
- Not recommended in patients with narrow-angle glaucoma due to increased risk of mydriasis
- During or within 14 days of taking a MAOI

Viloxazine

- Should not be administered together with a MAOI or within 2 weeks of discontinuing a MAOI
- Should not be administered together with a sensitive CYP1A2 substrate or a CYP1A2 substrate with a narrow therapeutic range

Toxicity

- See p. 45
- Atomoxetine: Symptoms may include anxiety, tremulousness, dry mouth, seizures, and prolonged QTc interval
- Viloxazine: Symptoms include drowsiness, impaired consciousness, diminished reflexes, increased heart rate

Lab Tests/Monitoring

- Atomoxetine: Blood pressure, pulse, height, weight, suicidal thoughts or behaviors. Liver function tests with any symptoms or sign of liver dysfunction
- Viloxazine: Blood pressure, pulse, height, weight, suicidal thoughts or behaviors

Use in Pregnancy◊

- Effect of atomoxetine on humans unknown
- Discontinue viloxazine when pregnancy is recognized unless the benefits of therapy outweigh potential risk. Evidence of fetal toxicity in animal studies

Breast Milk

- Unknown if atomoxetine or viloxazine is excreted in human milk

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Selective Norepinephrine Reuptake Inhibitors (cont.)

Nursing Implications

Atomoxetine

- Measure pulse and blood pressure at baseline and periodically during treatment
- Monitor for increased irritability, anger, depression or suicidal ideation
- Monitor growth and weight during treatment
- Monitor for signs of liver toxicity (pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms)
- Manufacturer recommends capsules of atomoxetine should not be opened (drug powder may irritate handler's eyes)
- Give atomoxetine with or after meals to minimize stomach ache, nausea, and vomiting

Viloxazine

- Measure pulse and blood pressure at baseline and periodically during treatment
- Monitor for increased irritability, anger, mood changes or suicidal ideation
- Monitor growth and weight during treatment
- Manufacturer recommends capsules of viloxazine should not be cut, crushed or chewed but may be opened and contents sprinkled on soft food (e.g., applesauce) prior to administration

Patient Instructions

- For detailed patient instructions on atomoxetine and viloxazine, see the Patient and Caregiver Information Sheets (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Antiarrhythmic	Quinidine	Increased level of atomoxetine due to inhibited metabolism via CYP2D6
Antidepressant		
SSRI	Fluoxetine, paroxetine	Increased plasma level and half-life of atomoxetine due to inhibited metabolism via CYP2D6
NDRI	Bupropion	Increased plasma level and half-life of atomoxetine due to inhibited metabolism via CYP2D6
MAOI	Phenelzine, tranylcypromine	Do not administer concurrently or within 2 weeks of discontinuing a MAOI
Antiviral	Ritonavir, delavirdine	Increased atomoxetine level due to inhibited metabolism via CYP2D6
β-Agonist	Albuterol/salbutamol, levalbuterol	Can potentiate cardiovascular effects, resulting in increased blood pressure and heart rate
CYP1A2 substrate	Clozapine, duloxetine, ramelteon, tizanidine	With viloxazine, sensitive CYP1A2 substrates with a narrow therapeutic range are contraindicated. Moderately sensitive CYP1A2 substrates should be avoided due to increased exposure
Dextromethorphan (DM)		Competitive inhibition of DM metabolism via CYP2D6, with potential for increased plasma level of either drug
QT-prolonging agent	Antiarrhythmics (e.g., amiodarone, sotalol), antimalarials (e.g., chloroquine, mefloquine), antipsychotics (quetiapine, thioridazine, ziprasidone), dolasetron, methadone, tacrolimus	Possible additive prolongation of QT interval with atomoxetine
Stimulant	Methylphenidate, amphetamine, and related products	Possible potentiation of hypertension and tachycardia. However, combination use recommended as an option by some ADHD guidelines following monotherapy trials with each agent

Comparison of Drugs for ADHD

	Methylphenidate	Dexmethylphenidate	Amphetamine Salts/Dextroamphetamine/ Lisdexamfetamine/Methamphetamine	Atomoxetine	Viloxazine
Pharmacology	Selectively inhibits presynaptic transporters (i.e., reuptake) for DA and NE – dependent on normal neuronal activity Increases levels of synaptic DA and NE	Selectively inhibits presynaptic transporters (i.e., reuptake) for DA and NE – dependent on normal neuronal activity Increases levels of synaptic DA and NE	Competitive inhibitor and pseudosubstrate for presynaptic transporters (i.e., reuptake) for DA, NE, and 5-HT (though primarily DA). Main amphetamine effects are: 1) depletion of vesicular dopamine, 2) reversal of presynaptic DA transporters, and 3) presynaptic DA transporter inhibition	Selectively blocks reuptake of NE; increases NE and DA in prefrontal cortex	Selectively blocks reuptake of NE; increases NE and DA in prefrontal cortex
Dosing ADHD	Start with 2.5–5 mg bid and increase by 2.5–5 mg weekly Usual dose: 10–60 mg/day or 0.25–1 mg/kg/day body weight (divided doses); up to 3 mg/kg/day has been used in children Concerta: 18 mg q a.m.; can increase by 18 mg weekly to a maximum of 72 mg/day (some references support a maximum of 90 mg daily in adolescents) Aptensio XR/Biphentin: 10–20 mg q a.m.; can increase by 10 mg weekly to a maximum of 80 mg/day Cotempla XR-ODT: 17.3 mg q a.m., then increase by 8.6–17.3 mg in weekly intervals to maximum of 51.8 mg/day Daytrana transdermal patch: Week 1, apply 27.5 mg patch (for 9 h/day); increase dose in weekly intervals as necessary Foquest: 25 mg q a.m., then increase in 5-day intervals to maximum of 70 mg/day (85 mg/day for adolescents in US labelling)	Over age 6: Start with 2.5 mg bid and can increase weekly in 2.5–5 mg increments to a maximum of 20 mg/day (divided dose, given at least q 4 h) Usual dose: 5–20 mg daily divided bid When switching from methylphenidate, the starting dose of dexmethylphenidate should be half that of methylphenidate	*Amphetamine:* Adzenys XR-ODT: Children: 6.3 mg q a.m. Increase by 3.1 or 6.3 mg weekly to maximum of 18.8 mg/day for children or 12.5 mg/day for adolescents. Adults: 12.5 mg q a.m. Dyanavel XR: Over age 6: Start with 2.5–5 mg q a.m. May increase by 2.5–10 mg every 4–7 days to a maximum of 20 mg/day Evekeo: Age 3–5: Start with 2.5 mg and increase by 2.5 mg weekly. Over age 6: Start with 5 mg and increase by 5 mg weekly. Usual maximum: 40 mg/day *Dextroamphetamine:* Age 3–5: Start with 2.5 mg and increase by 2.5 mg weekly. Over age 6: Start with 5 mg and increase by 5 mg weekly. Usual dose: 2.5–40 mg/day or 0.1–0.8 mg/kg (divided doses); Spansules can be opened and sprinkled on food Adderall: 2.5–5 mg to start and increase by 2.5–5 mg every 3–7 days up to 30 mg/day (given every 4–7 h). In adults up to 40 mg/day (in divided doses) Adderall XR: 10–30 mg q a.m. Mydayis: 12.5 mg q a.m. Increase by 12.5 mg weekly to maximum of 25 mg/day for adolescents or 50 mg/day for adults Xelstrym transdermal patch: Week 1, apply 4.5 mg patch (for 9 h/day); increase dose in weekly intervals as necessary	Dosing is based on body weight *Children up to 70 kg:* Canadian labeling: Initiate at 0.5 mg/kg/day for 7–14 days. Based on tolerability, increase to 0.8 mg/kg/day for 7–14 days, and then to 1.2 mg/kg/day, given once daily or bid in the morning and late afternoon. Do not exceed 1.4 mg/kg or 100 mg/day, whichever is less US labeling: 0.5 mg/kg/day for 3 days, then increase to 1.2 mg/kg/day if tolerated *Adolescents and adults over 70 kg:* Canadian labeling: Initiate at 40 mg/day for 7–14 days. Based on tolerability, increase to 60 mg/day for 7–14 days, and then to 80 mg/day, given once daily or divided bid in the morning and late afternoon. If response is inadequate after 2–4 weeks, the dose can be increased to a maximum of 100 mg/day US labeling: 40 mg/day for 3 days, then increase to 80 mg/day. May increase to maximum of 100 mg/day in 2–4 weeks to achieve optimal response	Children: 100 mg daily for 1 week, then may increase in 100 mg increments weekly to maximum of 400 mg/day depending on response and tolerability Adolescents: 200 mg daily for 1 week, then may increase to 400 mg/day depending on response and tolerability

Comparison of Drugs for ADHD (cont.)

	Methylphenidate	Dexmethylphenidate	Amphetamine Salts/Dextroamphetamine/ Lisdexamfetamine/Methamphetamine	Atomoxetine	Viloxazine
	Quillivant XR/Quillichew ER: 20 mg q a.m.; may increase by 10–20 mg weekly to a maximum of 60 mg/day		*Lisdexamfetamine:* Children and adolescents: start with 20–30 mg q a.m. and can adjust by 10–20 mg increments in 7-day intervals to a maximum of 60 mg/day (Canada) or 70 mg/day (USA) *Methamphetamine:* Start with 5 mg daily bid and increase by 5 mg/week. Usual dose: 20–25 mg/day – in divided doses; Gradumet given once daily		
Depression	10–30 mg/day	–	Dextroamphetamine: 5–60 mg/day	–	–
Narcolepsy	10–60 mg/day (usual dose: 10 mg 2–3 times/day)	–	Dextroamphetamine: 5–60 mg/day	–	–
Pharmacokinetics					
Bioavailability	30% (range 11–52%)	22–25%	*Amphetamine/Dextroamphetamine*: > 90% *Lisdexamfetamine*: 96.4% *Methamphetamine*: 65–70%	63–94%	88% (compared to (unmarketed) immediate-release formulation)
Peak plasma level	IR (regular) tablets: 0.3–4 h SR tabs: 1 h Aptensio XR/Biphentin: 2 h first peak, 7 h second peak Foquest: 11.5 h Concerta: 1 h initial peak, 6.8 h second peak ACT Methylphenidate ER: 6.5 h Apo-Methylphenidate ER: 4.63 h PMS-Methylphenidate ER: 6.5 h[B] Metadate CD: 1.5 h first peak, 4.5 h second peak Quillichew ER: 5 h Quillivant XR: 5 h Cotempla XR-ODT: 5 h	1–1.5 h (fasting)	*Amphetamine*: Adzenys XR-ODT: *d-amphetamine*: 5 h (7 h with food) Dyanavel XR: 4 h Evekeo: within 4 h *Dextroamphetamine*: Tablets 1–4 h, Spansules: 6–10 h Adderall: 1–2 h Adderall XR: 7 h Mydayis: 8 h *Lisdexamfetamine* capsules: 1 h, *d-amphetamine*: 3.5 h; chewable tablets: 1 h, *d-amphetamine*: 4.4 h	1–2 h CYP2D6 poor metabolizers: 3–4 h	5 h
Protein binding	8–15%	12–15%	12–15%	Atomoxetine: 98% hydroxyatomoxetine metabolite: 69%	76–82%
Onset of effects	0.5–2 h Absorption from GI tract is slow and incomplete	0.5–2 h	0.5–2 h Readily absorbed from the GI tract Adderall: Saccharate and aspartate salts have a delayed onset	Delayed up to 4 weeks, but then continuously effective with ongoing administration	1 week

	Methylphenidate	Dexmethylphenidate	Amphetamine Salts/Dextroamphetamine/ Lisdexamfetamine/Methamphetamine	Atomoxetine	Viloxazine
Plasma half-life	IR (regular) tablets: 2.9 h mean (range: 2–4 h) SR tablets and Concerta: 3.4 h mean Cotempla XR-ODT: 4 h Daytrana: 3–4 h after removal of patch Foquest: 7 h Metadate CD: 6.8 h mean Quillichew ER: 5.2 h Quillivant XR: 5.6 h	2.2 h	Dyanavel XR: contains d-amphetamine and L-amphetamine with half-lives of 12.4 h and 15.1 h, respectively Adderall: 6–8 h *Dextroamphetamine*: 6–8 h in acidic pH, 18.6–33.6 h in alkaline pH Xelstrym: 6.4–11.5 h after removal of patch *Lisdexamfetamine* (parent, inactive): 1 h; *dextroamphetamine* (metabolite, active): 10–13 h *Methamphetamine*: 6.5–15 h	Atomoxetine = 5 h (CYP2D6 poor metabolizers = 21.6 h) hydroxyatomoxetine = 6–8 h (CYP2D6 poor metabolizers = 34–40 h)	7 h
Duration of action	IR (regular) tablets: 3–5 h SR: Theoretically 5–8 h, but 3–5 h practically Extended-release formulations: 8–12 h Foquest: 16 h	6–7 h	*Amphetamine*: Dyanavel XR: up to 13 h Evekeo: 4–6 h Adderall: 5–7 h Adderall XR: 12 h Mydayis: 16 h *Dextroamphetamine*: 6–8 h in acidic pH, 18.6–33.6 h in alkaline pH *Lisdexamfetamine*: under 1 h; d-amphetamine (after conversion): 10–13 h *Methamphetamine*: 6.5–15 h	Approx. 24 h	24 h
Metabolism	Hepatic via carboxylesterase CES1A1 to minimally active metabolite Weak CYP2D6 inhibitor		Minor CYP2D6 substrate (*lisdexamfetamine* converted to active *d-amphetamine* on erythrocytes)	Metabolized primarily by CYP2D6; also by CYP2C19	CYP2D6; UGT1A9; UGT2B15
Hepatic impairment	No change	No change	No change	Moderate: Reduce dose by 50% Severe: Reduce dose by 75%	Not recommended
Renal impairment	No adjustment	No adjustment	Decreased excretion	No adjustment	Severe: Reduce dose by 50%
Effect of Food	Metadate CD: Delayed T_{max} by 1 h Concerta: Delayed T_{max} by 1 h and reduced C_{max} by 10–30% Foquest: no change	–	Decreased extent of absorption Adzenys XR-ODT: T_{max} increased by 2–2.5 h, C_{max} reduced by 19% *Lisdexamfetamine* (capsules): No change	T_{max} delayed by 3 h	–
High-fat meal	Aptensio XR/Biphentin: diminished second peak level, C_{max} increased by 28%, AUC by 19% Cotempla XR-ODT: C_{max} decreased 24%, AUC decreased 16%, T_{max} shortened by 0.5 h Metadate CD: C_{max} increased by 30%	Delayed T_{max}	Dyanavel XR: T_{max} increased by 1 h, C_{max} by 2%, AUC by 6% Mydayis: T_{max} increased by 5 h; extent of absorption not affected *Lisdexamfetamine* (chewable tablets): C_{max} and AUC decreased by 5–7%, T_{max} delayed by 1 h	C_{max} 37% lower	T_{max} delayed by 2 h, C_{max} 9% lower, AUC 8% lower

Comparison of Drugs for ADHD (cont.)

	Methylphenidate	Dexmethylphenidate	Amphetamine Salts/Dextroamphetamine/ Lisdexamfetamine/Methamphetamine	Atomoxetine	Viloxazine
	Ritalin and Ritalin LA: T_{max} delayed Quillichew ER: T_{max} unchanged, C_{max} increased by 20%, AUC by 4% Quillivant XR: T_{max} increased by 1 h, C_{max} by 28%, AUC by 19%				
Adverse Effects (Dose related)					
CNS	Nervousness (16%), anxiety, insomnia (up to 28%), restlessness, activation, irritability (up to 26%), headache (up to 14%), tearfulness, drowsiness (10%), rebound depression, may exacerbate mania or psychosis (See Precautions p. 33) Cases of suicidal thoughts, hallucinations, and psychotic or violent behavior reported with Concerta Tourette's disorder, tics (up to 10% at higher doses) Social withdrawal, dullness, sadness, and irritability reported in children with autism	Drowsiness, headache Fever (5%) Arthralgia, dyskinesias (See Precautions p. 33)	Nervousness, insomnia, activation, restlessness, anxiety, emotional lability, mania (with high doses), dysphoria, irritability, headache, confusion, delusions, rebound depression; may exacerbate mania or psychosis (See Precautions p. 33) Headache Tremor, Tourette's disorder, tics – usually with higher doses	Insomnia, dizziness, fatigue, headache, emotional lability Less common: Drowsiness, irritability, depression, tremor, aggression Reports of psychotic/manic symptoms (hallucinations, delusions, and mania) in children and adolescents with no prior history of psychotic illness Case reports of tics	Somnolence, headache, fatigue, insomnia, fever, irritability, suicidal thoughts and behaviors
GI	Abdominal pain (up to 23%), nausea, vomiting, and diarrhea (over 10%), anorexia (up to 41%, dose-related)	Abdominal pain (15%), nausea, anorexia (6%)	Abdominal pain common; nausea, vomiting, anorexia	Upper abdominal pain, nausea, vomiting, anorexia	Nausea, vomiting, abdominal pain, decreased appetite, weight loss
Cardio-vascular	Increased heart rate and blood pressure at start of therapy, dizziness (13%), hypotension, palpitations (See Precautions p. 33)	Increased heart rate and blood pressure at start of therapy (See Precautions p. 33)	Increased heart rate and blood pressure at start of therapy, dizziness, palpitations (See Precautions p. 33)	Small increases in heart rate and blood pressure at start of treatment (See Precautions p. 39)	Increases in heart rate and blood pressure
Anti-cholinergic	Dry mouth, blurred vision	Blurred vision	Dry mouth, dysgeusia, blurred vision	Dry mouth, constipation, mydriasis, urinary retention	–

	Methylphenidate	Dexmethylphenidate	Amphetamine Salts/Dextroamphetamine/ Lisdexamfetamine/Methamphetamine	Atomoxetine	Viloxazine
Endocrine	Growth delay (height and weight), may occur initially but tends to normalize over time (unless high chronic doses used), weight loss	Growth delay, weight loss	Growth delay (height and weight), may occur initially but tends to normalize over time (unless high chronic doses used), weight loss, impotence, changes in libido	Sexual dysfunction, weight loss	–
Other	Upper respiratory infections: Pharyngitis (4%), sinusitis (3%), rhinitis (13%), cough (4%), fever Rash; contact sensitization/dermatitis Daytrana transdermal patch application site reactions: redness, itching, blistering Leukopenia, blood dyscrasias, anemia, hair loss, priapism	Cough, upper respiratory infections, priapism	Urticaria, anemia Xelstrym transdermal patch application site reactions: rash, pain, pruritus, burning sensation, erythema, discomfort, edema, swelling	Cases of liver damage with elevated AST/ALT and bilirubin in adults and children Pruritus, rhinitis, priapism	Upper respiratory tract infection
Toxicity	CNS overstimulation with vomiting, agitation, tremors, hyperreflexia, convulsions, confusion, hallucinations, delirium, cardiovascular effects (e.g., hypertension, tachycardia); seizures reported Supportive therapy should be given	CNS overstimulation with vomiting, agitation, tremors, hyperreflexia, convulsions, confusion, hallucinations, delirium, cardiovascular effects (e.g., hypertension, tachycardia) Supportive therapy should be given	Restlessness, dizziness, increased reflexes, tremor, insomnia, irritability, assaultiveness, hallucinations, panic, cardiovascular effects, circulatory collapse, convulsions, and coma Supportive therapy should be given	Anxiety, tremulousness, dry mouth; case of seizures & QTc prolongation Supportive therapy should be given	Drowsiness, impaired consciousness, diminished reflexes, increased heart rate Supportive therapy should be given
Use in Pregnancy	No evidence of teratogenicity reported	Safety not established	High doses have embryotoxic and teratogenic potential; use of amphetamine in pregnant animals has been associated with permanent alterations in the central noradrenergic system of the neonate Increased risk of premature delivery and low birth weight; withdrawal reactions in newborn reported	Safety not established	Discontinue when pregnancy is recognized unless benefits of therapy outweigh potential risk. Evidence of fetal toxicity in animal studies
Breastfeeding	No data	No data	Excreted into breast milk; recommended not to breastfeed	No published experience with this drug during breastfeeding; however, there have been reports of no serious adverse effects in 2 breastfed infants	No data

[B] Not marketed in Canada

α_2 agonists

Product Availability*

Generic Name	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Clonidine	Norepinephrine/Agonist	Catapres, Dixarit[C]	Tablets: 0.025 mg[C], 0.1 mg, 0.2 mg, 0.3 mg[B]	Safety and efficacy not established in children under age 12
		Kapvay[B]	Extended-release tablets: 0.1 mg	Safety and efficacy not established in children under age 6
		Catapres TTS[B]	Transdermal patch: 0.1 mg/24 h, 0.2 mg/24 h, 0.3 mg/24 h	Safety and efficacy not established in children under age 12
Guanfacine	Norepinephrine/Agonist	Tenex[B]	Tablets: 1 mg, 2 mg	Safety and efficacy not established in children under age 12
		Intuniv[B], Intuniv XR[C]	Extended-release tablets: 1 mg, 2 mg, 3 mg, 4 mg	Approved for children age 6 and above, NOT approved in adults

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

- 👍 ADHD (clonidine (Kapvay) and guanfacine (Intuniv, Intuniv XR)) – meta-analysis of studies suggests a moderate benefit in children and adolescents; reduced hyperarousal, agitation, aggression, impulsivity, and sleep disturbances; useful in patients with concurrent tic disorders or conduct disorder; minimal benefit for patients with primarily inattentive symptoms
- 👍 Some benefit in combination with stimulants; may help ameliorate sleep disturbances caused by psychostimulants (Caution – see Drug Interactions p. 48)
- 👍 Hypertension (IR formulations; guanfacine – USA)
- May improve behavior or impulsivity when used alone or in combination with methylphenidate (Caution – see Drug Interactions p. 48)
- Autism – reported to be safe and effective for controlling hyperactivity, impulsivity, and inattention in children and adults[14] (guanfacine XR); clonidine used commonly for similar purposes
- Aggression and impulsivity – reported to have synergistic effect with anticonvulsant regimens in controlling these behaviors
- Generalized anxiety disorder (GAD), panic attacks, phobic disorders, and obsessive-compulsive disorders: Of some benefit; may augment effects of SSRIs and cyclic antidepressants in social anxiety disorder; helpful for symptoms of hyperarousal, hypervigilance, aggression, and irritability of PTSD
- May relieve antipsychotic-induced asthenia and improve symptoms of tardive dyskinesia
- May help decrease clozapine-induced sialorrhea
- Heroin, cocaine, and nicotine withdrawal: Used to reduce agitation, tremor, and diaphoresis, and to increase patient comfort. Opioid antagonists (e.g., naltrexone) as well as dicyclomine (for stomach cramps) and cyclobenzaprine (for muscle cramps) often given concomitantly

General Comments

- Reduces the hyperactive/impulsive and aggressive symptoms of ADHD but may be less effective for inattention problems; considered generally less effective than psychostimulants and thus second-line treatments, though may be beneficial for some patients who have not responded to stimulant treatment or those with comorbid tic disorder
- In anxiety disorders, psychological symptoms respond better than somatic symptoms; anxiolytic effects may be short-lived

Pharmacology

- Mechanism of action for the treatment of ADHD is unknown; agonizing α_{2A} receptors in the prefrontal cortex appears to improve "signal-to-noise ratio"

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

- Clonidine is a relatively nonselective α_2-adrenergic agonist (α_{2A}, α_{2B}, and α_{2C} receptors). It also has affinity for imidazoline receptors, which may be responsible for some of its sedating and hypotensive action
- Guanfacine is a more selective agonist for postsynaptic α_{2A} receptors in the prefrontal cortex. It has less sedating and hypotensive effects compared to clonidine
- Both clonidine and guanfacine stimulate α_2-adrenergic receptors in the brain stem. This reduces sympathetic outflow from the CNS and decreases peripheral resistance, renal vascular resistance, heart rate, and blood pressure

Dosing

- ADHD:
  - Clonidine IR: 3–10 micrograms/kg body weight per day (0.05–0.4 mg/day) in 3–4 divided doses
  - Clonidine XR: initially 0.1 mg/day, may adjust by increments no larger than 0.1 mg/day every week to maximum of 0.4 mg/day based on clinical response. Doses above 0.1 mg/day should be divided equally, or with the higher portion of the split dose given at bedtime
  - Guanfacine IR: 0.5–4 mg/day divided bid
  - Guanfacine XR: initially 1 mg once daily; may adjust by increments no larger than 1 mg/week to maximum of 4 mg/day in children or 7 mg/day as monotherapy in adolescents (maximum 4 mg/day in adolescents when adjunct to stimulant treatment). Clinical response is associated with doses of 0.05–0.08 mg/kg/day. Doses up to 0.12 mg/kg/day may provide additional benefit
- Antisocial behavior/aggression: Clonidine: Children: 0.1–0.4 mg/day as tablets (IR: in divided doses) or transdermal patch; adults: 0.4–0.6 mg/day
- Anxiety disorders: Clonidine: 0.15–0.5 mg/day (IR: in 3–4 divided doses)
- Drug dependence: Clonidine IR: 0.1–0.3 mg tid to qid for up to 7 days; nicotine withdrawal: 0.1 mg bid to 0.4 mg/day for 3–4 weeks
- Tic disorders: Clonidine IR: 3–5 micrograms/kg body weight per day in 2–4 divided doses; guanfacine IR: 0.5 mg tid to maximum of 4 mg/day in 3 divided doses

Pharmacokinetics

- Clonidine is well absorbed orally and percutaneously (when patch applied to the arm or chest)
- Peak plasma level of oral clonidine occurs in 1–3 h (IR) or 7–8 h (XR); therapeutic plasma concentrations of clonidine transdermal patch occur within 2–3 days
- Clonidine plasma half-life is 8–12 h in children and 12–20 h in adults; in patients with impaired renal function, half-life range is 18–41 h. Elimination half-life is dose dependent
- Guanfacine is metabolized via CYP3A4; peak plasma level of oral guanfacine occurs in 1–4 h (IR) or 5 h (XR); 4–8 h in adults; half-life is 14–18 h in children and adolescents, 18±4 h in adults
- Bioavailability is reduced with guanfacine XR tablets compared to IR tablets, therefore products are not considered interchangeable

Onset & Duration of Action

- Oral clonidine IR tablets: Onset of effects occurs in 30–60 min and effects last about 4–6 h (except for XR formulations)
- Clonidine transdermal patch: Therapeutic plasma concentrations are attained within 2–3 days and effects last for 7 days

Adverse Effects

- With clonidine and guanfacine, sedation, dizziness, bradycardia, and hypotension (with cases of syncope) are common on initiation (monitor BP and heart rate). Reduced rate of these adverse effects with XR formulations
- Less common with both drugs: anxiety, irritability, decreased memory, headache, dry mouth, and lack of energy
- Dermatological reactions reported in up to 50% of patients using transdermal clonidine patch
- Clonidine and guanfacine may increase agitation and produce depressive symptoms
- Case reports of mania induced by guanfacine[15]

D/C Discontinuation Syndrome

- Withdrawal reactions may occur after abrupt cessation of long-term clonidine or guanfacine therapy (over 1–2 months)
- Taper clonidine and guanfacine (e.g., reduce dose by 25% every 3–7 days) on drug discontinuation to prevent rebound hypertension and insomnia, as well as tic rebound in patients with Tourette's disorder
- Cases of rebound psychotic symptoms reported with both drugs

Precautions

- Case reports (4) of sudden death with combination of methylphenidate and clonidine, but causal relationship not established; FDA recommended removal of drug interaction statement regarding methylphenidate and clonidine[16]

α_2 agonists (cont.)

- Clonidine and guanfacine extended-release formulations evaluated in combination with stimulants in safety studies and now FDA approved for adjunctive use with long-acting stimulants (Health Canada: guanfacine XR only)
- Use with caution in patients with or at risk of cerebrovascular disease, chronic hepatic or renal impairment or any condition that may predispose to syncope
- Use caution when prescribing/transcribing doses of clonidine: high potential for 10-fold dosing errors due to inadvertent decimal misplacement when converting doses between units of micrograms and milligrams
- Do not use clonidine drug powder for compounding suspensions. 1000-fold overdoses reported when preparing compounded clonidine suspensions from drug powder due to confusion when converting between units of micrograms and milligrams[17]

Toxicity

- Signs and symptoms of clonidine or guanfacine overdose occur within 60 min of drug ingestion (with IR tablets; may be delayed with XR tablets) and may persist for up to 48 h
- Symptoms include transient hypertension followed by hypotension, bradycardia, weakness, pallor, sedation, vomiting, hypothermia; can progress to CNS depression, diminished or absent reflexes, apnea, respiratory depression, cardiac conduction defects, seizures, and coma

Treatment

- Supportive and symptomatic

Use in Pregnancy◊

- Clonidine: Animal studies suggest teratogenic effects; no adequate well-controlled studies of clonidine in pregnant women. Clonidine passes the placental barrier and may lower the heart rate of the fetus. Transient rise in blood pressure in the newborn cannot be excluded postpartum
- Guanfacine: No adequate well-controlled studies of guanfacine in pregnant women

Breast Milk

- Clonidine is distributed into breast milk; effects on infant unknown
- It is unknown whether guanfacine is distributed into breast milk
- If used by nursing mothers, observe milk-fed infants for somnolence and sedation

Nursing Implications

- Clonidine and guanfacine should not be discontinued suddenly due to risk of rebound hypertension and insomnia (reduce dose by 25% every 3–7 days)
- Advise patients not to break, split, chew or crush XR tablets (drug release may occur more rapidly, with increased risk for adverse effects)
- Should be taken with a full glass of water. Advise patient to maintain adequate hydration unless instructed to restrict fluid intake
- Handle the used transdermal patch carefully (fold in half with sticky sides together for disposal)
- Should the transdermal patch begin to loosen from the skin, apply adhesive overlay over the system to ensure good adhesion over the period of application
- Monitor for skin reactions around area when transdermal patch is applied
- Monitor for dizziness/lightheadedness and possibly blood pressure (sitting/standing) after initiation or dose increase
- Assess potential for interactions with other CNS depressants. Do not discontinue abruptly; taper, decreasing dose gradually to prevent rebound hypertension
- Bioavailability is reduced with XR tablets compared to IR tablets, therefore products and their respective dosing guidelines are not interchangeable

Patient Instructions

- For detailed patient instructions on clonidine and guanfacine, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Class of Drug	Example	Interaction Effects
Antibiotic	Clarithromycin, erythromycin	Decreased clearance and increased plasma level of guanfacine due to inhibition of CYP3A4 metabolism
	Rifampin	Decreased guanfacine levels due to CYP3A4 induction; monitor for signs and symptoms of altered response. With the XR formulation, higher dosages (up to 8 mg/day) and dose increments (2 mg/week) may be required
Anticonvulsant	Carbamazepine	Decreased guanfacine levels due to CYP3A4 induction; monitor for signs and symptoms of altered response. With the XR formulation, higher dosages (up to 8 mg/day) and dose increments (2 mg/week) may be required
	Divalproex, valproic acid	Increased valproate levels; may be due to competition between valproate and guanfacine metabolite (3-hydroxy guanfacine) for glucuronidation enzymes
Antidepressant	Bupropion, desipramine	α_2 agonist withdrawal may result in excess circulating catecholamines; use caution in combination with noradrenergic or dopaminergic antidepressants
	Desipramine, imipramine, SNRI	Inhibition of antihypertensive effect of α_2 agonist by the antidepressant
Antifungal	Itraconazole, ketoconazole	Decreased clearance and increased plasma level of guanfacine due to inhibition of CYP3A4 metabolism
Antihypertensive	Hydrochlorothiazide, ramipril	Additive hypotension
β-blocker	Propranolol	Additive bradycardia, increased risk for rebound hypertension with abrupt discontinuation of α-2 agonist
CNS depressant	Alcohol, antihistamines	Additive CNS depressant effects
Grapefruit juice		Possible decreased clearance and increased plasma level of guanfacine due to inhibition of CYP3A4 metabolism
H_2 antagonist	Cimetidine	Decreased clearance and increased plasma level of guanfacine due to inhibition of CYP3A4 metabolism
Protease inhibitor	Indinavir, ritonavir	Decreased clearance and increased plasma level of guanfacine due to inhibition of CYP3A4 metabolism
Stimulant	Dextroamphetamine, methylphenidate	Additive effect on hyperactivity and aggression associated with ADHD Kapvay (clonidine XR) and Intuniv/Intuniv XR (guanfacine XR) are approved for adjunctive use with long-acting stimulants

Augmentation Strategies in ADHD

Nonresponse in ADHD

- Ascertain whether diagnosis is correct
- Ascertain if patient is adherent with therapy (speak with caregivers, check with pharmacy for late refills, count remaining pills in container and compare to prescription fill date)
- Ensure dosage prescribed is therapeutically appropriate and tailor regimen to have peak serum levels occur at those times of the day that symptoms are most prominent
- Consider trying a stimulant from an alternate class (methylphenidate or amphetamine) if the first trial was ineffective and the patient was adhering to therapy recommendations before moving on to second-line treatments

Factors Complicating Response

- Concurrent medical or psychiatric condition, e.g., anxiety disorder, bipolar disorder, conduct disorder, autism spectrum disorder, learning disability
- Concurrent prescription drugs may interfere with efficacy, e.g., antipsychotics (see Drug Interactions pp. 35–36, 40, 48)
- Metabolic inducers (e.g., carbamazepine) may decrease the plasma level of methylphenidate or guanfacine
- High intake of acidifying agents (e.g., fruit juices, vitamin C) may decrease the efficacy of amphetamine preparations
- Substance use, including alcohol and marijuana, may make management difficult; need to discontinue substance use to optimize treatment outcomes
- High level of adverse effects with atomoxetine may be due to CYP2D6 poor metabolism
- Poor efficacy with atomoxetine may be due to CYP2D6 ultrarapid metabolism
- Side effects to medication

Augmentation Strategies in ADHD (cont.)

- Psychosocial factors may affect response; nonpharmacological treatment approaches (e.g., behavior modification, psychotherapy, and education) can increase the probability of response

Augmentation Strategies

Methylphenidate/ Dexmethylphenidate/ Dextroamphetamine + α_2 agonist

- Additive effect on hyperactivity, aggression, mood lability, and sleep problems; studies indicate efficacy in 50–80% of patients. Has been found helpful in patients with concomitant tic disorders, conduct disorder or oppositional defiant disorder [monitor ECG, heart rate, and blood pressure with combination]
- Kapvay (clonidine XR) and Intuniv/Intuniv XR (guanfacine XR) are approved for adjunctive use with stimulant medications

Psychostimulants + Antidepressants

- Tricyclics (imipramine, nortriptyline, and desipramine) useful in refractory patients or those with concomitant enuresis or bulimia; they may reduce abnormal movements in patients with tic disorders. There is an increase in the incidence of adverse effects, including cardiovascular, GI, anticholinergic effects, and weight gain; use caution and limit quantities prescribed in patients at risk of overdose
- SSRIs or venlafaxine may be effective in adult patients with concomitant mood or anxiety disorders (e.g., PTSD)
- Bupropion used to augment effects of psychostimulants and in patients with concomitant mood disorder, substance use disorder, or conduct disorder. May cause dermatological reactions, exacerbate tics, and increase seizure risk

Psychostimulants + Atomoxetine

- Use in patients who have partial relief of symptoms with maximally tolerated doses of either stimulant or atomoxetine alone. The combination may permit lower stimulant doses and allows robust coverage as well as coverage early and late in the day
- Monitor for increased blood pressure, tachycardia, weight loss, and reduced growth velocity

Psychostimulants + Antipsychotics

- Second-generation antipsychotics (low doses of risperidone, aripiprazole or quetiapine) may be useful in patients with comorbid symptoms of dyscontrol, aggression, hyperactivity, and tics. Ensure appropriate metabolic monitoring of antipsychotic therapy completed and discontinue antipsychotic treatment if excessive increases in blood pressure, weight, cholesterol, triglyceride or fasting glucose occur. Stimulants do not mitigate the effects of antipsychotics on weight and metabolic parameters
- Low doses of haloperidol or risperidone have been used in patients with concurrent Tourette's disorder

Psychostimulants + Mood Stabilizers

- Combination used in patients with comorbid bipolar disorder, conduct disorder, impulsivity, and aggression; infrequent case reports in children include the use of lithium, carbamazepine, and valproate – the possibility of drug interactions should be considered (see Drug Interactions pp. 35–36); limited likelihood of benefit

Psychostimulants + Buspirone

- Open studies suggest buspirone may improve rage attacks, impulsivity, inattention, and disruptive behavior at doses of 15–30 mg daily

Further Reading

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ANTIDEPRESSANTS

Classification

- Antidepressants can be classified as follows:

Pharmacological Class	Examples	Page
Cyclic Antidepressants [A]		
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	See p. 53
Norepinephrine Dopamine Reuptake Inhibitor (NDRI)	Bupropion	See p. 67
Selective Serotonin-Norepinephrine Reuptake Inhibitor (SNRIs)	Desvenlafaxine, duloxetine, venlafaxine	See p. 73
Serotonin-2 Antagonists/Serotonin Reuptake Inhibitors (SARIs)	Nefazodone, trazodone	See p. 81
Serotonin-1A Partial Agonist/Serotonin Reuptake Inhibitor (SPARI)	Vilazodone	See p. 88
Serotonin Modulator and Stimulator (SMS)	Vortioxetine	See p. 92
Noradrenergic/Specific Serotonergic Agent (NaSSA)	Mirtazapine	See p. 97
Nonselective Cyclic Agents (Mixed Reuptake Inhibitor/Receptor Blockers)	Amitriptyline, desipramine, imipramine, nortriptyline	See p. 102
Monoamine Oxidase Inhibitors		
Reversible MAO-A Inhibitor (RIMA)	Moclobemide	See p. 112
Irreversible MAO (A&B) Inhibitors (MAOI)	Phenelzine, tranylcypromine	See p. 115
Irreversible MAO-B Inhibitor	Selegiline	See p. 122
NMDA Receptor Antagonist	Esketamine	See p. 125

[A] Cyclic antidepressants are currently classified according to their effect on brain neurotransmitters. These neurotransmitter effects determine the antidepressants' spectrum of activity and adverse effects (see table p. 128).

General Comments

☞ **Antidepressants are associated with a small (2–3%) risk of hostility or suicidal ideation and associated behaviors in children, adolescents, and young adults (aged up to 24 years). Risk for suicide should be closely assessed and monitored during the initial weeks of antidepressant therapy**
In patients with major depression, treatment selection should consider safety in overdose (i.e., consider using newer antidepressant agents rather than nonselective cyclic, bupropion, and MAOI antidepressants, caregivers securing medication, limit prescription quantities) and close monitoring. Recently, bupropion was shown to have higher risk of serious outcomes in overdose compared to SSRIs

- Many studies examining previously published RCTs of SSRI medications have cast some doubt on the validity of some of the boxed warnings issued on antidepressants in 2004–2006 for risks of increasing suicidal ideation.[1, 2] A 2015 meta-analysis showed that most of the suicidality effect in antidepressants is due to treatment selection effects, and is much smaller in magnitude than previously reported.[3] In some studies, time to first suicidal thought is significantly increased with SSRI treatment. Newer meta-analyses show no significant association of antidepressant treatment in adolescents and suicidality, and newer estimates of risk could be as low as 9 per 1,000[4]
- Risk of switching to mania with antidepressants in children with **bipolar disorder** or risk for bipolar disorder is higher than in adult population; one study showed a risk of 9.3% per year of manic switch[5]
- Some antidepressants are associated with restlessness or psychomotor agitation prior to seeing any change in core symptoms of depression
- Though some randomized double-blind, controlled trials and systematic reviews suggest otherwise, on average, all antidepressants are equally efficacious at reducing symptoms of depression. Overall effects of antidepressants are modest when the effects of publication bias are considered. Compared to placebo, the overall effect size of treatment is reported as being 0.56 for treatment of anxiety and 0.2 for treatment of depression, though high placebo responses in multi-site adolescent depression RCTs contribute significantly to this finding[4]
- On the basis of some RCTs[6] and the TADS trial[7, 8] it has been suggested that fluoxetine may offer a more favorable benefit-to-risk ratio in pediatric depression, despite the fact that only some of the clinician-rated measures indicated a difference favoring fluoxetine

- Different antidepressant classes may be combined in patients with a partial response or in refractory cases; however, consideration of, and additional monitoring for, the potential interactions such as serotonin syndrome is necessary
- Prophylaxis of depression is most effective if the therapeutic dose is maintained; continued therapy with all classes of antidepressants has been shown to significantly reduce risk of relapse
- Tolerance (tachyphylaxis or "poop-out" syndrome) has been reported in 10–20% of patients on various antidepressants, despite adherence to therapy. Possible explanations include adaptations in the CNS, increase in disease severity or pathogenesis, loss of placebo effect, unrecognized rapid-cycling, incorrect diagnosis, comorbid substance use, anxiety disorders, ADHD or eating disorders. Check compliance with therapy; dosage adjustment may help; switching to an alternate antidepressant (p. 137) or augmentation strategies (p. 139) have also been tried
- A landmark study for treatment of depression, STAR*D, showed that about 1 in 3 patients reached remission in 10 weeks of treatment, and another 2 in 10 responded to treatment. After switching treatments, another 25% of patients became symptom-free with one switch. In total, approximately 50% of all patients in the study became symptom-free after two treatment trials; over the course of the maximum four antidepressant trials (the first two being SSRI, then switching outside the class, then augmentation) almost 70% became symptom-free. This study specifically excluded adolescents[9]

Therapeutic Effects

- Elevation of mood, improved appetite and sleep patterns, increased physical activity, improved clarity of thinking, better memory; decreased feelings of guilt, worthlessness, helplessness, and inadequacy; decrease in delusional preoccupation and ambivalence. Co-occurring therapeutic effects on anxiety, obsessions, eating disorders, and some sexual dysfunctions

Selective Serotonin Reuptake Inhibitors (SSRIs)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/ Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Citalopram	Phthalane derivative	Serotonin/ Reuptake inhibitor	Celexa	Tablets: 10 mg, 20 mg, 30 mg[C], 40 mg Capsules[B]: 30 mg Oral disintegrating tablets[B]: 40 mg Oral solution[B]: 10 mg/5 mL	Safety and efficacy not established in children and adolescents under age 18
Escitalopram	Phthalane derivative	Serotonin/ Reuptake inhibitor	Cipralex[C], Lexapro[B] Cipralex Meltz[C]	Tablets: 5 mg, 10 mg, 15 mg[C], 20 mg Oral solution[B]: 5 mg/5 mL Oral disintegrating tablets: 10 mg, 20 mg	Approved in the USA for children age 12 and above in major depressive disorder Safety and efficacy not established in children and adolescents under age 18
Fluoxetine	Bicyclic	Serotonin/ Reuptake inhibitor	Prozac Prozac Weekly[B]	Capsules: 10 mg, 20 mg, 40 mg, 60 mg[C] Oral solution: 20 mg/5 mL Tablets[B]: 10 mg, 20 mg, 60 mg Capsules, delayed-release pellets: 90 mg	Approved in the USA for children age 7 and above in obsessive-compulsive disorder and age 8 and above in major depressive disorder
Fluoxetine/olanzapine	Bicyclic	Serotonin/ Reuptake inhibitor Dopamine, serotonin/ Antagonist	Symbyax[B]	Capsules: Fluoxetine 25 mg with 6 mg, or 12 mg olanzapine; fluoxetine 50 mg with 6 mg or 12 mg olanzapine	Approved in the USA for children age 10 and above in acute treatment of depressive episodes in bipolar I disorder

Selective Serotonin Reuptake Inhibitors (SSRIs) (cont.)

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/ Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Fluvoxamine	Monocyclic	Serotonin/ Reuptake inhibitor	Luvox Luvox CR[B]	Tablets: 25 mg[B], 50 mg, 100 mg Extended-release capsules: 100 mg, 150 mg	Approved in the USA for children age 8 and above in obsessive-compulsive disorder
Paroxetine hydrochloride	Phenylpiperidine	Serotonin/ Reuptake inhibitor	Paxil Paxil CR	Tablets: 10 mg, 20 mg, 30 mg, 40 mg[B] Oral suspension[B]: 10 mg/5 mL Controlled-release tablets: 12.5 mg, 25 mg, 37.5 mg[B]	Safety and efficacy not established in children and adolescents under age 18
Paroxetine mesylate[B]	Phenylpiperidine	Serotonin/ Reuptake inhibitor	Pexeva Brisdelle	Tablets: 10 mg, 20 mg, 30 mg, 40 mg Capsules: 7.5 mg	Safety and efficacy not established in children and adolescents under age 18
Sertraline	Tetrahydronaphthyl-methylamine	Serotonin/ Reuptake inhibitor	Zoloft	Capsules: 25 mg[C], 50 mg[C], 100 mg[C], 150 mg[B], 200 mg[B] Tablets[B]: 25 mg, 50 mg, 100 mg Oral concentrate[B]: 20 mg/mL	Approved in the USA for children age 6 and above in obsessive-compulsive disorder

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- 👍 Depression (USA: fluoxetine – age 8 and above; escitalopram – age 12 and above)
- 👍 Bipolar depression (USA: fluoxetine/olanzapine combination – age 10 and above)
- 👍 Obsessive-compulsive disorder (OCD) (USA: sertraline – age 6 and above; fluoxetine – age 7 and above; fluvoxamine – age 8 and above)
- No SSRIs are approved for use in children and adolescents in Canada
- SSRIs have also been used in the treatment of persistent depressive disorder, social anxiety disorder, anxiety, panic disorder, bulimia, Tourette's disorder, and ADHD; preliminary data suggest efficacy in some children with autism spectrum disorder and selective mutism; negative trial in adolescents with comorbid cannabis use disorder and MDD

In adults:

- 👍 Major depressive disorder (MDD) (Canada: all; USA: citalopram, escitalopram, fluoxetine, paroxetine, sertraline)
- 👍 MDD, recurrent: Prophylaxis
- 👍 Bulimia nervosa (fluoxetine, sertraline)
- 👍 Obsessive-compulsive disorder (OCD) (fluvoxamine, fluoxetine, paroxetine, escitalopram (Canada only), sertraline)
- 👍 Panic disorder with or without agoraphobia (paroxetine, sertraline, fluoxetine)
- 👍 Social anxiety disorder (paroxetine, sertraline)
- 👍 Posttraumatic stress disorder (PTSD) (paroxetine, sertraline)
- 👍 Premenstrual dysphoric disorder (PMDD) (paroxetine, sertraline)
- 👍 Generalized anxiety disorder (GAD) (escitalopram, paroxetine)

‡ Indications listed here do not necessarily apply to all SSRIs or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

- Depressive episodes associated with bipolar I disorder and treatment-resistant depression (fluoxetine/olanzapine combination)
- Moderate-to-severe vasomotor symptoms of menopause (low-dose paroxetine mesylate in USA; may be a first-choice alternative for females who are not suitable for, or refuse, hormone therapy)
- Dysthymia/persistent depressive disorder
- Binge-eating disorder – double-blind studies suggest efficacy of fluoxetine, fluvoxamine, and citalopram
- Borderline personality disorder – treatment of self-injurious behavior, aggression, impulsive behavior, and behavior disturbances
- Body dysmorphic disorder – benefit reported
- Postpartum depression – open trial suggests sertraline may prevent recurrence in females with a prior history
- Autism spectrum disorder in adults (fluoxetine)[10] and selective mutism – preliminary data suggest efficacy
- Trichotillomania
- Cannabis use disorder – fluoxetine (preliminary efficacy data in patients with comorbid depression and alcohol use disorder), escitalopram (negative trial; 50% dropout rate)
- Betel-quid (betel nut) use disorder – preliminary findings (escitalopram)
- Chronic fatigue syndrome – open label trials have shown 70% effectiveness but not replicated in RCTs
- Premature ejaculation
- Raynaud's phenomenon

General Comments

- Efficacy for major depressive disorder (MDD) in children and adolescents NOT clearly demonstrated in controlled trials with paroxetine; no data with fluvoxamine
- See p. 52 for comments on antidepressants and suicidality
- In the TORDIA (Treatment of Resistant Depression in Adolescents) RCT, outcomes for adolescents who were treatment resistant to an SSRI were randomized to switch to a different medication (SSRI or venlafaxine) or a different medication plus CBT.[11] There were no differences in outcomes; about 40% of all treatment-resistant patients achieved remission in 24 weeks.[6] However, the TORDIA study demonstrated effectively that response at 6 weeks was strongly predictive of overall response, suggesting that earlier intervention among non-responders is important[6]
- Response to SSRIs may be more delayed in OCD relative to depression or anxiety disorders; response is dose-related, with better clinical responses associated with higher doses, although lower doses may be effective in preventing relapse

Pharmacology

- Exact mechanism of antidepressant action unknown; SSRIs, through inhibition of serotonin reuptake, increase concentrations of serotonin in the synapse, which causes downregulation of post-synaptic receptors (e.g., 5-HT_{2A}). Some SSRIs can also affect other neurotransmitters, e.g., some SSRIs also inhibit the reuptake of norepinephrine (i.e., fluoxetine, paroxetine), while others inhibit the reuptake of dopamine (i.e., sertraline) or antagonize muscarinic cholinergic receptors (e.g., paroxetine)
- Escitalopram is an active, (S)-enantiomer of racemic citalopram; more potent and selective than citalopram in inhibiting serotonin reuptake; six times less potent than citalopram in binding to the histamine (H1) and muscarinic receptors; dose-dependent QTc prolongation was found for both escitalopram and citalopram

Dosing

- See p. 133
- Microdosing (for example, 2.5 mg or 5 mg doses of fluoxetine) is not appropriate for initial therapy unless there are specific considerations (see below); the starting dose for children has been established through randomized controlled trials and need not be halved or quartered. Dosage should be decreased (by 50%) in patients with significant hepatic impairment, as plasma levels can increase up to 3-fold
- In kidney impairment, sertraline levels may increase by 50%; use 50% of the standard dose of paroxetine if creatinine clearance is 10–50 mL/min, and 25% of the standard dose if creatinine clearance is less than 10mL/min
- Higher doses than those used in depression may be required in the treatment of anxiety disorders, OCD, eating disorders, and PTSD
- Lower starting dose may be effective for panic disorder and should be considered, as patients may be more sensitive to stimulant effects
- Dosing interval of every 2 to 7 days has been used with fluoxetine in prophylaxis of depression; once weekly dosing used in the maintenance treatment of panic disorder
- Intermittent dosing (during luteal phase of menstrual cycle) found effective for the treatment of premenstrual dysphoric disorder

Selective Serotonin Reuptake Inhibitors (SSRIs) (cont.)

Pharmacokinetics

- See p. 133
- SSRIs are absorbed relatively slowly but completely (time to peak plasma concentration is 3–8 h); most undergo little first-pass effect
- Peak plasma level and bioavailability of sertraline capsules are 30% higher (25% and 40%, respectively) when drug taken with food, as first-pass metabolism is reduced; food does not significantly change the bioavailability of sertraline oral concentrate or tablets
- SSRIs are highly bound to plasma protein (fluoxetine, paroxetine, and sertraline) and will displace other drugs from protein binding although this is rarely clinically significant (see Interactions, p. 61)
- Metabolized primarily by the liver; all SSRIs affect CYP450 enzymes (least: citalopram and escitalopram) and will affect the metabolism of other drugs metabolized by this system (see Interactions, p. 61). Fluoxetine and paroxetine have been shown to decrease their own metabolism over time; half-life of fluoxetine is increased with chronic administration. Clearance of all SSRIs reduced in patients with liver cirrhosis
- Fluoxetine as well as its active metabolite, norfluoxetine, have the longest half-lives (up to 70 h and 330 h, respectively); this has implications for reaching steady-state drug levels as well as for drug withdrawal and drug interactions
- Controlled-release paroxetine is enteric-coated and formulated for controlled dissolution; suggested to be better tolerated than the immediate-release formulations in regards to GI effects, especially at start of therapy. No difference in efficacy or pharmacokinetics has been confirmed in pediatric patients

Onset & Duration of Action

- SSRIs are long-acting drugs and can be given in a single daily dose, usually in the morning; may cause sedation in some patients and can be prescribed at night. When total daily dose of fluvoxamine exceeds 100 mg, it should be given in 2 divided doses, with the larger portion administered at bedtime
- Therapeutic effect typically seen after 28 days (although some patients may respond sooner); increasing the dose too rapidly due to absence of therapeutic effect can result in higher doses than necessary and higher rate of adverse effects
- Tolerance to effects seen in some patients after months of treatment ("poop-out syndrome" or tachyphylaxis) (see p. 53)

Adverse Effects

- The pharmacological and adverse effect profile of SSRIs is related to their *in vivo* affinity for and activity on neurotransmitters/receptors (see Table p. 128)
- For incidence of adverse effects at therapeutic doses see chart (p. 130)
- Incidence may be greater in early days of treatment; patients adapt to many side effects over time
- Rule out withdrawal symptoms of previous antidepressant – can be misattributed to side effects of current drug
- Children are more prone to behavioral adverse effects including: Agitation, restlessness (32–46%), activation, hypomania (up to 13%), insomnia (up to 21%), irritability, social disinhibition (up to 25%)
- See p. 52 for comments on antidepressants and suicidality

CNS Effects

- Headache common, worsening of migraines [Management: Acetaminophen prn]
- Seizures reported, primarily in patients with underlying seizure disorder (risk 0.04–0.3%); dose related
- Activation, excitement, impulse dyscontrol, anxiety, agitation, and restlessness; more frequent at higher doses; psychosis or panic reactions may occur; isolated reports of antidepressants causing motor activation, aggression, depersonalization, **suicidal urges** (see p. 52), and potential to harm others; may increase risk of violent crime in high-risk patients (e.g., younger, male, history of violent crime)
- Insomnia: Decreased REM sleep, prolonged sleep onset latency, reduced sleep efficacy, and increased awakenings with all SSRIs; increased dreaming, nightmares, sexual dreams and obsessions reported with fluoxetine [Management: May respond to clonazepam or cyproheptadine 2 mg]; case reports of somnambulism with paroxetine
- Drowsiness – more common with fluvoxamine and paroxetine; prescribe bulk of dose at bedtime
- Precipitation of hypomania or mania (up to 10% of patients with a history of bipolar disorders – less frequent if patient receiving mood stabilizers); increased risk in patients with comorbid substance use disorder
- Lethargy, apathy or amotivational syndrome (asthenia) reported – may be dose related and is reversible; more likely with SSRIs than SNRIs [Management: Prescribe bulk of dose at bedtime or consider alternative medication]

- Case reports of cognitive impairment, decreased attention
- Case reports of visual hallucinations with fluoxetine, fluvoxamine, paroxetine, and sertraline
- Fine tremor [Management: May respond to dose reduction]
- Akathisia
- Dystonia, dyskinesia, parkinsonism or tics
- Tinnitus
- Myoclonus, spasticity, restless legs syndrome
- Dysphasia, stuttering
- Nocturnal bruxism reported – may result in morning headache or lead to damage to teeth [Management: May respond to buspirone up to 50 mg/day]
- Paresthesias; may be caused by pyridoxine deficiency [Management: Pyridoxine]; "electric-shock-like" sensations
- Yawning reported with citalopram, escitalopram (dose-related), fluoxetine, paroxetine, and sertraline

Anticholinergic Effects

- Case reports of urinary retention, urgency, incontinence, or cystitis
- Case report of acute angle closure with paroxetine in patient with narrow-angle glaucoma

Cardiovascular Effects

- Citalopram and escitalopram cause dose-dependent QTc interval prolongation. Citalopram should not be prescribed at doses greater than 40 mg/day, and 20 mg/day in individuals with liver impairment, or if combined with CYP2C19 inhibitors. Similarly, the dose of escitalopram should be limited to 20 mg/day in adolescents and to 10 mg/day if combined with CYP2C19 inhibitors. Citalopram use is discouraged in patients with congenital long QTc syndrome. Patients with congestive heart failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesemia because of concomitant illness or drugs are at higher risk of developing torsades de pointes
- Rare reports of tachycardia, palpitations, hypertension, and atrial fibrillation
- Bradycardia
- Dizziness
- Slowing of sinus node reported with fluoxetine; caution in sinus node disease and in patients with serious left ventricular impairment; case reports of QTc prolongation with fluoxetine (two mechanisms proposed: Direct blockade of the hERG potassium ion channels and disruption of hERG protein expression on the cell membrane)
- Increased LDL cholesterol levels reported with paroxetine and sertraline

Hematologic Effects

- Bleeding disorders including petechiae, purpura (1% risk with fluoxetine); thrombocytopenia with fluoxetine; bruising, nosebleeds, and bleeding after surgery (and need for blood transfusion) reported with all SSRI drugs; rarely: Microscopic hematuria, intracranial hemorrhage (conflicting data) and postpartum hemorrhage; increased bleeding attributed to inhibition of serotonin uptake by platelets; increased GI bleed attributed to increase in gastric acid secretion; risk increased in older individuals, those with a history of GI bleed or in combination with drugs such as NSAIDs, ASA, anticoagulants or antiplatelet drugs (see Interactions p. 10–15); GI bleed risk decreased with use of proton pump inhibitors[12]
- Rare blood dyscrasias including neutropenia and aplastic anemia
- In surgical patients, a small evidence base suggests SSRI use is associated with bleeding and adverse outcomes. In coronary bypass surgery, SSRI use has been associated with increased bleeding risk. Similar findings have been seen in orthopedic surgical procedures. Receiving SSRIs in the perioperative period is associated with higher odds for bleeding.[13] Note: There are no high-quality prospective studies examining the risk–benefit profile for cessation of SSRIs and risk of surgical bleeding

Endocrine & Metabolic Effects

- Can induce SIADH with hyponatremia; can result in nausea, fatigue, headache, cognitive impairment, confusion, and seizures; risk increases with age (up to 32% incidence), female sex, low body weight, smoking, and concomitant diuretic use
- Monitoring of serum sodium is suggested in those with a history of hyponatremia or on other agents associated with hyponatremia, such as diuretics, or with comorbid conditions associated with hyponatremia, such as heart failure
- Elevated prolactin – risk increased in females (up to 22% reported in females taking fluoxetine); cases of galactorrhea and gynecomastia
- SSRIs do not typically affect blood glucose; however, reports of increased and decreased blood glucose are available
- One meta-analysis found that weight loss occurred with acute treatment with most of the SSRIs but this was not sustained with chronic treatment. Weight gain reported: Up to 18% of individuals gain more than 7% of body weight with chronic use – reported more frequently in females (more common with paroxetine)[14]
- Preliminary evidence that SSRIs slightly decrease thyroid function, but evidence quality is low and clinical magnitude is unclear[15]

Selective Serotonin Reuptake Inhibitors (SSRIs) (cont.)

GI Effects

- A result of inhibition of 5-HT reuptake (activation of 5-HT_3 receptors)
- Nausea; vomiting – generally decreases over time due to gradual desensitization of 5-HT_3 receptors [Management: May respond to taking drug with meals, lowering dose, or switching to the delayed/controlled-release formulation]
- Diarrhea, bloating – usually transient and dose-related; may be more frequent with fluoxetine 90 mg delayed-release pellets taken once weekly
- Decreased appetite and weight loss frequently reported early in treatment – more pronounced in overweight patients and those with carbohydrate cravings
- Weight gain reported, particularly with paroxetine
- 2–4 times higher risk of upper GI bleeding with SSRIs, especially if combined with NSAIDs (risk increased 12-fold) or ASA
- Case reports of stomatitis with fluoxetine; glossodynia (burning mouth syndrome) reported during treatment with fluoxetine, sertraline

Urogenital & Sexual Effects

- Sexual dysfunction should be well screened and managed because it is not always fully explored; could negatively impact treatment prognosis, and is a common cause of medication non-adherence; treatment emergent sexual dysfunction should be differentiated from depression- and anxiety-related sexual dysfunction
- A result of increased serotonergic transmission by way of the 5-HT_{2A} receptor which results in reduced dopaminergic transmission, acetylcholine (ACh) blockade, and reduced nitric oxide levels – appears to be dose-related; risk increased with age and concomitant drug use
- All three phases of the sexual cycle may be affected: Reduced interest and desire for sex; erectile dysfunction in males and diminished arousal in females; and difficulty in attaining orgasm in both sexes
- Paroxetine may be more likely than other SSRIs to cause sexual dysfunction (up to 75% of patients) and fluvoxamine may have a modest advantage for anorgasmia (at dose below 100 mg daily)
- Phosphodiesterase inhibitors such as sildenafil have been shown in RCTs to be effective in overcoming erectile dysfunction and orgasmic problems induced by SSRIs in adult males, and in reducing adverse sexual effects including reversal of anorgasmia in adult females, with similar adverse events to the general population
- Cases of priapism in both males and females reported with citalopram, fluoxetine, paroxetine, and sertraline
- Cases of spontaneous orgasm with yawning
- Case of painful ejaculation (fluoxetine)

Hypersensitivity Reactions

- Rare
- Rash (up to 1% incidence), urticaria, psoriasis, pruritus, edema, photoallergy/photosensitivity (cross-sensitivity between SSRIs has been suggested); rare cases of Stevens-Johnson syndrome
- Serum sickness-like reaction
- Increased hepatic enzyme levels, hyperbilirubinemia, jaundice, hepatitis
- Pneumonitis

Other Adverse Effects

- Sweating is most likely with paroxetine (a result of norepinephrine-reuptake inhibition) [Management: Daily showering; in severe cases: Drysol solution, oxybutynin, clonidine, guanfacine, or benztropine; drug may need to be changed]
- Rhinitis common
- Hepatic effects – infrequent, usually modest elevations in liver enzymes that are often self-limited and do not require dose modification or discontinuation although rare cases of acute failure and chronic hepatitis have been reported; onset varies, usually within 2–24 weeks and pattern of presentation has ranged from hepatocellular to cholestatic or mixed; immunoallergic features are uncommon
- Epistaxis
- Case reports of alopecia
- Case reports of exacerbation of Raynaud's syndrome
- Sporadic cases of eosinophilic pneumonia, idiopathic pulmonary fibrosis, granulomatous lung disease, and diffuse alveolar damage
- There is a growing body of evidence to suggest an increased, dose-dependent risk of fractures in females and older adults taking SSRIs[16, 17, 18]; effects in children and adolescents unknown. When prescribing SSRIs, the increased risk of fractures must be considered, including risk of falls and potential fracture risk

D/C Discontinuation Syndrome

- Abrupt discontinuation of high doses may cause a syndrome consisting of *somatic symptoms:* Dizziness (exacerbated by movement), lethargy, nausea, vomiting, diarrhea, headache, fever, sweating, chills, malaise, incoordination, insomnia, vivid dreams; *neurological symptoms:* Myalgia, paresthesias, dyskinesias, "electric-shock-like" sensations, visual discoordination; *psychological symptoms:* Anxiety, agitation, crying, irritability, confusion, slowed thinking, disorientation; rarely aggression, impulsivity, hypomania, and depersonalization; cases of mania reported following antidepressant taper, despite adequate concomitant mood-stabilizing treatment
- Most likely to occur within 1–7 days after a short half-life drug stopped or dose drastically reduced, and typically disappears within 3 weeks
- Incidence (of 2–78%) is related to half-life of antidepressant – reported most frequently with paroxetine, least with fluoxetine; attributed to rapid decrease in 5-HT availability

☞ **THEREFORE THESE MEDICATIONS SHOULD BE WITHDRAWN GRADUALLY AFTER PROLONGED USE. Taper antidepressant no more rapidly than by 25% per week (or nearest dose possible) and monitor for recurrence of depressive symptoms (except for fluoxetine, which can be tapered more rapidly due to its prolonged half-life)**

Management

- Re-institute drug and taper more slowly
- Substitution with a single dose of fluoxetine (10–20 mg) can help in the withdrawal process due to its very long half-life
- Consider utilizing a liquid or compounded formulation to allow for smaller incremental dosing adjustments if necessary

Precautions

- Monitor all patients for worsening depression and suicidal thinking especially at start of therapy or following an increase or decrease in dose
- May impair the mental and physical ability to perform hazardous tasks (e.g., driving a car or operating machinery)
- May induce manic reactions in up to 10% of patients with bipolar disorder – reported more frequently with fluoxetine; because of risk of increased cycling, bipolar disorder is a relative contraindication unless a mood stabilizer is added

☞ **SEROTONIN SYNDROME**

Use of SSRIs with other serotonergic agents may result in serotonin syndrome – usually occurs within 24 h of medication administration (but can occur within minutes to hours). Be particularly suspicious if symptoms appear around a change in dose or suspected overdose. Symptoms can be grouped into the following categories:

- COGNITIVE: Headache, agitation, confusion, coma
- AUTONOMIC: Sweating, fever, tachycardia, nausea, diarrhea, chills/shivering
- SOMATIC: Myoclonus, hyperreflexia, tremor

Serotonin syndrome may progress to rhabdomyolysis, coma, and death, and it is important to recognize that non-antidepressants or other serotonergic drugs can contribute to the syndrome (see Drug Interactions pp. 61–66) – common non-antidepressant drugs include: Amphetamines, dextromethorphan, fentanyl, hallucinogens, L-dopa, meperidine, metoclopramide, oxycodone, risperidone, and tramadol [Treatment: Stop medication and administer supportive care]. Residual symptoms such as muscle aches may last for up to 8 weeks in SSRIs with long half-lives

- Fluoxetine, fluvoxamine, and paroxetine affect CYP450 and will inhibit the metabolism (and elevate the levels) of drugs metabolized by this system; sertraline will inhibit metabolism at higher doses (e.g., > 100 mg/day) (see Drug Interactions, pp. 61–66)
- Treatment with medications that inhibit the serotonin transporter may be associated with abnormal bleeding, particularly when combined with NSAIDs, ASA or other medications that affect coagulation

Toxicity

- SSRIs generally have a low probability of causing dose-related toxicity; symptoms include: Nausea, vomiting, tremor, myoclonus, irritability (one fatality reported with dose of 6000 mg of fluoxetine; seizure reported in adolescent after ingestion of 1880 mg of fluoxetine); much more favorable toxicity profile compared to tricyclic antidepressants
- Rapid onset of seizures with QTc interval prolongation is common with citalopram; citalopram and escitalopram are more likely to cause cardiotoxicity than other SSRIs. Cardiac arrest and torsades de pointes have been reported with citalopram and toxicity has occurred in adults ingesting as little as 100–190 mg
- Apart from citalopram, there is no clear difference in QTc prolongation risk among other SSRIs based on currently available data. Overall, the average QTc prolongation of SSRIs is approximately 6 msec at therapeutic dosages, much lower than with most medications for which a QTc warning or awareness exist[19]
- Altered mental state, QTc prolongation, bradyarrhythmias, syncope, and seizures reported following an overdose of citalopram; fatal outcome in 6 adult patients with citalopram 840–3920 mg (some had also taken other sedative drugs or alcohol); fatalities reported with overdoses of citalopram and moclobemide when co-prescribed
- Case of serotonin syndrome reported after overdose of 8000 mg of sertraline

Selective Serotonin Reuptake Inhibitors (SSRIs) (cont.)

Management

- Treatment: Symptomatic and supportive
- Citalopram and escitalopram overdose – asymptomatic patients should have continuous ECG monitoring and monitoring of vital signs for 6 h; symptomatic patients until resolution of symptoms

Use in Pregnancy◊

- Despite extensive studies on the effects of SSRIs in pregnancy, conflicting views on possible adverse effects on the course of pregnancy and on the newborn remain, likely because of the complex and confounding role of factors such as maternal illness itself and stress. Additionally, because depression in late pregnancy is a major predictor for potentially life-threatening postpartum depression, it is advisable to weigh the benefits of treatment against possible hazards. Overall, this is an individualized decision, but the risk associated with treatment discontinuation in those at high risk of relapse seems to outweigh the potential risks, as severe maternal illness may negatively affect the child's development
- In a meta-analysis of 115 studies (16 included), fluoxetine and paroxetine were associated with increased risk of major malformations. Sertraline and citalopram were not significantly associated with congenital malformation[20]
- Paroxetine should be avoided due to increased risk of cardiac malformation
- Absolute risk of cardiac malformations in a 2014 study was higher in females who used antidepressants in pregnancy (9 per 1000) vs. females who did not (7.2 per 1000), an absolute risk difference of 0.2%[21]
- Fetal echocardiography should be considered for females exposed to paroxetine in early pregnancy (Level B evidence).[22]
- A 2011 FDA review concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and pulmonary hypertension
- Possible increased risk of miscarriage; with escitalopram, teratogenic effects have been reported in animal studies[23]
- If possible, avoid SSRIs during first trimester; when stopping the SSRI, taper the dose gradually to minimize adverse fetal outcome; with fluoxetine be aware of long half-life of metabolite, norfluoxetine
- Reports of an increase in premature births and poor neonatal adaptation when drug taken in the third trimester
- Neonates exposed to SSRIs (especially paroxetine) in the third trimester (after 20th week) have developed complications upon delivery including: Jitteriness, restlessness, irritability, tremors, feeding difficulties, changes in muscle tone, respiratory distress, persistent pulmonary hypertension (6-fold increased risk), temperature instability, seizures (with fluoxetine these are related to blood level of fluoxetine and norfluoxetine)[24]
- Higher plasma levels of paroxetine reported in infants whose mothers also received clonazepam
- Meta-analysis supports an increased risk of autism spectrum disorder in children of mothers exposed to SSRIs during pregnancy[25]

Breast Milk

- Although all SSRIs may be secreted in breast milk, concentrations are generally low and overall, infant exposure relatively limited so SSRIs are all considered compatible; however, when initiating treatment during breastfeeding, sertraline and paroxetine are considered preferred agents as they have the most research combined with low to undetectable levels; fluoxetine is well-researched but exhibits the highest breast milk concentrations and its long half-life increases risk of accumulation in the infant, making it less advisable in this scenario
- Fluoxetine and citalopram appear in breast milk in therapeutic levels; CAUTION: Infant can receive up to 17% of maternal dose of fluoxetine and up to 9% of maternal dose of citalopram. Escitalopram, citalopram, and fluoxetine are not preferred agents for a nursing mother starting a new antidepressant. Fluoxetine: Colic, fussiness, and drowsiness reported in breastfed infants, but no adverse effects on development found in a few infants followed for up to a year. Citalopram and escitalopram: Drowsiness and irritability reported in breastfed infants
- Paroxetine and fluvoxamine are present in very low concentrations in plasma of breastfed infants; sertraline detected in breast milk, especially if mother on dose of 100 mg or higher. In a review, these three agents were considered compatible with breastfeeding[26]
- The American Academy of Pediatrics considers SSRIs as "drugs whose effect on nursing infants is unknown but may be of concern"
- Mothers who are already stabilized on an SSRI at delivery should not be discouraged from breastfeeding, nor is there evidence that would advise switching agents in the context of stable psychiatric condition

Nursing Implications

- Psychotherapy and education are also important in the treatment of depression; effects of CBT can be comparable to antidepressants with possibly longer lasting effects

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

- Monitor therapy by watching for adverse effects and mood and activity level changes, including worsening of suicidal thoughts, especially at start of therapy or following an increase or decrease in dose
- Be aware that the medication reduces the degree of depression and may increase psychomotor activity; this may create concern about suicidal behavior
- Watch for increased bruising, nosebleeds, or evidence of GI bleed, especially in patients also taking ASA or NSAIDs, corticosteroids or anticoagulants
- Excessive ingestion of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis
- Extended/controlled-release fluvoxamine, paroxetine and fluoxetine products should not be broken, crushed or chewed but swallowed whole, with water
- Sertraline capsule should be given with food (increases bioavailability by 40%), but no bioavailability change is seen with the tablet or oral concentrate formulations; food reduces incidence of nausea with all SSRIs
- Ingestion of grapefruit juice while taking fluvoxamine, and sertraline may increase the plasma level of these drugs
- SSRIs (exception: fluoxetine) should not be stopped suddenly due to risk of precipitating withdrawal reactions

Patient Instructions

- For detailed patient instructions on SSRI antidepressants, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
α_2 adrenergic agonist	Tizanidine	DO NOT COMBINE with fluvoxamine. Increased AUC of tizanidine (14- to 103-fold), increased C_{max} (5- to 32-fold), and half-life (3-fold) with fluvoxamine due to inhibition of metabolism via CYP1A2
Anorexiant	Phentermine, sibutramine	Case reports of mania, psychosis, and serotonin syndrome in combination
Antiarrhythmic	Flecainide, mexiletine, propafenone	Increased plasma level of antiarrhythmic with fluoxetine and paroxetine due to inhibited metabolism via CYP2D6
	Lidocaine, quinidine	Increased plasma level of antiarrhythmic possible with fluoxetine, fluvoxamine, sertraline, and paroxetine due to inhibited metabolism via CYP3A4
Antibiotic	Azithromycin	Additive QTc prolongation
	Clarithromycin	Additive QTc prolongation; case of delirium with fluoxetine; case of serotonin syndrome with citalopram
	Erythromycin	Additive QTc prolongation; increased plasma level of citalopram due to inhibited metabolism via CYP3A4 is possible; case of serotonin syndrome with sertraline
	Linezolid	Monitor for increased serotonergic effects due to linezolid's weak MAO inhibition
Anticoagulant	Apixaban, dabigatran, rivaroxaban	Increased risk of bleeding
	Warfarin	Increased risk of bleeding; increased bleeding time and INR response due to decreased platelet aggregation secondary to depletion of serotonin in platelets
		65% increase in plasma level of warfarin with fluvoxamine due to accumulation of R-warfarin through inhibited metabolism (via CYP1A2 and 3A4) and decreased clearance of S-isomer (via CYP2C9)

Selective Serotonin Reuptake Inhibitors (SSRIs) (cont.)

Class of Drug	Example	Interaction Effects
Anticonvulsant	Barbiturates	Barbiturate metabolism inhibited by fluoxetine; reduced plasma level of SSRIs due to enzyme induction by barbiturate
	Carbamazepine, phenytoin, phenobarbital	Decreased plasma level of SSRIs; half-life of paroxetine decreased by 28% Increased plasma level of carbamazepine or phenytoin due to inhibition of metabolism with fluoxetine and fluvoxamine; elevated phenytoin level with sertraline and paroxetine Increased nausea with fluvoxamine and carbamazepine
	Divalproex, valproate, valproic acid	Increased plasma level of valproate (up to 50%) with fluoxetine Valproate may increase plasma level of fluoxetine
	Topiramate	Case reports of angle-closure glaucoma
Antidepressant		
NDRI	Bupropion	Additive antidepressant effect in refractory patients. Bupropion may reverse SSRI-induced sexual dysfunction. Case of hypersexual behavior in combination with fluoxetine Cases of anxiety, panic, delirium, tremor, myoclonus, and seizure reported with fluoxetine due to inhibited metabolism of bupropion and/or fluoxetine (via CYP3A4 and 2D6), competition for protein binding, and additive pharmacological effects
SNRI	Duloxetine	Combination with SSRIs that inhibit CYP1A2 (e.g., fluvoxamine) or CYP2D6 (e.g., paroxetine, fluoxetine) can result in increased levels of duloxetine, with possible increase in blood pressure, anticholinergic effects, and serotonergic effects
	Venlafaxine	Reports that combination with SSRIs that inhibit CYP2D6 (e.g., paroxetine, fluoxetine) can result in increased levels of venlafaxine, with possible increase in blood pressure, anticholinergic effects, and serotonergic effects
SARI	Trazodone	Additive antidepressant effect Elevated plasma level of SARI; increased serotonergic effects Increased level of mCPP metabolite of trazodone and nefazodone with paroxetine (via inhibition of CYP2D6), resulting in increased anxiogenic potential
NaSSA	Mirtazapine	Combination reported to alleviate insomnia with low mirtazapine doses (under 30 mg) and augment antidepressant response May mitigate SSRI-induced sexual dysfunction and "poop-out" syndrome Increased sedation, serotonergic effects, and weight gain in combination Increased mirtazapine level (up to 4-fold) reported in combination with fluvoxamine due to inhibited metabolism
Nonselective cyclic	Amitriptyline, desipramine, imipramine	Elevated plasma level of cyclic antidepressant with fluoxetine, fluvoxamine, and paroxetine due to release from protein binding and inhibition of oxidative metabolism; can occur with higher doses of sertraline Imipramine metabolite (desipramine) increased by 50% with citalopram and escitalopram
	Clomipramine	Additive antidepressant effect in treatment-resistant patients. Via CYP1A2 inhibition, fluvoxamine reduces conversion of clomipramine to desmethylclomipramine (adrenergic/cardiotoxic metabolite) and is sometimes co-prescribed intentionally for this effect Increased serotonergic effects
RIMA	Moclobemide	Combined therapy may have additive antidepressant effect in treatment-resistant patients; use caution and monitor for serotonergic effects; case reports of serotonin syndrome, especially with citalopram and escitalopram
Irreversible MAOI	Phenelzine, tranylcypromine	Serotonin syndrome (see p. 59) and death reported with combined use. Allow SSRI to washout for 4–6 elimination half-lives before prescribing MAOI. Suggest waiting 5 weeks when switching from fluoxetine to MAOI and vice versa

Class of Drug	Example	Interaction Effects
Antiemetic (5-HT_3 antagonist)	Alosetron	DO NOT USE with fluvoxamine as plasma level of alosetron increased 6-fold and half-life increased 3-fold due to inhibited metabolism via CYP3A4
	Dolasetron, granisetron, ondansetron	Reports of serotonin syndrome Potential for additive QTc prolongation
Antifungal	Fluconazole, ketoconazole	Decreased C_{max} of ketoconazole by 21% with citalopram 2 cases of life-threatening serotonin syndrome reported with citalopram[27]
	Terbinafine	Increased paroxetine exposure (AUC 2.5-fold) via CYP2D6 inhibition by terbinafine
Antihistamine	Diphenhydramine	Increased plasma levels of fluoxetine and paroxetine possible due to inhibited metabolism via CYP2D6 Additive CNS effects
Antiparkinsonian	Benztropine Procyclidine	Increased plasma level of benztropine with paroxetine Increased plasma level of procyclidine with paroxetine (by 40%)
Antiplatelet	Clopidogrel	Increased risk of bleeding (by 54%)
Antipsychotic	General	May worsen extrapyramidal effects and akathisia, especially if antidepressant added early in the course of antipsychotic therapy Increased plasma level of antipsychotic due to inhibition of metabolism via CYP1A2 (potent – fluvoxamine), 2D6 (potent – fluoxetine and paroxetine), and/or 3A4 (fluvoxamine). Monitor for increased antipsychotic adverse effects (e.g., sedation, orthostatic hypotension, EPSE) when starting and antipsychotic efficacy when stopping SSRI. Adjust antipsychotic dose as needed. Alternatively, consider using an SSRI with no or weak effects on CYPs such as citalopram, escitalopram, and sertraline (at doses of 100 mg/day or less) or use an SSRI that does not affect the specific CYP enzyme which metabolizes the specific antipsychotic
First generation	Chlorpromazine, fluphenazine, haloperidol, perphenazine	Haloperidol levels: 20–35% higher with fluoxetine; 23–60% higher with fluvoxamine; 28% higher with sertraline Perphenazine peak levels 2- to 13-fold higher with paroxetine Case report of QTc prolongation and patient collapsing with concurrent chlorpromazine and fluoxetine Increased risk of QTc prolongation, EPS, and akathisia
	Pimozide	Pimozide levels: AUC increased by 151% and peak level increased by 62% with paroxetine; AUC and peak level increased by 40% with sertraline. Case reports of bradycardia with concurrent use of pimozide and fluoxetine Pimozide level also increased when combined with citalopram, escitalopram, or fluvoxamine, increasing risk of QTc prolongation – DO NOT COMBINE
	Thioridazine	3-fold increase in thioridazine levels with fluvoxamine DO NOT COMBINE citalopram, escitalopram, fluoxetine, or paroxetine with thioridazine due to risk of additive QTc prolongation
Second generation	Asenapine	Asenapine peak level increased by 13% and AUC increased by 29% with fluvoxamine. Asenapine (a weak inhibitor of CYP2D6) increases paroxetine exposure by ~ 2-fold. Reduce paroxetine dose by 50% if asenapine added
	Clozapine	Clozapine levels: With fluoxetine, 41–76% higher clozapine levels plus 38–45% higher norclozapine levels; one fatality reported; case report of acute myocarditis after addition of clozapine to fluoxetine and lithium. With fluvoxamine, 3- to 11-fold higher levels. With paroxetine, no change to 41% increase in clozapine plus 45% increase in norclozapine. With sertraline, 41–76% clozapine increase plus 45% norclozapine increase; one fatal arrhythmia reported but causality unclear
	Iloperidone	Iloperidone AUC increased by ~ 1.6- to 3-fold in the presence of fluoxetine or paroxetine. Reduce iloperidone dose by 50% if fluoxetine or paroxetine added
	Olanzapine	Olanzapine levels: With fluoxetine, 16% increase in peak concentration; not clinically significant. In the USA, olanzapine/fluoxetine is available as a combination product. With fluvoxamine, 2.3- to 4-fold increase in olanzapine levels; consider use of an SSRI with less effect on CYP1A2 or use lower olanzapine doses and monitor for adverse effects (e.g., EPS, hypersalivation)

Selective Serotonin Reuptake Inhibitors (SSRIs) (cont.)

Class of Drug	Example	Interaction Effects
	Paliperidone, risperidone, ziprasidone	Case reports of dose-related mania when risperidone or ziprasidone added to SSRI Risperidone levels: With fluoxetine, 2.5- to 8-fold increased levels and case report of TD. With paroxetine, 3- to 9-fold higher levels and cases of serotonin syndrome; consider using an alternative SSRI. Case reports of serotonin syndrome and/or NMS with fluvoxamine and trazodone plus sertraline Case report of serotonin syndrome with ziprasidone and citalopram CAUTION; possible additive prolongation of QTc interval and associated life-threatening cardiac arrhythmias. Factors that further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia
Third generation	Aripiprazole, brexpiprazole, cariprazine	When combined with fluoxetine or paroxetine, due to inhibited metabolism via CYP2D6, reduce aripiprazole and brexpiprazole dose by 50%. No dose adjustment required with cariprazine, as it is primarily a CYP3A4 substrate Cases of NMS, akathisia, dystonia, and myxedema coma with SSRIs combined with aripiprazole
Antitubercular	Rifampin	Case reports of SSRI withdrawal symptoms and decreased therapeutic efficacy of sertraline and citalopram due to CYP3A4 induction
Anxiolytic		
Benzodiazepine	Alprazolam, diazepam, bromazepam	Increased plasma level of benzodiazepine metabolized by CYP3A4; alprazolam (by 100% with fluvoxamine and 46% with fluoxetine), bromazepam, triazolam, midazolam, and diazepam; small (13%) decrease in clearance of diazepam reported with sertraline Increased sedation, psychomotor and memory impairment
Buspirone		Increased plasma level of buspirone (3-fold increase in AUC) with fluvoxamine Case report of possible serotonin syndrome with fluoxetine
β-blocker	Metoprolol, propranolol	Decreased heart rate and syncope (additive effect) reported Increased side effects, lethargy, and bradycardia with fluoxetine, fluvoxamine, and paroxetine due to decreased metabolism of the β-blocker via CYP2D6 (5-fold increase in propranolol level reported with fluvoxamine) Increased metoprolol level with citalopram (by 100%) and with escitalopram (by 50%)
	Pindolol	Increased concentration of serotonin at postsynaptic sites; faster onset of therapeutic response Increased half-life of pindolol (by 28%) with fluoxetine; increased plasma level with paroxetine due to inhibited metabolism via CYP2D6
Caffeine		Increased caffeine levels with fluvoxamine due to inhibited metabolism via CYP1A2; half-life increased from 5 to 31 h Increased jitteriness and insomnia
Calcium channel blocker	Nifedipine, verapamil	Increased side effects (headache, flushing, edema) due to inhibited clearance of calcium channel blocker via CYP3A4 with fluoxetine, fluvoxamine, sertraline, and paroxetine
	Diltiazem	Bradycardia in combination with fluvoxamine
Cannabis/marijuana		Case report of mania in combination with SSRI Association of negative treatment benefits in anxiety and mood disorders
CNS depressant	Alcohol, antihistamines	Potentiation of CNS effects; low risk
	Chloral hydrate	Increased sedation and side effects with fluoxetine due to inhibited metabolism of chloral hydrate
Corticosteroid	Dexamethasone, prednisone	Increased risk of GI bleed
Cyclobenzaprine		Increased side effects of cyclobenzaprine with fluoxetine due to inhibited metabolism; observe for QTc prolongation
Cyproheptadine		Report of reversal of antidepressant and antibulimic effects of fluoxetine and paroxetine Potent serotonin antagonist

Class of Drug	Example	Interaction Effects
DDAVP (desmopressin)		Water intoxication and hyponatremia in rare cases
Digoxin		Case report of digoxin AUC decreased by 18% with paroxetine
Ergot alkaloid	Dihydroergotamine	Increased serotonergic effects with IV use – AVOID. Oral, rectal, and subcutaneous routes can be used, with monitoring
	Ergotamine	Elevated ergotamine levels possible due to inhibited metabolism via CYP3A4 with fluoxetine and fluvoxamine
Ginkgo biloba		Possible increased risk of petechiae and bleeding due to combined anti-hemostatic effects
Grapefruit juice		Decreased metabolism via CYP3A4 of fluvoxamine and sertraline resulting in increased plasma levels
H_2 antagonist	Cimetidine	Inhibited metabolism and increased plasma level of sertraline (by 25%), paroxetine (by 50%), citalopram, and escitalopram
Hallucinogen	LSD	Recurrence or worsening of flashbacks reported with fluoxetine, sertraline, and paroxetine
Hormone	Oral contraceptive	Increased activity of combined oral contraceptive possible with fluoxetine and fluvoxamine due to inhibited metabolism
Hypnotic/sedative	Ramelteon	DO NOT COMBINE with fluvoxamine; increased peak level (70-fold) and AUC (190-fold) of ramelteon due to inhibited metabolism via CYP1A2
	Zolpidem	Case reports of hallucinations and delirium when combined with sertraline, fluoxetine, and paroxetine Administration of sertraline resulted in faster onset of action and increase in peak plasma concentration of zolpidem
Immunosuppressant	Cyclosporine	Decreased clearance of cyclosporine with sertraline due to competition for metabolism via CYP3A4
Insulin		Increased insulin sensitivity reported
Kava kava		Case report of lethargic state with paroxetine
Licorice		Increased serotonergic effects possible via MAO inhibition by licorice constituents
Lithium		Increased serotonergic effects Caution with fluoxetine and fluvoxamine; neurotoxicity and seizures reported Increased tremor and nausea reported with sertraline and paroxetine Additive antidepressant effect in treatment-resistant patients
L-tryptophan		May result in central and peripheral toxicity, hypermetabolic syndrome (serotonin syndrome – see Precautions p. 59)
MAO-B inhibitor	Selegiline (L-deprenyl)	Case reports of serotonin syndrome (see p. 53), hypertension, and mania when combined with fluoxetine
Melatonin		Increased levels of melatonin with fluvoxamine due to inhibited metabolism via CYP1A2 or 2C9; endogenous melatonin secretion increased
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome (see Precautions p. 59)
Metoclopramide		Report of increased extrapyramidal and serotonergic effects
NSAID	ASA, ibuprofen, naproxen	Increased risk of upper GI bleed with combined use (risk increased up to 12-fold (large adult cohort study))
Opioid	Codeine, oxycodone, hydrocodone	Decreased analgesic effect with fluoxetine and paroxetine due to inhibited metabolism to active moiety – morphine, oxymorphone, and hydromorphone, respectively (interaction may be beneficial in the treatment of dependence by decreasing morphine and analog formation and opiate reinforcing properties)
	Dextromethorphan	Visual hallucinations reported with fluoxetine; fluoxetine and paroxetine may inhibit metabolism via CYP2D6; monitor for increased serotonergic effects
	Methadone	Increased risk of QTc prolongation Elevated plasma level of methadone (by 10–100%) reported with fluvoxamine
	Morphine, fentanyl	Enhanced analgesia
	Pentazocine	Report of excitatory toxicity (serotonergic) with fluoxetine and pentazocine

Selective Serotonin Reuptake Inhibitors (SSRIs) (cont.)

Class of Drug	Example	Interaction Effects
	Tramadol[28]	Increased risk of seizures and serotonin syndrome Possible decreased analgesic effect with SSRIs that inhibit CYP2D6 (fluoxetine, paroxetine) due to decreased conversion to the active M1 metabolite
Proguanil		Increased plasma level of proguanil with fluvoxamine due to inhibited metabolism via CYP2C19
Protease inhibitor	Fosamprenavir/ritonavir Ritonavir	Decreased plasma level of paroxetine Increased plasma level of sertraline due to competition for metabolism; moderate increase in level of fluoxetine and paroxetine. Serotonin syndrome reported in combination with high dose of fluoxetine Cardiac and neurological side effects reported with fluoxetine due to elevated ritonavir level (AUC increased by 19%)
Proton pump inhibitor	Omeprazole	Increased plasma level of citalopram due to inhibited metabolism via CYP2C19
Selective norepinephrine reuptake inhibitor	Atomoxetine	SSRIs that strongly inhibit CYP2D6 (fluoxetine, paroxetine) can significantly increase atomoxetine C_{max} (3.5-fold), AUC (6.5-fold), and half-life (2.5-fold). Atomoxetine dose reduction recommended
Sildenafil		Possible enhanced hypotension due to inhibited metabolism of sildenafil via CYP3A4 with fluoxetine and fluvoxamine
Smoking (tobacco)		Increased metabolism of fluvoxamine (by 25%) via CYP1A2
Statin	Lovastatin, simvastatin Pravastatin	Increased plasma level of statin with fluoxetine, fluvoxamine, sertraline, and paroxetine due to inhibited metabolism via CYP3A4 Synergistic effect on increasing blood glucose (paroxetine)
St. John's wort		May augment serotonergic effects – several reports of serotonin syndrome (see p. 59). AVOID combination
Stimulant	Amphetamines Methylphenidates	Fluoxetine and paroxetine increased plasma concentrations of amphetamines through CYP2D6 inhibition. Increased risk of seizures No pharmacokinetic interaction. Increased risk of seizures Case reports of serotonin syndrome (see p. 59) when combined with sertraline and paroxetine
Sulfonylurea antidiabetic agent	Glyburide, tolbutamide	Increased hypoglycemia reported in diabetics Increased plasma level of tolbutamide due to reduced clearance (up to 16%) with sertraline
Tamoxifen		Inhibitors of CYP2D6 (paroxetine, fluoxetine) appear to reduce the conversion of tamoxifen to its active metabolite (endoxifen) and may decrease the therapeutic efficacy of this drug
Theophylline and derivatives		Increased plasma level of theophylline/aminophylline with fluvoxamine due to decreased metabolism via CYP1A2
Thyroid drug	Triiodothyronine (T_3-liothyronine)	Antidepressant effect potentiated
Tolterodine		Decreased oral clearance of tolterodine (by up to 93%) with fluoxetine
Triptan	Rizatriptan, sumatriptan	Risk of serotonin syndrome when SSRI combined with triptan (0.6 cases per 10,000 person-years of exposure)

Norepinephrine Dopamine Reuptake Inhibitor (NDRI)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Bupropion	Monocyclic agent (aminoketone)	Norepinephrine, dopamine/Reuptake inhibitor (NET, DAT), releaser (NE, DA)	Wellbutrin[B]	Tablets: 75 mg, 100 mg	Safety and efficacy not established in children and adolescents under age 18
			Wellbutrin SR, Zyban[C],[D]	Sustained-release tablets: 100 mg, 150 mg, 200 mg[B]	
			Aplenzin[B]	Extended-release tablets: 174 mg, 348 mg, 522 mg (as hydrobromide salt)	
			Forfivo XL[B]	Extended-release tablets: 450 mg	
			Wellbutrin XL	Extended-release tablets: 150 mg, 300 mg	

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. * Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Marketed as aid in smoking cessation (as 150 mg)

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications in children and adolescents
- ADHD – randomized, controlled studies suggest benefit in children; primarily in individuals with simple ADHD or with comorbid depression
- There are no randomized controlled trials for MDD, and only 6 studies in ADHD, including 235 patients, making it very difficult to assess the tolerability of bupropion[29]
- Smoking cessation – when adhered to (only 74% in adolescents), a study of 312 nicotine-using adolescent boys demonstrated a 13.9% abstinence rate at 6 months[30]

In adults:

- 👍 Major depressive disorder (MDD)
- 👍 Smoking cessation
- 👍 Seasonal affective disorder (SAD)
- 👍 Weight loss (taken in combination with naltrexone)
- 👍 MDD, recurrent: Prophylaxis
- 👍 Bipolar disorder: Depressed phase (use with an antimanic agent)
- Sexual dysfunction (e.g., reduced sexual desire, anorgasmia, erectile problems) induced by SSRIs/SNRI: Mitigating effect (sustained-release products may be less effective than regular-release formulations)
- Persistent depressive disorder and chronic fatigue syndrome – efficacy reported
- Social phobia – case reports of efficacy
- ADHD – controlled studies suggest benefit in adults; primarily in individuals with simple ADHD or with comorbid depression, cigarette smoking or active substance use disorder
- Weight gain secondary to antipsychotics – reduced body weight in patients on olanzapine or risperidone in a small study
- Trichotillomania – case report of benefit
- Substance use disorders (e.g., cocaine, alcohol[31], cannabis) – negative trial for cannabis
- Neuropathic pain – randomized control studies suggest benefit

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Norepinephrine Dopamine Reuptake Inhibitor (NDRI) (cont.)

General Comments

- Bupropion was shown to have higher risk of serious outcomes in overdose compared to SSRIs
- May enhance energy and motivation early in treatment due to effects on norepinephrine and dopamine; reported to improve neurocognitive function in patients with depression
- See p. 52 for comments on antidepressants and suicidality
- SR/XL preparations appear to be better tolerated than IR preparation and are associated with decreased risk of seizures and lower risk of sexual dysfunction in adults
- Bupropion does not potentiate the sedative effects of alcohol
- Pilot study of bupropion in adolescent methamphetamine abuse was discontinued due to statistically significant worsening of methamphetamine abstinence[32]
- Lower likelihood compared to other antidepressants to impair sexual functioning
- Case reports of recreational abuse of bupropion via oral, intranasal, and intravenous administration; abusers report receiving a "high" similar to cocaine abuse, but of lesser intensity

Pharmacology

- Inhibits the reuptake of primarily norepinephrine (and dopamine to a lesser extent) into presynaptic neurons
- Bupropion's major metabolite (hydroxybupropion), which in humans is present at blood levels 10- to 20-fold higher than bupropion, blocks only norepinephrine reuptake

Dosing

- See p. 133
- Dosage in children: Initiate at 75–100 mg daily (depending on product availability) and increase gradually to a maximum of 300 mg daily (in divided doses)
- Immediate-release bupropion and SR formulation should be prescribed in divided doses, with a maximum of 150 mg per dose; XL formulation formulated for once daily dosing
- Initiate doses for depression at 75–150 mg/day (depending on product availability). The dose may be increased to 300 mg/day in patients who do not respond to 150 mg/day but in depression studies of bupropion SR at doses of 100–150 mg/day patients experienced improvement of depression. Clinical response did not improve with increasing dose, indicating a flat dose-response relationship in the range of doses studied
- In ADHD, begin at 75–100 mg/day (depending on product availability) and titrate dose gradually to a maximum of 300 mg/day in divided doses; up to 4 weeks may be required for maximum drug effect. Higher doses may be used in older adolescents and adults
- Manufacturer maximum dosing recommendation differs by country: Canada = 300 mg/day, USA = 450 mg/day
- Forfivo XL for treatment of depression may only be used after initial titration with other bupropion products; patients receiving 300 mg daily of bupropion HCL (as immediate-release, SR or XL) for at least 2 weeks and requiring a dose increase, or patients already taking 450 mg daily of bupropion HCL may switch to Forfivo XL 450 mg daily
- Aplenzin (bupropion hydrobromide): Initial dosing of 174 mg daily and may increase on day 4 (for treatment of depression) or on day 7 (for treatment of SAD) to 348 mg daily; maximum dose is 522 mg daily; bupropion HCL (as immediate-release, SR or XL): 150 mg, 300 mg, 450 mg is equivalent to bupropion hydrobromide 174 mg, 348 mg, 522 mg, respectively
- For smoking cessation: Initial dosing of 150 mg daily for 3 days, then 150 mg twice daily. Treatment should continue for 1 week before target quit date and continue for 7–12 weeks
- In renal impairment, reduce dose and frequency and monitor for adverse effects such as insomnia, dry mouth, or seizures that could indicate higher than normal levels; Forfivo XL not recommended in renal impairment
- In mild to moderate hepatic impairment (Child-Pugh Grade A or B), initiate treatment at the lowest recommended dose. In patients with severe hepatic impairment, use with extreme caution. Forfivo XL not recommended

Pharmacokinetics

- Rapid absorption with peak concentration occurring within 2 h after administration of immediate-release tablets, 3 h after administration of sustained-release tablets, 5 h after administration of extended-release tablets; peak plasma concentration of sustained-release preparation is 50–85% that of the immediate-release tablets after single dosing, and 25% after chronic dosing

- Protein binding 80–85%
- Metabolized predominantly by the liver, primarily via CYP2B6 and to a lesser extent by other isoenzymes – 6 metabolites; 3 are active
- Bupropion and hydroxybupropion inhibit CYP2D6
- Elimination half-life: 11–14 h; with chronic dosing: 21 h (mean)

Onset & Duration of Action

- Therapeutic effect typically seen after 28 days (though effects may be sooner in some patients)

Adverse Effects

- See chart on p. 130 for incidence of adverse effects

CNS Effects

- Insomnia; vivid dreams and nightmares reported; decreased REM latency and increased REM sleep
- Agitation, anxiety, irritability, dysphoria, aggression, hostility, depersonalization, coupled with urges of self-harm or harm to others
- Precipitation of hypomania or mania felt to be less likely than with other cyclic antidepressants; increased risk in bipolar patients with comorbid substance use disorder
- Can exacerbate psychotic symptoms
- Very high doses can result in CNS toxicity including delirium, confusion, impaired concentration, hallucinations, delusions, EPSE, and seizures
- Reported to exacerbate symptoms of OCD
- Short-term memory loss reported
- Risk of seizures with SR formulation at doses of 100–300 mg/day = 0.1% and at doses of 400 mg/day = 0.4%. With the IR formulation, the seizure incidence was 0.4% with dosing of 300–450 mg/day and the risk increases almost 10-fold with dosing of 450–600 mg/day. Anorexic and bulimic patients, those with a history of alcohol withdrawal seizures or current alcohol abuse are at higher risk
- Disturbance in gait, fine tremor, myoclonus
- Headache, arthralgia (4%), neuralgias (5%), myalgia
- Tinnitus reported
- Reversible dyskinesia reported; may aggravate neuroleptic-induced tardive dyskinesia

Anticholinergic Effects

- No appreciable affinity for cholinergic receptors
- Occur rarely
- Mydriasis
- Dry mouth
- Constipation

Cardiovascular Effects

- Modest sustained increases in blood pressure reported in adults and children (more likely in patients with pre-existing hypertension)
- Orthostatic hypotension, dizziness occurs occasionally, especially when bupropion added to SSRI
- Palpitations
- Case of transient ischemic attacks reported
- Rare cases of myocarditis, myocardial infarction, and cardiac death

Endocrine & Metabolic Effects

- Menstrual irregularities reported (up to 9% risk)
- Cases of hypoglycemia, hyperglycemia, SIADH

Other Adverse Effects

- May exacerbate tics in patients with ADHD and evoke tics in patients with Tourette's disorder
- Urticarial or pruritic rashes have been reported (in up to 17% of youths); rare cases of erythema multiforme and Stevens-Johnson syndrome
- Anaphylactoid reactions with pruritus, urticaria, angioedema, and dyspnea (up to 0.3%)
- Reports of serum sickness-like reactions
- Urinary frequency
- Nausea, anorexia, and weight loss with acute and long-term treatment
- Rarely febrile neutropenia
- Alopecia
- Sweating

Norepinephrine Dopamine Reuptake Inhibitor (NDRI) (cont.)

- Case report of rhabdomyolysis in a patient with hepatic dysfunction
- Case reports of liver failure
- Delayed hypersensitivity reactions with arthralgia, myalgia, fever, and rash

D/C Discontinuation Syndrome

- Abrupt discontinuation may cause a syndrome consisting of dizziness, lethargy, nausea, vomiting, diarrhea, headache, fever, sweating, chills, malaise, incoordination, insomnia, vivid dreams, myalgia, paresthesias, dyskinesias, "electric-shock-like" sensations, visual discoordination, anxiety, irritability, confusion, slowed thinking, disorientation; rarely aggression, impulsivity, hypomania, and depersonalization
- Most likely to occur within 1–7 days after drug stopped or dose drastically reduced, and typically disappears within 3 weeks
- Cases of mania amd acute dystonia reported after abrupt discontinuation

Precautions

- Contraindicated in patients with a history of anorexia or bulimia, undergoing alcohol or benzodiazepine withdrawal or with other conditions predisposing to seizures (arteriovenous malformation, severe head injury, severe stroke, CNS tumor, CNS infection, or abrupt discontinuation of barbiturates or antiepileptics)
- Monitor all patients for worsening depression and suicidal thoughts, especially at the start of therapy and following an increase or decrease in dose
- May lower the seizure threshold; therefore, administer cautiously to patients with organic brain disease and when combining with other drugs that may lower the seizure threshold; contraindicated in patients with a history of or current seizure disorder. To minimize seizures with regular-release bupropion, do not exceed a dose increase of 100 mg in a 3-day period. No single dose should exceed 150 mg for the immediate-release or the sustained-release preparation
- Use with caution (i.e., use lower dose and monitor regularly) in patients with hepatic impairment
- Zyban, marketed for smoking cessation, contains bupropion – DO NOT COMBINE with other bupropion products
- Caution in patients with narrow-angle glaucoma

Toxicity

- Recently, bupropion was shown to have higher risk of serious outcomes in overdose compared to SSRIs
- Commonly causes agitation, drowsiness, vomiting, hallucinations (auditory and visual), tremors, seizures, prolonged QTc prolongation, and sinus tachycardia; rarely causes hypotension, serious cardiac dysrhythmia
- Seizures and prolonged QTc may be delayed in onset by 18 h with SR/XL formulations
- Report of a 14-year-old female who ingested 15 g of bupropion XL – resulted in hyperglycemia, respiratory acidosis, agitation, status epilepticus, prolonged QT devolving into pulseless ventricular tachycardia and briefly V Fib, requiring a total of 5 cardioversions and 1 defibrillation; QT interval eventually narrowed after supportive care and lidocaine infusion (magnesium was ineffective)
- Rare reports of death following massive overdose, preceded by uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest
- A 2017 review showed 21 reported deaths among 8000 accidental/intentional exposures to bupropion in the pediatric population[33]

Management

- Single dose of activated charcoal if patient presents within 1 h of ingestion
- Isolated unintentional bupropion ingestion of less than 10 mg/kg in children may not require referral to a health care facility[34]
- Supportive treatment
- Monitor ECG and vital signs for 18 h as well as EEG
- Replete potassium and magnesium as necessary if QTc interval is prolonged
- Benzodiazepines are first-line therapy for seizures
- Guidelines weakly recommend lipid emulsion therapy in the setting of life-threatening bupropion toxicity refractory to conventional therapies[35]

Use in Pregnancy◊

- Conflicting evidence regarding slightly elevated risk of ventricular septal defect[36]
- Small study demonstrated an increase in spontaneous abortion but no increase in malformation[37]
- No harm to fetus reported in animal studies; no teratogenic effects reported in humans following use of bupropion in the first trimester[38]

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Breast Milk

- Bupropion and metabolites are secreted in breast milk; infant can receive up to 10.6% of maternal dose
- Seizures (2 infants, both at 6 months of age) and sleep disturbances reported in breastfed infants
- Infants of mothers using psychotropic medications should be monitored daily for changes in sleep, feeding patterns, and behavior as well as infant growth and neurodevelopment
- If a patient is breastfeeding and requires the addition of an antidepressant, other agents may be preferable as first-line options; however, maternal use of bupropion is not considered a reason to discontinue breastfeeding

Nursing Implications

- Risk of seizures increases if any single dose exceeds 150 mg (immediate-release or sustained-release formulations) or if total daily dose exceeds 300 mg; doses above 150 mg daily should be given in divided doses, preferably 8 h or more apart
- Advise patient not to split, crush or chew SR/XL formulations; crushing or chewing them destroys the slow-release activity of the product, increases seizure risk due to increased peak level
- Can be administered with or without food
- Bupropion degrades rapidly on exposure to moisture, therefore tablets should not be stored in an area of high humidity
- Monitor therapy by watching for adverse effects and mood and activity level changes including worsening depression and suicidal thoughts, especially at the start of therapy or following an increase or decrease in dose
- If the patient is taking bupropion in divided doses and has trouble sleeping, ensure that the last dose of bupropion is no later than 1500 h
- Ensure the patient is not currently being treated for smoking cessation with Zyban (also contains bupropion)

Patient Instructions

- For detailed patient instructions on bupropion, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Alcohol		Post-marketing reports of adverse neuropsychiatric events/reduced alcohol tolerance and hypersensitivity reactions. Avoid alcohol while taking bupropion
Amantadine		Increased side effects, including excitement, restlessness, and tremor due to increased dopamine availability
Antiarrhythmic (Type 1c)	Flecainide, propafenone	Increased plasma level of antiarrhythmic due to inhibited metabolism via CYP2D6
Antibiotic	Ciprofloxacin, linezolid	Seizure threshold may be reduced Case report of severe intraoperative hypertension in combination with linezolid via MAO inhibition
Anticholinergic	Orphenadrine	Altered levels of either drug due to competition for metabolism via CYP2B6
Anticonvulsant	Carbamazepine, phenytoin, phenobarbital	Decreased plasma level of bupropion and increased level of its metabolite hydroxybupropion due to increased metabolism by the anticonvulsant
	Valproate	Increased level of hydroxybupropion due to inhibited metabolism; level of bupropion not affected
Antidepressant		
SSRI	Fluoxetine	Case of delirium, anxiety, panic, and myoclonus with fluoxetine due to inhibited metabolism of bupropion and/or fluoxetine (via CYP2D6 and 3A4), competition for protein binding, and additive pharmacological effects Additive antidepressant effect in treatment-refractory patients; bupropion may mitigate SSRI-induced sexual dysfunction
SNRI	Venlafaxine	3-fold increase in venlafaxine level due to inhibited metabolism via CYP2D6, and reduction of level of O-desmethylvenlafaxine metabolite Potentiation of noradrenergic effects
SMS	Vortioxetine	May increase vortioxetine levels significantly. Recommend reducing dose by 50% when combining

Norepinephrine Dopamine Reuptake Inhibitor (NDRI) (cont.)

Class of Drug	Example	Interaction Effects
Nonselective cyclic	Clomipramine, desipramine, imipramine, nortriptyline	Elevated imipramine level (by 57%) and nortriptyline level (by 200%) with combination; desipramine peak plasma level and half-life increased 2-fold due to decreased metabolism (via CYP2D6) Seizure threshold may be reduced
Irreversible MAOI	Phenelzine	DO NOT COMBINE – dopamine metabolism inhibited; washout of 14 days recommended between drug
Antimalarial	Mefloquine, chloroquine	Seizure threshold may be reduced
Antipsychotic		
First generation	Chlorpromazine, haloperidol, thioridazine	Seizure threshold reduced Increased plasma level of thioridazine and haloperidol due to decreased metabolism via CYP2D6 Increased risk of QT prolongation, ventricular arrhythmia, and sudden death. DO NOT COMBINE. Washout of 14 days recommended between drugs
Second generation	Iloperidone, risperidone	Inhibits CYP2D6, leading to decreased metabolism of antipsychotic – risk of delirium Seizure threshold reduced Increased risk of QT prolongation, ventricular arrhythmia, and sudden death
Third generation	Aripiprazole, brexpiprazole, cariprazine	When combined with bupropion, due to inhibited metabolism via CYP2D6, reduce aripiprazole and brexpiprazole dose by 50%. No dose adjustment required with cariprazine, as it is primarily a CYP3A4 substrate Seizure threshold reduced
β-blocker	Metoprolol	Increased plasma level of β-blocker possible due to inhibited metabolism via CYP2D6
Corticosteroid (systemic)	Dexamethasone, prednisone	Seizure threshold may be reduced
Ginkgo biloba		Seizure threshold may be reduced
Hormone	Estrogen/Progesterone	Decreased metabolism of bupropion via inhibition of CYP2B6; interaction with combined oral contraceptive is unlikely to be clinically significant
L-dopa		Increased adverse effects, including excitement, restlessness, nausea, vomiting, and tremor due to increased dopamine availability Case reports of neurotoxicity
MAO-B inhibitor	Selegiline	Lower risk of dopamine metabolism inhibition with selegiline in doses below 10 mg than with irreversible MAOIs
Nicotine (transdermal)		Combination reported to promote higher rates of smoking cessation than either drug alone Increased risk of hypertension with combination
Nitrogen mustard analog	Cyclophosphamide, ifosfamide	Altered levels of either drug due to competition for metabolism via CYP2B6
Opioid	Meperidine, tramadol	Increased risk of seizures Possible decreased analgesic effect due to decreased conversion to the active M1 metabolite of tramadol
Protease inhibitor	Efavirenz, nelfinavir, ritonavir	Increased plasma level of bupropion due to decreased metabolism via CYP2B6; risk of seizure
Selective norepinephrine reuptake inhibitor	Atomoxetine	Increased plasma level and half-life of atomoxetine due to inhibited metabolism via CYP2D6
St. John's wort		Case report of orofacial dystonia due to additive effect on serotonin reuptake
Stimulant	Amphetamines Methylphenidates	Increased plasma concentrations of amphetamines through CYP2D6 inhibition. Increased risk of seizures No pharmacokinetic interaction. Increased risk of seizures
Sympathomimetic	Pseudoephedrine	Report of manic-like reaction with pseudoephedrine Seizure threshold may be reduced

Class of Drug	Example	Interaction Effects
Tamoxifen and derivatives		Combination appears to reduce the conversion of tamoxifen to its active metabolite (endoxifen) via inhibition of CYP2D6 and may decrease the therapeutic efficacy of this drug
Theophylline		Seizure threshold may be reduced
Zolpidem		Case reports of visual hallucinations with combination

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Desvenlafaxine	Anisole (phenol ether)	Serotonin, norepinephrine/ Reuptake inhibitor	Pristiq	Extended-release tablets: 25 mg[B], 50 mg, 100 mg	Safety and efficacy not established in children and adolescents under age 18
Duloxetine	Anisole (phenol ether)	Serotonin, norepinephrine/ Reuptake inhibitor	Cymbalta	Capsules, delayed-release pellets: 20 mg[B], 30 mg, 60 mg	Approved in the USA for children age 7 and above in generalized anxiety disorder, and for adolescents age 13 and above in fibromyalgia
			Drizalma Sprinkle[B]	Capsules, delayed-release pellets: 20 mg, 30 mg, 40 mg, 60 mg	Approved in the USA for children age 7 and above in generalized anxiety disorder
Venlafaxine	Anisole (phenol ether)	Serotonin, norepinephrine/ Reuptake inhibitor	Effexor[B]	Tablets: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg	Safety and efficacy not established in children and adolescents under age 18
			Effexor XR	Extended-release tablets[B]: 37.5 mg, 75 mg, 150 mg, 225 mg Extended-release capsules: 37.5 mg, 75 mg, 150 mg	
Levomilnacipran	Phenylacetamide (benzeneoid)	Serotonin, norepinephrine/ Reuptake inhibitor	Fetzima	Extended-release capsules: 20 mg, 40 mg, 80 mg, 120 mg	Safety and efficacy not established in children and adolescents under age 18
			Fetzima Titration[B]	Extended-release capsules (28-pack): 20 mg, 40 mg	

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada

Indications‡ (👍 approved)

In children and adolescents:

- 👍 Generalized anxiety disorder (GAD) (duloxetine in patients age 7 years and above – USA)
- 👍 Pain due to fibromyalgia (duloxetine in patients age 13 and above – USA)
- Social anxiety disorder – efficacy shown with venlafaxine
- Depression – not superior to placebo (venlafaxine, duloxetine, desvenlafaxine)

‡ Indications listed here do not necessarily apply to all SNRIs or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (cont.)

- Conduct disorder – venlafaxine (preliminary data)
- ADHD – venlafaxine (open trial)
- Autism spectrum disorder – venlafaxine (open trial)

In adults:

- Major depressive disorder (MDD) – all
- Generalized anxiety disorder (GAD) (venlafaxine and duloxetine)
- Social anxiety disorder (venlafaxine)
- Panic disorder with or without agoraphobia (venlafaxine)
- Pain due to diabetic peripheral neuropathy (duloxetine)
- Pain due to fibromyalgia (duloxetine)
- Chronic musculoskeletal pain including osteoarthritis of the knee and low back pain (duloxetine)
- Bipolar disorder: Depressed phase; short term venlafaxine monotherapy for bipolar type II depressive episodes
- Treatment-resistant depression, persistent depressive disorder, postpartum depression, and melancholic depression
- ADHD in children and adults – potential for benefit with venlafaxine and duloxetine (evidence is weak for these indications)
- OCD – double-blind and open trials report efficacy with duloxetine and higher doses of venlafaxine
- PTSD (venlafaxine, duloxetine)
- Premenstrual dysphoric disorder
- Negative symptoms of schizophrenia – duloxetine adjunct to risperidone (DBPC-RCT), levomilnacipran adjunct to antipsychotic (case report)
- Cannabis use disorder – venlafaxine worsened abstinence in patients with cannabis use disorder and MDD or persistent depressive disorder
- Chronic fatigue syndrome – case reports of efficacy of venlafaxine and duloxetine
- Hot flashes in menopausal females – double-blind and open-label studies have shown reduction by venlafaxine, desvenlafaxine, and duloxetine
- Migraine and tension headaches
- Urinary incontinence, stress induced (duloxetine)
- Vasomotor symptoms (moderate to severe) and neuropathic pain – desvenlafaxine has shown effect but for the latter possibly at doses higher than for depression
- Binge-eating (duloxetine) – preliminary data
- Persistent genital arousal disorder – case report (duloxetine)

General Comments

- A DBPC-RCT demonstrated duloxetine 30–120 mg/day for 10 weeks was more effective than placebo in patients 7–17 years of age with GAD
- Duloxetine 60–120 mg/day for 10 weeks failed to demonstrate efficacy in two DBPC-RCTs in patients 7–17 years of age with MDD; a recent DBPC-RCT has also shown duloxetine 40–60 mg/day for 6 weeks was not superior to placebo in patients 9–17 years of age with MDD in Japan
- Venlafaxine XR 37.5–225 mg/day for 16 weeks demonstrated efficacy in a DBPC-RCT in patients 8–17 years of age with social anxiety disorder
- Recommend against first-line/routine use of venlafaxine in pediatric depression. A 2016 meta-analysis of 5 pediatric studies showed no superior efficacy compared to placebo. The TORDIA study included venlafaxine as a potential agent for third-line switching in refractory depression, with an acceptable 25% response rate[39]
- In adults only, a meta-analysis of trials with venlafaxine versus SSRI for depression showed superiority in achieving remission and response but with higher rates of discontinuation due to adverse effects. Results not reproduced in other meta-analyses[40]
- Desvenlafaxine 25, 35, or 50 mg/day (based on weight) for 8 weeks failed to demonstrate efficacy in two DBPC-RCTs in patients 7–17 years of age with MDD
- Desvenlafaxine is the major active metabolite of venlafaxine and does not undergo metabolism via CYP2D6. This may result in a reduced risk of drug interactions and susceptibility to genetic polymorphism
- Levomilnacipran has not been studied in children and adolescents
- Levomilnacipran is the more active enantiomer of milnacipran, an SSRI approved for the treatment of fibromyalgia (USA)
- See p. 52 for comments on antidepressants and suicidality

Pharmacology

- Potent uptake inhibitors of serotonin and norepinephrine; venlafaxine inhibits norepinephrine reuptake at doses above 225 mg, while duloxetine has equal affinity to both norepinephrine and serotonin transporter "reuptake" proteins; inhibition of dopamine reuptake occurs at high doses
- Levomilnacipran has approximately 2-fold greater potency for inhibition of norepinephrine relative to serotonin reuptake. Compared with desvenlafaxine, duloxetine, and venlafaxine, levomilnacipran has more than 10-fold higher selectivity for norepinephrine relative to serotonin reuptake inhibition
- The higher selectivity of levomilnacipran for norepinephrine occurs at lowest effective dose; as dose is titrated upwards, levomilnacipran has equipotent effects on 5-HT and NE transporters and no effects on dopamine transporters

Dosing

- See p. 134
- Dosing based on adult data, unless specified otherwise
- Desvenlafaxine: Initiate drug at 50 mg once daily – usual maintenance dose; dose may be increased to 100 mg/day if needed and patient is tolerating it, however, a meta-analysis[41] of registration trials showed no increased efficacy with doses greater than 50 mg/day; adverse effects and discontinuations increase with dose. In patients with renal insufficiency (CrCl 30–50 mL/min), use maximum of 50 mg/day; if less than 30 mL/min, use 50 mg every other day
- Duloxetine: GAD (age 7 years and above): Initiate drug at 30 mg daily for 2 weeks, then may increase by 30 mg every 2 weeks, up to 120 mg daily. MDD: Initiate drug at 30 mg daily, with a target dose of 60 mg daily within 1–2 weeks. In a study of non-remitters (on 60 mg duloxetine) randomly reassigned to continue on 60 mg or 120 mg for an additional 8 weeks, remission was achieved in 30% with no advantage to the 120 mg dose.[42] AVOID in severe renal insufficiency as AUC increased 100% and metabolites increase up to 9-fold; in hepatic disorders, AUC increased 5-fold and half-life increased 3-fold
- Levomilnacipran: Initiate drug at 20 mg once daily for 2 days, increase to 40 mg once daily, may then be increased in increments of 40 mg at intervals of 2 or more days; maintenance: 40–120 mg once daily; maximum: 120 mg/day. In patients with renal insufficiency (CrCl 30–59 mL/min), use maximum of 80 mg/day; if CrCl 15–29 mL/min, use maximum of 40 mg/day. Use not recommended in end-stage renal disease (ESRD). No adjustments necessary for any hepatic impairment
- Venlafaxine: Social anxiety disorder (age 8 years and above): Initiate drug at 37.5 mg daily (XR formulation) for 1 week, then may increase by 37.5 mg at 1–2 week intervals if needed and tolerated; maximum (per weight): 112.5 mg/day (25–39 kg), 150 mg/day (40–50 kg), 225 mg/day ($\geq$ 50 kg). MDD: Initiate drug at 37.5–75 mg (once daily for XR formulation, twice daily for immediate-release formulation) and increase after 1 week in increments no greater than 75 mg q 4 days, up to 225 mg/day for moderately depressed patients. There is very limited evidence at higher doses (375 mg/day) in severely depressed inpatients. Decrease dose by 50% in hepatic disease and by 25–50% in renal disease. For panic disorder, start at 37.5 mg/day

Pharmacokinetics

- See p. 134
- Desvenlafaxine: Well absorbed from GI tract; food has no effect on absorption; peak plasma concentration reached in about 7.5 h and mean half-life is about 11 h. Metabolized primarily in the liver by UGT conjugation and, to a lesser extent, by CYP3A4. Steady state achieved in 4 days
- Duloxetine: Can be given with or without meals, although food delays T_{max} by 6–10 h. There is a 3 h delay in absorption and a 30% increase in clearance with an evening dose as compared to a morning dose. Bioavailability is reduced by about 30% in smokers. Duloxetine is metabolized by CYP1A2 and 2D6 and is an inhibitor of CYP2D6; elimination half-life increased from 12 h (mean) to 47.8 h (mean) in patients with liver impairment
- Levomilnacipran: Can be given with or without food; bioavailability is 92%. Peak plasma concentration C_{max} is reached in 6–8 h and mean half-life is about 12 h. Metabolized in the liver primarily by CYP3A4 with minor contributions by CYP2C8, CYP2C19, CYP2D6 to inactive metabolites. Levomilnacipran and its metabolites are eliminated primarily by renal excretion. Approximately 58% of dose is excreted in urine as unchanged levomilnacipran. N-desethyl levomilnacipran is the major metabolite excreted in urine and accounts for approximately 18% of the dose. The metabolites are inactive. Displays linear pharmacokinetics over the therapeutic dosage range (and up to 300 mg). No clinically relevant effects of gender, age, body weight, or hepatic impairment on pharmacokinetics
- Venlafaxine: Well absorbed from GI tract, food has no effect on absorption; absorption of XR formulation is slow (15 $\pm$ 6 h); peak plasma level (C_{max}) reached by parent drug in 1–3 h and by active metabolite (O-desmethylvenlafaxine, ODV) in 2–6 h; with XR formulation, C_{max} reached by parent drug in 6 h and metabolite in 8.8 h (mean). Elimination half-life of oral tablet: Parent = 3–7 h and metabolite = 9–13 h; XR elimination half-life is dependent on absorption half-life (15 h mean). Steady state of parent and metabolite reached in about 3 days. Parent drug metabolized by CYP2D6 and is also a weak inhibitor of this enzyme; ODV metabolite is metabolized by CYP3A3/4

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (cont.)

Onset & Duration of Action

- Therapeutic effect is typically seen after 28 days (though some patients may respond sooner)

Adverse Effects

- Generally dose-related; see chart p. 130 for incidence of adverse effects

CNS Effects

- May cause behavior activation and aggravate symptoms of hyperactivity in children and adolescents
- Both sedation and insomnia reported; prolonged sleep onset latency, disruption of sleep cycle, decreased REM sleep, increased awakenings, reduced sleep efficiency, vivid nightmares
- Headache common
- Nervousness, agitation, hostility, suicidal urges; epidemiological studies have shown that venlafaxine-treated patients have a higher burden of suicide risk than SSRI-treated patients
- Asthenia, fatigue, difficulty concentrating, decreased memory – more likely with higher doses of venlafaxine
- Risk of hypomania/mania estimated to be 0.5% with venlafaxine, 0.1% with desvenlafaxine in Phase 2 and 3 studies, 0.1% with duloxetine in placebo-controlled trials (adult data); caution in bipolar patients with comorbid substance use disorder
- 10–30% of patients on venlafaxine who improve initially can have breakthrough depression after several months ("poop-out syndrome") – an increase in dosage or augmentation therapy may be of benefit
- Seizures reported rarely (0.3%) with venlafaxine
- Case reports of restless legs syndrome (venlafaxine, duloxetine) and myoclonus (venlafaxine)
- Extrapyramidal side effects reported[43]
- Yawning - case reports (venlafaxine, duloxetine)

Anticholinergic Effects

- Dry mouth common
- Urinary retention; cases of urinary frequency and incontinence in females on venlafaxine; dose-related side effect of levomilnacipran, with case reports indicating successful treatment with tamsulosin
- Constipation
- Mydriasis; cases of elevated intraocular pressure in patients with narrow-angle glaucoma

Cardiovascular Effects

- Increased blood pressure – class effect. Venlafaxine/desvenlafaxine: Modest, sustained increase in blood pressure can occur, usually within 2 months of dose stabilization; seen in over 3% of individuals on less than 100 mg/day of venlafaxine, up to 13% of individuals on doses above 300 mg/day of immediate-release drug, and 3–4% with sustained-release product. Duloxetine is associated with case reports of increase in blood pressure and, rarely, hypertensive crisis.
- Tachycardia; increase by 4 beats/min
- Dizziness common, hypotension occasionally reported
- QTc prolongation: At therapeutic doses, SNRIs do not have clinically significant concern, but can occur in overdose, in use with other medications, or in patients with cardiovascular disease

Hematological Effects

- Increased risk of bleeding attributed to uptake inhibition of serotonin; upper GI bleed; rare: intracranial, postpartum, and intraoperative hemorrhage and microscopic hematuria

Endocrine & Metabolic Effects

- No weight gain reported
- Minor changes in blood glucose and cholesterol are infrequently noted with all SNRIs; duloxetine capsules contain sucrose, therefore should not be used in patients with fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency
- SIADH and hyponatremia risk similar to SSRIs
- Case of galactorrhea (duloxetine)

GI Effects

- Nausea occurs frequently at start of therapy and tends to decrease after 1–2 weeks; less frequent with XR formulation of venlafaxine; 22–43% incidence with duloxetine – most common side effect; levomilnacipran had a 17% incidence of nausea, the most commonly reported side effect
- Increased risk of upper GI bleed
- Case report of glossodynia (burning mouth syndrome) in a female taking venlafaxine

Urogenital & Sexual Effects

- Sexual side effects reported include: Decreased libido, delayed orgasm/ejaculation, anorgasmia, no ejaculation, and erectile dysfunction (see SSRIs p. 58 for suggested treatments); reports of long-lasting sexual dysfunction despite discontinuation
- Risk increased with increasing age, use of higher doses, and concomitant medication
- Priapism reported
- No large studies comparing venlafaxine to SSRIs but one small study found that rates of sexual dysfunction for venlafaxine were between those for moclobemide and the SSRIs paroxetine and sertraline
- Duloxetine and desvenlafaxine appear to have fewer sexual dysfunction effects than the SSRIs
- Levomilnacipran causes dose-related erectile dysfunction, ejaculatory disorder, and testicular pain; spontaneous reports of sexual dysfunction were greater than with placebo
- Case of painful ejaculation (venlafaxine)

Other Adverse Effects

- Sweating (in over 10%)
- Hepatotoxicity – duloxetine and venlafaxine: Cases of hepatitis accompanied by abdominal pain, hepatomegaly, and serum transaminase concentrations more than 20 times the upper limit of normal, with or without jaundice, have been reported during post-marketing surveillance. Elevation in serum transaminase concentrations has in some cases required the discontinuation of duloxetine and venlafaxine
- Epistaxis, bruising and abnormal bleeding with venlafaxine
- Venlafaxine: Case reports of breast engorgement and pain, SIADH with hyponatremia, Stevens-Johnson syndrome
- Duloxetine: Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, can occur
- Myoclonic jerks can occur with venlafaxine
- Case of acquired hemophilia A with desvenlafaxine

D/C Discontinuation Syndrome

- Abrupt discontinuation may cause a syndrome consisting of dizziness, lethargy, nausea, vomiting, diarrhea, headache, fever, sweating, chills, malaise, incoordination, insomnia, vivid dreams, myalgia, paresthesias, dyskinesias, "electric-shock-like" sensations, tinnitus, visual discoordination, anxiety, irritability, confusion, slowed thinking, disorientation; rarely aggression, impulsivity, hypomania, and depersonalization
- Most likely to occur within 1–7 days after drug stopped or dose drastically reduced, and typically disappears within 3 weeks
- Cases of inter-dose withdrawal reported with venlafaxine immediate-release tablet; withdrawal reactions also reported with XR formulation; withdrawal from venlafaxine can be problematic, with symptom severity occasionally preventing cessation of the medication even when prolonged taper is used
- Case of mania reported following venlafaxine taper, despite adequate concomitant mood stabilizing treatment
- Although levomilnacipran studies reported comparable rates of discontinuation symptoms between active treatment and placebo, gradual titration still recommended

☞ **THEREFORE THESE MEDICATIONS SHOULD BE WITHDRAWN GRADUALLY (OVER SEVERAL WEEKS) AFTER PROLONGED USE**

Management

- Suggested to taper slowly over a 2–6-week period, depending on how long the individual has been taking the SNRI
- Substituting one dose of fluoxetine (10 or 20 mg) near the end of the taper may help in the withdrawal process due to its very long half-life
- To withdraw desvenlafaxine, increase the dosing interval by giving it every other day, then increase this interval gradually

Precautions

- Monitor all patients for worsening depression and suicidal thoughts, especially at start of therapy and following an increase or decrease in dose
- Risk of hypomania/mania estimated to be 0.5% with venlafaxine, 0.1% with desvenlafaxine in phase 2 and 3 studies, 0.1% with duloxetine in placebo-controlled trials; caution in bipolar disorder with comorbid substance use
- Serotonin syndrome may occur, particularly when used with other agents that affect serotonergic neurotransmission
- Treatment with medications that inhibit the serotonin transporter may be associated with abnormal bleeding, particularly when combined with NSAIDs, ASA, anticoagulants or other medications that affect coagulation
- Do not use in patients with uncontrolled hypertension, as SNRIs can cause modest, sustained increases in blood pressure [BP monitoring recommended for all patients]

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (cont.)

- AVOID duloxetine in patients with severe renal insufficiency (CrCl below 30 mL/min)
- AVOID duloxetine in patients with underlying liver disease; DO NOT USE in patients with substantial alcohol use, chronic liver disease or hepatic insufficiency
- AVOID levomilnacipran in end-stage renal disease

Toxicity

- Symptoms of toxicity include vomiting, excess adrenergic stimulation, mydriasis, tachycardia, hypotension, arrhythmias, increase in QTc interval, bowel dysmotility, decreased level of consciousness, seizures – increased risk of fatal outcomes following overdose
- A 2015 review of pediatric ingestions of venlafaxine reported to Poison Control Centers showed common effects include gastrointestinal, mental status changes, and tachycardia. A dose of 65 mg/kg resulted in moderate-to-severe adverse effects. At doses ranging from 1500 mg to 7500 mg, seizures occurred[44]
- Delayed onset rhabdomyolysis
- Fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine alone, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, serotonin syndrome, seizures, vomiting, and tachycardia
- There is limited clinical experience with desvenlafaxine overdose in humans. No cases of fatal acute overdose reported in premarketing clinical trials. The most common symptoms associated with desvenlafaxine overdose are headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine is the major active metabolite of venlafaxine. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that of tricyclic antidepressants
- Cardiac toxicity and serotonin syndrome reported in an adult woman who ingested 3 g of levomilnacipran

Use in Pregnancy◊

- No teratogenic effects reported in humans with venlafaxine; there may be a trend toward higher rates of spontaneous abortion; use of duloxetine during pregnancy is associated with an increased risk of spontaneous abortion; one study suggests an absolute risk of 18%, and another suggests a 3-fold relative risk
- SNRI exposure in late pregnancy was associated with a 1.7-fold increased risk for postpartum hemorrhage[45]
- A 2015 population-based cohort study demonstrated no specific venlafaxine teratogenicity; however, when included in the larger "serotonergic antidepressant" category there was a 13% increase in birth defects[46]
- A 2013 prevention study showed associations of venlafaxine in the periconceptual period and anencephaly, atrial septal defect, coarctation of the aorta, cleft palate, and gastroschisis[47]
- Neonates exposed to venlafaxine and desvenlafaxine in third trimester have developed complications upon delivery including respiratory distress, temperature instability, feeding difficulties, agitation, irritability, changes in muscle tone, and seizures
- No developmental toxicity or other signs of toxicity were observed in an infant exposed to duloxetine during the second half of gestation and during breast-feeding in the first 32 days after birth[48]
- There are no adequate well-controlled studies of levomilnacipran in pregnant females

Breast Milk

- The total dose of venlafaxine and its ODV metabolite ingested by a breastfed infant can be as high as 9.2% of the maternal dose
- An exclusively breastfed infant would receive an estimated 5.7–7.4% of the maternal weight-adjusted dose of desvenlafaxine[48]
- Most infants exposed to venlafaxine and desvenlafaxine in breast milk have no adverse reactions and develop normally, although there are a few cases of drowsiness and agitation
- Duloxetine has very low excretion into breast milk, infant would receive less than 1% of the maternal dose and steady-state concentrations in breast milk are about one-fourth of those in maternal plasma; no reports of adverse reactions in breastfed infants, but experience is limited
- The effect of levomilnacipran on lactation and nursing in humans is unknown; with the racemic form, milnacipran, breastfed infant would receive less than 5% of the maternal dose

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Nursing Implications

- A gradual titration of dosage at start of therapy will minimize nausea
- Psychotherapy and education are also important in the treatment of depression
- Monitor therapy by watching for adverse effects as well as mood and activity level changes including worsening of suicidal thoughts, especially at start of therapy or following an increase or decrease in dose; keep physician informed
- Be aware that the medication may increase psychomotor activity; this may create concern about suicidal behavior
- Excessive ingestion of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis
- Instruct patient not to chew or crush the extended-release venlafaxine tablets/capsules, the extended-release desvenlafaxine tablets, the extended-release levomilnacipran capsules or the delayed-release duloxetine capsules; patients should swallow these sustained-release products whole. Venlafaxine XR capsules may be opened and the contents sprinkled onto applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water
- If a dose is missed, do not attempt to make it up; continue with regular daily schedule
- SNRIs should not be stopped suddenly due to risk of precipitating a withdrawal reaction; desvenlafaxine can be withdrawn by gradually increasing the dosing interval
- Patients taking desvenlafaxine may see an "empty" tablet in their stool since the tablet shell does not dissolve

Patient Instructions

- For detailed patient instructions on SNRI antidepressants, see the Patient and Caregiver Information Sheet (details on p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Alcohol		Increased risk of psychomotor impairment and hepatotoxicity
α_2 agonist	Clonidine	Inhibition of antihypertensive effect of clonidine
Antiarrhythmic	Flecainide, propafenone	Increased plasma level of venlafaxine and duloxetine due to inhibited metabolism via CYP2D6 Duloxetine may increase plasma levels of propafenone
	Quinidine	Increased plasma level of duloxetine due to inhibited metabolism via CYP2D6
Antibiotic	Ciprofloxacin, enoxacin	Increased plasma level of duloxetine due to inhibition of metabolism via CYP1A2
	Clarithromycin	Increased plasma level of levomilnacipran due to inhibited metabolism via CYP3A4. Do not exceed a maximum of 80 mg/day
	Linezolid	Due to weak MAOI activity of linezolid, monitor for increased serotonergic and noradrenergic effects
Anticholinergic	Antiparkinsonian agents, antipsychotics, etc.	Increased anticholinergic effects
Anticoagulant	Apixaban, dabigatran, rivaroxaban, warfarin	Case reports of significant decreases in international normalized ratio (INR) with duloxetine Increased risk of bleeding possible due to decreased platelet aggregation
Anticonvulsant	Carbamazepine	Levomilnacipran peak level decreased by 26%, AUC decreased by 29% via induction of CYP3A4
	Stiripentol	Strong CYP3A4 inhibitors may increase levomilnacipran concentrations significantly. Do not exceed a maximum of 80 mg/day
Antidepressant		
SSRI	Fluoxetine, paroxetine	Reports that combination with SSRIs that inhibit CYP2D6 can result in increased levels of venlafaxine and duloxetine, with possible increases in blood pressure, anticholinergic effects, and serotonergic effects
	Fluvoxamine	6-fold increase in AUC, 2.5-fold increase in peak level, and 3-fold increase in half-life of duloxetine due to inhibited metabolism via CYP1A2 (AVOID concomitant use)

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (cont.)

Class of Drug	Example	Interaction Effects
NDRI	Bupropion	3-fold increase in venlafaxine plasma level due to inhibited metabolism via CYP2D6 and reduction in level of O-desmethylvenlafaxine metabolite Potentiation of noradrenergic effects Bupropion may mitigate SNRI-induced sexual side effects
SARI	Nefazodone	May increase plasma level of levomilnacipran through inhibition of CYP3A4
	Trazodone	Case report of serotonin syndrome with venlafaxine
NaSSA	Mirtazapine	Case report of serotonin syndrome with venlafaxine
Nonselective cyclic	Desipramine	Desipramine (metabolite) clearance reduced by 20% with venlafaxine; desipramine level increased 3-fold with duloxetine Increased levels of cyclic antidepressants metabolized by CYP2D6 possible with duloxetine
	Imipramine	Imipramine peak level and AUC increased by 40% with venlafaxine
	Trimipramine	Case report of seizure in combination with venlafaxine – postulated to be a result of inhibited metabolism via CYP2D6
RIMA	Moclobemide	Enhanced effects of norepinephrine and serotonin; CAUTION – no data on safety with combined use
Irreversible MAOI	Phenelzine	AVOID; possible hypertensive crisis and serotonergic reaction
Antifungal	Fluconazole, itraconazole, ketoconazole	Strong CYP3A4 inhibitors may increase levomilnacipran concentrations significantly; ketoconazole peak level increased by 39% and AUC by 57%. Do not exceed a maximum of 80 mg/day
Antihistamine	Diphenhydramine	Decreased metabolism of venlafaxine via CYP2D6
Antiplatelet	Clopidogrel	Increased risk of upper GI bleeding with combined use
Antipsychotic	General	Increased levels of antipsychotics metabolized by CYP2D6 possible with duloxetine
First generation	Haloperidol	Haloperidol peak level and AUC increased with venlafaxine; no change in half-life
	Thioridazine	Venlafaxine plasma level increased and concentration of ODV metabolite decreased Increased plasma levels of thioridazine and other phenothiazines possible with duloxetine due to inhibition of CYP2D6 – AVOID duloxetine and CAUTION with other SNRIs due to possible additive prolongation of QTc interval
Second generation	Clozapine	Increased levels of both clozapine and venlafaxine possible due to competitive inhibition of CYP2D6 and/or CYP3A4. A study with venlafaxine doses of 150 mg/day or less suggests no clinically significant interaction. Case report of NMS/serotonin syndrome
	Risperidone	Increased AUC of risperidone by 32% and decreased renal clearance by 20% with venlafaxine
Third generation	Aripiprazole	Case report of parkinsonism with venlafaxine 225 mg/day and aripiprazole 15 mg/day
Antiretrovirals	Delavirdine, efavirenz	Strong CYP3A4 inhibitors may increase levomilnacipran concentrations significantly. Do not exceed a maximum of 80 mg/day Moderate CYP3A4 inhibitors may increase levomilnacipran concentrations
	Indinavir	Both increases (by 13%) and decreases (by 60%) in total concentration (AUC) of indinavir reported with venlafaxine
	Ritonavir	Moderate decrease in clearance of venlafaxine
β-blocker	Propranolol	Increased plasma level of venlafaxine due to competition for metabolism via CYP2D6
Calcium channel blocker	Nicardipine	Strong CYP3A4 inhibitors may increase levomilnacipran concentrations significantly. Do not exceed a maximum of 80 mg/day
	Verapamil	Moderate CYP3A4 inhibitors may increase levomilnacipran concentrations
H_2 antagonist	Cimetidine	Increased plasma level of venlafaxine due to decreased clearance (by 43%); peak concentration increased by 60% Increased plasma level of duloxetine due to inhibited metabolism
Hypnotic/sedative	Zolpidem	Case report of delirium and hallucinations with venlafaxine
Lithium		Case report of serotonin syndrome with venlafaxine (see p. 59)

Class of Drug	Example	Interaction Effects
Licorice		Increased serotonergic effects possible
Lomitapide		Moderate CYP3A4 inhibitors may increase levomilnacipran levels
L-tryptophan		Additive effects with duloxetine in treatment-resistant patients May potentiate the risk of serotonin syndrome. Monitor for increased serotonergic effects
MAO-B inhibitor	Selegiline	Case reports of serotonergic reaction with venlafaxine
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome (see Precautions)
Metoclopramide		Case report of extrapyramidal and serotonergic effects with venlafaxine
NSAID	ASA, ibuprofen, naproxen	Increased risk of upper GI bleed with combined use
Opioid	Dextromethorphan Meperidine, tramadol	Increased risk of serotonin syndrome Increased risk of seizures and serotonin syndrome
Smoking (tobacco)		Decreased duloxetine levels due to CYP1A2 induction by cigarette smoking
St. John's wort		May augment serotonergic effects – increased risk of serotonin syndrome
Stimulant	Dextroamphetamine Methylphenidate	Case report of serotonin syndrome with venlafaxine Potentiated effect in the treatment of depression and ADHD
Tolterodine		C_{max} and half-life of tolterodine increased; no effect on active metabolites
Triptan	Rizatriptan, sumatriptan	Risk of serotonin syndrome when SSRI combined with triptan is 0.6 cases per 10,000 person-years of exposure; 95% CI, 0.0–1.5)

Serotonin-2 Antagonists/Reuptake Inhibitors (SARIs)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Nefazodone[B]	Phenylpiperidine	Serotonin/Antagonist and agonist	Serzone	Tablets: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	Safety and efficacy not established in children and adolescents under age 18
Trazodone	Triazolopyridine	Serotonin/Multimodal	Desyrel	Tablets: 50 mg, 75 mg[C], 100 mg, 150 mg, 300 mg[B]	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications in children and adolescents
- Trazodone used in acute and chronic treatment of insomnia and night terrors, and in MDD and behavior disturbances in children (agitation, aggression)

In adults:

‡ Indications listed here do not necessarily apply to all SARIs or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Serotonin-2 Antagonists/Reuptake Inhibitors (SARIs) (cont.)

- Major depressive disorder (MDD)
- Persistent depressive disorder
- Secondary depression in other mental illnesses (e.g., schizophrenia, dementia)
- MDD, recurrent: Prophylaxis
- Agoraphobia associated with panic disorder
- Social anxiety disorder
- Posttraumatic stress disorder (PTSD)
- Insomnia
- Antipsychotic-induced akathisia
- Bulimia
- Benzodiazepine abuse
- Schizophrenia: Negative symptoms (trazodone)
- Behavioral and psychological symptoms of dementia (BPSD)
- Cannabis use disorder – negative trial (nefazodone)
- Impotence, erectile dysfunction (trazodone), anorgasmia (nefazodone)
- Fibromyalgia, in open-label studies – monitor for tachycardia
- Diabetic neuropathy

General Comments

- Nefazodone withdrawn in Canada in 2003 due to risk of hepatotoxicity
- Trazodone increases slow-wave (stage 3–4) sleep
- Monitor all patients for worsening depression and/or suicidal thoughts

Pharmacology

- Exact mechanism of action unknown; equilibrate the effects of biogenic amines through various mechanisms; cause downregulation of β-adrenergic receptors
- Trazodone[50]: Potent antagonist of the 5-HT_{2A} receptor as well as a dose-dependent blockade of serotonin transporter; also blocks 5-HT_{2C}, α_1 (5 times more potent than nefazodone), and H_1 receptors
- Nefazodone: An analogue of trazodone; inhibits neuronal reuptake of serotonin and norepinephrine; also blocks 5-$HT_{2A/C}$ receptors and α_1 receptors; has no significant affinity for α_2, β-adrenergic, 5-HT_{1A}, cholinergic, dopaminergic, or benzodiazepine receptors

Dosing

- See p. 134
- Initiate drug at a low dose and increase every 3–5 days to a maximum tolerated dose based on side effects; there is a wide variation in dosage requirements; prophylaxis is most effective if therapeutic dose is maintained
- Trazodone doses of 25–100 mg at bedtime used in chronic sleep disorders
- Trazodone should be taken on an empty stomach when used for sedation, as food delays absorption, but otherwise should be taken after a light meal or snack to reduce side effects
- XR formulation (Oleptro) dosing: 150–375 mg daily, should be given on an empty stomach in the late evening, caplets can be halved along score line but should not be crushed or chewed

Pharmacokinetics

- See p. 134
- Completely absorbed from the GI tract; food significantly delays (from 1 h to several hours) and decreases peak plasma effect of trazodone
- Nefazodone bioavailability only 20% due to high first-pass metabolism; can be given without regard to meals
- Large percentage metabolized by first-pass effect
- Highly bound to plasma protein (trazodone 85–95%; nefazodone over 99%)
- Metabolized primarily by the liver; half-life of nefazodone is dose dependent, varying from 2 h at 100 mg/day to 4–5 h at 600 mg/day; half-life and AUC of nefazodone and hydroxy metabolite doubled in patients with severe liver impairment

- Trazodone metabolized by CYP3A4 to active metabolite m-chlorophenylpiperazine (mCPP); elimination half-life 4–9 h in adults; steady state reached in about 3 days
- Nefazodone is a potent inhibitor of CYP3A4 and may decrease the metabolism of drugs metabolized by this isoenzyme (see Interactions pp. 86–87)
- Regular ingestion of grapefruit juice while taking nefazodone may affect the antidepressant plasma levels (see Interactions pp. 86–87)

Onset & Duration of Action

- Therapeutic effect is typically seen after 28 days (though some patients may respond sooner)
- Sedative effects are seen within a few hours of oral administration; decreased sleep disturbance reported after a few days

Adverse Effects

- The pharmacological and adverse effect profile of SARI antidepressants is dependent on their affinity for and activity on neurotransmitters/receptors (see table p. 128)
- See chart p. 130 for incidence of adverse effects at therapeutic doses; incidence of adverse effects may be greater in early days of treatment; patients adapt to many adverse effects over time

CNS Effects

- A result of antagonism at histamine H_1 receptors and α_1 adrenoreceptors
- Occur frequently
- Drowsiness (most common adverse effect; reported in 20–50%) [Management: Prescribe bulk of dose at bedtime]
- Weakness, lethargy, fatigue
- Conversely, excitement, agitation, and restlessness have occurred
- Confusion, disturbed concentration, and disorientation
- Nefazodone increases REM sleep and sleep quality
- Improved psychomotor and complex memory performance reported with nefazodone after single doses; dose-related impairment noted after repeated doses
- Precipitation of hypomania or mania, increased risk in bipolar patients with comorbid substance use disorder
- Psychosis, panic reactions, anxiety or euphoria may occur
- Fine tremor
- Seizures can occur rarely following abrupt drug increase or after drug withdrawal; risk increases with high plasma levels
- Myoclonus; includes muscle jerks of lower extremities, jaw, and arms, and nocturnal myoclonus – may be severe in up to 9% of patients [If severe, clonazepam, valproate or carbamazepine may be of benefit]
- Dysphasia, stuttering
- Disturbance in gait, parkinsonism, dystonia
- Headache; worsening of migraine reported with trazodone and nefazodone

Anticholinergic Effects

- A result of antagonism at muscarinic receptors
- Include dry eyes, blurred vision, constipation, dry mouth [see p. 105 for treatment suggestions]

Cardiovascular Effects

- A result of antagonism at α_1 adrenoreceptors, muscarinic, 5-$HT_{2A/C}$, and H_1 receptors, and inhibition of sodium fast channels
- Risk increases with high plasma levels
- Bradycardia reported with nefazodone
- Dizziness (10–30%), orthostatic hypotension, and syncope
- Trazodone can exacerbate ischemic attacks; arrhythmias reported (with doses above 200 mg/day) including torsades de pointes
- Cases of QTc prolongation with trazodone and nefazodone (by inhibiting hERG potassium ion channels); contraindicated in heart block or post-myocardial infarction

Endocrine & Metabolic Effects

- Decreases in blood sugar levels reported (nefazodone)
- Can induce SIADH with hyponatremia
- Weight gain reported with trazodone; rare with nefazodone

GI Effects

- A result of inhibition of 5-HT uptake and M_1 receptor antagonism
- Peculiar taste, “black tongue,” glossitis

Serotonin-2 Antagonists/Reuptake Inhibitors (SARIs) (cont.)

- Nausea, vomiting
- Reports of upper GI bleeding

Urogenital & Sexual Effects

- A result of altered dopamine (D_2) activity, 5-HT_2 blockade, inhibition of 5-HT reuptake, α_1 blockade, and M_1 blockade
- Sexual adverse effects occur rarely
- Testicular swelling, painful ejaculation, retrograde ejaculation, increased libido; spontaneous orgasm with yawning (trazodone)
- Priapism with trazodone (0.01–0.1% of males) and nefazodone due to prominent α_1 blockade in the absence of anticholinergic activity; trazodone has 5 times more potent α_1 blockade, thus nefazodone has a lower potential to cause priapism; trazodone-induced priapism can occur at dosages ranging 50–400 mg, with the majority occurring at a dosage of 150 mg or less, within first 4 weeks; cases of clitoral priapism with trazodone and nefazodone
- Case of penile amputation secondary to trazodone-induced priapism in a patient with clotting disorder and history of DVT; carefully administer and closely monitor in patients with coagulopathy or clotting disorders

Hypersensitivity Reactions

- Rare
- Rash, urticaria, pruritus, edema, blood dyscrasias

Other Adverse Effects

- Jaundice, hepatitis, hepatic necrosis and hepatic failure reported with therapeutic doses of nefazodone (laboratory evidence includes: Increased levels of ALT, AST, GGT, and bilirubin and increased international normalized ratio (INR)) – cases of liver failure and death reported. Recommend baseline and periodic liver function tests with nefazodone. Monitor for signs of hepatotoxicity
- Cases of palinopsia with both trazodone and nefazodone and scotoma with nefazodone – may be dose related
- Rare reports of alopecia with nefazodone
- Case reports of burning sensations in various parts of the body with nefazodone

D/C Discontinuation Syndrome

- Very little information is published related to low-dose trazodone (< 200 mg daily) and withdrawal syndrome risk. Rebound insomnia possible
- Abrupt discontinuation may cause a syndrome consisting of dizziness, lethargy, nausea, vomiting, diarrhea, headache, fever, sweating, chills, malaise, incoordination, insomnia, vivid dreams, myalgia, paresthesias, dyskinesias, "electric-shock-like" sensations, visual discoordination, anxiety, irritability, confusion, slowed thinking, disorientation; rarely aggression, impulsivity, hypomania, and depersonalization
- Most likely to occur within 1–7 days after drug stopped or dose drastically reduced, and typically disappears within 3 weeks
- Paradoxical mood changes reported on abrupt withdrawal, including hypomania or mania

☞ **THEREFORE THESE MEDICATIONS SHOULD BE WITHDRAWN GRADUALLY AFTER PROLONGED USE**

Management

- Reinstitute the drug at a lower dose and gradually reduce in small amounts over several days[51]

Precautions

- May induce manic reactions in patients with bipolar disorder and rarely in unipolar depression; because of risk of increased cycling, bipolar disorder is a relative contraindication
- May impair the mental and physical ability to perform hazardous tasks (e.g., driving a car or operating machinery); will potentiate the effects of alcohol
- Trazodone is a substrate for CYP3A4 and its metabolism can be inhibited by CYP3A4 inhibitors; nefazodone is a potent inhibitor of CYP3A4 (see Interactions pp. 86–87)
- SARIs may cause suicidal ideation, hostility, and psychomotor agitation in children and adolescents. Monitor all patients for worsening depression and suicidal thinking
- Use caution in combination with drugs that prolong the QTc interval
- May be arrhythmogenic in patients with a history of cardiac disease
- Treatment with medications that inhibit the serotonin transporter may be associated with abnormal bleeding, particularly when combined with NSAIDs, ASA, anticoagulants, or other medications that affect coagulation
- May lower the seizure threshold; therefore, administer cautiously to patients with a history of convulsive disorders, organic brain disease or a predisposition to convulsions (e.g., alcohol withdrawal)

- Priapism (approximately 0,45% in 6,000 patients) has occurred with trazodone requiring surgical intervention in one third of cases; one case of trazodone-induced priapism requiring penile amputation in a patient with clotting disorder and history of DVT; carefully administer and closely monitor in patients with coagulopathy or clotting disorders
- Use nefazodone cautiously in patients in whom excess anticholinergic activity could be harmful (e.g., urinary retention, narrow-angle glaucoma)
- Use nefazodone with caution in patients with respiratory difficulties, since antidepressants with anticholinergic properties can dry up bronchial secretions and make breathing more difficult
- Use caution in prescribing nefazodone for patients with a history of alcoholism or liver disorder. Monitor liver function tests at baseline and periodically during treatment, and at first symptom or clinical sign of liver dysfunction
- Combination with SSRIs can lead to increased plasma level of trazodone. Combination therapy has been used in the treatment of resistant patients; use caution and monitor for serotonin syndrome
- Use caution when switching from trazodone (antidepressant doses) to fluoxetine and vice versa (see Interactions pp. 86–87, and Switching Antidepressants p. 137)

Toxicity

- Acute poisoning results in drowsiness, ataxia, nausea, vomiting; deep coma as well as arrhythmias (including torsades de pointes) and AV block reported; no seizures reported
- Retrospective review of 84 cases of children ≤ 6 years of age who ingested trazodone unintentionally showed 62% had no clinical effects, 34% had minor effects (vomiting, dizziness, headache), and 4% had moderate effects (ataxia, slurred speech, priapism). No major adverse effects or deaths were observed. Children should be referred for further evaluation in acute unintentional trazodone ingestions of doses ≥ 6 mg/kg

Use in Pregnancy◊

- Trazodone in high doses was found to be teratogenic and toxic to the fetus in some animal species; trazodone and nefazodone found not to increase rates of malformations in humans above the baseline of 1–3%
- If possible, avoid during first trimester

Breast Milk

- Limited data suggests that trazodone levels in milk are low and would not be expected to cause any adverse effects in breastfed infants, especially when maternal doses of 100 mg or less are used at bedtime for sleep
- Exclusively breastfed infant would receive up to 6.2% of the maternal weight-adjusted dosage of nefazodone; drowsiness, lethargy, poor feeding, and low body temperature were reported in a breastfed 9-week-old preterm infant with maternal dosage of 300 mg/day

Nursing Implications

- Psychotherapy and education are also important in the treatment of depression
- Monitor therapy by watching for adverse side effects and mood and activity level changes, including worsening of suicidal thoughts; keep physician informed
- Be aware that the medication reduces the degree of depression and may increase psychomotor activity; this may create concern about suicidal behavior
- Expect a lag time of 28 days before antidepressant effects will be noticed
- Reassure patient that drowsiness and dizziness usually subside after first few weeks; if dizzy, patient should get up from lying or sitting position slowly, and dangle legs over edge of bed before getting up
- Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis
- These drugs should not be stopped suddenly due to risk of precipitating withdrawal reactions; withdrawal syndrome expected to be minimal and may include return to insomnia for low-dose (< 200 mg nightly) trazodone
- Because these drugs can cause drowsiness, caution patient that activities requiring mental alertness should not be performed until response to the drug has been determined
- With nefazodone, monitor for signs of hepatotoxicity, including nausea, vomiting, fatigue, pruritus, jaundice, and dark urine
- Trazodone should be taken on an empty stomach when used for sedation, as food delays absorption, but otherwise should be taken after a light meal or snack to reduce side effects
- Instruct patient to avoid ingestion of grapefruit juice, as the blood level of trazodone and nefazodone may increase

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Serotonin-2 Antagonists/Reuptake Inhibitors (SARIs) (cont.)

Patient Instructions

- For detailed patient instructions on SARI antidepressants, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Alcohol		Short-term or acute use reduces first-pass metabolism of antidepressant and increases its plasma level; chronic use induces metabolizing enzymes and decreases its plasma level
Antibiotic	Linezolid	Monitor for increased serotonergic effects due to weak MAOI activity of linezolid
	Macrolides (clarithromycin, erythromycin)	Increased plasma level and decreased clearance of trazodone reported via CYP3A4 inhibition by clarithromycin; reduction in trazodone dose may be necessary when used concurrently
Anticholinergic	Antihistamines, antiparkinsonian agents	Increased anticholinergic effect; may increase risk of hyperthermia, confusion, urinary retention, blurred vision, constipation
Anticoagulant	Apixaban, dabigatran, rivaroxaban	Increased risk of bleeding possible
	Warfarin	Case reports of altered INR with trazodone
Anticonvulsant	Carbamazepine, phenytoin	Increased plasma level of carbamazepine or phenytoin, possibly due to competitive inhibition of metabolism via CYP3A4 with trazodone Increased plasma level of carbamazepine with nefazodone due to inhibited metabolism via CYP3A4
	Carbamazepine, barbiturates, phenytoin	Decreased plasma level of trazodone and its mCPP metabolite (by 76% and 60%, respectively, with carbamazepine) and of nefazodone, due to enzyme induction via CYP3A4
Antidepressant		
SSRI	Fluoxetine, fluvoxamine, paroxetine, sertraline	Elevated SSRI plasma level (due to release from protein binding and inhibition of oxidative metabolism); monitor plasma level and for signs of toxicity Nefazodone metabolite (mCPP) level increased 4-fold with fluoxetine; case report of serotonin syndrome with combination Nefazodone may reverse SSRI-induced sexual dysfunction and may enhance sleep
SNRI	Levomilnacipran	Nefazodone may increase plasma level of levomilnacipran through inhibition of CYP3A4
	Venlafaxine	Combined use may increase risk of serotonin syndrome
NaSSA	Mirtazapine	Case report of priapism lasting 19 h with combined use; previously tolerated each agent as monotherapy
RIMA	Moclobemide	Monitor for serotonergic effects
Irreversible MAOI	Phenelzine, tranylcypromine	Monitor for serotonergic effects
Antifungal	Ketoconazole	Increased plasma level of trazodone due to inhibited metabolism via CYP3A4
Antihypertensive	Methyldopa, reserpine	Decreased antihypertensive effect due to inhibition of α-adrenergic receptors
	Clonidine, guanfacine	Additive hypotension and sedation
	Acetazolamide, thiazide diuretics	Hypotension augmented

Class of Drug	Example	Interaction Effects
Antipsychotic	General	Increased risk of QT interval prolongation, torsades de pointes, and sudden cardiac death Potential for additive adverse effects (e.g., sedation, orthostatic hypotension)
First generation	Pimozide	Elevated pimozide levels and cardiac arrhythmias may occur with combination
Second generation	Clozapine, olanzapine, risperidone	Increased plasma levels of clozapine (case report) Case reports of NMS and serotonin syndrome
	Lurasidone, quetiapine	Nefazodone may significantly increase antipsychotic levels due to inhibition of CYP3A4
Third generation	Aripiprazole, brexpiprazole, cariprazine	Nefazodone may significantly increase antipsychotic levels due to inhibition of CYP3A4
Anxiolytic	Alprazolam, triazolam	Increased plasma levels of alprazolam (by 200%) and triazolam (by 500%), due to inhibited metabolism via CYP3A4 by nefazodone
	Buspirone	Concomitant use increases the risk of serotonin syndrome
Calcium channel blocker	Amlodipine	Elevated amlodipine level due to inhibited metabolism via CYP3A4 with nefazodone
Cardiac glycoside	Digoxin	Increased digoxin plasma level, with possible toxicity
CNS depressant	Alcohol, antihistamines, benzodiazepines, hypnotics	Increased sedation, CNS depression
Cholestyramine		Decreased absorption of antidepressant, if given together
Ginkgo biloba		Case report of coma with trazodone (postulated to be due to excess stimulation of GABA receptors)
Grapefruit juice		Decreased metabolism of trazodone and nefazodone via CYP3A4
L-tryptophan		Additive antidepressant effect; monitor for serotonergic effects
MAO-B inhibitor	Selegiline	Reports of serotonergic reactions
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome (see Precautions)
Opioid	Dextromethorphan	Increased risk of serotonin syndrome
	Meperidine, tramadol	Increased risk of seizures and serotonin syndrome
Protease inhibitor	Ritonavir, indinavir	Increased plasma levels of trazodone and nefazodone due to decreased metabolism (with ritonavir, trazodone clearance decreased 52%)
Sildenafil		Possible enhanced hypotension due to inhibited metabolism of sildenafil via CYP3A4 with nefazodone
Statins	Atorvastatin, pravastatin, simvastatin	Inhibited metabolism of statins by nefazodone (via CYP3A4); increased plasma level and adverse effects – myositis and rhabdomyolysis reported
St. John's wort		May augment serotonergic effects. AVOID combination
Sulfonylurea	Glyburide	Increased hypoglycemia
Triptan	Rizatriptan, sumatriptan	Inadequate data available to determine risk of serotonin syndrome with addition of a triptan to SARIs. However, given the seriousness of serotonin syndrome, caution is warranted

Serotonin-1A Partial Agonist/Serotonin Reuptake Inhibitor (SPARI)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name	Dosage Forms and Strengths	Monograph Statement
Vilazodone	Indolalkylamine	Serotonin/Multimodal	Viibryd	Tablets: 10 mg, 20 mg, 40 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. * Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),

Indications‡ (👍 approved)

In children and adolescents:
- No approved indications in children and adolescents

In adults:
- 👍 Major depressive disorder (MDD)
- 👍 Generalized anxiety disorder (GAD)
- 👍 Cannabis use disorder – negative trial; worsened cravings (preliminary data)

General Comments

- Two double-blind, placebo-controlled trials in children and adolescents aged 7–17 years with MDD did not find vilazodone effective over placebo
- A new class of antidepressants (SPARI) incorporating two mechanisms of action but its clinical profile remains similar to SARIs and SSRIs. Based on the limited available 8-week clinical data it remains unclear whether vilazodone has any safety or efficacy advantages compared to other serotonergic antidepressant agents
- The efficacy of vilazodone (over placebo) for MDD was established in four 8–10-week, RCTs in adult patients; 41–58% of patients on vilazodone had a response compared to 31–47% of patients who received placebo
- The efficacy of vilazodone (over placebo) for generalized anxiety disorder (GAD) was studied in two 10-week, RCTs in adult patients; 46–55% of patients on vilazodone had a response compared to 42–48% of patients who received placebo
- In a 28-week RCT, fixed-dose (20 mg/day, 40 mg/day, or placebo) trial, the time to relapse with vilazodone was not statistically different from placebo

Pharmacology

- Dual 5-HT_{1A} receptor partial agonist and 5-HT reuptake inhibitor. Vilazodone has greater affinity for the 5-HT_{1A} receptor (IC_{50} = 0.2nM) compared to serotonin itself; it's affinity for the 5-HT reuptake pump (IC_{50} = 0.5nM) is comparatively lower
- 5-HT_{1A} agonism produces a more rapid desensitization of presynaptic 5-HT_{1A} autoreceptors

Dosing

- No pediatric dosing has been established; doses of 15–30 mg once daily were not effective for children and adolescents with MDD
- Adults: 10 mg once daily with food for 7 days, followed by 20 mg once daily for an additional 7 days, then increase to 40 mg once daily
- Some adult patients were unable to reach 40 mg in clinical trials due to lack of tolerability
- No dosage adjustment required in renal insufficiency or moderate liver impairment
- Give with food as absorption decreased by up to 50% in fasting state

Pharmacokinetics

- See p. 134
- The pharmacokinetics of vilazodone (5–80 mg) are dose proportional. Vilazodone concentrations peak at a median of 4–5 h (T_{max}) after administration and decline with a terminal half-life of approximately 25 h

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

- The bioavailability is 72% with food. Administration with food (high-fat or light meal) increases oral bioavailability (C_{max} increased by approximately 147–160% and AUC increased by approximately 64–85%)
- Distribution: Vilazodone is widely distributed and approximately 96–99% protein bound
- Metabolism and elimination: Elimination of vilazodone is primarily by hepatic metabolism through CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in urine and 2% of the dose recovered in feces as unchanged vilazodone. CYP3A4 is primarily responsible for its metabolism, with minor contributions from CYP2C19 and CYP2D6. Vilazodone has no active metabolites

Adverse Effects

CNS Effects

- Headache was a common side effect (over 10%) but this was no different than placebo
- In pooled analysis of pivotal trials, dizziness was also a common side effect (16.5% vs. 3.3% placebo), as were insomnia (11.1% vs. 5.4%), fatigue (8.7% vs. 3%), and lethargy (6.8% vs. 0.5%)
- Restlessness and abnormal dreams reported in initial trials
- Effects on sleep were specifically investigated in a randomized crossover study with 10 healthy young males (20 mg single dose); slow-wave sleep increased in the first and third one-third of the night, whereas wakefulness was enhanced in the second and third one-third of the night; rapid eye movement almost totally disappeared in patients receiving vilazodone

Cardiovascular Effects

- A thorough ECG study in healthy volunteers found that vilazodone had no clinically significant effect on heart rate, PR interval, or QTc interval, indicating a low potential for it to induce cardiac arrhythmias[53]

Endocrine & Metabolic Effects

- No statistically significant weight gain in the two pivotal trials; mean weight increase in the long-term study was 1.7 kg
- Increased appetite reported, but incidence was low and not significantly different to placebo
- In one GAD trial, a higher percentage of vilazodone-treated patients compared to placebo-treated patients shifted from normal baseline values to high values at the end of treatment for total cholesterol (18% vs. 11%), glucose (10% vs. 4%), and triglycerides (19% vs. 12%)[54]

GI Effects

- Diarrhea (> 25%), nausea (> 20%)
- Vomiting, dyspepsia, abdominal pain, dry mouth, and flatulence also reported

Urogenital & Sexual Effects

- Partial agonism at 5-HT_{1A} receptors may lower the risk of sexual adverse effects compared to SSRIs
- Spontaneously-reported sexual side effects were generally more frequent with vilazodone than placebo in 8- or 10-week trials, decreased libido being most common (4% vs. less than 1% in males and 2% vs. less than 1% in females for vilazodone 40 mg once daily); in open-label treatment with vilazodone for 1 year, the most frequent sexual function-related adverse effects were decreased libido (4.2%), erectile dysfunction (4.2%), delayed ejaculation (3.1%), and abnormal orgasm (2.3%)
- In 3 trials prospectively evaluating sexual dysfunction using validated scales, over half of the participants had baseline sexual dysfunction; scores for those whose MADRS score was reduced by ≥ 50% improved in all treatment groups with a small numerical (but not statistically significant) difference between vilazodone (20 mg/40 mg) and placebo relative to citalopram 40 mg

Other Adverse Effects

- Dry mouth, hyperhidrosis
- Night sweats, blurred vision, and dry eyes relatively common
- Dose-dependent hyponatremia (case report)

D/C Discontinuation Syndrome

- Abrupt discontinuation may cause a syndrome consisting of dizziness, lethargy, nausea, vomiting, diarrhea, headache, fever, sweating, chills, malaise, incoordination, insomnia, vivid dreams, myalgia, paresthesias, dyskinesias, “electric-shock-like” sensations, visual discoordination, anxiety, irritability, confusion, slowed thinking, disorientation; rarely aggression, impulsivity, hypomania, and depersonalization
- Most likely to occur within 1–7 days after drug stopped or dose drastically reduced, and typically disappears within 3 weeks
- Paradoxical mood changes reported on abrupt withdrawal, including hypomania or mania

☞ **THEREFORE THIS MEDICATION SHOULD BE WITHDRAWN GRADUALLY AFTER PROLONGED USE**

Management

- Reinstitute the drug at a lower dose and taper gradually over several days

Serotonin-1A Partial Agonist/Serotonin Reuptake Inhibitor (SPARI) (cont.)

Precautions

- Strong CYP3A4 inhibitors can result in elevated plasma levels of vilazodone; alternatively, potent inducers of CYP3A4 can lower plasma levels of the drug and decrease its effectiveness
- Boxed warning regarding increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders
- Contraindicated in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days
- Similar to other antidepressants, vilazodone labeling carries warnings about serotonin syndrome, seizures, abnormal bleeding, activation of mania/hypomania (reported in 0.1% of patients in clinical trials), and SIADH/hyponatremia
- Dose tapering is recommended when the drug is discontinued
- May impair platelet aggregation, resulting in increased risk of bleeding events, particularly if used concomitantly with ASA, NSAIDs, warfarin, or other anticoagulants
- If urgent treatment with linezolid or IV methylene blue is required in a patient already receiving vilazodone and potential benefits outweigh potential risks, discontinue vilazodone promptly and monitor for serotonin syndrome for 2 weeks or until 24 h after the last dose of linezolid or IV methylene blue, whichever comes first. May resume vilazodone 24 h after the last dose of linezolid or IV methylene blue

Toxicity

- In a review of all serotonergic poisonings of children (age 6 and under) in the USA, vilazodone accounted for only 5.9% of all exposures but resulted in the highest proportion of health care facility admission, with a 20-fold increased risk of moderate to major toxic outcomes. Several severe outcomes, such as seizure and coma, were more common in vilazodone compared to SSRIs[55]
- The median dose associated with major effects was 50 mg; half of children with a major effect ingested less than 40 mg
- Case series of 8 children (19 months to 3 years of age) ingesting partially chewed tablets–940 mg of vilazodone presented with symptoms; most common symptoms were agitation, somnolence, tachycardia, nausea, vomiting, and seizures; 3 children developed serotonin syndrome; all 8 children required hospital admission (7 in ICU)
- Case report of a 22-month-old, 8.8 kg child ingesting up to 920 mg vilazodone (unwitnessed) who developed serotonin syndrome and elevated creatine kinase; managed with supportive care, benzodiazepines (ineffective), and dexmedetomidine – patient recovered 74 h following ingestion. Vilazodone level was detected. Urine toxicology screening was positive for amphetamines but confirmatory testing was negative; the possibility of false-positive amphetamine screenings when an overdose of vilazodone is suspected should be investigated
- Case report of a 15-year-old adolescent ingesting 780 mg vilazodone who developed serotonin syndrome and QRS prolongation; managed with supportive care and sodium bicarbonate
- The adverse reactions associated with overdose at doses of 200–280 mg as observed in adult clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation

Management

- Benzodiazepines for seizures, serotonin syndrome or sedation after intubation, and other forms of sedation; respiratory support with oxygen or intubation have been noted as therapeutic in a subset of ingestions[56]

Use in Pregnancy◊

- There are no adequate, well-controlled studies of vilazodone in pregnant females and no human data regarding vilazodone concentrations in breast milk
- One published case report of vilazodone used in pregnancy: 32-year-old woman unexpectedly became pregnant while on 40 mg/day, continued treatment and gave birth to a healthy child. The child experienced transient neonatal jaundice but none of the irritability or feeding or respiratory difficulties reported with other serotonergic antidepressants[57]

Breast Milk

- No human data regarding vilazodone concentrations in breast milk

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Nursing Implications

- Vilazodone should be taken with food for full absorption
- Instruct patient to avoid ingestion of grapefruit juice, as the blood level of vilazodone may increase
- May see antidepressant effects after 1 week

Patient Instructions

- For detailed patient instructions on vilazodone, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Antibiotic	Clarithromycin, erythromycin	Increased plasma level of vilazodone due to inhibition of metabolism via CYP3A4; reduce dose to maximum of 20 mg
	Linezolid	May enhance serotonergic effect. May increase risk for serotonin syndrome
Anticoagulant	Apixaban, dabigatran, rivaroxaban, warfarin	May enhance the anticoagulant effect of some anticoagulants
Antidepressant		
MAOI	Moclobemide, phenelzine, tranylcypromine	Risk of serotonin syndrome. Contraindicated if used concurrently or within 14 days of stopping
Antiemetic	Metoclopramide	May enhance serotonergic effect. Risk of serotonin syndrome
Antifungal	Ketoconazole	Increased plasma level of vilazodone due to inhibition of metabolism via CYP3A4; reduce dose to maximum of 20 mg
Antipsychotic	Pimozide	May enhance antipsychotic side effects due to inhibition of metabolism via CYP3A4
Anxiolytic	Buspirone	May enhance serotonergic effect. Risk of serotonin syndrome
Calcium channel blocker	Verapamil	Increased plasma level of vilazodone due to inhibition of metabolism via CYP3A4; reduce dose to maximum of 20 mg
Cardiac glycoside	Digoxin	C_{max} of digoxin increased significantly when co-administered with vilazodone, monitoring of digoxin plasma concentrations and possible digoxin dosage reduction may be required
CYP450 enzyme inducer	Carbamazepine, phenytoin, rifampin	May induce the metabolism of vilazodone due to induction of metabolism via CYP3A4
Grapefruit juice		Increased plasma level of vilazodone possible due to inhibition of metabolism via CYP3A4
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome (see Precautions)
NSAID	ASA, ibuprofen, naproxen	May impair platelet aggregation, resulting in increased risk of bleeding events
Opioid	Dextromethorphan, meperidine	May enhance serotonergic effect. May increase risk for serotonin syndrome
	Tramadol	May increase seizure risk
Protease inhibitor	Indinavir, ritonavir	Increased plasma level of vilazodone due to inhibition of metabolism via CYP3A4; reduce dose to maximum of 20 mg
St. John's wort		May augment serotonergic effects and cause serotonin syndrome. AVOID combination
Stimulant	Methylphenidate	May enhance serotonergic effect. Risk of serotonin syndrome
Triptan	Rizatriptan, sumatriptan	Inadequate data available to determine risk of serotonin syndrome with addition of a triptan to SPARI. However, given the seriousness of serotonin syndrome, caution is warranted

Serotonin Modulator and Stimulator (SMS)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name	Dosage Forms and Strengths	Monograph Statement
Vortioxetine	Bisarylsulfanyl amine	Serotonin/Multimodal	Trintellix	Tablets: 5 mg, 10 mg, 20 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications in children and adolescents
- Major depressive disorder (MDD): Vortioxetine did not show efficacy greater than placebo in a DBPC-RCT[58]
- Narcolepsy and cataplexy with comorbid depression: Improvement in all conditions (case report)

In adults:

- 👍 Major depressive disorder (MDD)
- Generalized anxiety disorder (GAD): Conflicting results
- Social anxiety disorder: Preliminary results
- Panic disorder: Preliminary results; panic disorder induced by COVID-19 (case report)
- Posttraumatic stress disorder (PTSD): No benefit shown in two small trials
- Obsessive-compulsive disorder (OCD): Positive case reports; monotherapy or combined with aripiprazole
- Binge-eating disorder with comorbid MDD: Improvement in both conditions (pilot study)
- Schizophrenia: Improved negative symptoms (adjunct to risperidone in DBPC-RCT); improved cognition and positive symptoms (adjunct to clozapine in open-label study)
- ADHD: Negative trial
- Sleep disturbance: Preliminary results
- Cognitive impairment: Positive studies
- Chronic neuropathic pain: Positive studies
- Irritable bowel syndrome: Improved quality of life in a small study

General Comments

- Structurally related to buspirone, citalopram, and ondansetron, each of which shares some mechanisms of action with vortioxetine
- Vortioxetine 10–20 mg/day for 8 weeks failed to demonstrate efficacy greater than placebo in a DBPC-RCT in 616 patients 12–17 years of age with MDD and who did not respond to brief psychosocial intervention in the lead-in period[58]
- Non-US-based trials demonstrated efficacy for MDD at lower doses (5 mg) compared to US trials (adults)
- A network meta-analysis of 24 studies does not indicate greater benefits or fewer harms of vortioxetine compared with other antidepressants
- As with other antidepressants, vortioxetine carries the warning regarding clinical worsening, suicidality, and unusual changes in behavior. See p. 52 for comments on antidepressants and suicidality

Pharmacology

- The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications

- Based on PET data, the mean 5-HT transporter occupancy in the raphe nuclei was approximately 50% at 5 mg/day, 65% at 10 mg/day, and increased to above 80% at 20 mg/day
- Nonclinical data indicate that vortioxetine inhibits the serotonin transporter protein (K_i = 1.6) and, in decreasing order of affinity, acts as a 5-HT_3 antagonist (K_i = 3.7), 5-HT_{1A} receptor agonist (K_i = 15), 5-HT_7 antagonist (K_i = 19), 5-HT_{1B} receptor partial agonist (K_i = 33), and 5-HT_{1D} receptor antagonist (K_i = 54)
- Often referred to as a multimodal antidepressant because it has partial agonist and antagonist effects, plus inhibits serotonin reuptake
- 5-HT_{1A} agonism produces a more rapid desensitization of presynaptic 5-HT_{1A} autoreceptors
- 5-HT_3 affinity for vortioxetine is greater than that of mirtazapine and olanzapine but it is lacking in H_1 affinity, which may explain the significant rates of nausea despite strong 5-HT_3 antagonist activity
- Serotonergic modulation of glutamate neurotransmission via 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, and 5-HT_7 receptors has been postulated as a potential mechanism of action for relief of depression-related cognitive dysfunction

Dosing

- See p. 135
- Initial dose of 10 mg once daily without regard to meals; increase to 20 mg once daily after one week as tolerated because higher doses showed better treatment effects in trials conducted in the USA; consider 5 mg once daily for patients who do not tolerate higher doses
- MDD in adolescents: 5 mg daily for 2 days, then increase by 5 mg every 2 days to target 10 mg or 20 mg daily[58]
- Maintenance dose: 5–20 mg once daily
- A 6-month open-label extension study in pediatric patients showed dosing between 5 and 20 mg daily as suitable for this population[59, 60]
- In known CYP2D6 poor metabolizers, the maximum recommended dose is 10 mg/day
- No dose adjustment necessary on the basis of age, renal function or mild–moderate renal impairment
- Vortioxetine can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation, if possible

Pharmacokinetics

- See p. 135
- Displays linear pharmacokinetics (up to 60 mg after multiple doses); bioavailability (75%) is NOT affected by food
- Vortioxetine concentrations peak in 7–11 h (T_{max}). Widely distributed and about 98% protein bound
- Elimination half-life is 57–66 h. Elimination is via hepatic metabolism, primarily through oxidation (CYP2D6 is the major isoenzyme responsible for metabolism) with subsequent glucuronic acid conjugation. The major metabolite has no clinical activity and a minor metabolite has the capacity to inhibit the serotonin transport protein, but it has limited ability to penetrate blood/brain barrier
- In healthy patients, oral clearance was approximately 2-fold higher in extensive (i.e., normal) metabolizers compared to poor CYP2D6 metabolizer; no clinically relevant differences in overall incidence of adverse events in clinical trials. Routine CYP2D6 genotyping is not required before starting vortioxetine
- Vortioxetine or its metabolites have not shown any potential for clinically meaningful CYP enzyme inhibition or induction. It is also not considered a P-glycoprotein substrate, nor does it have any P-glycoprotein inhibitory effects
- Steady state levels occur in about 14 days
- Excretion via urine (59%) and feces (26%). Negligible amounts of unchanged drug remain in urine

Adverse Effects

- In an adolescent DBPC-RCT common adverse effects were (in descending incidence) nausea, headache, vomiting, nasopharyngitis, diarrhea, dizziness; suicidal ideation was below 1% in 10 mg group and 1.9% in 20 mg group, and 1.3% in fluoxetine 20 mg reference group[58]
- In a short-term pediatric open-label study of vortioxetine for 14–20 days[59], most common adverse effects were headache (25%), nausea (23%), sedation (23%), and common adverse effects were (in descending incidence) upper abdominal pain, fatigue, vomiting, decreased appetite, and irritability. In a 6-month extension study[60], most common adverse effects were headache (27%) and nausea (20%), and common adverse effects were (in descending incidence) dysmenorrhea (females), vomiting, toothache, upper respiratory tract infection, and weight gain

CNS Effects

- Fatigue, sedation or somnolence possible but not common
- During short-term clinical trials in patients with no history of seizure disorders, seizures were reported in less than 0.1% of patients receiving vortioxetine
- Headaches common in adolescents (12.4–15.9%); common in adult maintenance trials

Serotonin Modulator and Stimulator (SMS) (cont.)

- One industry-sponsored RCT suggests vortioxetine (at 10 mg/day over a 15-day period) has no significant impact on cognitive and psychomotor performance in the context of driving
- Although symptoms of mania/hypomania were seen in less than 0.1% of patients treated with vortioxetine in pre-marketing trials, caution is still warranted in using vortioxetine in patients with a personal or family history of bipolar disorder, mania or hypomanic symptoms
- Suicidal ideation in adolescents (< 1–1.9%)
- Irritability (pediatric open label study)
- Dystonia (Meige syndrome in case reports)
- Restless legs syndrome (case report)
- Reversible cerebral vasoconstriction syndrome (Call-Fleming syndrome) (case report)

Cardiovascular Effects

- No significant effects on blood pressure, heart rate, and ECG parameters were seen in pre-marketing trials at doses up to 40 mg/day

Endocrine & Metabolic Effects

- No significant effect on body weight as measured by the mean change from baseline (5.8% of patients in one long-term trial reported a mean weight increase of 1 kg)
- Decreased appetite (pediatric open label study)
- Dysmenorrhea (pediatric open label study)
- Amenorrhea (case report)

GI Effects

- Nausea was the most common adverse effect (14.3–19.3% in adolescents; 20.9–30.2% in adults); generally dose-related and usually transient, with a median duration of 10–16 days
- Diarrhea common, also dry mouth, constipation, vomiting, abdominal discomfort, dyspepsia, and flatulence
- Liver test abnormalities in a small proportion of patients (less than 1%) on long-term vortioxetine therapy but elevations are usually mild, asymptomatic, and transient, reversing even with continuation of medication. No instances of acute liver injury with jaundice attributable to vortioxetine reported, but the total experience with its use has been limited

Urogenital & Sexual Effects

- Impact on sexual dysfunction appears to be dose related; limited comparative evidence suggests rates are likely lower relative to SSRIs of SNRIs when using 5–10 mg/day
- When trials used the ASEX rating scale to evaluate sexual dysfunction in patients without baseline sexual dysfunction, rates were higher: Incidence of treatment-related sexual dysfunction (TRSD) across the dosing range was 22–34% for females and 16–29% for men

Hypersensitivity Reactions

- Rash and urticaria reported infrequently
- Rare post-marketing reports of angioedema and allergic dermatitis

Other Adverse Effects

- Generalized pruritus, hyperhidrosis, nasopharyngitis, and arthralgia relatively common
- Toothache (pediatric open label study)
- Upper respiratory infection (pediatric open label study)
- Hemoptysis, cough, and chest pain (case report)

D/C Discontinuation Syndrome

- In clinical trials, vortioxetine doses of 10 mg, 15 mg, and 20 mg daily were abruptly discontinued, with non-significant differences in the Discontinuation–Emergent Signs and Symptoms checklist total scores vs. placebo (likely explained by long elimination half-life)
- However, because of individual variation and sensitivity, some may still experience withdrawal symptoms. Most likely to occur within the first week after drug stopped or dose drastically reduced, and typically disappears within 1 week

☞ **THEREFORE THIS MEDICATION SHOULD BE WITHDRAWN GRADUALLY AFTER PROLONGED USE**

Management

- Reinstitute the drug at a lower dose and taper more gradually

Precautions

- Strong CYP2D6 inhibitors can result in elevated plasma levels of vortioxetine. Vortioxetine should be reduced by 50% in the presence of strong inhibitors such as bupropion, fluoxetine, and paroxetine

- Although CYP3A4 is not a primary metabolic pathway, the product label recommends increasing the dose of vortioxetine when a strong CYP3A4 inducer such as carbamazepine, phenytoin or rifampin is co-administered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose
- Contraindicated in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days. Using MAOIs within 21 days of stopping treatment with vortioxetine is also contraindicated
- As with other serotonergic antidepressants, serotonin syndrome (see p. 59) may occur with vortioxetine, both when taken alone and especially when co-administered with other serotonergic agents. If such symptoms occur, discontinue the medications and initiate supportive treatment. If concomitant use of vortioxetine with other serotonergic drugs is clinically warranted (note that linezolid or intravenous methylene blue use is specifically mentioned as a contraindication), patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases
- As with other antidepressants, vortioxetine should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy
- Treatment with medications that inhibit the serotonin transporter may be associated with abnormal bleeding, particularly when combined with NSAIDs, ASA or other medications that affect coagulation

Toxicity

- Ingestion of vortioxetine in the dose range of 40–75 mg in adults has caused an aggravation of the following adverse reactions: Nausea, postural dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing. Management of overdose should consist of treating clinical symptoms and relevant monitoring

Use in Pregnancy◊

- In a case series of 17 pregnancies, there were three miscarriages, two terminations, and one still birth in vortioxetine treated mothers. In a single case report, a healthy baby was delivered following 1 month of exposure to vortioxetine 5 mg
- Adverse events were observed in animal reproduction studies. Non-teratogenic effects in the newborn following serotonergic exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyperreflexia, jitteriness, irritability, constant crying, and tremor. In the majority of instances, such complications began immediately or soon (less than 24 h) after delivery. Symptoms may be due to the toxicity of serotonergic antidepressants or a discontinuation syndrome – although no specific reports of such exist to date related specifically to vortioxetine exposure, it may be a possibility
- Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension (PPHN) in the newborn. Although no studies have investigated the association of PPHN with vortioxetine treatment, this potential risk cannot be ruled out, taking into account the related mechanism of action (increase in serotonin concentrations)

Breast Milk

- An exclusively breastfed infant would receive weight-adjusted dosages of 1.1% for 10 mg and 1.7% for 20 mg vortioxetine
- No reports of adverse reactions in three breastfed infants (1, 2, and 6 months of age)

Nursing Implications

- Psychotherapy and education are also important in the treatment of depression
- Monitor therapy by watching for adverse side effects and mood and activity level changes, including worsening of suicidal thoughts; keep physician informed
- Be aware that as the medication reduces the degree of depression it may increase psychomotor activity; this may create concern about suicidal behavior
- Expect a lag time of up to 28 days before antidepressant effects are noticed
- Reassure patient that most early side effects usually subside after the first few weeks; if dizzy, patient should get up from lying or sitting position slowly and dangle legs over edge of bed before getting up
- Excessive use of caffeinated foods, drugs, or beverages may increase anxiety and agitation and confuse the diagnosis
- Should not be stopped suddenly due to risk of precipitating withdrawal reactions
- May cause false positive results for urine methadone depending on the assay used

Patient Instructions

- For detailed patient instructions on vortioxetine, see the Patient and Caregiver Information Sheet (details p. 429)

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Serotonin Modulator and Stimulator (SMS) (cont.)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Antibiotic	Linezolid	May enhance serotonergic effect. May increase risk for serotonin syndrome (see Precautions)
Anticoagulant	Apixaban, dabigatran, rivaroxaban, warfarin	Increased risk of bleeding; increased prothrombin ratio or INR response due to decreased platelet aggregation secondary to depletion of serotonin in platelets
Antidepressant		
SSRI	Fluoxetine, paroxetine	May increase vortioxetine levels significantly. Recommend reducing dose by 50% when combining with these strong CYP2D6 inhibitors
NDRI	Bupropion	May increase vortioxetine levels significantly. Recommend reducing dose by 50% when combining Case report of enhancing vortioxetine efficacy and tolerability, and reducing tablet quantity and cost in a patient with OCD
Antifungal	Fluconazole, ketoconazole	Moderate to strong CYP2C9/2C19/3A4 inhibitors can increase AUC and C_{max} of vortioxetine only modestly (15–46%), therefore no dosage adjustment is recommended but monitoring may be warranted
CYP450 inducers	Carbamazepine, phenytoin, rifampin	May reduce vortioxetine levels due to CYP3A4 induction Strong CYP inducer rifampin decreased the exposure of vortioxetine by 72%
CYP450 inhibitors	Protease inhibitors, quinidine	Strong CYP2D6 inhibitors can increase vortioxetine levels significantly. Recommend reducing vortioxetine dose by 50% when combining
DDAVP (desmopressin)		Increased risk of hyponatremia if combined with vortioxetine
Diuretic	Hydrochlorothiazide	Increased risk of hyponatremia if combined with vortioxetine
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome (see Precautions)
NSAID	ASA, ibuprofen, naproxen	Increased risk of abnormal bleeding
Opioid	Dextromethorphan, meperidine, tramadol	Increased risk of serotonin syndrome
St. John's wort		May augment serotonergic effects and cause serotonin syndrome. AVOID combination May reduce vortioxetine levels due to CYP3A4 induction

Noradrenergic/Specific Serotonergic Antidepressant (NaSSA)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Mirtazapine	Tetracyclic agent	Norepinephrine, serotonin/Multimodal	Remeron	Tablets: 7.5 mg[B], 15 mg, 30 mg, 45 mg	Safety and efficacy not established in children and adolescents under
			Remeron SolTab[B], Remeron RD[C]	Oral disintegrating tablets: 15 mg, 30 mg, 45 mg	

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparation may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications in children and adolescents
- Anorexia nervosa – negative case-control study
- Anxiety – a pilot double-blind RCT showed no benefit over placebo in patients 5–17 years old with autism
- Catatonia – case report of improvement in catatonia and mood in an adolescent with MDD and catatonia

In adults:

- 👍 Major depressive disorder (MDD) (with or without comorbid anxiety)
- SSRI-induced sexual dysfunction and "poop-out" syndrome (see p. 53) may be mitigated by mirtazapine
- Panic disorder, generalized anxiety disorder, social anxiety disorder, somatoform disorder, OCD[62], PTSD, persistent depressive disorder, and pre-menstrual dysphoric disorder – preliminary reports of efficacy[63]
- Autism spectrum disorder (ASD) – open-label study suggests improvement in symptoms of aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia
- Schizophrenia – mirtazapine may benefit negative symptoms; sexual dysfunction (orgasmic dysfunction) due to first-generation antipsychotic use[64]
- Akathisia – double-blind RCT showed improvement with addition of low-dose (15 mg) mirtazapine
- Substance use disorder (methamphetamine) – addition of mirtazapine to substance use counseling decreased methamphetamine use among active users and was associated with decreases in sexual risk taking despite low to moderate medication adherence
- Catatonia – case report of improvement in a patient with MDD
- Agitation in dementia – negative double-blind RCT
- Fibromyalgia – a study of 430 adults with fibromyalgia showed mirtazapine (15 mg daily for one week, then 30 mg daily) decreased pain by 30% from baseline and there was an improvement in pain-related quality of life[65]
- Insomnia
- Nausea/vomiting, refractory gastroparesis, functional dyspepsia, appetite stimulation
- Prevention of postspinal anesthesia shivering in gynecological surgeries – positive RCT

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Noradrenergic/Specific Serotonergic Antidepressant (NaSSA) (cont.)

General Comments

- Reduces sleep latency and prolongs sleep duration due to H_1 and 5-$HT_{2A/C}$ blockade – may be helpful in treating depression with prominent insomnia or agitation
- Has mild anxiolytic/sedating effects at lower doses
- A Cochrane review found mirtazapine was more effective at 2 weeks and at the end of acute-phase treatment than SSRIs and venlafaxine and was more likely to cause weight gain or increased appetite and somnolence than SSRIs but less likely to cause nausea or vomiting and sexual dysfunction
- Monitor all patients for worsening depression and suicidal thinking

Pharmacology

- Presynaptic α_2-adrenergic antagonist effects, which result in increased release of norepinephrine and serotonin. It is also a potent antagonist of 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and H_1 receptors and a moderate peripheral α_1-adrenergic and muscarinic antagonist; it does not inhibit the reuptake of norepinephrine or serotonin

Dosing

- See p. 135
- Initiate at 7.5–15 mg daily for a minimum of one week before considering further dose increases since mirtazapine has a half-life of 20–40 h. Dosing should be individualized, and approved dosing range for adults with MDD is 15–45 mg daily
- The dose is best administered at bedtime, daytime sedation can be minimized by slow titration

Pharmacokinetics

- Bioavailability is approximately 50% due to gut wall and hepatic first-pass metabolism; food slightly decreases absorption rate
- Oral disintegrating tablets dissolve on the tongue within 30 seconds; can be swallowed with or without water, chewed, or allowed to dissolve
- Peak plasma level achieved in 2 h
- Protein binding of 85%
- Extensively metabolized via CYP1A2, 2D6, and 3A4; desmethyl metabolite has some clinical activity
- Half-life 20–40 h – significantly longer in females than in males
- Hepatic clearance decreased by 40% in patients with cirrhosis
- Clearance reduced by 30–50% in patients with renal impairment

Onset & Duration of Action

- Therapeutic effect is typically seen after 28 days (though some effects may be seen sooner), especially on symptoms related to sleep and appetite
- Meta-analysis of double-blind trials in adults with depression suggests an earlier onset of efficacy with mirtazapine than with SSRIs although no difference in number of responders at study end[62]

Adverse Effects

- See p. 131
- Somnolence, hyperphagia, and weight gain are the most commonly reported side effects[63]

CNS Effects

- Fatigue, sedation in over 30% of patients; less sedation at doses above 15 mg due to increased effect on α_2 receptors and increased release of NE (based on limited evidence)
- Shown to impair driving performance and decreased psychomotor functioning during acute treatment phase although a prospective randomized study in depressed patients using a simulator showed a significant improvement in performance and decrease in crash rates
- Insomnia, agitation, hostility, depersonalization, restlessness, and nervousness reported occasionally, coupled with urges of self-harm or harm to others
- Increases slow-wave sleep and decreases stage 1 sleep. Reported to shorten sleep onset latency, improve sleep efficiency and increase total sleep time; vivid dreams reported; case reports of REM sleep behavior disorder with hallucinations and confusion; case report of somnambulism on dose increase

- Case report of panic attack during dose escalation
- Rarely delirium, hallucinations, psychosis
- Seizures (very rare – 0.04%)
- Restless legs syndrome (case report)

Anticholinergic Effects

- Dry mouth frequent; thirst, constipation [for treatment suggestions see Nonselective Cyclic Antidepressants, p. 105]
- Increased sweating, blurred vision, and urinary retention reported rarely

Cardiovascular Effects

- Hypotension, hypertension, vertigo, tachycardia, and palpitations reported rarely
- Edema 1–2%
- QTc prolongation and torsades de pointes reported, with most cases in association with overdose or in patients with other risk factors for QTc prolongation, including concomitant use of QTc-prolonging medication

Endocrine & Metabolic Effects

- Carbohydrate craving, increased appetite and leptin concentrations, and weight gain (of over 4 kg) reported in over 16% of patients (due to potent antihistaminic properties); occur primarily in the first 4 weeks of treatment and may be dose related – may be of benefit in depressed patients with marked anorexia
- May be less likely than SSRIs to cause SIADH/hyponatremia
- Increases in plasma cholesterol, to over 20% above the upper limit of normal, seen in 15% of patients; increases in non-fasting triglyceride levels (7%)

GI Effects

- Rare reports of bitter taste, dyspepsia, nausea, vomiting, and diarrhea
- Decreased appetite and weight loss occasionally reported

Other Adverse Effects

- Sexual dysfunction occurs occasionally; risk increased with age, use of higher doses, and concomitant medication
- Rates of sexual dysfunction in a naturalistic study were citalopram 60%, venlafaxine 54.5%, paroxetine 54.2%, fluoxetine 46.2%, and mirtazapine 18.2%
- Increased sweating
- Rare reports of tremor, hot flashes
- Transient elevation of ALT reported in about 2% of patients; cases of hepatitis
- Febrile neutropenia (1.5% risk) and agranulocytosis (0.1%) reported; monitor WBC if patient develops signs of infection [some recommend testing CBC at baseline and annually]
- Cases of joint pain or worsening of arthritis reported
- Myalgia and flu-like symptoms in 2–5% of patients
- Case of palinopsia reported
- Cases of pancreatitis and of gall-bladder disorder
- Cases of rhabdomyolysis reported with mirtazapine used alone, in combination with risperidone, and in overdose
- Reports of venous thromboembolism including deep vein thrombosis
- Cases of paradoxical tremors, akathisia, dystonia, and dyskinesia reported

D/C Discontinuation Syndrome

- Abrupt discontinuation may cause a syndrome consisting of dizziness, lethargy, nausea, vomiting, diarrhea, headache, fever, sweating, chills, malaise, incoordination, insomnia, vivid dreams, myalgia, paresthesias, dyskinesias, "electric-shock-like" sensations, visual discoordination, anxiety, irritability, confusion, slowed thinking, disorientation; rarely aggression, impulsivity, hypomania, and depersonalization
- Most likely to occur within 1–7 days after drug stopped or dose drastically reduced, and typically disappears within 3 weeks
- Case report of hypomania, akathisia, and panic attack

☞ **THEREFORE THIS MEDICATION SHOULD BE WITHDRAWN GRADUALLY AFTER PROLONGED USE**

Management

- Reinstitute drug at a lower dose and taper gradually over several days

Noradrenergic/Specific Serotonergic Antidepressant (NaSSA) (cont.)

Precautions

- May cause suicidal ideation, hostility, and psychomotor agitation in children and adolescents. Monitor all patients for worsening depression and suicidal thinking
- Cases of QT prolongation and torsades de pointes; caution in patients with risk factors such as known cardiovascular disease, family history of QT prolongation, and concomitant use of QT-prolonging medications
- Caution in patients with compromised liver function or renal impairment
- Monitor WBC if patient develops signs of infection; a low WBC requires discontinuation of therapy
- May induce manic reactions in patients with bipolar disorder and rarely in unipolar depression
- While mirtazapine does not inhibit the serotonin transporter, there appears to be a slightly elevated risk of GI bleeding in adult patients compared to patient not taking antidepressants (OR = 1.17, 95% CI 1.01–1.38)[66]

Toxicity

- Low liability for toxicity in overdose if taken alone; CNS depression with disorientation and prolonged sedation with tachycardia and changes in blood pressure
- Post-marketing reports of QTc prolongation and torsades de pointes in overdose
- A retrospective case analysis of 117 overdoses (median dose 450 mg) found that 30% experienced tachycardia but no significant ECG changes, no increased risk of seizures; 28% experienced drowsiness or reduced level of consciousness, no specific treatment required

Use in Pregnancy◊

- Limited data suggest no major teratogenic effects in humans
- Although some evidence suggests higher rate of spontaneous abortions, preterm births, and low birth weight, no adjustment has been made for depressive symptoms, a known risk factor
- No long-term outcome data or evidence available on neonatal abstinence syndrome

Breast Milk

- Mirtazapine and its metabolite are secreted into breast milk in low concentrations (e.g., 1.9% of the maternal weight-adjusted dose)
- Very limited information regarding outcomes, no apparent short-term adverse effects but small sample size (less than 50 published cases) makes overall safety index unknown. Not enough data available to come to a conclusion on the safety of mirtazapine during lactation[67]
- If a patient is breastfeeding and requires the addition of an antidepressant, other agents may be preferable as first-line options; however, maternal use of mirtazapine is not considered a reason to discontinue breastfeeding

Nursing Implications

- Psychotherapy and education are also important in the treatment of depression
- Monitor therapy by watching for adverse effects and mood and activity level changes, including worsening of suicidal thoughts
- Signs and symptoms of infections (e.g., sore throat, fever, mouth sores, elevated temperature) should be reported to the physician as soon as possible
- Because mirtazapine can cause drowsiness, caution patient not to perform activities requiring mental alertness until response to this drug has been determined
- Mirtazapine should not be stopped suddenly due to risk of precipitating a withdrawal reaction

Patient Instructions

- For detailed patient instructions on mirtazapine, see Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Class of Drug	Example	Interaction Effects
Antibiotic	Linezolid	Monitor for increased serotonergic and noradrenergic effects due to linezolid's weak MAO inhibition
Anticoagulant	Warfarin	May increase INR; monitor
α_2 adrenergic agonist	Clonidine, guanfacine	Antihypertensive effect may be antagonized by mirtazapine
Anticonvulsant	Carbamazepine, phenytoin	Decreased plasma level of mirtazapine by 60% with carbamazepine and 46% with phenytoin due to induction of metabolism via CYP3A4
Antidepressant		
SSRI	Fluoxetine, sertraline	Combination reported to alleviate insomnia and augment antidepressant response; may have activating effects May mitigate SSRI-induced sexual dysfunction and "poop-out" syndrome Three cases of patients developing restless legs syndrome after taking mirtazapine and fluoxetine
	Fluvoxamine	Increased serotonergic effects possible; case reports of increased mirtazapine concentrations (3- to 4-fold) Increased sedation and weight gain reported with combination
SNRI	Venlafaxine	Increased plasma level of mirtazapine (3- to 4-fold) due to inhibited metabolism Case report of serotonin syndrome (see p. 59)
SARI	Trazodone	Case report of priapism lasting 19 h with combined use; previously tolerated each agent as monotherapy
Irreversible MAOI	Phenelzine, tranylcypromine	Possible serotonergic reaction; DO NOT COMBINE
Irreversible MAO-B inhibitor	Rasagiline, selegiline	Possible serotonergic reaction
Antiemetic (5-HT$_3$ antagonist)	Dolasetron, granisetron, ondansetron	Case reports of serotonin syndrome
Antifungal	Ketoconazole	Increased peak plasma levels of mirtazapine (by about 40%)
Antipsychotic	Olanzapine	Case report of status epilepticus with mirtazapine and olanzapine; and of serotonin syndrome with mirtazapine, tramadol, and olanzapine Potential for additive metabolic adverse effects (e.g., increased cholesterol, sedation) and increased appetite
CNS depressant	Alcohol, benzodiazepines, opioid analgesics, etc.	Impaired cognition and motor performance
H$_2$ antagonist	Cimetidine	Increased serum levels of mirtazapine (by 61%), dose adjustments of mirtazapine may be required
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome
Opioid	Dextromethorphan, meperidine, tramadol	Increased risk of serotonin syndrome
Smoking (tobacco)		Significantly decreased levels of mirtazapine
Stimulant	Dextroamphetamine, methylphenidate, phentermine	May increase agitation and risk of mania, especially in patients with bipolar disorder
St. John's wort		May augment serotonergic effects and cause serotonin syndrome. AVOID combination May reduce mirtazapine levels due to CYP3A4 induction

Nonselective Cyclic Antidepressants

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Amitriptyline[D]	Tricyclic antidepressant (TCA)	Serotonin, norepinephrine/Multimodal	Elavil	Tablets: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg[B]	Not recommended in children under age 12
Clomipramine	Tricyclic antidepressant (TCA)	Serotonin, norepinephrine/ Reuptake inhibitor	Anafranil	Tablets[C]: 10 mg, 25 mg, 50 mg Capsules: 25 mg, 50 mg, 75 mg[B]	Approved in children age 10 and older for OCD Safety and efficacy not established for other disorders
Desipramine	Tricyclic antidepressant (TCA)	Norepinephrine/Reuptake inhibitor	Norpramin	Tablets: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg[B]	Safety and efficacy not established in children and adolescents under age 18
Doxepin	Tricyclic antidepressant (TCA)	Norepinephrine, serotonin/Multimodal	Sinequan	Capsules: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg[B] Oral concentrate[B]: 10 mg/mL	Not recommended in children under age 12
			Silenor	Tablets: 3 mg, 6 mg	Safety and efficacy not established in children and adolescents under age 18
			Zonalon[B],[E]	5% topical cream	Safety and efficacy not established in children and adolescents under age 18
Imipramine hydrochloride	Tricyclic antidepressant (TCA)	Serotonin, norepinephrine/ Reuptake inhibitor	Tofranil	Tablets: 10 mg, 25 mg, 50 mg, 75 mg[C]	Approved in children age 6 and older for enuresis Safety and efficacy not established for other disorders
Imipramine pamoate	Tricyclic antidepressant (TCA)	Serotonin, norepinephrine/ Reuptake inhibitor	Tofranil PM[B]	Capsules: 75 mg, 100 mg, 125 mg, 150 mg	Safety and efficacy not established in children and adolescents under age 18
Nortriptyline	Tricyclic antidepressant (TCA)	Norepinephrine/Reuptake inhibitor	Aventyl[C], Pamelor[B]	Capsules: 10 mg, 25 mg, 50 mg[B], 75 mg[B] Oral solution[B]: 10 mg/5 mL	Safety and efficacy not established in children and adolescents under age 18
Protriptyline[B]	Tricyclic antidepressant (TCA)	Norepinephrine/Reuptake inhibitor	Vivactil	Tablets: 5 mg, 10 mg	Safety and efficacy not established in children and adolescents under age 18
Trimipramine	Tricyclic antidepressant (TCA)	Serotonin, dopamine/Antagonist	Surmontil	Tablets[C]: 12.5 mg, 25 mg, 50 mg, 100 mg Capsules: 25 mg[B], 50 mg[B], 75 mg[C], 100 mg[B]	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Available in combination with perphenazine and also in combination with chlordiazepoxide in the USA, [E] Indicated for moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus

Indications‡ (👍 approved)

In children and adolescents:

- 👍 OCD in children age 10 and older (clomipramine)
- 👍 Enuresis in children age 6 and older (imipramine)
- Tricyclics have been tried in pediatric patients with variable success in treating the following:
  - ADHD – a 2014 Cochrane Review concluded that desipramine improves core symptoms of ADHD, but cautioned against its mainstream use due to potential cardiac effects[68]
  - MDD – a 2013 Cochrane Review concluded that tricyclic drugs are not useful in treating depression in children and had only marginal evidence to support the use of tricyclic drugs to treat depression in adolescents[69]
  - Obsessive-compulsive disorder (OCD)
  - Panic disorder
  - Separation anxiety disorder
  - Bulimia nervosa
  - Tourette's disorder (clomipramine)
  - Prophylaxis for migraine headaches – a NIH-funded study found no difference in migraine reduction between amitriptyline, topiramate, or placebo (CHAMP study)[70, 71]

In adults (selected indications):

- 👍 Major depressive disorder (MDD): Acute treatment and maintenance (amitriptyline, desipramine, imipramine, nortriptyline; clomipramine – Canada only); treatment resistant (doxepin)
- 👍 Secondary depression in other mental illnesses (e.g., schizophrenia, dementia)
- 👍 Bipolar disorder: Depressed phase (desipramine, doxepin)
- 👍 Obsessive-compulsive disorder (OCD) (clomipramine)
- 👍 Enuresis (imipramine)
- 👍 Depression and/or anxiety associated with alcoholism or organic disease (doxepin)
- 👍 Psychoneuroses with MDD (doxepin)
- 👍 Insomnia (doxepin marketed in low dose, i.e., 3 and 6 mg at bedtime, for difficulty with sleep maintenance)
- Panic disorder with or without agoraphobia (clomipramine, imipramine)
- Persistent depressive disorder – efficacy reported (imipramine, desipramine)
- Depression, poststroke (nortriptyline)
- Posttraumatic stress disorder (PTSD) – efficacy against intrusive symptoms reported
- Generalized anxiety disorder (GAD) (imipramine)
- Bulimia nervosa (desipramine, imipramine)
- ADHD not responsive to other agents
- Premenstrual dysphoric disorder (clomipramine, nortriptyline)
- Sialorrhea induced by clozapine (amitriptyline)
- Smoking cessation (nortriptyline), alone or in combination with nicotine patch. Nortriptyline (25–75 mg/day) appears as effective as bupropion for smoking cessation and has been recommended as second-line therapy for treating smoking dependence
- Pain management, including migraine prophylaxis, neuropathic pain, diabetic neuropathy, postherpetic neuralgia, chronic oral-facial pain, and adjuvant analgesic; may help with sleep problems associated with fibromyalgia and other pain syndromes (i.e., amitriptyline)
- Temporomandibular joint disorders
- Premature ejaculation (clomipramine)
- Interstitial cystitis (amitriptyline)
- Functional dyspepsia (amitriptyline)
- Irritable bowel syndrome (amitriptyline, desipramine, imipramine, nortriptyline)

General Comments

- In patients with risk of suicide, treatment selection should consider safety in overdose (i.e., consider using newer antidepressants rather than nonselective cyclic and MAOIs). Prescription quantities should be consistent with safe patient care

‡ Indications listed here do not necessarily apply to all nonselective cyclic antidepressants or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Nonselective Cyclic Antidepressants (cont.)

- Meta-analysis of double-blind RCTs of tricyclics for treating MDD in pediatric patients suggested that those treated with tricyclics had a similar response to patients assigned to the placebo arm of the studies[72]
- Prior to treatment, a baseline ECG is recommended. When an effective daily dose is reached, a steady-state serum level and ECG should be done. Consider a follow-up ECG at any dose change and a plasma level every few months
- The US FDA defines the following ECG and examination values as unsafe in children treated with tricyclics: (a) PR interval above 200 ms, (b) QRS interval more than 30% above a baseline (or over 120 ms), (c) BP above 140 mmHg systolic or 90 mmHg diastolic, (d) Heart rate above 130 beats/min at rest
- Sudden death (rare) reported with desipramine, even with therapeutic plasma levels; plasma levels may be higher by 42% in children than adults at the same dose
- Studies suggest improved outcomes in panic disorder with combination of imipramine and psychotherapy (adults)
- Presence of hallucinations or delusions are negative predictors of response to TCAs

Pharmacology

- Exact mechanism of action unknown; equilibrate the effects of biogenic amines through various mechanisms (such as reuptake blockade); tertiary amine agents (amitriptyline, clomipramine, doxepin, imipramine, trimipramine) have greater affinity for serotonin transporter blockade; secondary amine agents (desipramine, nortriptyline, protriptyline) have greater affinity for norepinephrine transporter blockade
- Cause downregulation of β-adrenergic receptors
- The action in the treatment of enuresis may involve inhibition of urination due to the anticholinergic effect and CNS stimulation, resulting in easier arousal by the stimulus of a full bladder
- Low-dose doxepin's histamine (H_1) blockade enables its use as a sedative and in urticaria
- Tricyclics may exert analgesic effects through blockade of sodium channels

Dosing

- There is a wide variation in dosage requirements (partially dependent on plasma levels) (see p. 135)
- Adults: Start drug at a low dose (10–25 mg) and increase gradually by 10–25 mg every 4–5 days to a maximum dose of 3–5 mg/kg (tricyclics) based on side effects – TCAs demonstrate a dose-response relationship
- Children: In pain disorders such as migraine headaches, start amitriptyline at 0.25 mg/kg/day and increase up to 1 mg/kg/day
- Once steady state is reached, give drug as a single bedtime dose; use divided doses if patient develops nightmares. An exception to bedtime dosing can be made for protriptyline, which is usually given in the morning
- Prophylaxis is most effective if therapeutic dose is maintained
- Imipramine pamoate is mg equivalent to imipramine hydrochloride in dosage; imipramine pamoate should not be used in children for its higher risk of acute overdose due to the high unit potency (i.e., 75 mg, 100 mg, 125 mg and 150 mg capsules)
- Hepatic disease: CAUTION may require a lower dosage
- Renal disease: CAUTION may require a lower dosage

Pharmacokinetics

- See p. 135
- Completely absorbed from the GI tract
- Large percentage metabolized by first-pass effect
- Metabolized primarily by the liver (e.g., CYP2D6); inhibition or use in poor metabolizers may experience up to 8-fold increase in plasma concentrations, resulting in increased adverse effects (e.g., cardiac toxicity, anticholinergic, etc.)
- Highly lipophilic; concentrated primarily in myocardial and cerebral tissue
- Highly bound to plasma protein
- Most tricyclics have linear pharmacokinetics, i.e., a change in dose leads to a proportional change in plasma concentration; occasional case of non-linear pharmacokinetics reported
- Elimination half-life: See p. 135; steady state reached in about 5 days
- Pharmacokinetics may vary between males and females; data suggest that plasma levels of TCAs may be reduced in female patients prior to menstruation

- Concurrent ingestion of TCAs with high-fiber foods or laxatives (e.g., bran, psyllium) can result in decreased absorption of the antidepressant
- Amitriptyline is metabolized to nortriptyline; they have equal antidepressant activity

Onset & Duration of Action

- Tricyclics and related drugs are long acting; they may be given in a single daily dose, usually at bedtime (except protriptyline, which is usually given in the morning)
- Therapeutic effect is typically seen after 4 weeks (though some patients may respond sooner)
- Sedative effects are seen within a few hours of oral administration, with lessened sleep disturbance after a few days
- Occasionally patients may report loss of antidepressant response or "poop-out syndrome" [Management: Check compliance with therapy; optimize dose (plasma level may be useful); may need to change drug]

Adverse Effects

- The pharmacological and side effect profile of cyclic antidepressants is dependent on their affinity for and activity on neurotransmitters/receptors (see table p. 128)
- See chart p. 130 for incidence of adverse effects at therapeutic doses of specific agents; incidence of adverse effects may be greater in early days of treatment; patients adapt to many side effects over time

CNS Effects

- A result of antagonism at histamine H_1 receptors and α_1 adrenoreceptors
- Drowsiness is the most common side effect; weakness, lethargy, and fatigue occur. Conversely, excitement, agitation, restlessness, and insomnia have been reported
- Secondary amines reduce sleep efficiency and increase wake time after sleep onset; tertiary amines improve sleep continuity; decrease REM sleep (except for trimipramine); vivid dreaming or nightmares can occur, especially if all the medication is given at bedtime
- Confusion, disturbed concentration, disorientation, delirium, delusions, and hallucinations can occur (especially with higher doses)
- Dizziness
- Headache
- Precipitation of hypomania or mania (in patients with a history of bipolar disorder – less frequent in patients receiving mood stabilizers), episode acceleration (in up to 67% of patients), psychosis, panic reactions, anxiety or euphoria may occur
- Anxiety, euphoria, panic reactions, and hostility may occur
- Fine tremor, dose-dependent
- Disturbance in gait, parkinsonism, and dystonia
- Akathisia; can also occur following abrupt drug withdrawal; reported with imipramine and desipramine
- Tinnitus – more likely with serotonergic agents
- Paresthesias reported with tricyclics (approximate risk 4%)
- Myoclonus – more likely with serotonergic agents; includes muscle jerks of lower extremities, jaw, and arms, and nocturnal myoclonus – may be severe in up to 9% of patients [If severe, clonazepam, valproate or carbamazepine may be of benefit]
- Seizures (more common in children with autism spectrum disorder and patients with eating disorder) can occur following abrupt drug increase or after drug withdrawal; risk increases with high plasma levels; case of status epilepticus in a child with frontal lobe epilepsy symptoms mistaken for anxiety and parasomnia (imipramine)
- Dysphasia, stuttering

Anticholinergic Effects

- A result of antagonism at muscarinic receptors (ACh)
- Common side effects associated with TCAs
- Dry mucous membranes; may predispose patient to monilial infections and dental caries [Management: Sugar-free gum and candy, oral lubricants (e.g., MoiStir, OraCare D), pilocarpine tablets (10–15 mg/day) or mouthwash (4 drops of 4% solution to 12 drops water swished in mouth and spat out), bethanechol; oral hygiene]
- Blurred vision
- Dry eyes [Management: Artificial tears, but employ caution with patients wearing contact lenses; these patients manage dry eyes with their usual wetting solutions or comfort drops]
- TCAs can induce or exacerbate existing hiatus hernia; TCAs should be discontinued if gastroesophageal reflux develops
- Constipation (frequent in children on therapy for enuresis) [Management: Increase bulk and fluid intake, fecal softener, bulk laxative, PEG 3350]
- Urinary retention, delayed micturition [Management: Bethanechol 10–30 mg tid]

Nonselective Cyclic Antidepressants (cont.)

- Confusion, disturbed concentration, disorientation, delirium, delusions, and hallucinations (especially with higher doses)
- Hyperthermia; increased risk when combined with other anticholinergics or drugs that affect thermoregulation

Cardiovascular Effects

- A result of antagonism at α_1 adrenoreceptors, muscarinic, 5-HT_2, and H_1 receptors and inhibition of fast sodium channels
- Risk increases with high plasma levels
- Prolonged conduction time by delaying the inward sodium current into cardiomyocytes, thereby slowing cardiac depolarization and lengthening the QTc interval; contraindicated in heart block or post-myocardial infarction. Nortriptyline may not affect the QTc interval at therapeutic doses
- Orthostatic hypotension [Management: Sodium chloride tablets, caffeine, fludrocortisone (0.1 mg/day), midodrine (2.5–5 mg tid), use of support stockings]
- May cause hypertension in patients with bulimia
- Tachycardia; may be more pronounced in younger patients
- Arrhythmias, syncope, thrombosis, thrombophlebitis, stroke, and congestive heart failure have been reported on occasion

Endocrine & Metabolic Effects

- Both increases and decreases in blood sugar levels reported
- Weight gain (in up to 30% of patients with chronic use; average gain of up to 7 kg (adults) – weight gain is linear over time and is often accompanied by a craving for sweets) [Management: Nutritional counseling, exercise, dose reduction, changing antidepressant]
- Hyperprolactinemia, menstrual irregularities, amenorrhea, and galactorrhea (clomipramine)
- Can induce SIADH with hyponatremia; rare in children and adolescents

GI Effects

- A result of inhibition of 5-HT uptake and ACh antagonism
- Anorexia, nausea, vomiting, and diarrhea
- Increased pancreatic enzymes
- Constipation (see Anticholinergic Effects, p. 105)
- Peculiar taste, "black tongue," glossitis

Urogenital & Sexual Effects

- A result of altered dopamine activity, 5-HT_2 blockade, inhibition of 5-HT reuptake, α_1 blockade, and ACh blockade
- Decreased libido, impotence, and anorgasmia
- Testicular swelling, painful ejaculation, retrograde ejaculation, increased libido, and priapism; spontaneous orgasm with yawning (clomipramine)
- Breast engorgement and breast tissue enlargement in males and females

Hypersensitivity Reactions

- Rare
- Drug fever, edema, erythema, petechiae, pruritus, rash, urticaria
- Photosensitivity, skin hyperpigmentation (imipramine (13 case reports)[73], desipramine)
- Rarely agranulocytosis, eosinophilia, leukopenia, purpura, and thrombocytopenia

Other Adverse Effects

- Asymptomatic increases in aminotransferases, jaundice, hepatitis
- Excessive sweating [Management: Daily showering; in severe cases: Drysol solution, terazosin 1–10 mg daily, oxybutynin up to 5 mg bid, clonidine 0.1 mg bid; drug may need to be changed]
- Rare reports of alopecia

D/C Discontinuation Syndrome

- Occurs most frequently with clomipramine; likely due to removal of serotonergic activity; cholinergic and adrenergic rebound may also contribute
- Abrupt withdrawal from high doses may cause a "flu-like" syndrome consisting of fever, fatigue, sweating, coryza, malaise, myalgia, headache; anxiety, agitation, hypomania or mania, insomnia, vivid dreams, as well as dizziness, nausea, vomiting; akathisia and dyskinesia also reported
- Most likely to occur 24–48 h after withdrawal, or after a large dosage decrease
- Paradoxical mood changes reported on abrupt withdrawal, including hypomania or mania

☞ **THESE MEDICATIONS SHOULD THEREFORE BE WITHDRAWN GRADUALLY AFTER PROLONGED USE**

Management

- Reinstitute drug (at slightly lower dose) and gradually taper dose over several days (e.g., by 25 mg every 3–5 days)
- Alternatively, can treat specific symptoms:

- Cholinergic rebound (e.g., nausea, vomiting, sweating) [Management: Ginger, benztropine 0.5–2 mg prn]
- Anxiety, agitation, insomnia [Management: Benzodiazepine 0.5–2 mg prn, lorazepam 0.5–2 mg prn]
- Neurological symptoms: Akathisia [Management: Propranolol 10–20 mg tid to qid]; dyskinesia [Management: Clonazepam 0.5–2 mg prn]; dystonia [Management: Benztropine 0.5–2 mg prn]

Precautions

- The therapeutic margin is low (lethal dose is about 3 times the maximum therapeutic dose); prescribe limited quantities
- **Contraindicated**
  - Within 14 days of stopping an MAOI
  - If hypersensitive to TCAs
  - In acute recovery phase of myocardial infarction and in heart block
- May lower the seizure threshold; therefore, administer cautiously to patients with a history of convulsive disorders, eating disorder, organic brain disease or a predisposition to convulsions (e.g., alcohol withdrawal)
- Patients with existing cardiovascular disease
- Patients in whom excess anticholinergic activity could be harmful (e.g., prostatic hypertrophy, urinary retention, narrow-angle glaucoma)
- Patients with respiratory difficulties, since antidepressants with anticholinergic properties can dry up bronchial secretions and make breathing more difficult
- May impair the mental and physical ability to perform hazardous tasks (e.g., driving a car or operating machinery); will potentiate the effects of alcohol
- May induce manic reactions in up to 50% of patients with bipolar disorder (BD); because of risk of increased cycling, BD is a relative contraindication
- Combination of cyclic antidepressants with SSRIs can lead to increased plasma level of the cyclic antidepressant. Combination therapy has been used in the treatment of resistant patients; use of serotonergic cyclic antidepressants with SSRIs can cause serotonin syndrome (see p. 59)

Toxicity

- Overdose can cause higher rates of hospitalization and fatality in comparison to other antidepressants
- Symptoms of toxicity are extensions of the common adverse effects: Anticholinergic, CNS stimulation followed by CNS depression, myoclonus, hallucinations, respiratory depression, and seizures
- Cardiac irregularities occur and are most hazardous; duration of QRS complex on the electrocardiogram (ECG) reflects the severity of the overdose; if it equals or exceeds 0.12 sec, it should be considered a danger sign (normal range 0.08–0.11 sec); TCA poisoning is evident by arrhythmia (both tachyarrhythmias and bradyarrhythmias) and hypotension; QT prolongation possibly leading to torsade de pointes; life-threatening arrhythmias are typically the final cause of death
- Patients with cardiac disease, eating disorders or renal disease, as well as children are more susceptible to TCA cardiotoxicity
- Hypoxia, electrolyte abnormalities, and/or acid–base imbalances can occur

Management

- Hospitalize; monitor and provide supportive treatment
- Activated charcoal (25–100 g if patient presents within 2 h); in cardiac arrest patients, there will be decreased splanchnic circulation, thus decreased absorption; when there is return of spontaneous circulation, there may be a repeat absorption of the ingested TCA; thus activated charcoal should still be given after the 2-hour window has passed
- DO NOT GIVE IPECAC due to possibility of rapid neurological deterioration and high incidence of seizures
- Benzodiazepines should be used for seizures; Diazepam IV is the drug of choice for convulsions
- Main treatment for severe or life-threatening toxicity is hypertonic sodium bicarbonate; it narrows QRS complex, improves blood pressure and acidemia, and helps control ventricular arrhythmias

Use in Pregnancy◊

- Clomipramine, nortriptyline, and possibly others cross the placenta
- Neonatal withdrawal syndrome may develop in 20–50% of neonates due to *in utero* TCA exposure; withdrawal symptoms may include insomnia, temperature instability, convulsions, tachypnea, dyspnea, restlessness, arrhythmias, emesis, tachycardia, aberrant stool, urine retention, decreased tone, cyanosis, apathy, unstable blood pressure, and agitation
- Fetal malformations and developmental delay reported in children of mothers who received TCAs during pregnancy
- Avoid TCAs during first trimester if possible

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Nonselective Cyclic Antidepressants (cont.)

- Urinary retention in neonate has been associated with antidepressant use in third trimester
- Dosage required to achieve therapeutic plasma level may increase during the third trimester
- A meta-analysis of TCA exposure during pregnancy demonstrated no significant increase in spontaneous abortion rate[74]

Breast Milk

- TCAs are secreted into breast milk and it is estimated that the baby will receive up to 4% of the mother's dose (relative infant dose; conservative safety cutoff suggested to be 5% for psychotropics); infant serum levels are generally low or undetectable; half-life of antidepressant is increased in neonate 3- to 4-fold
- Nortriptyline is one of the preferred antidepressants – relative infant dose of ~ 1.3%; 44 breastfed infants (newborn to 3.5 months old) had no adverse effects with maternal dosages of 25–175 mg/day; 27 of these infants were followed between 15–71 months and found to have normal growth and development
- Amitriptyline – relative infant dose of ~ 1%; 23 breastfed infants had no adverse effects with maternal dosages of 75–175 mg/day; one case of a 15-day-old infant developing extreme drowsiness whose mother was taking 10 mg/day
- Clomipramine – relative infant dose of ~ 1.3%; cases of breastfed infants having no adverse effects on growth and development (studied up to 71 months of age) with maternal dosages of 75–175 mg/day. In a case series of 10 infants experiencing neonatal withdrawal syndrome (maternal dosages of 37.5–125 mg/day throughout pregnancy), there were no difference in withdrawal symptoms between breastfed and non-breastfed infants, likely due to small amount of drug that is excreted into breast milk
- Imipramine – relative infant dose of ~ 2.9%; 30 breastfed infants were followed for 15 days to 3 years in 5 studies and found to have normal growth and development with maternal dosages of 25–225 mg/day
- Doxepin is contraindicated in breastfeeding; metabolite concentration reported to reach similar plasma level in infant as in mother; two case reports of adverse effects in breastfed infants (i.e., a 9-day-old infant had poor sucking and swallowing, hypotonia, vomiting, and weight loss; an 8-week old infant had drowsiness and respiratory depression) and only one report of no adverse effects. Maternal use of topical doxepin cream is likely compatible as long as it is applied away from the breasts so that the infant cannot ingest the drug directly

Nursing Implications

- Psychotherapy and education are also important in the treatment of MDD
- Monitor therapy by watching for adverse side effects and mood and activity level changes; keep physician informed
- Be aware that the medication reduces the degree of depression and may increase psychomotor activity; this may create concern about suicidal behavior
- Expect a lag time of 4 weeks before antidepressant effects will be noticed
- Check for constipation; increase fluids and increase bulk in diet to lessen constipation; instruct the patient to avoid ingesting high-fiber foods or laxatives (e.g., bran, psyllium) concurrently with medication, as this may reduce the antidepressant level
- Reassure patient that drowsiness and dizziness usually subside after first few weeks; if dizzy, patient should get up from lying or sitting position slowly, and dangle legs over edge of bed before getting up
- Because these medications can cause sedation, caution patient not to perform activities requiring alertness until response to the drug has been determined
- Expect a dry mouth; suggest frequent mouth rinsing with water, and sour or sugarless hard candy or gum
- Artificial tears may be useful for patients who complain of dry eyes (or wetting solutions for those wearing contact lenses)
- Monitor for urinary retention
- Excessive use of caffeinated foods, drugs, or beverages may increase anxiety and agitation and confuse the diagnosis
- Caution patient not to stop the drug suddenly due to risk of precipitating a withdrawal reaction

Patient Instructions

- For detailed patient instructions on cyclic antidepressants, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
ACE inhibitor	Enalapril	Increased plasma level of clomipramine due to decreased metabolism
Alcohol		Short-term or acute use reduces first-pass metabolism of antidepressant and increases its plasma level; chronic use induces metabolizing enzymes and decreases its plasma level Increased sedation, CNS depression
Anesthetic	Enflurane	Report of seizures with amitriptyline
Antiarrhythmic	Procainamide, propafenone, quinidine	Increased TCA plasma level due to CYP2D6 inhibition
Antibiotic	Linezolid	Monitor for increased serotonergic and noradrenergic effects due to linezolid's weak MAO inhibition
	Macrolides	Additive QT prolongation, arrhythmia
	Rifampin	Decreased plasma level of antidepressant due to induction of CYP metabolism
Anticholinergic	Antihistamines, antiparkinsonian agents, antipsychotics	Increased anticholinergic effect; may increase risk of hyperthermia, confusion, urinary retention, dry mouth, blurred vision, constipation
Anticoagulant	Apixaban, dabigatran, rivaroxaban	Increased risk of bleeding possible with serotonergic agents
	Warfarin	Increased international normalized ratio (INR) with tricyclics
Anticonvulsant	Carbamazepine, barbiturates, phenytoin	Decreased plasma level of tricyclics due to enzyme induction; increased levels of carbamazepine
	Divalproex, valproate, valproic acid	Increased TCA plasma level
	Phenobarbital	Increased plasma level of phenobarbital with clomipramine
Antidepressant		
SSRI	Citalopram, escitalopram	Possible additive prolongation of QTc interval
	Fluvoxamine	Via CYP1A2 inhibition, fluvoxamine reduces conversion of clomipramine to desmethylclomipramine (adrenergic/cardiotoxic metabolite) and is sometimes co-prescribed intentionally for this effect
	Fluoxetine, paroxetine, sertraline	Elevated TCA plasma level (due to release from protein binding and inhibition of oxidative metabolism); monitor plasma level and for signs of toxicity
NDRI	Bupropion	Elevated imipramine level (by 57%), desipramine level (by 82%), and nortriptyline level (by 200%) with combination via CYP2D6 inhibition by bupropion Combined use lowers seizure threshold
Irreversible MAOI	Isocarboxazid, phenelzine, selegiline, tranylcypromine	If used together, do not add cyclic antidepressants to MAOI: Start cyclic antidepressant first or simultaneously with MAOI; for patients already on MAOI, discontinue MAOI 10–14 days before starting combination therapy Serotonin syndrome and deaths have been reported. DO NOT COMBINE
Antifungal	Fluconazole, ketoconazole	Increased TCA plasma level due to inhibited metabolism (89% with amitriptyline; 70% with nortriptyline); 20% increase with imipramine and no increase with desipramine
	Terbinafine	Increased TCA plasma level due to CYP2D6 inhibition
Antihistamine	Diphenhydramine	Increased TCA plasma level possible (e.g., amitriptyline, desipramine, clomipramine, imipramine) due to inhibition of CYP2D6 metabolism Additive CNS effects and anticholinergic effects
Antihypertensive	Clonidine, guanfacine, methyldopa	Decreased antihypertensive effect due to inhibition of α-adrenergic receptors Abrupt discontinuation of clonidine may precipitate hypertensive crisis
	Acetazolamide, thiazide diuretics	Hypotension augmented
	Labetalol	Increased plasma level of imipramine (by 54%) and desipramine

Nonselective Cyclic Antidepressants (cont.)

Class of Drug	Example	Interaction Effects
Antipsychotic		
First generation	Chlorpromazine, fluphenazine, haloperidol, perphenazine, pimozide, thioridazine, zuclopenthixol	Haloperidol and phenothiazines may increase TCA plasma level. TCAs may increase the plasma level of chlorpromazine. Clinical significance unknown DO NOT COMBINE pimozide or thioridazine with TCAs; NOT recommended with phenothiazines or zuclopenthixol CAUTION with all other FGAs. Possible additive prolongation of QTc interval and associated life-threatening cardiac arrhythmias Additive sedation, hypotension, and anticholinergic effects
Second generation	Clozapine	Possible serotonin syndrome reported in a patient taking clomipramine following the withdrawal of clozapine
	Quetiapine, ziprasidone	Possible additive prolongation of QTc interval
Anxiolytic	Alprazolam	Increased plasma levels of desipramine and imipramine with alprazolam (by 20% and 31%, respectively)
	Buspirone	Concomitant use of serotonergic agents (clomipramine, amitriptyline) increases the risk of serotonin syndrome
	Triazolam	Desipramine and triazolam: Report of hypothermia (neither drug causes this effect alone); triazolam potentiates anorexic effect of desipramine
Calcium channel blocker	Diltiazem, verapamil	Increased imipramine plasma level (by 30% and 15%, respectively); increased level of trimipramine
	Nifedipine	May antagonize the efficacy of antidepressant drugs
Cannabis/marijuana		Case reports of tachycardia, lightheadedness, confusion, mood lability, and delirium with nortriptyline and desipramine May evoke cardiac complications in youth
CNS depressant	Alcohol, antihistamines, benzodiazepines, hypnotics	Increased sedation, CNS depression
Cholestyramine		Decreased absorption of antidepressant due to binding by cholestyramine, if given together
Evening primrose oil		May lower seizure threshold
Grapefruit juice		Decreased conversion of clomipramine to metabolite due to inhibition of CYP3A4
H_2 antagonist	Cimetidine	Increased plasma level of antidepressant; for desipramine, inhibition of hydroxylation occurs only in rapid metabolizers
Hormone	Estrogen/progesterone oral contraceptive	Increased TCA plasma level due to decreased metabolism Reduced clearance of combined oral contraceptive possible with amitriptyline due to inhibited metabolism
Insulin		Decreased insulin sensitivity reported with amitriptyline
Lithium		Additive antidepressant effect, may increase risk of neurotoxicity
L-tryptophan		Additive effects in treatment-resistant patients May potentiate the risk of serotonin syndrome. Monitor for increased serotonergic effects
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome
Opioid	Codeine	Marked inhibition of conversion of codeine to morphine (active moiety) with amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline
	Dextromethorphan	Increased risk of serotonin syndrome
	Meperidine, tramadol	Increased risk of seizures and serotonin syndrome
	Methadone	Increased plasma level of desipramine (by about 108%) Potential for additive QTc prolongation
	Morphine	Enhanced analgesic effect

Class of Drug	Example	Interaction Effects
Oxybutynin		Increased metabolism of clomipramine (may be due to induction of CYP3A4) and additive anticholinergic effects
Protease inhibitor	Ritonavir	Increased TCA plasma level due to decreased metabolism (AUC of desipramine increased by 145%; peak plasma level increased by 22%)
Proton pump inhibitor	Omeprazole	Increased TCA plasma level due to inhibited metabolism
Stimulant	Methylphenidate	TCA plasma level may be increased Used together to augment antidepressant effect and response to symptoms of ADHD Cardiovascular effects increased with combination, in children – monitor Case reports of neurotoxic effects with imipramine, but considered rare – monitor Decreased seizure threshold Elevated heart rate and diastolic pressure (by 20–30%); increased risk of arrhythmia
St. John's wort		Decreased amitriptyline concentration May augment serotonergic effects and cause serotonin syndrome. AVOID combination
Sulfonylurea	Glyburide	Increased hypoglycemia
Sympathomimetic	Epinephrine, norepinephrine (levarterenol), phenylephrine Isoproterenol	Enhanced pressor response from 2- to 8-fold; benefit may outweigh risks in anaphylaxis May increase likelihood of arrhythmias
Tamoxifen		Decreased plasma level of doxepin (by 25%), possibly due to induced metabolism via CYP3A4
Triptan	Sumatriptan, zolmitriptan	Possible risk of serotonin syndrome when combined with TCAs with serotonergic activity (e.g., clomipramine)
Zolpidem		Case report of visual hallucinations in combination with desipramine In one study, 5 of 8 patients on imipramine experienced anterograde amnesia

Monoamine Oxidase Inhibitors

General Comments

- Monoamine oxidase inhibitors can be classified as follows:

Chemical Class	Agent	Page
Reversible Inhibitor of MAO-A (RIMA)	Moclobemide[C]	See p. 112
Irreversible MAO (A&B) Inhibitors (MAOIs)	Isocarboxazid[B] Phenelzine Tranylcypromine	See p. 115 See p. 115 See p. 115
Irreversible MAO-B inhibitor	Selegiline	See p. 122

[B] Not marketed in Canada, [C] Not marketed in the USA

Reversible Inhibitor of MAO-A (RIMA)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name(A)	Dosage Forms and Strengths	Monograph Statement
Moclobemide(C)	Reversible Inhibitor of MAO-A (RIMA)	Serotonin, norepinephrine, dopamine/ Enzyme inhibitor	Manerix	Tablets: 100 mg, 150 mg, 300 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), (A) Generic preparations may be available, (C) Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications in children and adolescents; moclobemide has almost no data in children and adolescents and should be limited in its use

In adults:

- 👍 Major depressive disorder (MDD)
- Persistent depressive disorder
- Seasonal affective disorder (SAD), chronic fatigue syndrome, and obsessive-compulsive disorder (OCD) – weak evidence suggests efficacy
- Social anxiety disorder
- ADHD – open label studies
- Betel-quid (betel nut) use disorder – preliminary findings

General Comments

- Safety and efficacy in children and adolescents have not been adequately studied
- Increases REM sleep

Pharmacology

- Inhibits the action of MAO-A enzyme that metabolizes the neurotransmitters serotonin, norepinephrine, and dopamine; in chronic doses over 400 mg daily, will produce 20–30% inhibition of MAO-B in platelets
- Inhibition is reversible within 24 h
- Combined therapy with cyclic antidepressants or lithium may increase antidepressant effect

Dosing

- Starting dose: 75–100 mg daily; further increase should wait at least 1 week, as bioavailability increases over the first week. Usual dose range: 150–600 mg daily in divided doses
- Should be taken after meals to minimize tyramine-related responses (e.g., headache)
- Hepatic disease: Decreases clearance [Management: Reduce dose by 50–66% in patients with severe hepatic impairment]
- Renal disease: Use with caution, does not affect dosing

Pharmacokinetics

- See p. 136
- Rapidly absorbed from gut, high first-pass effect with absorption increasing from 50% with first dose to approximately 90% after 2 weeks
- Relatively lipophilic, but at low pH is highly water-soluble
- Low plasma-protein binding (50% – albumin)
- Peak level seen between 0.7 and 1.1 h in the absence and presence of food, respectively
- Plasma level increases in proportion to dose; blockade of MAO-A correlates with plasma concentration

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

- Metabolized by oxidation; partial metabolism primarily via CYP2C19
- Elimination half-life 1–3 h; clearance decreased as dosage increased because of auto-inhibition or metabolite-induced inhibition
- Moclobemide may inhibit its own metabolism or a metabolite may inhibit the metabolism of the parent compound

Onset & Duration of Action

- Therapeutic effects are typically seen after 28 days

Adverse Effects

- See table p. 132

CNS Effects

- Most common: Insomnia, sedation, headache, and dizziness
- Increased stimulation (restlessness, anxiety, agitation, and aggression) can occur – dose related
- Hypomania reported, especially in patients with bipolar disorder
- Tremor

Anticholinergic Effects

- Dry mouth, blurred vision

Cardiovascular Effects

- Hypotension, tachycardia

Endocrine & Metabolic Effects

- Reports of galactorrhea in females; increased prolactin levels in males
- Both weight loss and weight gain

GI Effects

- Nausea, vomiting, abdominal pain, and constipation

Urogenital & Sexual Effects

- Incidence of sexual dysfunction (24% compared to 62% for SSRIs) in adults[75]

D/C Discontinuation Syndrome

- Case report of moclobemide discontinuation syndrome presenting with influenza-like symptoms (muscle cramps, shivering, neck pain, headache, nausea, hot flush without fever)

Precautions

- Hypertensive patients should avoid ingesting large quantities of tyramine-rich foods
- Hypertensive reactions may occur in patients with thyrotoxicosis or pheochromocytoma
- Use caution when combining with serotonergic drugs as serotonin syndrome has been reported (see p. 59) with CNS irritability, increased muscle tone, myoclonus, diaphoresis, and elevated temperature (see Interactions, p. 114)
- Reduce dose by 50–66% in patients with severe liver impairment

Toxicity

- Symptoms same as adverse effects, but intensified: Drowsiness, disorientation, stupor, hypotension, tachycardia, hyperreflexia, grimacing, sweating, agitation, and hallucinations; serotonin syndrome reported, convulsions
- Fatalities have occurred when combined with citalopram or clomipramine in overdose

Management

- Gastric lavage, emesis, activated charcoal may be of benefit
- Monitor vital functions, supportive treatment

Use in Pregnancy◊

- Data on safety in pregnancy is lacking
- Animal studies have not shown any particular adverse effects on reproduction

Breast Milk

- Moclobemide is secreted into breast milk at about 1–4% of maternal dose
- Nine breastfed infants with maternal dosages of 150–900 mg/day had no adverse effects in weight gain, milestones, and behavioral effects
- Four breastfed infants with maternal dosages of 300–1200 mg/day were followed up in the neonatal period and at 1 year postpartum; one infant developed severe gastroesophageal reflux, thus stopped breastfeeding at 2 months; two infants breastfed beyond 12 months

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Reversible Inhibitor of MAO-A (RIMA) (cont.)

Nursing Implications

- If patient has difficulty sleeping, ensure last dose of moclobemide is no later than 1700 h
- It is not necessary to maintain a special diet when moclobemide is prescribed in low to moderate doses; however, excessive amounts of foods with high tyramine content can lead to blood pressure risk and headache (see lists pp. 119–120)
- Administer moclobemide after food to minimize side effects; a big meal should not be consumed after taking moclobemide
- Warn patient not to self-medicate with over-the-counter drugs or herbal preparations, but to consult physician or pharmacist to prevent drug-drug interactions
- Patients should be instructed to recognize signs of hypertensive crisis (e.g., headache, neck stiffness, palpitations, etc.)

Patient Instructions

- For detailed patient instructions on moclobemide, see the Patient and Caregiver Information Sheet (details p. 429)

Food Interactions

- No particular precautions are required with low to moderate doses; however, excessive consumption of tyramine-containing food should be avoided to minimize hypertension risk
- Adults prescribed doses above 600 mg/day should minimize the use of tyramine-rich foods (see lists pp. 119–120)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Anesthetic	Spinal/local anesthetics containing epinephrine	Stop antidepressant two days prior to anesthetic use
Antibiotic	Linezolid	Monitor for increased serotonergic and noradrenergic effects due to linezolid's weak MAO inhibition; AVOID concomitant use
Anticholinergic	Antiparkinsonian drugs	Increased atropine-like effects
Antidepressant	General	MAOIs may enhance the adverse effects of other antidepressants
SSRI	Citalopram, escitalopram, fluoxetine, fluvoxamine	Use cautiously and monitor for serotonergic adverse effects, especially with citalopram and escitalopram Higher incidence of insomnia may occur; increased headache reported with fluvoxamine Fluoxetine and fluvoxamine can inhibit the metabolism of moclobemide
NDRI	Bupropion	Enhanced neurotoxic (central adrenergic) and hypertensive effects; AVOID
SNRI, SARI	Nefazodone, venlafaxine	Enhanced effects of serotonin and/or norepinephrine; no data on safety with combination
Nonselective cyclic	Desipramine, nortriptyline	Additive antidepressant effect in treatment-resistant patients Potentiation of weight gain, hypotension, and anticholinergic effects; use cautiously and monitor for serotonergic adverse effects
	Clomipramine	Enhanced serotonergic effects – AVOID
Irreversible MAOI	Phenelzine, tranylcypromine	Concurrent use CONTRAINDICATED
Antipsychotic	Chlorpromazine, clozapine, methotrimeprazine, quetiapine	Additive hypotension, particularly with low-potency FGAs such as chlorpromazine. Start with a lower dose of antipsychotic, titrate slowly, and monitor for orthostatic hypotension Antipsychotics may enhance serotonergic effects resulting in serotonin syndrome
Anxiolytic	Buspirone	Buspirone may increase the adverse effects of MAOIs (e.g., increased blood pressure); AVOID MAOIs may potentiate the activity of buspirone via inhibition of serotonin metabolism; serotonergic reaction possible
H_2 antagonist	Cimetidine	Decreased metabolism of moclobemide; plasma level can double
Lithium		Additive antidepressant effect in treatment-resistant patients

Class of Drug	Example	Interaction Effects
L-tryptophan		Serotonin syndrome possible; AVOID (see p. 59)
MAO-B inhibitor	Selegiline	CAUTION with combination; dietary restrictions recommended as both A + B MAO enzymes will be inhibited
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome
Opioids and related drugs	Dextromethorphan, pentazocine	Vertigo, tremor, nausea, and vomiting reported; increased risk of serotonin syndrome – AVOID COMBINATION
	Meperidine	Serotonergic reaction/syndrome, increased restlessness; death reported with meperidine – AVOID COMBINATION
	Tramadol	May enhance neuroexcitatory effects, increasing the risk of seizures and serotonin syndrome
Selective norepinephrine reuptake inhibitor	Atomoxetine	MAOIs may enhance the neurotoxic effects of atomoxetine; AVOID
Stimulant	Amphetamine, methylphenidate	Increased blood pressure and enhanced effects if used over prolonged periods or at high doses; AVOID
St. John's wort		May augment serotonergic effects and cause serotonin syndrome. AVOID
Sympathomimetic	Amphetamine, ephedrine, epinephrine L-dopa, methylphenidate, salbutamol	Increased blood pressure and enhanced effects if used over prolonged periods or at high doses; AVOID
Triptan	Rizatriptan	Decreased metabolism of rizatriptan; AUC and peak plasma level increased by 119% and 41%, respectively, and AUC of metabolite increased by 400%
	Sumatriptan, zolmitriptan	Possibly increased serotonergic effects

Irreversible Monoamine Oxidase (A&B) Inhibitors (MAOIs)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Isocarboxazid[B]	Hydrazine derivative	Serotonin, norepinephrine, dopamine/ Enzyme inhibitor	Marplan	Tablets: 10 mg	Not recommended in children and adolescents under age 16
Phenelzine	Hydrazine derivative	Serotonin, norepinephrine, dopamine/ Enzyme inhibitor	Nardil	Tablets: 15 mg	Safety and efficacy not established in children and adolescents under age 18 Not recommended under age 16 in Canada
Tranylcypromine	Non-hydrazine derivative	Serotonin, norepinephrine, dopamine/ Enzyme inhibitor	Parnate	Tablets: 10 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada

Indications‡ (👍 approved)

In children and adolescents:

- 👍 Major depressive disorder (MDD) unresponsive to other antidepressants (USA: isocarboxazid in age 16 and over)
- Almost no pediatric or adolescent data exists for monoamine oxidase inhibitors, so they should be used very rarely

‡ Indications listed here do not necessarily apply to all MAOIs or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Irreversible Monoamine Oxidase (A&B) Inhibitors (MAOIs) (cont.)

In adults:

- Depression, atypical
- Major depressive disorder (MDD) unresponsive to other antidepressants
- Bipolar depression, atypical (anergic)
- MDD in patients with borderline personality disorder
- Persistent depressive disorder
- Phobia: Phobic anxiety states or social anxiety disorder
- Panic disorder: Prophylaxis
- Obsessive-compulsive disorder (OCD)
- Posttraumatic stress disorder (PTSD) – efficacy reported (phenelzine)
- Generalized anxiety disorder (GAD) – positive case report (tranylcypromine)
- Schizophrenia, chronic: May improve negative symptoms
- Herpes: Possible antiherpetic effect
- Prostate cancer (recurrent, hormone-sensitive) – open-label study (phenelzine)

General Comments

- Safety and efficacy in children and adolescents have not been adequately studied
- Ability of patient to adhere to dietary and drug restrictions should be assessed before prescribing
- Monitor BP and heart rate
- Combined therapy with cyclic antidepressants or lithium may increase antidepressant effect but caution as combination has resulted in serotonin syndrome and malignant hyperpyrexia

Pharmacology

- Nonselective inhibition of MAO-A and -B enzymes, which are involved in oxidative deamination of serotonin, norepinephrine, and dopamine; cause down-regulation of β-adrenoceptors
- MAOI enzyme inhibition is irreversible and lasts about 10 days
- Tranylcypromine is a structural analogue of amphetamine; higher doses can have more amphetamine-like effects

Dosing

- See p. 136
- Due to short half-life, bid or more frequent dosing required (see individual agents); give doses in the morning and mid-day to avoid overstimulation and insomnia (occasionally cause sedation)
- Percentage of MAO enzyme inhibited is related to dose
- Hepatic disease – AVOID
- Renal disease – CAUTION, may require lower doses

Pharmacokinetics

- See p. 136
- Rapidly absorbed from the GI tract, metabolized by the liver and excreted almost entirely in the urine
- Peak plasma level of tranylcypromine occurs within 1–2 h and correlates with elevations in supine blood pressure, orthostatic drop of systolic blood pressure, and rise in pulse rate. Blood pressure elevation correlates with dose
- With long-term use, irreversible MAOIs can impair own metabolism, resulting in nonlinear pharmacokinetics and potential for drug accumulation

Onset & Duration of Action

- May require up to 2 weeks to reach maximum MAO inhibition
- Duration of MAO inhibition can be up to 2 weeks after discontinuation of phenelzine; 10 days for tranylcypromine
- Energizing effect often seen within a few days
- Tolerance to anti-panic effects reported

Adverse Effects

• See p. 132

CNS Effects

- Most common: Dizziness, drowsiness, (phenelzine most sedating), fatigue, headache (without blood pressure increase), hyperreflexia, and sleep disturbance that can occur early on [Management: Slowing dosage titration, dividing dosing, bedtime dosing]
- Other symptoms include akathisia, confusion, disorientation, memory loss, and nystagmus
- Stimulant effect includes agitation, anxiety, hyperexcitability, manic symptoms, precipitation of psychosis, and restlessness (may be more prevalent with higher doses of tranylcypromine)
- Increased sleep onset latency and reduced sleep efficiency; REM sleep decreased and may be eliminated at start of therapy, rebound REM of up to 250% above baseline reported on drug withdrawal
- Hypomania and mania: In patients with bipolar disorder, risk up to 35%; lower risk with concomitant use of a mood stabilizer; in MDD, risk about 4%
- Paresthesias or "electric-shock-like" sensations; carpal tunnel syndrome (numbness) reported; may be due to vitamin B6 deficiency [Management: Pyridoxine 50–150 mg/day]
- Myoclonic jerks, especially during sleep (10–15%), tremor, muscle tension, cramps, akathisia (dose-related) [cyproheptadine may be helpful for cramps or jerks; clonazepam or valproate are useful for nocturnal myoclonus]
- Drug dependence, addiction (case reports with tranylcypromine)

Anticholinergic Effects

- Constipation common [Management: Increase bulk and fluid intake, fecal softener, bulk laxative, PEG 3350]
- Dry mouth
- Urinary retention

Cardiovascular Effects

- Dizziness, weakness, orthostatic hypotension – usually temporary but if persistent, may need to discontinue drug [Management: Fludrocortisone 0.1–0.2 mg/day]
- Occasionally, hypertensive patients may experience a rise in blood pressure
- Edema in lower extremities [Management: Restrict sodium; support hose; amiloride 5–10 mg/day up to bid, frequent monitoring for hypotension]

Hematological Effects

- Normocytic, normochromic anemia, agranulocytosis, thrombocytopenia, and neutropenia reported

Endocrine & Metabolic Effects

- Hyponatremia and SIADH reported
- Increased appetite and weight gain
- Hypoglycemia reported
- Increased prolactin (phenelzine, tranylcypromine) and galactorrhea (phenelzine) reported

GI Effects

- Most common are anorexia, nausea, and vomiting

Urogenital & Sexual Effects

- Urinary frequency, incontinence, and retention reported
- Impotence, anorgasmia, decreased libido, ejaculation difficulties [Management: See SSRIs p. 58]
- May diminish sperm count
- Rarely priapism

Other Adverse Effects

- Elevated transaminase levels; rare reports of liver toxicity
- Rare reports of hair loss with tranylcypromine

Hypertensive Crisis

- Can occur with irreversible MAOIs due to ingestion of incompatible foods (containing substantial levels of tyramine) or drugs (see lists pp. 119–120)
- Not related to dose of drug

Signs and Symptoms

- Occipital headache, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils and photophobia, sudden nose bleed, tachycardia, bradycardia, and constricting chest pain
- Case reports of intracranial hemorrhage due to hypertensive crisis in patients on tranylcypromine ingesting tyramine containing food (e.g., cheeses, aged meats, soy sauce, beer)

Management

- Withhold medication and notify physician immediately
- Monitor vital signs, clinical status, and ECG

Irreversible Monoamine Oxidase (A&B) Inhibitors (MAOIs) (cont.)

- Sublingual captopril 12.5–25 mg may decrease blood pressure (occasionally drastically – monitor)
- Phentolamine is an alternative parenteral treatment
- Patient should stand and walk, rather than lie down, during a hypertensive reaction; BP will drop somewhat

D/C Discontinuation Syndrome

- Occurs occasionally 1–4 days after abrupt withdrawal
- Reports of muscle weakness, swift relapse of depression, agitation, vivid nightmares, headache, palpitations, nausea, sweating, irritability, and myoclonic jerking; acute organic psychosis with visual, auditory, and tactile hallucinations reported (phenelzine); delirium reported (high dose of tranylcypromine)
- REM rebound occurs (up to 250% above baseline)
- Maintain dietary and drug restrictions for at least 10 days after stopping MAOI

Precautions

- **Monitor for worsening of depression or suicidal ideation, especially during initiation of therapy or with dose changes**
- CONTRAINDICATED in patients with history of liver disease or abnormal liver function tests
- Should not be administered to patients with cerebrovascular disease, cardiovascular disease, or history of hypertension
- Use with caution in patients with hyperthyroidism, impaired renal function, or history of seizures
- Should not be used alone in patients with marked psychomotor agitation
- When changing from one MAOI to another, or to a tricyclic antidepressant, allow a minimum of 10 medication-free days
- Discontinue at least 10–14 days before an incompatible drug or food is given
- Discontinue at least 7–10 days before elective surgery (tranylcypromine: 7 days; phenelzine, isocarboxazid: 10 days); may also want to discontinue use prior to ECT
- Hypertensive crisis can occur if given concurrently with certain drugs or foods (see lists pp. 119–120)
- Use caution when combining with serotonergic drugs as serotonin syndrome has been reported (see p. 59)

Toxicity

- Symptoms same as side effects but intensified
- Severe cases progress to extreme dizziness and shock due to effects on cardiac conduction
- Overdose, whether accidental or intentional, can be fatal: Patient may be symptom-free up to 6 h, then progress to restlessness-coma-death – therefore, close medical supervision is indicated for 48 h following an overdose

Use in Pregnancy◊

- The human pregnancy experience is too limited to adequately assess the risk of MAOIs; however, increased incidence of malformations shown with use in first trimester. Recommend to AVOID MAOI use during pregnancy
- Case reports of tranylcypromine combined with other psychotropic drugs demonstrated fetal death and fetal autopsy revealing facial dysmorphism, ocular hypertelorism, cardiac defects, atrio-ventricular septal defect, and placental infarct

Breast Milk

- Limited data on tranylcypromine, phenelzine, or isocarboxazid in breastfeeding; molecular weight is low enough to expect excretion into breast milk; other antidepressants are preferred in breastfeeding
- Tranylcypromine – a breastfed infant with maternal dosage of 100–120 mg/day developed abdominal distension and feeding intolerance at 2 weeks; mother was also taking pimozide, diazepam, and alprazolam during pregnancy and postpartum; symptoms resolved upon discontinuation of breastfeeding

Nursing Implications

- Advise patients to inform other physicians and their dentist that they are taking a MAOI
- Educate patient regarding foods and drugs to avoid; a diet sheet should be provided for each patient
- Warn patient not to self-medicate with over-the-counter drugs or herbal preparations, but to consult physician or pharmacist to prevent drug-drug interactions

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

- Monitor BP, heart rate, diet, and weight; orthostatic hypotension is common
- Educate patient to report headache; measure pulse and blood pressure, and report increases to physician immediately
- If patient has difficulty sleeping, ensure last dose of MAOI is no later than 1500 h
- Assess each patient's risk for abuse and misuse prior to prescribing tranylcypromine and monitor for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy

Patient Instructions

- For detailed patient instructions on MAOIs, see the Patient and Caregiver Information Sheet (details p. 429)

Food Interactions

There are many serious food and drug interactions that may precipitate a hypertensive crisis; maintain dietary and drug restrictions for at least 10 days after stopping MAOI

☞ **MAKE SURE ALL FOOD IS FRESH, STORED PROPERLY, AND EATEN SOON AFTER BEING PURCHASED – refrigerated products will show an increase in tyramine content after several days**

- Never consume food that is fermented or possibly "off"
- Avoid restaurant sauces, gravy, and soup

Foods to avoid (high tyramine content):

- All matured or aged cheeses (e.g., camembert, cheddar, blue, brie, Roquefort, Stilton)
- Broad bean pods (e.g., Fava) – contain dopamine
- Concentrated yeast extracts (e.g., Marmite)
- Dried salted fish, pickled herring
- Packet soup (especially miso)
- Fermented or pickled vegetables (e.g., sauerkraut, kimchi)
- Aged/smoked meats – sausage (especially salami, mortadella, pastrami, summer sausage), other unrefrigerated fermented meats, game meat that has been hung, liver
- Soy sauce or soybean condiments, tofu, tempeh
- Tap (draft) beer, unpasteurized beer (includes beer with visible sediments); tyramine contents similar regardless of alcohol content/nonalcoholic
- Improperly stored or spoiled meats, poultry or fish

It is SAFE to use in moderate amounts (only if fresh):

- Cottage cheese, cream cheese, farmer's cheese, processed cheese (e.g., American cheese slices, Cheez Whiz), ricotta, Havarti, Boursin, brie without rind, gorgonzola
- Liver (as long as it is fresh), fresh or processed meats (e.g., hot dogs, bologna), poultry, or fish
- Sour cream
- Soy milk
- Salad dressings
- Worcestershire sauce
- Yeast-leavened bread

Reactions have also been reported with the following (moderate tyramine content) – use moderately with caution:

- Smoked fish, caviar, snails, tinned fish, shrimp paste
- Yogurt
- Meat tenderizers
- Homemade red wine, Chianti, canned/bottled beer, sherry, champagne
- Cheeses (e.g., Parmesan, muenster, Swiss, gruyere, mozzarella, feta)
- Pepperoni
- Overripe fruit: Bananas, avocados, raspberries, plums, tomatoes, canned figs or raisins, orange pulp
- Meat extract (e.g., Bovril, Oxo)
- Asian foods
- Spinach, eggplant

Irreversible Monoamine Oxidase (A&B) Inhibitors (MAOIs) (cont.)

Over-the-counter drugs: DO NOT USE without prior consultation with doctor or pharmacist:

- Cold remedies, decongestants (including nasal sprays and drops), some antihistamines and cough medicines containing dextromethorphan or codeine
- Opioid painkillers (e.g., products containing codeine, meperidine, or tramadol)
- All stimulants (Wake-ups, Nodoz)
- All appetite suppressants
- Anti-asthma drugs (Primatine P)
- Sleep aids and sedatives (Sominex, Nytol)
- Yeast, dietary supplements (e.g., Ultrafast, Optifast)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Anesthetic, general		MAOIs may exaggerate the hypotension and CNS effects of anesthetics; discontinue 10 days prior to elective surgery
Antibiotic	Linezolid	Monitor for increased serotonergic and noradrenergic effects due to linezolid's weak MAO inhibition
Anticholinergic	Antiparkinsonian agents, antihistamines	Severe reactions reported, including prolonged and intensifying some anticholinergic effects Increased atropine-like effects
Anticonvulsant	Carbamazepine	Possible decrease in metabolism and increased plasma level of carbamazepine with phenelzine
Antidepressant		Serotonin syndrome and death reported with serotonergic antidepressants; AVOID
SSRI	Fluoxetine, paroxetine, sertraline	Do not use within 5 weeks following fluoxetine treatment and 2 weeks of other SSRIs
NDRI	Bupropion	Metabolism of dopamine inhibited; AVOID
SNRI	Venlafaxine	Metabolism of serotonin and norepinephrine inhibited; AVOID
SARI	Trazodone	Monitor for serotonergic effects
SPARI	Vilazodone	Possible serotonergic reaction; AVOID
SMS	Vortioxetine	Possible serotonergic reaction; AVOID
NaSSA	Mirtazapine	Possible serotonergic reaction; AVOID
Nonselective cyclic	Amitriptyline, desipramine	If used together, do not add cyclic antidepressant to MAOI. Start cyclic antidepressant first or simultaneously with MAOI. For patients already on MAOI, discontinue the MAOI for 10–14 days before starting combination therapy Combined cyclic and MAOI therapy has increased antidepressant effects and will potentiate weight gain, hypotension, and anticholinergic effects Serotonin syndrome and deaths have been reported
	Clomipramine	Serotonin syndrome (see p. 59) reported; AVOID
	Imipramine	Case report of fatal serotonin syndrome with tranylcypromine; AVOID
Antihypertensive	ACE-inhibitors, α-blockers, β-blockers	MAOIs should not be administered with hypotensive agents as marked hypotension may occur
Antipsychotic	General	Additive hypotension and anticholinergic effects
	Quetiapine, ziprasidone	Case reports of serotonin syndrome
Anxiolytic	Buspirone	Several cases of increased blood pressure reported; AVOID; discontinue MAOIs at least 10 days before initiation of buspirone

Class of Drug	Example	Interaction Effects
Atropine		Prolonged action of atropine
CNS depressant	Alcohol, barbiturates, sedatives	May enhance CNS depression
Diuretic	Chlorthalidone, hydrochlorothiazide	MAOIs should not be administered with hypotensive agents as marked hypotension may occur
Ginseng		May cause headache, tremulousness or hypomania; case report of irritability and visual hallucinations with combination
Insulin		Enhanced hypoglycemic response through stimulation of insulin secretion and inhibition of gluconeogenesis
L-dopa		Increase in storage and release of dopamine and/or norepinephrine Headache, hyperexcitability, hypertension, and related symptoms reported
Licorice		Increased serotonergic effects possible
Lithium		Increased serotonergic effects
L-tryptophan		Reports of serotonin syndrome (see p. 59) with hyperreflexia, tremor, myoclonic jerks, and ocular oscillations; AVOID
MAO-B inhibitor	Selegiline	Increased serotonergic effects
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue. Risk for serotonin syndrome (see Precautions)
Muscle relaxant	Succinylcholine	Phenelzine may prolong muscle relaxation by inhibiting metabolism
Nicotine		Low doses of tranylcypromine reported to inhibit nicotine metabolism by competitive inhibition via CYP2A6
Opioids and related drugs	Dextromethorphan, diphenoxylate, meperidine, tramadol Morphine Tramadol	Excitation, sweating, and hypotension reported; may lead to development of encephalopathy, convulsions, coma, respiratory depression, and serotonin syndrome. If an opioid is required, meperidine should not be used; institute other opioids cautiously Case report of serotonin syndrome (see p. 59 with phenelzine Increased risk of seizures and serotonin syndrome
Reserpine		Central excitatory syndrome and hypertension reported due to central and peripheral release of catecholamines
Stimulants	MDMA ("Ecstasy"), MDA Modafinil	Case reports of serotonin syndrome (see p. 59) and hypertensive crisis Two case reports of severe hypertensive crisis and 1 case report of serotonin syndrome (see p. 59) with tranylcypromine
St. John's wort		Increased serotonergic effects possible
Sulfonylureas	Glyburide	Enhanced hypoglycemic response
Sympathomimetic	*Indirect-acting:* amphetamine, dopamine, ephedrine, methylphenidate, pseudoephedrine, tyramine *Direct-acting:* epinephrine, isoproterenol, norepinephrine (levarterenol), salbutamol Phenylephrine	Release of large amounts of norepinephrine with hypertensive reaction; AVOID No interaction Increased pressor response
Tetrabenazine		Central excitatory syndrome and hypertension reported due to central and peripheral release of catecholamines
Triptan	Rizatriptan, sumatriptan, zolmitriptan	Serotonin syndrome (see p. 59); AVOID; recommended that 2 weeks elapse after discontinuing an irreversible MAOI before using triptans

Irreversible MAO-B Inhibitor

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Selegiline	Levo-acetylenic derivative of phenethylamine	Dopamine, norepinephrine, serotonin/ Enzyme inhibitor	Eldepryl Zelapar[B]	Capsules[B]/tablets: 5 mg Orally disintegrating tablets: 1.25 mg	Safety and efficacy not established in children and adolescents under age 18
Selegiline transdermal[B]	Levo-acetylenic derivative of phenethylamine	Dopamine, norepinephrine, serotonin/ Enzyme inhibitor	EMSAM	Transdermal patch: 6 mg/24 h, 9 mg/24 h, 12 mg/24 h	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada

Indications‡ (👍 approved)

In children and adolescents:

- Adolescents – a double-blind, placebo-controlled study of selegiline in depressed adolescents showed no difference between treatment and placebo

In adults:

- 👍 Major depressive disorder (MDD) (patches – USA only)
- 👍 Parkinson's disease (oral) – adjunct for patients who exhibit deterioration in the quality of their response to levodopa with or without carbidopa (USA and Canada), or in newly diagnosed patients before symptoms begin to affect the patient's social or professional life (Canada only)
- Cocaine use: Selegiline may reduce physiological and subjective effects

General Comments

- In patients presenting with depression and a high risk of suicide, treatment selection should consider safety in overdose (i.e., consider using newer antidepressant agents rather than nonselective cyclic, bupropion, and MAOI antidepressants). Prescription quantities should be consistent with safe patient care
- Oral formulation approved in low doses for the treatment of Parkinson's disease; higher doses required for treatment of MDD
- Transdermal patches contain 1 mg of selegiline per cm^2 and deliver approximately 0.3 mg of selegiline per cm^2 over 24 h
- Dietary restrictions are not required at lowest doses; use caution at higher doses as selegiline loses its selectivity for MAO-B inhibition
- May produce false-positive drug screen (*l*-amphetamine metabolites)

Pharmacology

- Transdermal selegiline provides sustained plasma concentrations of the parent compound, increasing the amount of drug delivered to the brain and decreasing metabolite production
- At low doses, selegiline irreversibly inhibits MAO-B, which is involved in oxidative deamination of dopamine in the brain and also inhibits the uptake of dopamine
- At higher doses, selegiline inhibits both MAO-A and B, which are involved in the catabolism of norepinephrine, dopamine, and serotonin. In vivo animal models using the transdermal patch suggest that both MAO-A and MAO-B inhibition is required for antidepressant effects
- The transdermal formulation allows for targeted inhibition of central nervous system MAO-A and MAO-B with minimal effects on MAO-A in the GI (gut wall) and hepatic systems, avoiding first-pass effect, reducing the risk of interactions with tyramine-rich foods
- Induces antioxidant enzymes and decreases the formation of oxygen radicals; it interferes with early apoptotic signaling events induced by various kinds of insults in cell cultures, protecting cells from apoptotic death

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Dosing

- See p. 136
- Transdermal patches should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 h. Avoid using the same site on consecutive days
- The 6 mg/24 h patch is the recommended starting and target dose. If dose increases are indicated for individual patients, they should occur in dose increments of 3 mg/24 h (up to a maximum dose of 12 mg/24 h) at intervals of no less than 2 weeks
- No adjustment in dosage necessary in moderate hepatic or renal insufficiency

Pharmacokinetics

- See p. 136
- On average, 25–30% of the selegiline content is systemically delivered over 24 h (range ~ 10–40%) following dermal application
- Absorption of selegiline is similar when transdermal selegiline is applied to the upper torso or upper thigh; the drug is not metabolized in human skin
- Transdermal selegiline bypasses the GI tract, thus avoids inhibiting MAO-A in the GI tract; patient sensitivity to dietary tyramine is more than 20 times less than with oral tranylcypromine, the effect of avoiding excessive amounts of tyramine entering the bloodstream
- Transdermal dosing avoids extensive first-pass metabolism, resulting in substantially higher selegiline exposure and lower exposure to metabolites compared to oral dosing
- Selegiline is approximately 90% bound to plasma protein
- Steady-state selegiline plasma concentrations are achieved within 5 days of daily dosing
- Extensively metabolized by CYP450 enzymes including CYP2B6, CYP2C9, and CYP3A4/5 and CYP2A6
- Selegiline is initially metabolized via N-dealkylation or N-depropargylation to form N-desmethylselegiline or R(–)-methamphetamine, respectively. Both of these metabolites can be further metabolized to R(–)-amphetamine
- Selegiline and N-desmethylselegiline produce a concentration-dependent inhibition of CYP2D6 at 10–250 micromolar and CYP3A4/5 at 25–250 micromolar; CYP2C19 and CYP2B6 were also inhibited at concentrations $\geq$ 100 micromolar. All inhibitory effects of selegiline and N-desmethylselegiline occurred at concentrations that were several orders of magnitude higher than clinical concentrations
- Mean half-lives of selegiline and its three metabolites, R(−)-N-desmethylselegiline, R(−)-amphetamine, and R(−)-methamphetamine, range from 18 to 25 h

Onset & Duration of Action

- Therapeutic effects are typically seen within 4 weeks; a lack of an antidepressant response within 6–8 weeks may require a dosage increase or selegiline may not be effective

Adverse Effects

- See p. 132
- Insomnia is common [Management: Take the patch off before bedtime]
- Dermatological reactions are common at the site of application; usually erythema (24%) [Management: Rotate application sites]
- Diarrhea, pharyngitis, dizziness, lightheadedness, headache (18%); hypotension (10%); dry mouth
- Increased blood pressure at doses above 6 mg/24 h possible
- Increased anxiety, agitation, irritability, increase in suicidal thoughts; activation of mania/hypomania (0.4%)
- Weight loss of more than 5% of body weight (5% incidence)
- Decrease prolactin level in females with migraine and in patients taking neuroleptics; clinical relevance unknown

Contraindications

- Simultaneous administration of drugs with serotonergic properties (see Interactions, p. 124)
- Combination with sympathomimetic amines, amphetamines, cold products, and weight-reducing preparations that contain vasoconstrictors or local vasoconstrictors (i.e., cocaine or local anesthesia containing sympathomimetic vasoconstrictors)
- Carbamazepine, oxcarbazepine (see Interactions, p. 124)

Precautions

- Both adults and children with depression (whether under treatment or not) may experience worsening of their MDD, unusual changes in their behavior, and/or the emergence of suicidal ideation and behavior (see Nursing Implications p. 124 for monitoring)
- Although dietary restrictions are not required for the 6 mg/24 h dose, higher doses can negate drug selectivity and a pressor response can occur on exposure to tyramine-rich foods. Patients should observe dietary and drug restrictions for doses over 6 mg (as per irreversible MAO inhibitors p. 119)

Irreversible MAO-B Inhibitor (cont.)

- A 14-day washout is required between termination of selegiline and initiating an antidepressant with serotonergic activity; prevents serotonin syndrome (see Interactions p. 65 and Switching Antidepressants pp. 137–139)
- Patients should be carefully evaluated for a history of drug abuse; patients should be closely observed for signs of transdermal selegiline misuse or abuse (e.g., development of tolerance, increases in dose, or drug-seeking behavior)

Toxicity

- No information available on overdose by selegiline patches. Overdose with MAOI agents is typically associated with CNS and cardiovascular toxicity
- Delays of up to 12 h between ingestion of drug and appearance of symptoms may occur; peak effects may not be observed for 24–48 h
- Death has been reported following overdosage with MAOI agents; hospitalization and close monitoring during this period are essential

Management

- Symptomatic and supportive

Use in Pregnancy◊

- Very limited human data, avoid when possible
- A woman took selegiline 10 mg/day (along with levodopa 400 mg and benserazide 100 mg/day) throughout pregnancy; the child was followed for 10 years and no developmental abnormalities were found
- A woman used selegiline 6 mg/24 h patch during pregnancy; follow-up at 5 months of age found no developmental abnormalities

Breast Milk

- Unknown whether selegiline hydrochloride is excreted in human milk but low molecular weight suggests that it will be. Significant neurotoxicity observed in animals
- No level of selegiline or its metabolites detected in an infant's plasma on day 12 of breastfeeding with maternal dosage of 6 mg/24 h patch
- A woman took selegiline 10 mg/day (along with levodopa 400 mg and benserazide 100 mg/day) throughout pregnancy and while breastfeeding her child for only 3 days; the child was followed for 10 years and no developmental abnormalities were found
- A woman used selegiline 6 mg/24 h patch during pregnancy and postpartum; she exclusively breastfed her infant for an unknown time; follow-up at 5 months of age found no developmental abnormalities

Nursing Implications

- Dietary restrictions are not necessary at a dose of 6 mg/24 h; however, patients should be informed about the signs and symptoms associated with MAOI-induced hypertensive crisis and urged to seek immediate medical attention if these symptoms occur
- Follow MAOI dietary restrictions for doses over 6 mg/24 h
- Patients should be advised to immediately report severe headache, neck stiffness, palpitations or other atypical or unusual symptoms not previously experienced
- Advise patient to avoid exposing the application site of patches to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight, as this may result in an increase in the amount of selegiline absorbed from the patch, producing elevated serum levels
- Theoretically, there is a 3-day reservoir of drug in each patch; after removal, fold it so that sticky side sticks to itself; discard patches in a manner that prevents accidental application or ingestion by children, pets, etc.
- All patients being treated with antidepressants should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of therapy or following an increase or decrease in dose

Patient Instructions

- For detailed patient instruction on transdermal selegiline, see the Patient Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Class of Drug	Example	Interaction Effects
Antibiotic	Linezolid	Monitor for increased serotonergic and noradrenergic effects due to linezolid's weak MAO inhibition; AVOID
Anticonvulsant	Carbamazepine, oxcarbazepine	Increased level of selegiline metabolites *l*-amphetamine and *l*-methamphetamine (2-fold); AVOID
Antidepressant SSRI, SNRI, SARI, SPARI, SMS, NaSSA, tricyclic, RIMA, MAOI		Increased serotonergic effects with possibility of serotonin syndrome; AVOID
Anxiolytic	Buspirone	Several cases of elevated blood pressure have been reported; AVOID
Opioid	Dextromethorphan	Increased risk of serotonin syndrome; AVOID
	Meperidine	Stupor, muscular rigidity, severe agitation, and elevated temperature reported in some patients receiving the combination of selegiline and meperidine; AVOID
	Tramadol	Increased risk of seizures and serotonin syndrome; AVOID
St. John's wort		Increased serotonergic effects with possibility of serotonin syndrome; AVOID
Sympathomimetic	Amphetamines, dextroamphetamine, ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine	Risk of hypertensive crisis; AVOID
Triptan	Rizatriptan	Contraindicated during concurrent or recent (within 2 weeks) use of agents that inhibit MAO-A (this can occur with higher doses of selegiline)

NMDA Receptor Antagonist

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name	Dosage Forms and Strengths	Monograph Statement
Esketamine	NMDA receptor antagonist	Not listed/Antagonist	Spravato	Nasal spray: 28 mg of esketamine per device	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),

Indications‡ (👍 approved)

In children and adolescents:

- Safety and efficacy not established in children and adolescents
- One small randomized, midazolam-controlled, trial found intravenous ketamine effective for adolescents with treatment-resistant depression, but this needs to be replicated in larger studies[76]. A few small, uncontrolled studies or case reports using intravenous or intranasal (es)ketamine are also available for various child and adolescent psychiatric disorders[77]

In adults:

- 👍 Treatment-resistant major depressive disorder (MDD), in conjunction with an oral antidepressant

‡ Indications listed here do not necessarily apply to all SSRIs or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

NMDA Receptor Antagonist (cont.)

- Depressive symptoms in MDD with acute suicidal ideation and behavior (USA only) – no evidence for preventing suicide or decreasing suicidal ideation
- Not approved as an anesthetic agent

General Comments

- Must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of esketamine and post-administration observation for at least 2 h
- Due to the risk of serious adverse outcomes resulting from sedation and dissociation caused by esketamine administration, and the potential for abuse and misuse of the drug, it is only available through two restricted distribution systems: Spravato Risk Evaluation and Mitigation Strategy (REMS) in USA (1-855-382-6022 or online at https://www.spravatorems.com) and Janssen Journey in Canada (1-833-257-7191 or online at https://www.janssenjourneyhcp.ca)
- Monitor all patients for worsening depression and suicidal thinking
- May not be effective in patients of Japanese ancestry; efficacy not demonstrated in a phase II clinical trial

Pharmacology

- Esketamine, the more potent S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor
- The mechanism by which esketamine exerts its antidepressant effect is unknown
- The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor with lower affinity

Dosing

- Dosage adjustments should be made based on efficacy and tolerability
- Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment
- Induction phase (weeks 1–4, administered twice per week): Day 1 starting dose 56 mg; subsequent doses 56 mg or 84 mg
- Maintenance phase (weeks 5–8, administered once weekly): 56 mg or 84 mg. Dosing frequency should be individualized to the least frequent dosing to maintain remission/response
- Esketamine is for nasal use only. The nasal spray device delivers a total of 28 mg of esketamine. To prevent loss of medication, do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device

Pharmacokinetics

- The mean absolute bioavailability is approximately 48% following nasal spray administration
- Time to reach maximum esketamine plasma concentration is 20–40 min after the last nasal spray of the treatment session
- C_{max} inter-subject variability: 27–66%; C_{max} intra-subject variability: ~ 15%
- Mean steady-state Vd (IV route): 709 L
- Protein binding: 43–45%
- Brain-to-plasma ratio of noresketamine is 4–6 times lower than that of esketamine
- Half-life: 7–12 h
- Primarily metabolized to noresketamine via CYP2B6 and CYP3A4 and to a lesser extent via CYP2C9 and CYP2C19
- Noresketamine is metabolized via CYP-dependent pathways and certain subsequent metabolites undergo glucuronidation

Onset & Duration of Action

- In a 4-week study comparing esketamine (plus oral antidepressant) vs. intranasal placebo (plus oral antidepressant), a significant improvement in MADRS score was observed at 4 h with esketamine compared to placebo with the greatest treatment difference observed at 24 h
- Patients in stable remission who continued treatment with esketamine (plus oral antidepressant) experienced a statistically significant time to relapse of depressive symptoms than did patients on intranasal placebo (plus oral antidepressant)

Adverse Effects

- Dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increases, vomiting, and feeling drunk are the most commonly reported side effects (incidence ≥ 5% and at least twice that of placebo plus oral antidepressant)
- Approximately 5% of patients will discontinue treatment due to adverse effects

Contraindications

- Aneurysmal vascular disease or arteriovenous malformation, history of intracerebral hemorrhage, severe hepatic disease, or hypersensitivity to esketamine, ketamine, or any of the excipients
- Additional contraindication (Canada): Recent (within 6 weeks) major cardiovascular event (e.g., myocardial infarction or cerebrovascular accident)

Precautions

- Assess blood pressure prior to dosing. If baseline BP is elevated (e.g., more than 140 mmHg systolic, more than 90 mmHg diastolic), consider the risks of short-term increases in BP and benefit of esketamine. Do not administer esketamine if an increase in BP or intracranial pressure poses a serious risk. After dosing, reassess BP at approximately 40 min and subsequently as clinically indicated
- Monitor for sedation during concomitant treatment with esketamine and CNS depressants
- Due to risks of sedation and dissociation, patients must be monitored for at least 2 h after each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting
- Asses each patient's risk for abuse and misuse prior to prescribing esketamine and monitor for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy
- Monitor all patients for worsening depression and suicidal thoughts, especially during the initial few months of drug therapy and at times of dosage changes

Use in Pregnancy◊

- Not recommended during pregnancy
- Embryo-fetal toxicity in animal studies, thus potential for fetal harm in humans
- Insufficient data to draw conclusions about risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes

Breast Milk

- Esketamine is present in human milk; no data on effects on breastfed infants
- Neurotoxicity in juvenile animals, thus potential for neurotoxicity in breastfed infants

Nursing Implications

- Prior to esketamine administration, instruct patient not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep
- To prevent loss of medication, do not prime the device before use
- Instruct patient to blow nose before first device is delivered, recline at 45 degrees during administration of drug, close the opposite nostril while sniffing gently during esketamine administration, and repeat this process with the other nostril. If liquid drips out of nose after administration, do not blow nose, dab nose with a tissue
- If more than one spray device is used, allow a 5 min rest period between use of devices
- Assess blood pressure prior to and 40 min after esketamine administration
- Monitor for urinary tract and bladder symptoms during the course of esketamine treatment
- Monitor therapy by watching for adverse effects and mood/activity level changes, including suicidal thoughts

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Antidepressant		
Irreversible MAOI	Phenelzine, tranylcypromine	May increase blood pressure; AVOID
CNS depressant	Alcohol, benzodiazepines, opioids	May increase sedation; AVOID
Psychostimulant	Amphetamines, armodafinil, methylphenidate, modafinil	May increase sedation; AVOID

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Effects of Antidepressants on Neurotransmitters/Receptors*

	SSRIs						NDRI	SNRIs			SARIs	
	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Bupropion	Duloxetine	Levomilnacipran	Venlafaxine(*)	Nefazodone	Trazodone
NE reuptake block	+	+	++	++	+++	++	+	++++	+++	+	++	–
5-HT reuptake block	++++	++++	++++	++++	+++++	+++++	–	++++	+++	+++	++	++
DA reuptake block	–	–	+	–	++	+++	++	++	–	+	++	–
5-HT_{1A} blockade	–	?	–	–	–	–	–	+	–	–	+++	+++
5-HT_{2A} blockade	+	?	++	–	–	+	–	++	–	–	+++	+++
M_1(ACh) blockade	+	+	++	–	++	+	–	+	–	–	–	–
H_1 blockade	++	+	+	–	–	–	+	+	–	–	–	++
α_1 blockade	+	+	+	+	+	++	+	+	–	–	+++	+++
α_2 blockade	–	?	+	+	+	+	–	+	–	–	++	++
D_2 blockade	–	?	–	–	–	–	–	–	–	–	++	+
Selectivity	NE < 5-HT	NE < 5-HT	NE < 5-HT	NE < 5-HT	NE < 5-HT	NE < 5-HT	NE > 5-HT	NE < 5-HT	NE > 5-HT	NE < 5-HT	NE < 5-HT	NE < 5-HT

(*) Desvenlafaxine has similar effects on neurotransmitters as venlafaxine

	SPARI	SMS	NaSSA	Nonselective Cyclics							
	Vilazodone	Vortioxetine	Mirtazapine	Amitriptyline	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine
NE reuptake block	+++	++	+	+++	+++	+++++	+++	+++	++++	+++++	++
5-HT reuptake block	+++++	++++	–	+++	++++	++	++	+++	++	++	+
DA reuptake block	+++	+	–	+	+	+	+	+	+	+	+
5-HT_{1A} blockade	++++	+++(**)	+++	++	+	+	++	+	++	+	+
5-HT_{2A} blockade	+	–	+++	+++	+++	++	+++	+++	+++	+++	+++
M_1(ACh) blockade	+	–	++	+++	+++	++	+++	+++	++	+++	+++
H_1 blockade	++	–	++++	++++	+++	++	+++++	+++	+++	+++	+++++
α_1 blockade	++	–	++	+++	+++	++	+++	+++	+++	++	+++
α_2 blockade	+	–	+++	++	+	+	+	+	+	+	+
D_2 blockade	++	–	+	+	++	+	+	+	+	+	++
Selectivity	NE < 5-HT	NE < 5-HT	NE = 5-HT	NE > 5-HT	NE < 5-HT	NE > 5-HT	NE > 5-HT	NE > 5-HT	NE > 5-HT	NE > 5-HT	NE > 5-HT

(**) Vortioxetine is an agonist at the 5-HT_{1A} receptor

Key: K_i (nM) > 10,000 = –; 1000–10,000 = +; 100–1000 = ++; 10–100 = +++; 1–10 = ++++; 0.1–1 = +++++; ? = unknown

See also the National Institute of Mental Health's Psychoactive Drugs Screening Program. Available at http://pdsp.med.unc.edu

* The ratio of K_i values (inhibition constant) between various neurotransmitters/receptors determines the pharmacological profile for any one drug

Pharmacological Effects of Antidepressants on Neurotransmitters/Receptors

NE Reuptake Blockade	• Antidepressant effect • Adverse effects: Tremors, tachycardia, hypertension, sweating, insomnia, erectile and ejaculation problems • Potentiation of pressor effects of NE (e.g., sympathomimetic amines) • Interaction with guanethidine (blockade of antihypertensive effect)
5-HT Reuptake Blockade	• Antidepressant, anti-anxiety, anti-panic, anti-obsessional effect • Can increase or decrease anxiety, depending on dose • Adverse effects: Dyspepsia, nausea, headache, nervousness, akathisia, extrapyramidal effects, anorexia, sexual side effects • Potentiation of drugs with serotonergic properties (e.g., L-tryptophan); caution regarding serotonin syndrome
DA Reuptake Blockade	• Antidepressant, antiparkinsonian effect; may enhance motivation and cognition and mitigate against prolactin elevation • Adverse effects: Psychomotor activation, aggravation of psychosis
5-HT_{1A} Agonism	• Postulated to be associated with precognitive, anxiolytic, and antidepressant effects • Enhances dopamine release in prefrontal cortex
5-HT_{2A} Antagonism	• Sedation, prodopaminergic action may ameliorate EPS, and postulated to improve (not worsen) negative, cognitive, and mood symptoms • Enhances dopamine release in prefrontal cortex
5-HT_{2C} Antagonism	• Increased appetite, weight gain • Postulated to be associated with precognitive and antidepressant effects • Inhibits dopamine and norepinephrine release in prefrontal cortex
M_1 (ACh) Antagonism	• Adverse effects: Dry mouth, blurred vision, constipation, urinary retention, sinus tachycardia, QRS changes, memory disturbances, sedation, exacerbation/attack of narrow-angle glaucoma • Potentiation of effects of drugs with anticholinergic properties
H_1 Antagonism	• Antiemetic effect, anxiolytic effects • Adverse effects: Sedation, postural hypotension, weight gain
α_1 Antagonism	• Adverse effects: Postural hypotension, dizziness, reflex tachycardia, sedation • Potentiation of antihypertensives acting via α_1 blockade (e.g., prazosin, doxazosin, labetalol)
α_2 Antagonism	• May improve cognitive deficits and have antidepressant effects • Antagonism of presynaptic α_2-adrenergic receptors enhances serotonin and norepinephrine neurotransmission • Antagonism of antihypertensives acting as α_2 stimulants (e.g., clonidine) • Adverse effects: Sexual dysfunction, priapism
NMDA Antagonism	• Antidepressant effect • Adverse effects: Hypertension, dissociation, hallucinations, confusion

Frequency of Adverse Reactions to Antidepressants at Therapeutic Doses

Reaction	SSRIs						NDRI	SNRIs				SARIs	
	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Bupropion	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine	Nefazodone	Trazodone
CNS Effects													
Drowsiness, sedation	> 10%	> 2%	> 10%	> 10%	> 10%	> 10%	> 2%	> 10%	> 10%	–	> 10%	> 30%	> 30%
Insomnia	> 10%	> 10%	> 10%[a]	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 5%	> 10%[a]	> 2%	> 2%
Excitement, hypomania[1]	> 2%	< 2%	> 2%	> 10%	> 2%	> 10%	> 10%[b]	> 3%	> 2%	–	> 10%	> 2%	–[b]
Disorientation/confusion	< 2%	< 2%	> 10%	> 2%	< 2%	< 2%	> 2%	< 2%	–	–	> 2%	> 10%	< 2%
Headache	> 10%	< 2%	> 10%	> 10%	> 10%	> 10%	> 10%	> 3%	> 10%	> 10%	> 10%	> 30%	> 2%
Asthenia, fatigue	> 10%	> 2%	> 10%	> 10%	> 10%	> 2%	> 2%	> 10%	> 10%	–	> 10%	> 10%	> 10%
Anticholinergic Effects													
Dry mouth	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 5%	> 10%	> 10%	> 10%
Blurred vision	> 2%	< 2%	> 2%	> 2%	> 2%	> 2%	> 10%	> 3%	> 2%	< 2%	> 2%	> 10%	> 2%[c]
Constipation	> 2%	> 2%	> 2%	> 10%	> 10%	> 2%	> 10%	> 10%	> 10%	< 10%	> 10%	> 10%	> 2%
Sweating	> 10%	> 2%	> 2%	> 10%	> 10%	> 2%	> 10%	> 10%	> 10%	< 10%	> 10%	> 2%	–
Delayed micturition[2]	> 2%	–	> 2%	> 2%	> 2%	< 2%	> 2%	< 2%	< 2%	> 2%[d]	< 2%	< 2%	< 2%
Extrapyramidal Effects													
Unspecified	> 2%	< 2%	< 2%	> 2%[e]	> 2%	> 2%	< 2%	?	< 2%	< 2%	> 2%	< 2%	> 2%[e]
Tremor	> 2%	< 2%	> 10%	> 10%	> 10%	> 10%	> 10%	> 2%	> 2%	< 2%	> 2%	< 2%	> 2%
Cardiovascular Effects													
Orthostatic hypotension/dizziness	> 2%	> 2%	> 10%	> 2%	> 10%	> 10%	> 2%[f]	> 10%[f]	> 10%[f]	> 10%	> 10%[f]	> 10%	> 10%[g]
Tachycardia, palpitations	> 2%[h]	> 2%[h]	< 2%[h]	< 2%[h]	> 2%[h]	> 2%[h]	> 2%	> 3%	> 2%	> 2%	> 2%[i]	< 2%[h]	> 2%
ECG changes[3]	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	–	< 2%	< 2%[i]	< 2%	> 2%
Cardiac arrhythmia	< 2%	< 2%	< 2%[k]	< 2%	< 2%	< 2%	< 2%	< 2%	–	< 2%	< 2%	< 2%	> 2%[l]
GI distress	> 10%	> 10%	> 10%	> 30%	> 10%	> 30%	> 10%	> 30%	> 10%	> 20%	> 30%	> 10%	> 10%
Dermatitis, rash	< 2%	> 2%	> 2%	> 2%	< 2%	> 2%	> 2%	< 2%	> 2%	< 2%	> 2%	< 2%	< 2%
Weight gain (over 6 kg) [4]	> 2%	< 2%	> 2%[m]	> 2%[m]	> 10%[m]	≥ 2%[m]	< 2%[m]	?	> 2%	–	> 2%[m]	> 2%	> 2%
Sexual disturbances	> 30%	> 10%	> 30%[n]	> 30%	> 30%[n]	> 30%[n]	< 2%[n][o]	> 3%	> 30%	< 10%	> 30%[n]	> 2%	< 2%[n]
Seizures [5]	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%[p]	< 2%	< 2%	< 1%	< 2%	< 2%	< 2%

– None reported in literature perused, [1] More likely in bipolar patients, [2] Primarily in the elderly, [3] ECG abnormalities usually without cardiac injury, [4] With chronic treatment, [5] In nonepileptic patients; risk increased with elevated plasma levels, [a] Especially if given in the evening, [b] Less likely to precipitate mania, [c] Found to lower intraocular pressure, [d] Dose-related [e] Tardive dyskinesia reported (rarely), [f] Hypertension reported; may be more common in patients with pre-existing hypertension, [g] Less frequent if drugs given after meals, [h] Decreased heart rate reported, [i] Increased risk with higher doses, [k] Slowing of sinus node and atrial dysrhythmia, [l] Patients with pre-existing cardiac disease have a 10% incidence of premature ventricular contractions, [m] Weight loss reported initially, [n] Priapism reported, [o] Improved sexual functioning, [p] Higher incidence if doses used above 450 mg/day of bupropion or in patients with bulimia

Reaction	SPARI	SMS	NaSSA	Nonselective Cyclics							
	Vilazodone	Vortioxetine	Mirtazapine	Amitriptyline	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine
CNS Effects											
Drowsiness, sedation	< 2%	< 2%	> 30%[q]	> 30%	> 2%	> 2%	> 30%	> 10%	> 2%	< 2%	> 30%
Insomnia	< 2%	–	> 2%	> 2%	> 10%	> 2%	> 2%	> 10%	< 2%	> 10%	> 2%[r]
Excitement, hypomania[1]	< 2%	< 2%	> 2%	< 2%	< 2%	> 2%	< 2%	> 10%	> 2%	> 10%	< 2%
Disorientation/confusion	< 2%	–	> 2%	> 10%	> 2%	–	< 2%	> 2%	> 10%	–	> 10%
Headache	< 2%	> 5%	> 2%	> 2%	> 2%	< 2%	< 2%	> 10%	< 2%	–	> 2%
Asthenia, fatigue	< 2%	> 2%	> 10%	> 10%	> 2%	> 2%	> 2%	> 10%	> 10%	> 10%	> 2%
Anticholinergic Effects											
Dry mouth	< 2%	> 5%	> 30%	> 30%	> 30%	> 10%	> 30%	> 30%	> 10%	> 10%	> 10%
Blurred vision	< 2%	–	> 10%	> 10%	> 10%	> 2%	> 10%	> 10%	> 2%	> 10%	> 2%
Constipation	< 2%	> 5%	> 10%	> 10%	> 10%	> 2%	> 10%	> 10%	> 10%	> 10%	> 10%
Sweating	< 2%	> 5%	> 2%	> 10%	> 10%	> 2%	> 2%	> 10%	< 2%	> 10%	> 2%
Delayed micturition[2]	> 2%	< 2%	> 2%	> 2%	> 2%	–	< 2%	> 10%	< 2%	< 2%	< 2%
Extrapyramidal Effects											
Unspecified	< 2%	–	> 2%	> 2%[e]	< 2%[e]	< 2%	> 2%[e]	< 2%	–	–	< 2%
Tremor	< 2%	–	> 2%	> 10%	> 10%	> 2%	> 2%	> 10%	> 10%	> 2%	> 10%
Cardiovascular Effects											
Orthostatic hypotension/dizziness	< 2%	< 10%	> 2%	> 10%	> 10%	> 2%	> 10%	> 30%	> 2%	> 10%	> 10%
Tachycardia, palpitations	< 2%	–	> 2%	> 10%	> 10%	> 10%	> 2%	> 10%	> 2%	> 2%	> 2%
ECG changes[3]	< 2%	–	< 2%	> 10%[s]	> 10%[s]	> 2%[s]	> 2%[s]	> 10%[s]	> 2%[s]	> 10%[s]	> 10%[s]
Cardiac arrhythmia	< 2%	–	< 2%	> 2%	> 2%	> 2%	> 2%	> 2%	> 2%	> 2%	> 2%
GI distress	> 2%	> 30%	> 2%	> 2%	> 10%	> 2%	< 2%	> 10%	< 2%	–	< 2%
Dermatitis, rash	< 2%	> 2%	< 2%	> 2%	> 2%	> 2%	< 2%	> 2%	< 2%	< 2%	< 2%
Weight gain (over 6 kg)[4]	< 2%	–	> 30%	> 30%	> 10%	> 2%	> 10%	> 10%	> 2%	< 2%	> 10%
Sexual disturbances	< 2%	> 20%	> 2%	> 2%	> 30%	> 2%	> 2%	> 30%	< 2%	< 2%	< 2%
Seizures[5]	< 2%	–	< 2%	< 2%	< 2%[t]	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%

– None reported in literature perused, [1] More likely in bipolar patients, [2] Primarily in the elderly, [3] ECG abnormalities usually without cardiac injury, [4] With chronic treatment, [5] In nonepileptic patients, [e] Tardive dyskinesia reported (rarely), [q] Sedation decreased at higher doses (above 15 mg), [r] No effect on REM sleep, [s] Conduction delays: Increased PR, QRS or QTc interval, [t] Higher incidence if dose above 250 mg daily clomipramine

Frequency of Adverse Reactions to Antidepressants at Therapeutic Doses (cont.)

Reaction	RIMA	Irrev. MAOIs			Irrev. MAO-B Inhibitor
	Moclobemide	Isocarboxazid	Phenelzine	Tranylcypromine	Selegiline Transdermal
CNS Effects					
Drowsiness, sedation	> 2%	> 2%	> 10%	> 10%	< 2%
Insomnia	> 10%[(a)]	> 2%[(a)]	> 10%[(a)]	> 10%[(a)]	> 10%
Excitement, hypomania[1]	> 10%	> 2%	> 10%	> 10%	> 2%
Disorientation/confusion	> 2%	> 2%	> 2%	> 2%	< 2%
Headache	> 10%	> 10%	> 2%	> 10%	> 10%
Asthenia	< 2%	> 2%	< 2%	< 2%	< 2%
Anticholinergic Effects					
Dry mouth	> 10%	> 10%	> 30%	> 10%	> 2%
Blurred vision	> 10%	> 2%	> 10%	> 2%	< 2%
Constipation	> 2%	> 2%	> 10%	> 2%	> 2%
Sweating	> 2%	< 2%	–	> 2%	> 2%
Delayed micturition[2]	< 2%	> 2%	> 2%	> 2%	< 2%
Extrapyramidal Effects					
Unspecified	< 2%	> 2%	> 10%	< 2%	< 2%
Tremor	> 2%	> 10%	> 10%	> 2%	< 2%
Cardiovascular Effects					
Orthostatic hypotension/dizziness	> 10%	> 10%	> 10%	> 10%	> 2%[(y)]
Tachycardia	> 2%	–	> 10%[(h)]	> 10%[(h)]	< 2%
ECG changes[3]	> 2%	> 2%	< 2%[(u)]	< 2%[(u)]	< 2%
Cardiac arrhythmia	> 2%	> 2%	< 2%	< 2%	< 2%
GI distress (nausea)	> 10%	> 10%	> 10%	> 2%	> 2%
Dermatitis, rash	> 2%	> 2%	< 2%	> 2%	> 10%[(w)]
Weight gain (over 6 kg)[4]	< 2%	> 2%	> 10%	> 2%	> 2%[(m)]
Sexual disturbances	> 2%	> 2%	> 30%[(n)]	> 2%[(n)]	< 2%
Seizures[5]	< 2%	–	< 2%	–[(x)]	–

– None reported in literature perused, [1] More likely in bipolar patients, [2] Primarily in the elderly, [3] ECG abnormalities usually without cardiac injury, [4] With chronic treatment, [5] In nonepileptic patients, [(a)] Especially if given in the evening, [(h)] Decreased heart rate reported, [(m)] Weight loss reported, [(n)] Priapism reported, [(u)] Shortened QTc interval, [(w)] At site of patch application, [(x)] May have anticonvulsant activity, [(y)] Hypertension reported

Antidepressant Doses and Pharmacokinetics

Drug	Suggested Daily Pediatric Dose[1]	Comparable Dose (mg)[2]	Suggested Plasma Level (nmol/L)[2]	Bio-availability (%)[2]	Protein Binding (%)[2]	Peak Plasma Level (h) (T_{max})[2]	Elimination Half-life (h) ($T_{1/2}$)	Metabolizing Enzymes[3] (CYP450; other)	Enzyme Inhibition[4] (CYP450; other)
SSRIs									
Citalopram (Celexa)	Children: 10–20 mg Adolescents: 10–40 mg	10		80	80	4	23–45[a]	2D6[b][m], 2C19[m], 3A4[m]	2D6[w], 2C9[w], 2C19[w]
Escitalopram (Cipralex[C], Lexapro[B])	Children: 5–10 mg Adolescents: 5–20 mg	5		80	56	4–5 (metabolite = 14)	27–32[a] [c]	2D6[m], 3A4[m], 2C19[m]	2D6[w], 2C9[w], 2C19[w]
Fluoxetine (Prozac)	Children: 10–40 mg Adolescents: 10–40 mg Doses up to 80 mg in OCD, bulimia, autism[d]	10		72–85	94	6–8 (immediate release)	24–144 (parent)[a] 200–330 (metabolite)	1A2[w], 2B6[w], **2D6**[b] [p], 3A4[w], **2C9**[p], **2C19**[p], 2E1	1A2[m], 2B6[w], **2D6**[p], 3A4[b] [w], 2C9[w], 2C19[m]; P-gp
Fluvoxamine (Luvox)	Children: 25–200 mg Adolescents: 25–300 mg[d]	35		60	77–80	1.5–8	9–28[a]	1A2[w], 2D6	**1A2**[p], 2B6[w], 2D6[m], 3A4[w], 2C9[m], **2C19**[p]; P-gp
Paroxetine (Paxil)	Children: 5–10 mg Adolescents: 10–40 mg[d]	10		> 90	95	5.2 (immediate release)	3–65[a] [c]	**2D6**[p]; P-gp	1A2[w], **2B6**[p], **2D6**[p], 3A4[w], 2C9[w], 2C19[m]; P-gp
Paroxetine CR (Paxil CR)	Children: 12.5 mg Adolescents: 12.5–50 mg	12.5		> 90	95	C_{max} = 6–10 (CR)	15–20	**2D6**[p]; P-gp	1A2[w], **2B6**[p], **2D6**[p], 3A4[w], 2C9[w], 2C19[m]; P-gp
Sertraline (Zoloft)	Children: 25–200 mg Adolescents: 25–200 mg[d]	25		70	98	6	22–36 (parent) [a] [c] 62–104 (metabolite)	2B6, 2D6, **3A4**[p], 2C9, 2C19[m]; UGT2B7	1A2[w], 2B6[m], 2D6[w], 3A4[w], 2C9[w], **2C19**[p]; P-gp
NDRI									
Bupropion (Wellbutrin)[B]	Children: 75–150 mg Adolescents: 100–300 mg[e]	100[e]	75–350[f]	> 90	80–85	1.6 (immediate release)	10–14 (parent)[a]	1A2[w], **2B6**[p], 2D6[b], 3A4[w], 2C9[w], 2E1[m]	2D6[m]
Bupropion SR/XL (Wellbutrin SR/XL, Zyban)	Adolescents: 150–300 mg[e]	200[e]				3 (bupropion) 6 (metabolite) (SR)	20–27 (metabolites)		

Antidepressant Doses and Pharmacokinetics (cont.)

Drug	Suggested Daily Pediatric Dose[1]	Comparable Dose (mg)[2]	Suggested Plasma Level (nmol/L)[2]	Bio-availability (%)[2]	Protein Binding (%)[2]	Peak Plasma Level (h) (T_{max})[2]	Elimination Half-life (h) ($T_{1/2}$)	Metabolizing Enzymes[3] (CYP450; other)	Enzyme Inhibition[4] (CYP450; other)
Bupropion ER (Forfivo XL – only used after initial titration with other bupropion HCL products)[B]	450	450				5 (fasting); delayed in fed state			
Bupropion ER (Aplenzin)[B]	174–522 (HBr salt)	150–450 (HCl salt)				5			
SNRIs									
Venlafaxine (Effexor)[B]	18.75–225 mg 0.5–2.5 mg/kg/day Lower doses for anxiety disorders May use up to 3 mg/kg/day for ADHD	40		13	27	2 (immediate release)	3–7 (parent)[a] [c] 9–13 (metabolite)	**2D6**[p], 3A4[b] [w], 2C9, 2C19	2D6[w], 3A4[w]
Venlafaxine XR (Effexor XR)	37.5–225 mg					XR = 5.5	9–12 (absorption half-life)		
Desvenlafaxine (Pristiq)	50 mg	40		80	30	7.5	11[c]	**UGT**[p], 3A4	2D6
Duloxetine (Cymbalta)	30–120 mg	?		70	> 95	6	8–19[a] [c]	1A2, 2D6	2D6[m]
Levomilnacipran (Fetzima)	20–120 mg	?		92	22	6–8	12	2C8, 2C19, **3A4**	
SARIs									
Nefazodone (Serzone)[B]	Children: 50–200 mg Adolescents: 100–300 mg	130		99	15–23	2	2–5[g] (parent) 3–18 (metabolites)	2D6[b], **3A4**[p]	1A2[w], 2D6[w], **3A4**[p]; P-gp (acute dosing); inducer of P-gp
Trazodone (Desyrel)	Sleep: Age 0–3: 1 mg/kg/dose Age 3–12: 25–75 mg Adolescents: 25–100 mg Depression: Adolescents: Up to 300 mg	100		70–90	93	2	4–9	2D6[b], **3A4**[p]	2D6[w]; inducer of P-gp
SPARI									
Vilazodone (Viibryd)	Children: 10 mg Adolescents: 10–20 mg	10		72 with food (50 fasting)	96–99	4–5	~ 25	1A2[w], 2D6[w], **3A4**[p]	2C8[w], 2D6[w]

Drug	Suggested Daily Pediatric Dose[1]	Comparable Dose (mg)[2]	Suggested Plasma Level (nmol/L)[2]	Bio-availability (%)[2]	Protein Binding (%)[2]	Peak Plasma Level (h) (T_{max})[2]	Elimination Half-life (h) ($T_{1/2}$)	Metabolizing Enzymes[3] (CYP450; other)	Enzyme Inhibition[4] (CYP450; other)
SMS									
Vortioxetine (Trintellix)	5–20 mg[59, 60]	5		75	98	7–11	57	2A6, 2B6, 2C8, 2C9, 2C19, **2D6**, 3A4/5	–
NaSSA									
Mirtazapine (Remeron)	Children: 7.5–15 mg Adolescents: 15–45 mg	12.5		50	85	2	20–40[a] [c]	**1A2**[p], **2D6**[b] [p], **3A4**[p], 2C9	–
Nonselective cyclics									
Amitriptyline (Elavil)	Children: 10–100 mg Adolescents: 25–200 mg; maximum 1.5 mg/kg/day	30	250–825[f] [h]	43–48	92–96	2–8	10–46[a]	1A2[w], 2B6[w], 2D6[p], **3A4**[w], 2C9[w], **2C19**[p]; P-gp	1A2, 2D6[m], 3A4, 2C9[w], 2C19[m], 2E1; P-gp; UGT
Clomipramine (Anafranil)	Children: 10–100 mg Adolescents: 25–200 mg; can use 3 mg/kg/day	30	300–1000	98	98	2–6	17–37[a]	1A2, 2C19[w], **2D6**[p]	2D6[m]; UGT
Desipramine (Norpramin)	Children: 10–100 mg Adolescents: 25–300 mg; can use 3–5 mg/kg/day	50	400–1000[h]	73–92	73–92	2–6	12–76[a]	1A2, **2D6**[p], 3A4, 2C9[w], **2C19**[p]	2D6[m], 2C19[w], 2E1; P-gp
Doxepin (Sinequan)	Children: 10–100 mg Adolescents: 25–300 mg; can use 3–5 mg/kg/day	35	500–950[f]	89	89	2–6	8–36[a]	1A2[w], 2B6[w], **2D6**[p], 3A4[m], 2C9[w], 2C19[m]; UGT1A3; UGT1A4	–
Imipramine (Tofranil)	Children: 10–100 mg Adolescents: 25–200 mg; can use 2.5–5 mg/kg/day	35	500–800[f]	89	89	2–6	4–34[a]	**2D6**[p], 3A4[m], 2C9[w], 2C19[m]; UGT1A4	1A2, 2D6[m], 2C19[m], 2E1; P-gp; UGT1A3
Nortriptyline (Aventyl[C], Pamelor[B])	Children: 10–75 mg Adolescents: 25–150 mg; maximum 1.5 mg/kg/day	25	150–500[h]	89–92	89–92	2–6	13–88[a]	1A2, 2D6[m], 3A4[w], 2C19; P-gp	2D6, 2C19[w], 2E1
Protriptyline (Vivactil)[B]	Children: 5–10 mg Adolescents: 5–20 mg	15	350–700	90–96	90–96	12	54–124[a]	?	?
Trimipramine (Surmontil)	Children: 10–50 mg Adolescents: 25–100 mg	50	500–800	95	95	2–6	7–30[a]	2D6, 2C9, 2C19	2D6; P-gp

Antidepressant Doses and Pharmacokinetics (cont.)

Drug	Suggested Daily Pediatric Dose[1]	Comparable Dose (mg)[2]	Suggested Plasma Level (nmol/L)[2]	Bio-availability (%)[2]	Protein Binding (%)[2]	Peak Plasma Level (h) (T_{max})[2]	Elimination Half-life (h) ($T_{1/2}$)	Metabolizing Enzymes[3] (CYP450; other)	Enzyme Inhibition[4] (CYP450; other)
RIMA									
Moclobemide (Manerix)[C]	Children: 75–150 mg Adolescents: 100–300 mg	150	–	50–90 (after 2 weeks)	50	0.5–3.5	1–3[a]	**2C19** [p]	1A2[m], 2D6[m], 2C9, 2C19[m]
MAOI (irreversible)									
Isocarboxazid (Marplan)[B]	0.1–0.6 mg/kg/day	10	–	?	?	?	2.5	–	–
Phenelzine (Nardil)	0.3–1 mg/kg/day	15	–	?	?	0.75	1.5–4	2E1	–
Tranylcypromine (Parnate)	0.1–0.7 mg/kg/day	10	–	?	?	1.5	2.4[a]	–	1A2[w],**2A6**[p], 2D6[w], 2C9[w], 2C19[w], 3A4[w], 2E1[m]
MAO-B Inhibitor									
Selegiline Transdermal (EMSAM)[B]	Adolescents: 6–12 mg/24h	?	–	10–40	90	4	18–25	2A6, 2B6, 2C9, 3A4/5	2B6, 2D6, 3A4/5

[1] Suggested dosages are based on RCT data and/or authors' clinical judgment in the absence of approved pediatric dosing guidelines in manufacturers' prescribing information/product monographs, [2] Most of the data available is based on adult population, [3] Cytochrome P450 isoenzymes involved in drug metabolism, [4] CYP450 isoenzymes inhibited by the drug; magnitude may be influenced by drug dose and plasma concentration, and by genotype and basal metabolic capacity of each patient
[B] Not marketed in Canada, [C] Not marketed in the USA
[a] Increased in liver disorders – consider dose adjustment, [b] Specific to metabolite, [c] Increased in moderate to severe renal impairment – consider dose adjustment, [d] SSRIs have a flat dose response curve. For depression most patients respond to the initial (low) dose. Higher doses are used in the treatment of OCD, [e] Give in divided doses (maximum of 150 mg per dose), [f] Includes sum of drug and its metabolites, [g] Dose-dependent, [h] Established ranges for efficacy in major depressive disorder, [m] Moderate activity, [p] Potent activity, [w] Weak activity

P-gp = p-glycoprotein [*a transporter of hydrophobic substances in or out of specific body organs (e.g., block absorption in the gut)*]; UGT = uridine diphosphate glucuronosyl transferase [*involved in Phase II reactions (conjugation)*]

Switching Antidepressants

Antidepressant Nonresponse

- Ascertain diagnosis is correct; ascertain patient is adherent to treatment
- Ensure dosage prescribed is therapeutic; consider measuring plasma level; ensure there has been an adequate trial period, i.e., up to 6 weeks at a reasonable dose
- Regular, systematic assessment of the patient's response to drug therapy, with the use of measurement tools for symptoms, adverse effects, and patient adherence is useful to guide future clinical decisions[78]

Factors Complicating Response

- Concurrent medical or psychiatric illness, e.g., hypothyroidism, OCD
- Personality disorders lead to poor outcome; however, depression may evoke personality problems which may disappear when the depression is alleviated
- Substance use may make management difficult (e.g., cocaine); see CANMAT recommendations[79]
- Low folate levels associated with lack of remission, response and relapse
- Concurrent prescription drugs may interfere with efficacy (e.g., calcium channel blockers)
- Metabolic inducers (e.g., carbamazepine) or inhibitors (e.g., erythromycin) may affect plasma level of antidepressant
- Psychosocial factors and genetic variants may affect response

Switching Antidepressants

- Switching from one SSRI to another may offer enhanced response in previously nonresponsive patients
- 20–25% remission rate when switching from SSRI to another class of antidepressant or a different SSRI after failure of first SSRI (STAR*D studies)
- Use caution when switching to or from irreversible MAOIs (see Switching Antidepressants pp. 137–139)
- One study found significantly higher response rates when switching from imipramine to sertraline than vice versa and better tolerability[80]

Advantages of Switching

- Minimizes polypharmacy
- Decreased risk of drug interactions
- Second agent may be better tolerated
- Improved adherence
- Less costly

Disadvantages of Switching

- Lose partial efficacy of first agent
- Time required to taper first agent or need for a washout (risk of relapse)
- Delayed onset of action

Switching Strategies

- Many switching strategies exist. For additional guidance please see the following websites/pages:
  - https://www.switchrx.com
  - https://www.nps.org.au/assets/Products/Guidelines-switching-antidepressants_A3.pdf
  - https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/depress_appd.pdf
  - https://www.psychiatrienet.nl/switchtabel/show?id=SwitchAntidepressants

Switching Antidepressants (cont.)

Switching from		Switching to	Switching Method[a]
SSRI (not fluoxetine)	→	SSRI (including fluoxetine)	Direct switch, **OR** taper, stop, and switch
	→	NDRI, SPARI, clomipramine	Taper, stop, and switch
	→	SNRI	Taper, stop, and switch, **OR** cross-taper
	→	SARI, SMS, NaSSA, nonselective cyclics (not clomipramine)	Cross-taper
	→	RIMA, Irrev. MAOI, MAO-B	Taper, stop, washout (1–2 weeks), and switch
Fluoxetine	→	SSRI, NDRI, SPARI, SMS, nonselective cyclics (not clomipramine)	Taper, stop, washout (4–7 days), and switch
	→	SNRI	Taper, stop, and switch
	→	SARI	Cross-taper
	→	NaSSA	Taper, stop, washout (4–7 days), and switch **OR** cross-taper
	→	Clomipramine	Taper, stop, washout (2 weeks), and switch
	→	RIMA	Taper, stop, washout (5 weeks), and switch
	→	Irrev. MAOI, MAO-B	Taper, stop, washout (5–6 weeks), and switch
NDRI	→	SSRI (including fluoxetine), SNRI, SARI, SPARI, SMS, NaSSA, nonselective cyclics (including clomipramine)	Taper, stop and switch
	→	RIMA, Irrev. MAOI, MAO-B	Taper, stop, washout (1 week), and switch
SNRI	→	SSRI (not fluoxetine), SARI, SMS, NaSSA, nonselective cyclics (not clomipramine)	Cross-taper
	→	Fluoxetine, SPARI	Taper, stop and switch, **OR** cross-taper
	→	NDRI, SNRI, clomipramine	Taper, stop, and switch
	→	RIMA, Irrev. MAOI, MAO-B	Taper, stop, washout (1 week), and switch
SARI	→	SSRI (including fluoxetine), NDRI, SNRI, SPARI, SMS, NaSSA, nonselective cyclics (including clomipramine)	Cross-taper
	→	RIMA, Irrev. MAOI, MAO-B	Taper, stop, washout (1 week), and switch
SPARI[b]	→	SSRI (including fluoxetine), NDRI, SNRI, clomipramine	Taper, stop and switch
	→	SARI, SMS, NaSSA	Cross-taper
	→	Nonselective cyclics (not clomipramine)	Taper, stop, and switch **OR** cross-taper
	→	RIMA, Irrev. MAOI, MAO-B	Taper, stop, washout (2 weeks), and switch
SMS	→	SSRI (not fluoxetine)	Taper, stop, and switch **OR** cross-taper
	→	Fluoxetine, NDRI, clomipramine	Taper, stop and switch
	→	SNRI, SARI, SPARI, NaSSA, nonselective cyclics (not clomipramine)	Cross-taper
	→	RIMA, Irrev. MAOI, MAO-B	Taper, stop, washout (3 weeks), and switch
NaSSA	→	SSRI (including fluoxetine), SNRI, SPARI, nonselective cyclics (including clomipramine)	Taper, stop, and switch **OR** cross-taper
	→	NDRI	Taper, stop and switch
	→	SARI, SMS	Cross-taper
	→	RIMA	Taper, stop, washout (1 week), and switch
	→	Irrev. MAOI, MAO-B	Taper, stop, washout (2 weeks), and switch

Switching from		Switching to	Switching Method[a]
Nonselective cyclic	→	SSRI (including fluoxetine), NDRI, SNRI, SARI, SPARI, SMS, nonselective cyclics (including clomipramine)	Cross-taper
	→	NaSSA	Taper, stop, and switch **OR** cross-taper
	→	RIMA	Taper, stop, washout (1 week), and switch
	→	Irrev. MAOI, MAO-B	Taper, stop, washout (2 weeks), and switch
Clomipramine[c]	→	SSRI (not fluoxetine), SNRI, SPARI, SMS	Taper, stop and switch
	→	Fluoxetine	Taper, stop, washout (2–3 weeks), and switch
	→	NDRI, SARI, NaSSA, nonselective cyclics	Cross-taper
	→	RIMA	Taper, stop, washout (1 week), and switch
	→	Irrev. MAOIs, MAO-B	Taper, stop, washout (3 weeks), and switch
RIMA	→	SSRI (including fluoxetine), NDRI, SNRI, SARI, SMS, NaSSA, nonselective cyclics (including clomipramine), Irrev. MAOI, MAO-B	Taper, stop, washout (1 day), and switch
	→	SPARI	Taper, stop, washout (2 weeks), and switch
Irreversible MAOI[d]	→	SSRI (including fluoxetine), NDRI, SNRI, SARI, SPARI, SMS, NaSSA, nonselective cyclics (not clomipramine or imipramine), irrev. MAOI, MAO-B	Taper, stop, washout (2 weeks), and switch
	→	Clomipramine, imipramine	Taper, stop, washout (3 weeks), and switch
MAO-B	→	SSRI (including fluoxetine), NDRI, SNRI, SARI, SPARI, SMS, NaSSA, nonselective cyclics (not clomipramine or imipramine), irrev. MAOI, MAO-B	Taper, stop, washout (2 weeks), and switch
	→	Clomipramine, imipramine	Taper, stop, washout (3 weeks), and switch

[a] Switching Method:
Direct Switch: Stop the first antidepressant and start the new antidepressant the following day. Recommended if first antidepressant therapy duration is less than 6 weeks (interactions less likely) and/or switching to an antidepressant with similar mode of action (ameliorates withdrawal effects)
Taper, stop and switch: Gradually taper the first antidepressant and start the new antidepressant immediately after discontinuation. Recommended if first antidepressant therapy duration is more than 6 weeks
Taper, stop, washout, and switch: Gradually taper the first antidepressant and start the new antidepressant after a washout period
Cross-taper: Gradually taper down the first antidepressant and slowly simultaneously introduce and increase the dose of the new antidepressant
Speed of tapering and cross-taper is most commonly 1–2 weeks or longer and should be judged by monitoring tolerability of the individual patient,
[b] Vilazodone is both an SSRI and a partial agonist of the 5-hydroxytryptamine 1A receptors. Caution is advised when switching to and from vilazodone due to limited relevant information from studies, [c] Clomipramine should not be co-administered with SSRIs, venlafaxine or duloxetine (except under specialist use) and cross-tapering is not recommended, [d] Should not be commenced before all other antidepressants have been trialed due to risk of hypertensive crisis and serotonin syndrome. Allow washout period and monitor patients individually

Antidepressant Augmentation Strategies

Augmentation Strategies

According to the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines, Section 6: Special Populations, no augmentation strategies are suggested in children and adolescents[81]. The largest evidence base for antidepressant nonresponders in adults with MDD is the use of adjunctive atypical antipsychotics with at least 15 RCTs (in adults) to date[80]. However, no atypical antipsychotics are approved for this indication for children or adolescents in the USA or Canada and data is very limited

Advantages of Augmentation

- May have rapid onset of response
- Response greater than 50% with most combinations[9]
- No need to taper first agent or have a washout
- Avoids risk of withdrawal effects from first drug

Disadvantages of Augmentation

- Due to lack of clinical trials, clinical guidelines generally do not support augmentation efficacy in children and adolescents with MDD
- Increased potential for side effects

Antidepressant Augmentation Strategies (cont.)

- Increased risk of drug interactions
- Increased cost
- Decreased adherence possible due to need to take an increased number of tablets/capsules

Choosing Adjunctive Medications (Adults)

- Adjunctive medication for nonresponse or partial response to antidepressants in MDD, according to the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines[81]
- CANMAT levels of evidence within this guideline include: 1) Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled; 2) Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size; 3) Small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies; and 4) Expert opinion/consensus
- CANMAT Lines of Treatment:
  - First-line: Level 1 or 2 evidence, plus clinical support
  - Second-line: Level 3 evidence or higher, plus clinical support
  - Third-line: Level 4 evidence or higher, plus clinical support

First-line Adjunctive Medications (Adults)

- Aripiprazole: Initial dose 2–5 mg/day; recommended dose 5–10 mg/day; maximum dose 15 mg/day if necessary
- Quetiapine: Initial dose 50 mg/day; recommended dose 150–300 mg/day; maximum dose 300 mg/day
- Risperidone: 0.25 mg/day for 3 days; 0.5 mg/day on days 4–15, 1 mg/day on days 6–28. Increase to 2 mg/day

Second-line Adjunctive Medications (Adults)

- Brexpiprazole: Initial dose 0.5 mg/day; recommended dose 2 mg/day; maximum dose 3 mg/day
  - Due to limited evidence when guidelines were published, designated as second-line agent. Now may be considered a first-line option
- Bupropion: 150–300 mg/day
  - Of the 13 trials using bupropion as an adjunctive medication, 7 were open label
  - Of 5 studies with bupropion as an adjunctive to SSRIs, only one was a placebo-controlled RCT. In a three-arm study (bupropion monotherapy vs. escitalopram monotherapy, vs. bupropion + escitalopram), the combination of bupropion + escitalopram was not significantly better than either medication used as monotherapy, but there were more adverse events with the combination
  - There have been 2 studies using bupropion as an adjunctive to SNRIs. Positive results were found when bupropion was added to venlafaxine but not to when it was added to duloxetine
- Lithium: 600–1200 mg/day (levels 0.5–0.8 mmol/L)
  - Most lithium augmentation studies were with TCAs and had small sample sizes. Only three trials with lithium and SSRIs
  - A meta-analysis of 9 RCTs with 237 participants found overall comparison and the SSRI-only comparison to have significantly better efficacy than placebo. However, confidence intervals were wide, hence, Level 2 evidence for efficacy
- Mirtazapine: 30–60 mg/day
  - A meta-analysis of 23 trials with 2,435 participants, focusing on adverse events, found that an adjunctive antidepressant was associated with increased side effects compared to monotherapy, especially when adding mirtazapine or TCAs to SSRIs
- Modafinil
  - See p. 401
  - A meta-analysis of 4 trials involving 568 patients (of which only 2 with 211 patients were adjunctive trials) reported marginal evidence for efficacy in the modafinil-treated patients compared to placebo after an outlier was excluded
- Olanzapine: 2.5–10 mg/day
  - Considered second-line due to unfavorable metabolic profile
- Triiodothyronine: 25–50 micrograms/day
  - There have only been 2 RCTs with lithium as an augmentation agent
  - Although not placebo controlled, triiodothyronine was also evaluated in the STAR*D study. No differences in remission rate compared to lithium, but triiodothyronine was better tolerated and had lower dropout rates
  - If no response within 3 weeks, consider alternative strategies

Third-line Adjunctive Medications (Adults)

- Other antidepressants
- Other stimulants (e.g., methylphenidate, lisdexamfetamine)
  - 2 RCTs of lisdexamfetamine showed efficacy as an adjunctive agent for partial responders to SSRIs. However, 2 unpublished phase III trials with 830 participants were negative
- TCAs
  - Considered third-line due to higher side effect burden, arrhythmia risk in overdose
- Ziprasidone

Complementary Adjunctive Medications

- Folate (adult data)
  - Small overall benefits for unipolar depression; however, large doses (15 mg/day) of methylfolate as adjunctive therapy in MDD was found to have moderate to large benefits for depressive symptoms vs. placebo in a few small RCTs
  - Consider dietary enhancement first. Variance in active ingredients between manufacturer may limit efficacy
  - Clinical utility of MTHFR genotyping is unclear. Available evidence does not support additional benefits from L-methylfolate in patients with MTHFR genetic variants compared to those without
- Omega-3 fatty acids (see pp. 411–414)
  - Monotherapy double-blind RCT with 51 patients: In adolescents aged 12–19, omega-3 supplementation (1.2–3.6 g/day; EPA:DHA ratio 2:1) for 10 weeks was not superior to placebo in reducing depression severity, anhedonia, irritability, or suicidality. Both groups significantly improved depression severity
  - Monotherapy double-blind pilot trial with 20 patients: In children aged 6–12, omega-3 fatty acids at a dose of 600 mg/day (400 mg EPA, 200 mg DHA) significantly reduced scores on the CDRS-R at 16 weeks compared to placebo. Placebo response was uncharacteristically small for a pediatric depression trial
  - Adjuvant double-blind RCT with 60 patients: Trial of children aged 11–17; omega-3 adjuvant at a dose of 2400 mg/day (1000 mg EPA, 750 mg DHA) to standard antidepressant therapy significantly reduced depression rating scores after 6 and 12 weeks compared to omega-6 adjuvant. Reduction in score was greater in depressive disorder subgroup compared to mixed anxiety and depression disorder subgroup
  - Well tolerated in children and adolescents; mild gastrointestinal effects, foul breath, and unpleasant fishy taste reported; this may be reduced by taking an enteric-coated formulation
- S-Adenosyl-L-Methionine (SAMe) (adult data)
  - Adjunctive for mild to moderate MDD
  - Usual starting dose is 400 mg/day for the first 1–2 weeks, then increase by 200–400 mg/day every 5–7 days to maximum dose of 800 mg bid
  - Variance in active ingredients between manufacturers may limit efficacy

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ELECTROCONVULSIVE THERAPY (ECT)

Definition

- Non-invasive convulsive neurostimulation treatment, which therapeutic mechanism is mediated by the induction of a tonic-clonic generalized seizure by means of a brief current applied under general anesthesia
- Magnetic Seizure Therapy (MST) is a novel form of convulsive therapy under investigation that utilizes strong magnetic fields to elicit a generalized seizure[3]
- ECT is **not** to be confused with the administration of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive NON-convulsive neurostimulation treatment that induces a current by means of strong magnetic fields at subconvulsive thresholds (as opposed to MST); preliminary comparison of rTMS with ECT indicates that rTMS may be effective for major depression, but not with psychotic symptoms

Indications

- For the syndrome of catatonia, ECT is second-line treatment after the use of benzodiazepines[4]
- For the syndrome of malignant catatonia (catatonic features plus deteriorating autonomic vital signs, rigidity, hyperthermia), ECT is first-line treatment[4]
- Mood disorder, severe: May be necessary for childhood or early adolescent onset of severe mood disorder with suicide risk, if adequate trials of 2 or more antidepressants are ineffective; **should never be prescribed without consultation by a specialist in child and adolescent psychiatry**
- Major depressive disorder (MDD), refractory; especially when associated with high suicide risk, exhaustion caused by lack of nourishment/dehydration, severe agitation, depressive stupor, catatonia, delusions, nonresponse to one or more adequate trials of antidepressants or intolerance of therapeutic dosages
- Bipolar disorder: Depressed phase
- Bipolar disorder: Manic phase; adjunct to mood stabilizers and antipsychotics for severe mania (manic “delirium”) and rapid-cycling illness
- Severe psychotic disorders in patients with intellectual disability
- Intractable psychotic disorders; especially with concurrent catatonic and/or affective symptoms; adjunct to adequate dosage of antipsychotics for nonresponsive “positive” symptoms; after failed clozapine trial (response rate 50–60%)
- Schizoaffective disorder, first-episode psychosis; after nonresponse to adequate drug trials
- Schizophrenia, treatment resistant cases. Those presenting with catatonic features may respond particularly well. Reports of efficacy in phencyclidine-induced psychosis; ECT administered only for severe/prolonged illness
- Recent research supports ECT use in severe forms of self-injurious behavior in children and adolescents with neurodiversity[5]
- Has been used in some cases of treatment-refractory epilepsy in adults; descriptions of ECT use to treat super-refractory status epilepticus in children[6]

General Comments

- ECT technique in pediatric patients is very similar to that in adults with regards to main technical aspects such as electrode placement, stimulation parameters, anesthetic use. Side effect profile also similar to adults; main concern is the effect of ECT on the developing brain[7]
- ECT is reserved for the most severely ill children and adolescents and thus long-term side effects are difficult to ascertain as the improvement gained outweighs side effects
- Some jurisdictions do not permit the use of ECT for youth under a specific age
- Reviews suggest ECT is effective for mood disorders and generally well-tolerated in children and adolescents; rates of improvement and adverse effects similar to those in adults
- Education of patient and/or caregiver and informed consent must be obtained prior to treatment. It is very important to engage families/caregivers in the consent process and to provide information in a manner that patients and their families are able to understand
- In a survey of 19 adolescents who had received ECT, 84% reported that ECT had improved their illness, and 77% reported that ECT was worth having[8]
- The portrayal of ECT is common in popular media, with a review showing ECT being used in torture, memory erasure, and the vast majority occurring without anaesthesia or neuromuscular blockade (72%). This contributes to anti-ECT stigma in the general population[9]

Electroconvulsive Therapy (ECT) (cont.)

Therapeutic Effects

- The effects of ECT on catatonia have an extremely large effect size, however, there exists no good randomized controlled trial for ECT in catatonia and this may never occur due to ethical limitations[10]
- Vegetative symptoms of depression, such as insomnia and fatigue, and catatonic symptoms may respond initially; later improvement of affective symptoms, such as depressed mood and anhedonia; followed by improvement of cognitive symptoms, such as impaired self-esteem, helplessness, hopelessness, suicidal and delusional ideation
- Manic symptoms that respond include agitation, euphoria, motor overactivity, and thought disorder
- Some "positive" symptoms of schizophrenia and other psychoses may respond
- Most effective treatment for severe depression in that a substantial proportion of nonresponders to antidepressants do recover with ECT; "melancholic" and "psychotic" presentations respond best

Mechanism of Action

- Exact mechanism unknown, but induction of generalized tonic-clonic seizures is the necessary mediating mechanism
- Affects almost all neurotransmitters implicated in the pathogenesis of the mental disorders (norepinephrine, serotonin, acetylcholine, dopamine, GABA)
- Neurophysiological effects include increased transient permeability of the blood-brain barrier (see precautions with lithium), increased transient sympathetic tone with increased heart rate and blood pressure; with suppression of regional cerebral blood flow and neurometabolic activity; repeated administration of ECT increases the seizure threshold (i.e., it is more difficult to elicit a seizure, and hence its use in treatment-refractory epilepsy). The "anticonvulsant" effects may be related to psychiatric outcomes (inhibitory neurotransmitters are increased by ECT)
- Affects neuroendocrine substances (corticotropin releasing factor (CRF), adrenocorticotropic hormone (ACTH), thyrotropin releasing hormone (TRH), prolactin, vasopressin, metenkephalins, β-endorphins)

Dosage

- Square-wave, brief pulse devices should be used as they decrease side effect rates (sine wave devices may still be in use in developing countries)
- The preferred dosing method is titration. Starting dose may be lower than in adult population as seizure threshold is lower in children and adolescents, but no definite data has been published. Subsequent treatments require dose above seizure threshold but exact increase needed in pediatric populations is not established
- Dose is measured by charge/energy delivered in millicoulombs (mC) or joules (J). Total charge is determined by a combination of stimulation frequency, stimulation duration, pulse width, and dynamic impedance. A seizure lasting less than 15 sec is considered an aborted seizure and is an indication to re-stimulate. Adequate seizures have 15 sec duration or longer; extended seizure duration does not strongly correlate with psychiatric outcomes. Augmenting agents to trigger seizures are rarely needed in pediatric ECT
- Bitemporal stimulus electrode placement (regardless of the stimulus energy/charge) has been found more effective than unilateral placement; "high-energy" bilateral may be effective for nonresponse to "threshold" bilateral treatment
- Combination of ultrabrief stimulus pulse width with unilateral placement is associated with fewer cognitive side effects
- Unilateral stimulus pulse width may be effective with a generally lower seizure threshold and reduced cognitive side effects
- Change from bilateral to unilateral placement if the patient becomes unduly confused following bilateral treatment
- Gender, age, and electrode placement affect seizure threshold: Males have higher thresholds than females, thresholds increase with age and are greater with bilateral than unilateral ECT

Onset & Duration of Action

- Therapeutic effect may be evident within 3 treatments in some cases, while in other cases up to 20 treatments are needed to constitute an adequate trial. If there is no benefit after 12–15 treatments, it is unlikely that ECT will be effective
- There may be a lag between the subjective perception of improvement by others and patient (i.e., usually others perceive change in affect before patient notices subjective improvement in mood)
- Relapse rate following discontinuation is high (30–70%) within 1 year, partly dependent on degree of medication resistance pre-ECT; prophylactic antidepressants should be administered in almost all cases; "continuation" ECT for up to 6 months if antidepressant prophylaxis of rapid relapse is ineffective

Procedure

- Administer 3 times per week on alternate days; decrease frequency to twice weekly, if necessary, to reduce cognitive side effects (as effective as 3 times weekly although speed of response is slower)[11]
- ECT must always be administered under general anesthesia with partial neuromuscular blockade
- Induce light "sleep" anesthesia with methohexital[12, 13, 14, 15], which is the gold standard (may not be available in some countries or require special access regulatory approval); propofol may result in much briefer convulsions; may also raise seizure threshold; some data indicate worse outcomes with propofol[16]; reserve for patients with post-treatment delirium or severe nausea unresponsive to antiemetics)
- Induce neuromuscular blockade with succinylcholine or a short-acting non-depolarizing agent. Post-ECT myalgia may be due to insufficient relaxation or fasciculations (attenuate the latter if necessary with adjunctive non-depolarizing muscle relaxant (e.g., rocuronium), which necessitates a higher dosage of succinylcholine). Pediatric patients tend to require lower dose of muscle relaxant than adults
- If benzodiazepine treatment is being used concurrently (often in catatonia), withhold the benzodiazepine on the night and morning prior to ECT or consider use of IV flumazenil (benzodiazepine antagonist) immediately before application of ECT[17]
- Pretreat with atropine or glycopyrrolate if excess oral secretions and/or significant bradycardia anticipated (i.e., during "threshold" titration, patient on a β-blocker); treat with atropine if bradycardia develops post treatment
- Pretreat any concurrent physical illness which may complicate anesthesia (i.e., using antihypertensives, gastric acid/motility suppressants, hypoglycemics); special circumstances require anesthesia and/or internal medicine consultation
- If possible, discontinue or reduce dosage of all psychotropics with anticonvulsant properties (i.e., benzodiazepines, carbamazepine, valproate)
- Continue all other psychotropics, except MAOIs (see Contraindications p. 148), when clinically necessary
- Outpatient treatment can be administered if warranted by the clinical circumstances, if there is no medical/anesthesia contraindication, and if the patient can comply with the pre- and post-treatment procedural requirements

Adverse Effects

- Sparse data regarding cognitive side effects in children and adolescents
  - In one of the few studies formally addressing this question, impairment in concentration, attention, delayed verbal and visual recall and verbal fluency were present during the first 10 days of treatment, but these deficits were recovered fully over several months[18]
  - A comprehensive survey of 277 adult patients administered subjective memory surveys prior to and following ECT, with more (31.4%) showing improvements than deteriorations (16.2%). However, a majority (54.6%) retrospectively described ECT as harming their memory. This may have to do with negative expectations and patient attribution[19]
  - However, it is important to keep in mind that, in adults, there is:
    - Significant patchy amnesia for the period during which ECT is administered; may persist indefinitely
    - Retrograde amnesia for some events up to a number of months pre-ECT; may be permanent; uncommonly, longer periods of retrograde amnesia
    - Patchy anterograde amnesia for 3–6 months post-ECT; no evidence of permanent anterograde amnesia
    - Cognitive impairment (concentration and attention, verbal fluency, and delayed recall) reported in adolescents; recovered over several months. No evidence of long-term sequelae
    - Patients may rarely complain of permanent anterograde memory impairment; unknown if this is a residual effect of the ECT or an effect of residual symptoms of the illness for which ECT was prescribed
  - Ultrabrief pulse ECT seems to be associated with fewer subjective complaints of memory issues[19]
  - There is no evidence to suggest that ECT causes structural damage or adversely affects brain development in youth
- In adults, mortality rate 2–4 deaths per 100,000 treatments; in 9 studies after 2001, there was one death in 400,000 treatments. No mortality in 715 pediatric patients receiving ECT in a systematic review of 41 studies[20]
- Post-treatment delirium uncommon; usually of short duration (even less frequent in adolescents compared to adults)
  - Reported when more than one electric stimulus is used to induce a convulsion; after prolonged seizures
  - Due to concurrent drug toxicity (e.g., lithium, clozapine – see Drug Interactions p. 149)
  - May occur with too rapid pre-ECT discontinuation of some antidepressants
  - If occurs, consider propofol anesthesia for subsequent treatments
- Tachycardia and hypertension may be pronounced; duration of several minutes post-treatment
- Bradycardia (to the point of asystole) and hypotension may be pronounced if stimulus is subconvulsive
  - Increased risk if patient taking a β-blocker (e.g., propranolol)
  - Attenuated by the subsequent convulsion, atropine, and medication with anticholinergic effect

Electroconvulsive Therapy (ECT) (cont.)

- Post-treatment vagal "tone" may lead to significant bradycardia in young patients
- Prolonged seizures are more frequent in adolescents than adults; infrequent status epilepticus reported in adolescents after administration of ECT; monitor treatment with EEG until convulsion ends; seizures should be terminated after 3 min duration with anesthetic dosage of the induction agent, repeated if necessary, or with diazepam. Propofol may reduce risk of prolonged seizures
- Spontaneous seizures
  - Incidence of post-ECT epilepsy is approximately that found in the general population
- Headache and muscle pain common but not usually severe
  - Pretreat with rocuronium bromide (approximately 3 mg) for severe muscle pain
  - Headaches seem to be more frequent in adolescents
- Nausea common following ECT procedure; pre-treat with dimenhydrinate if severe
- Temporomandibular joint pain; may be reduced with bifrontal electrode placement (compared to standard bitemporal placement)
  - All patients should have a bite block inserted in their mouth during the electric stimulus and seizure to minimize jaw pain and prevent dental injury

Precautions

- Obtain pretreatment anesthesia consultation for all patients. Additional pre-treatment consultation may be needed if significant preexisting cardiovascular disease, potential gastro-esophageal reflux, compromised airway, and other circumstances which may complicate the procedure (e.g., personal or family history of significant adverse effects, or delay in recovery from general anesthesia); treat as indicated
- Monitor by ECG, pulse oximetry, and blood pressure, before, during, and after ECT; EEG during treatment
- Patients with insulin-dependent diabetes mellitus may have a reduced need for insulin after ECT, as ECT reduces blood glucose levels for several hours (may be related to pre-treatment fasting)
- 10–30% of bipolar depressed patients can switch to hypomania or mania following ECT; important to continue anti-manic medication if not unduly affecting the treatment procedure (i.e., increased seizure threshold)
- Concurrent use of lithium may be associated with delirium post-ECT (see p. 300); if lithium treatment is necessary, aim for a level at lower end of therapeutic range. If lithium dose is taken at night or in the morning, hold dose prior to ECT

Contraindications

Note: all contraindications should be regarded in the context of, and relative to, the risks of withholding ECT. None are absolute contraindications

- Rheumatoid arthritis complicated by erosion of the odontoid process
- Increased intracranial pressure
- Extremely loose teeth which may be aspirated if dislodged
- Other disorders associated with increased anesthetic risk (American Society of Anesthesiologists level 3 or 4)
- Concurrent administration of an irreversible MAOI, which may interact with anesthetic agents (although most reports have implicated meperidine as the interacting drug)
- Concurrent drug toxicity

Lab Tests/Monitoring

- Assess and document patient's capacity to consent to treatment; answer patient's questions about ECT; obtain signed and witnessed consent form (valid consent requires full disclosure to the patient of the nature of the procedure, all material risks and expected benefit of ECT and those of alternative available treatments, and the prognosis if no treatment is given); if patient incapable, get written consent from eligible substitute; involve parents/guardians in consent process
- Assess memory prior to treatment if there is evidence of significant cognitive impairment; reassess if treatment-emergent loss is unduly severe
- Physical examination
- Pregnancy test (females)
- CBC and differential when clinically indicated
- Electrolytes and creatinine for all patients on any diuretic, on lithium or with insulin-dependent diabetes, and as clinically indicated, including patients with a history of water intoxication
- ECG for all patients being treated for hypertension, or with a history of cardiac disease, and as clinically indicated

- Spinal X-rays for those patients with a history of compression fracture or other injury, significant back pain, and as clinically indicated; cervical spine X-rays for all patients with rheumatoid arthritis
- Sickle cell screening of all black patients of African descent; infectious hepatitis screening as clinically indicated
- Blood glucose on day of each treatment for patients with diabetes mellitus or taking insulin or hypoglycemic agents
- International Normalized Ratio (INR) and partial thromboplastin time (PTT) for all patients taking anticoagulants
- If patient is taking lithium, obtain serum lithium level before and periodically during course of ECT

Use in Pregnancy

- May be performed in all trimesters, associated with increased risk to fetus and obstetric complications; obtain obstetrical consultation; requires careful consideration of risks and benefits
- Fetal monitoring recommended
- Precaution: Increased risk of gastro-esophageal reflux

Nursing Implications

- Patients must be kept NPO (especially for solid food) for approximately 8 h before treatment; continuous observation of potentially non-compliant patients may be required. Essential medication (e.g., antihypertensives) may be administered with sip of water
- Dental appliances (excluding "fixed" braces) must be removed before treatment
- Observe and monitor vital signs until patient has recovered; patient should be oriented and alert before discharge from recovery room; patient should be advised not to operate a motor vehicle or potentially dangerous equipment/machinery/tools for 24 h post-ECT. Outpatients must be escorted home after treatment
- When possible, avoid prn benzodiazepines the night prior to and the morning of treatment

Patient Instructions

- For detailed patient and caregiver instructions on ECT, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below

Class of Drug	Example	Interaction Effects
Anesthetic	Propofol	Decreased seizure duration (may be very substantial); may increase seizure threshold
Anticonvulsant	Carbamazepine, lamotrigine, valproate	Increased seizure threshold with potential adverse effects of subconvulsive stimuli; it is possible to override the anticonvulsant effect with a modest increase in energy/charge of electric stimulus
Antidepressant		
SSRI, NDRI	Bupropion, fluoxetine	Prolonged seizures reported; clinical significance unknown. Concurrent administration not contraindicated
SARI	Trazodone	Prolonged seizures reported; clinical significance unknown. Concurrent administration not contraindicated Rare case reports of cardiovascular complications in patients with and without cardiac disease – more likely to occur at high dosages (i.e., above 300 mg/day)
Irreversible MAOI	Phenelzine	Possible need for a vasopressor agent for resuscitation requires that this combination be avoided, if possible
Antihypertensive	β-blockers (e.g., propranolol)	May potentiate bradycardia and hypotension with subconvulsive stimuli Confusion reported with combined use
Antipsychotic	Clozapine	Recent RCT shows ECT plus clozapine to be superior to clozapine alone for treatment-resistant schizophrenia. However, increased seizure duration reported in 16.6% of patients; spontaneous (tardive) seizures reported following ECT
Benzodiazepine	Clonazepam, diazepam, lorazepam	Increased seizure threshold with potential adverse effects of subconvulsive stimuli or abbreviated seizure May interfere with seizure quality
Caffeine		Increased seizure duration Reports of hypertension, tachycardia, and cardiac dysrhythmia

Electroconvulsive Therapy (ECT) (cont.)

Class of Drug	Example	Interaction Effects
Lithium		Lithium toxicity may occur, perhaps due to an increased permeability of the blood-brain barrier; decrease or discontinue lithium and monitor patient. Concurrent administration not contraindicated if lithium level within the therapeutic range (preferably lower end)
L-tryptophan		Increased seizure duration
Magnesium		Magnesium may increase seizure threshold. Avoid use of magnesium preparations prior to ECT
Theophylline		Increased seizure duration, status epilepticus. Concurrent administration not contraindicated if serum level within the therapeutic range

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ANTIPSYCHOTICS

Classification*

- Antipsychotics can be classified as follows:

Chemical Class	Agent	Page
First-Generation Antipsychotics (FGAs)[D]		See p. 158
Butyrophenone	Haloperidol	
Dibenzoxazepine	Loxapine	
Diphenylbutylpiperidine	Pimozide	
Phenothiazines		
– aliphatic	Example: Chlorpromazine	
– piperazine	Example: Perphenazine	
– piperidine	Example: Periciazine[C]	
Thioxanthenes	Example: Thiothixene	
Second-Generation Antipsychotics (SGAs)[A]		See p. 175
Alkyl-phenylketone	Lumateperone	
Benzisoxazole	Iloperidone[B], paliperidone, risperidone	
Benzisothiazol	Lurasidone	
Benzothiazolylpiperazine	Ziprasidone	
Dibenzodiazepine	Clozapine	
Dibenzooxepinopyrrole	Asenapine	
Dibenzothiazepine	Quetiapine	
Thienobenzodiazepine	Olanzapine	
Third-Generation Antipsychotics (TGAs)		See p. 206
N-arylpiperazine	Brexpiprazole	
Phenylpiperazine	Aripiprazole, cariprazine[B]	

[A] Formerly called "atypical," which describes antipsychotics that have a decreased incidence of EPSE at therapeutic doses; the boundaries, however, between "typical" and "atypical" antipsychotics are not definitive. "Atypical" antipsychotics (1) may have low affinity for D_2 receptors and are readily displaced by endogenous dopamine in striatum (e.g., clozapine, quetiapine); (2) may have high affinity for D_2 receptors and high muscarinic blockade-anticholinergic activity; (3) block both D_2 and 5-HT_2 receptors (e.g., risperidone, clozapine, olanzapine, quetiapine); (4) may have high affinity for D_4 receptors (e.g., clozapine, olanzapine, loxapine); (5) may lack a sustained increased prolactin response (e.g., clozapine, quetiapine, olanzapine); (6) may show mesolimbic selectivity (e.g., olanzapine, clozapine, quetiapine). [B] Not marketed in Canada. May be available through Health Canada's Special Access Programme. [C] Not marketed in the USA [D] Formerly called "typical" and "conventional."

General Comments

- Despite the categorization of first, second, or third generation, these classes are heterogeneous and differences exist in the pharmacology, adverse effect profiles, and cost of the agents within them. These differences often help guide individualized treatment decisions. A non-industry sponsored, randomized clinical trial comparing the effectiveness of a number of antipsychotics[1] suggests that some FGAs may be considered as appropriate first-line therapeutic alternatives. This has been reflected in a number of treatment guidelines, which suggest that selection of an antipsychotic agent should be tailored to best meet an individual's specific needs
- Generally, FGAs, especially high-potency agents, are associated with a higher incidence of extrapyramidal side effects (EPSE) and tardive dyskinesia (TD). Haloperidol, in particular, appears to be associated with more EPSE, even when lower doses are used. SGAs are less likely to result in EPSE and

* This classification system is under review.

TD but many are associated with a higher burden of metabolic adverse effects, most notably clozapine and olanzapine. The metabolic adverse effect burden appears to be even higher in children and adolescents than in adults. A systemic review found limited evidence for differences between antipsychotic classes and lipid abnormalities, and concludes that individual antipsychotics and not classes should likely be evaluated by their own risk profiles

- All classes have demonstrated efficacy in the treatment of positive symptoms of psychosis (e.g., hallucinations, delusions, hostility, and aggression) and relapse prevention
- Few comparative trials are available in first episode psychosis in children and adolescents, however, a network meta-analysis showed that, comparatively, clozapine, molindone, olanzapine, and risperidone demonstrated superior placebo-compared efficacy over aripiprazole, asenapine, lurasidone, paliperidone, quetiapine, and ziprasidone. In terms of tolerability, lurasidone seemed to separate as more favorable than other antipsychotics[2]
- No antipsychotic has demonstrated clinically significant efficacy to decrease primary negative symptoms of schizophrenia (i.e., affective flattening, alogia, amotivation, social withdrawal). Statistical differences were seen in one network meta-analysis[3] for clozapine, risperidone, lurasidone, and asenapine
- A recent systematic review showed no significant evidence that prodopaminergic agents like modafinil and methylphenidate reduce negative symptoms[4]
- Early response to antipsychotics (PANSS reduction $\geq$20% within first 2 weeks of therapy) in schizophrenia appears to effect ultimate response to therapy for adults. This finding has been replicated in adolescents taking olanzapine, quetiapine, and aripiprazole after 2–3 weeks of therapy.[5, 6, 7] In these studies, a response of less than 20% ("nonresponse") within 2 weeks on the much briefer PANSS-6 had similar predictive abilities as the larger PANSS-30
- There is currently insufficient evidence to support a clinically significant benefit of any antipsychotic class on cognitive symptoms. Certain adverse effects of these agents may impair cognition, especially via anticholinergic activity
- Accumulating evidence from studies suggests a correlation between early treatment of psychotic disorders and better prognosis
- Antipsychotics may have a number of off-label uses in children and adolescents, including psychosis, mood disorders, aggression, agitation, conduct disorder, intermittent explosive disorder, tic disorders; in autism, they are often utilized to reduce target symptoms of irritability, temper tantrums, psychomotor excitement, and severe hyperactivity
- Children and adolescents appear to be more sensitive to the effects of antipsychotics than adults, especially to metabolic adverse effects; initiate treatment with low doses and increase slowly; reassess dose and need for continued use regularly; monitor closely for metabolic and neurological adverse effects and drug-induced movement disorders
- Nonadherence or partial adherence to antipsychotic medication is a frequent problem, associated with increased relapse rates, hospitalization, and suicide in individuals with schizophrenia. Adherence is influenced by multiple factors (e.g., insight, adverse effects, cost, stigma, homelessness, substance use disorder)

Pharmacology

- See p. 160 (FGAs), p. 179 (SGAs), and p. 207 (TGAs) for specific pharmacological statements and the related charts listing effects on neurotransmitters/receptors p. 218
- Individual differences such as genetics, age, sex, comorbidities, and concomitant medications may impact the pharmacodynamic and pharmacokinetic profile (i.e., absorption, distribution, metabolism, elimination) of an antipsychotic and may account for individual variations of treatment response

Adverse Effects

- When individualizing therapy, the greater variation in adverse effect profiles observed among agents may play a more significant role in the selection of an antipsychotic than the smaller differences in efficacy profiles
- The differential affinities for various receptors and the rates of dissociation from receptors account for many observed adverse effects (i.e., theoretically, the faster an antipsychotic dissociates from the D_2 receptor, the lower the risk of EPSE and possibly TD) noted with antipsychotics. See detailed discussion of adverse effects associated with SGAs (pp. 183–189), TGAs (p. 209), FGAs (pp. 161–165) and related charts (pp. 219–219)
- When determining the need for an adverse effect-related intervention, consider the following:
  1) How serious is the adverse effect? (e.g., life-threatening adverse events such as agranulocytosis or neuroleptic malignant syndrome require immediate intervention)
  2) How bothersome is the adverse effect? (e.g., has the patient considered/developed nonadherence as a result of the adverse effect?)
  3) What interventions, if any, have been implemented in an attempt to resolve the adverse effect(s) and what was the outcome of these?
  4) What is the anticipated duration of treatment with the antipsychotic?

Antipsychotics (cont.)

5) What are the benefits (e.g., therapeutic alliance, better adherence, etc.) vs. risks (e.g., relapse, added cost, adverse events, etc.) associated with any potential intervention?

- Potential interventions may include:
  1) Discontinuing the antipsychotic
  2) Watchful waiting (in some instances, tolerance to the adverse effect may develop)
  3) Altering the administration schedule
  4) Lowering the antipsychotic dose
  5) Switching to an alternate antipsychotic
  6) Adding a non-pharmacological or pharmacological agent to treat the adverse effect
  7) Changing diet (e.g., eliminating caffeine intake where there is akathisia)

Lab Tests/Monitoring

- Monitoring frequencies proposed below are guidelines and should not replace good clinical judgment

Type	Details	Frequency
Initial history	Complete medical, substance use, smoking, and family history (including history of CVD, dyslipidemias, and glucose dysregulation/diabetes in first-degree relatives)	Baseline
Physical assessment	Physical exam	Baseline and annually
	Waist circumference, weight, and BMI	Baseline and routinely thereafter (e.g., monthly for first 3 months, then every 3 months thereafter while on a stable antipsychotic dose)
	Blood pressure and pulse	Baseline and regularly thereafter (e.g., at 1 week, 1 month, 3 months, and every 6 months thereafter). More frequent assessments may be necessary during dosage titration with asenapine, chlorpromazine, clozapine, quetiapine, risperidone, thioridazine, and ziprasidone
	Temperature	When clinically indicated
Clinical assessment	Hyperprolactinemia	Screen for symptoms (e.g., decreased libido, erectile or ejaculatory dysfunction, menstrual changes, galactorrhea) at baseline and routinely thereafter (e.g., 1 month, 3 months, 6 months, and 12 months, then annually thereafter)
	EPSE, TD, and other abnormal involuntary movements	Screen at baseline and routinely thereafter (e.g., at 2 weeks, monthly for 3 months, then every 6 months thereafter)
	Diabetes	Screen for symptoms (e.g., polydipsia, polyuria, polyphagia with weight loss, etc.) at baseline and routinely thereafter (e.g., baseline, at 3 months, 12 months, then annually thereafter)
	Sexual dysfunction	Screen at baseline and routinely (e.g., at 3 months, 6 months, and every 6 months thereafter)
	Sleep/sedation	Assess at baseline and routinely (e.g., at 2 weeks, 1 month, 2 months, 6 months, as clinically indicated thereafter)
	Anticholinergic effects	Screen for symptoms (e.g., confusion, constipation, dry eyes/mouth, blurred vision, urinary retention) at baseline and routinely as indicated (e.g., at 2 weeks, 1 month, 2 months, and as clinically indicated thereafter)

Type	Details	Frequency
Laboratory and other assessments	ECG	At baseline, along with serum potassium and magnesium levels in individuals with cardiac risk factors (e.g., heart disease – especially heart failure, recent MI, or preexisting conduction abnormalities; syncope; family history of early (before age 40) sudden cardiac death; or long QT syndrome) is recommended prior to prescribing antipsychotics with more definite associations/higher degrees of prolongation (e.g., chlorpromazine, haloperidol, pimozide, thioridazine, ziprasidone)
	EEG	If seizures or myoclonus occur
	Fasting blood glucose	At baseline and routinely (e.g., at 3 months, then at least annually thereafter). More frequent monitoring (baseline, at 3 months, then at least every 6 months) has been recommended. More frequent assessments may be required in patients with obesity, a family history of diabetes, or those who gain more than 5% of their body weight while on medication or experience a rapid increase in waist circumference
	A1c	If impaired fasting glucose or diabetes present; obtain q4 months in uncontrolled diabetes
	Fasting lipid profile	At baseline and routinely (e.g., at 3 months and at least annually thereafter). More frequent monitoring (baseline, at 3 months, then at least every 6 months) has been recommended
	Complete blood count	At baseline, annually, and as clinically indicated
	Liver function tests	At baseline and at 1 month, annually, and as clinically indicated
	Prolactin level	As clinically indicated if signs of hyperprolactinemia exist
	TSH (quetiapine only)	At baseline and every 6 months

Nursing Implications

- Nurses may assist in baseline and routine assessment of mental status (to identify target symptoms & their subsequent response to drug therapy), physiological parameters (including weight, waist circumference, BP, heart rate, temperature, presence of abnormal movements), as well as documentation of any comorbidities, concomitant medications, and issues around medication adherence
- Excessive use of caffeine or other stimulants may worsen anxiety and/or agitation and may counteract the beneficial effects of antipsychotics
- Adverse effects from therapy are a commonly cited reason for nonadherence
- Early onset (more common during the first 3 months of therapy) adverse effects include:
  - Anticholinergic effects: dry mouth, dry eyes, blurry vision, constipation, urinary retention, confusion/delirium
    - Frequent sips of water, chewing ice chips or sugarless gum, or artificial saliva products may relieve dry mouth. Artificial tears may relieve dry eyes. Blurred vision is usually transient; only near vision affected; if severe, pilocarpine eye drops may be prescribed
    - Anticholinergics reduce peristalsis and decrease intestinal secretions, leading to constipation; increasing fluids and bulk (e.g., bran, salads), as well as fruit in the diet is beneficial; increasing exercise may help; if necessary, docusate, osmotic laxative (e.g., PEG 3350), stimulant laxative (e.g., bisacodyl/senna), or lubiprostone may be used for chronic constipation
    - Monitor patient's intake and output; urinary retention can occur
  - Extrapyramidal side effects
    - Early-onset extrapyramidal side effects (EPSE) (e.g., acute dystonia, akathisia, and pseudoparkinsonism); acute dystonia typically occurs within the first few days and akathisia and pseudoparkinsonism within the first 6 weeks of treatment. These adverse effects are more commonly noted with FGAs, although they may occur with any antipsychotic. Anticholinergic agents (e.g., benztropine, trihexyphenidyl, procyclidine – Canada) may be used to prevent and/or treat some but not all of these conditions (see p. 244 for details on treatment)
    - The use of prophylactic anticholinergic medications to prevent EPSE is controversial as these agents can worsen anticholinergic adverse effects, including delirium. Young males taking risperidone or FGAs and individuals with a prior history of EPSE may be at a higher risk for developing EPSE and as such may be suitable candidates for prophylaxis on a temporary basis. If an anticholinergic is prescribed to treat EPSE, the need for continued use beyond 3 months should be reassessed periodically. While evidence conflicts, prophylactic anticholinergic use is usually avoided due to concern that regular use may increase risk of developing tardive dyskinesia
    - Hold dose and notify physician if patient develops acute dystonia, severe persistent EPSE (longer than a few hours), or has symptoms of jaundice or agranulocytosis (e.g., fever, sore throat, infection, cellulitis, weakness)
    - Be aware that akathisia can be misdiagnosed as anxiety or psychotic agitation and the incorrect treatment could be prescribed

Antipsychotics (cont.)

  - Postural hypotension, dizziness, and reflex tachycardia
    - Sitting on the side of the bed for a few minutes before rising or rising slowly from a seated position may help reduce falls
    - Hypotension may be compounded by concomitant administration of antihypertensives (e.g., propranolol, clonidine, guanfacine)
  - Somnolence, sedation
    - Caution patient not to perform activities requiring alertness until response to the drug has been determined
    - If drug is prescribed in the morning or during the day, suggest moving it to evening or bedtime and/or reduce dose
  - Activation: If drug is suspected of causing activation or restlessness or if patient has problems sleeping, evaluate for drug-induced akathisia; moving the dose to earlier in the day or dose reduction may be helpful
  - Weight gain and/or increased appetite may occur in patients receiving antipsychotics; proper diet, exercise, and avoidance of high-calorie beverages is important; monitor weight, waist circumference, and BMI during course of treatment
- Late-onset adverse effects include:
  - Metabolic effects: Dyslipidemias, glucose intolerance, type 2 diabetes mellitus (T2DM), weight gain; baseline and periodic evaluation of weight, waist circumference, BP, fasting blood glucose and lipid profiles recommended
  - Menstrual abnormalities, sexual dysfunction: Amenorrhea, sexual dysfunction including anorgasmia reported
  - Tardive movement disorders: Risk believed to increase with duration of treatment and total dose
  - Use the lowest effective dose for the shortest possible duration to minimize risk of development
  - Valbenazine and deutetrabenazine (vesicular monoamine transporter inhibitors) are FDA approved for TD in adults but unstudied in youth; consider discontinuing antipsychotic where feasible
- Other significant adverse effects (may not be time dependent) include:
  - Agranulocytosis/leukopenia/neutropenia
    - Can occur with all antipsychotic agents. Patients with low neutrophil counts should be monitored closely for fever and other signs of infection and treated accordingly
    - Discontinue antipsychotic use if persistent absolute neutrophil count less than 1.5×10^9/L
  - Diabetic Ketoacidosis
    - Has been noted to occur in individuals treated with antipsychotics despite no history of hyperglycemia
    - Signs/symptoms may include hypotension, tachycardia, fruity odor on breath, lethargy, shortness of breath, nausea, vomiting, abdominal pain, polyuria, polydipsia
  - Neuroleptic malignant syndrome (NMS)
    - Patients should avoid dehydration and exposure to extreme heat and humidity as antipsychotics affect the body's ability to regulate temperature
    - Signs of NMS may include autonomic instability, hyperpyrexia, altered mental status, rigidity, elevated creatine phosphokinase and elevated white blood cell count, and potentially renal failure
    - Antipsychotic should be discontinued immediately and supportive measures implemented
  - Seizures (typically dose related)
    - Use antipsychotics with caution in patients with seizure disorder, especially if poorly controlled
  - QTc prolongation/arrhythmia
    - Monitor patients for symptoms that may be associated with QTc interval prolongation (e.g., dizziness, fainting spells, palpitations, nausea, and vomiting). Symptomatic patients will require an ECG prior to starting antipsychotic
  - Photosensitivity reactions
    - Avoid by providing sunscreen agents with UVA protection and suggest that protective clothing be worn until response to sun has been determined; patients should wear UVA-protective sunglasses in bright sunlight
- Administration tips:
  - Injectables
    - Do not confuse short-acting injectables with their long-acting (depot) counterparts

- As with all parenteral drug products, injections should be inspected visually for appearance as per product monographs. Formulations that do not match manufacturer specifications regarding appearance or show evidence of leakage should not be used. Many of the new long-acting injectables are suspensions and must be used within a certain timeline once prepared and shaken vigorously prior to injection to ensure a homogeneous mixture (see individual product monographs or package inserts for details)
- Check patients on depot injections for indurations; Z-track administration technique is recommended for most depot injections

– Oral disintegrating tablets (ODT), sublingual tablets, and other special formulations
  - Clozapine (USA only), olanzapine, and risperidone are available in ODT formulations – tablets disintegrate in the mouth and are subsequently swallowed. These products are not absorbed sublingually. Because they start to disintegrate upon contact with moisture, ODT tablets should be handled carefully with dry hands (direct contact with hands should be avoided as much as possible)
  - If part tablets of olanzapine are required, break tablet carefully and wash your hands after this procedure. Avoid exposure to powder as dermatitis, eye irritation, and allergic reactions have been reported. Store broken tablet in tight, light-resistant container (tablet discolors) and use within 7 days
  - Asenapine is a sublingual tablet that should be dissolved under the tongue and not swallowed
  - Paliperidone is supplied in a non-absorbable shell that allows for extended release. The tablet should be swallowed whole and not chewed or crushed. The tablet shell may appear in the stool and is not a cause for concern
  - Seroquel XR is an extended release version of quetiapine and tablets must be swallowed whole and not chewed or crushed

– Food effects
  - Asenapine, lurasidone, and ziprasidone have low oral bioavailability. Asenapine is formulated in a sublingual formulation that requires patients not to eat or drink for 10 min after administration to maximize absorption. Conversely, the absorption of both lurasidone and ziprasidone is enhanced by food. A minimum intake of 350 calories (lurasidone) and 500 calories (ziprasidone) has been suggested
  - Avoid grapefruit juice and related citrus fruits with antipsychotics as it may interfere with drug effects. Risperidone solution should not be taken with tea or caffeine-containing soft drinks. Pectinate in apple juice reported to have a physical incompatibility with perphenazine and fluphenazine – unknown whether this interaction occurs with other antipsychotics

- For additional agent-specific administration instructions, see pp. 168–168 (FGAs), pp. 194–196 (SGAs), and p. 212 (TGAs)

Patient Instructions

- For detailed patient instructions on antipsychotics, see the Patient and Caregiver Information Sheets (details p. 429)

First-Generation Antipsychotics (FGAs)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/ Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Chlorpromazine	Aliphatic phenothiazine	Dopamine, serotonin/Antagonist	Largactil[C], Thorazine[B]	Tablets: 10 mg[B], 25 mg, 50 mg, 100 mg, 200 mg[B] Short-acting injection: 25 mg/mL[B]	Not recommended in children under 6 months
Flupenthixol (Flupentixol)[C]	Thioxanthene	Dopamine, serotonin/Antagonist	Fluanxol Fluanxol Depot	Tablets: 0.5 mg, 3 mg Long-acting injection (flupenthixol decanoate depot): 20 mg/mL, 100 mg/mL	Safety and efficacy not established in children and adolescents under age 18
Fluphenazine	Piperazine phenothiazine	Dopamine/Antagonist	Moditen[C], Prolixin[B] Modecate[C], Prolixin decanoate[B]	Tablets: 1 mg, 2 mg[C], 2.5 mg[B], 5 mg, 10 mg[B] Oral elixir[B]: 2.5 mg/5 mL Oral liquid concentrate[B]: 5 mg/mL Short-acting injection[B]: 2.5 mg/mL Long-acting injection (fluphenazine decanoate depot): 25 mg/mL[B], 100 mg/mL[C]	Safety and efficacy not established in children and adolescents under age 18
Haloperidol	Butyrophenone	Dopamine/Antagonist	Haldol Haldol Decanoate	Tablets: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg Oral solution[B]: 2 mg/mL Short-acting injection (haloperidol lactate): 5 mg/mL Long-acting injection (haloperidol decanoate depot): 50 mg/mL[B], 100 mg/mL	Not recommended in children under age 3
Loxapine	Dibenzoxazepine	Dopamine, serotonin/Antagonist	Adasuve[B] Loxapac[C] Loxitane[B] Xylac[C]	Inhalation powder: 10 mg in single-use inhaler Short-acting injection: 50 mg/mL Capsules: 5 mg, 10 mg, 25 mg, 50 mg Tablets: 2.5 mg, 5 mg, 10 mg, 25 mg, 50 mg	Safety and efficacy not established in children
Methotrimeprazine (Levomepromazine)[C]	Aliphatic phenothiazine	Not listed	Nozinan	Tablets: 2 mg, 5 mg, 25 mg, 50 mg Short-acting injection: 25 mg/mL	Safety and efficacy not established in children and adolescents under age 18
Periciazine[C]	Piperidine phenothiazine	Not listed	Neuleptil	Capsules: 10 mg, 20 mg Oral drops: 10 mg/mL	Dosage recommendations available for children age 5 and above
Perphenazine	Piperazine phenothiazine	Dopamine/Antagonist	Trilafon	Tablets: 2 mg, 4 mg, 8 mg, 16 mg	Safety and efficacy not established in children and adolescents under age 18
Pimozide	Diphenylbutyl-piperidine	Dopamine/Antagonist	Orap	Tablets: 1 mg[B], 2 mg, 4 mg[C]	Dosage recommendations available for children

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/ Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Thioridazine[B],[D]	Piperidine phenothiazine	Dopamine, serotonin/Antagonist	Mellaril	Tablets: 10 mg, 25 mg, 50 mg, 100 mg	Safety and efficacy not established in children and adolescents under age 18
Thiothixene[B]	Thioxanthene	Not listed	Navane	Capsules: 1 mg, 2 mg, 5 mg, 10 mg	Safety and efficacy not established in children and adolescents under age 12
Trifluoperazine	Piperazine phenothiazine	Dopamine, serotonin/Antagonist	Stelazine	Tablets: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg[C]	Dosage recommendations available for children age 6–12
Zuclopenthixol[C]	Thioxanthene	Dopamine/Antagonist	Clopixol Clopixol Acuphase Clopixol Depot	Tablets: 10 mg, 25 mg Short/intermediate-acting injection (zuclopenthixol acetate depot): 50 mg/mL Long-acting injection (zuclopenthixol decanoate depot): 200 mg/mL	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Restricted to treatment-refractory schizophrenia in adults

Indications[a‡] (👍 approved)

Schizophrenia and Psychotic Disorders

- 👍 Schizophrenia (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, trifluoperazine – Canada and USA; methotrimeprazine, zuclopenthixol – Canada; thiothixene – USA)
- 👍 Chronic schizophrenia in which the main manifestations do not include excitement, agitation or hyperactivity (flupenthixol, pimozide – Canada)
- 👍 Acute agitation associated with schizophrenia (loxapine inhalation powder – USA)
- 👍 Rapid control of acute manifestations of schizophrenia and acute psychotic episodes (short-acting injectable FGAs, e.g., haloperidol short-acting injection, zuclopenthixol acetate – Canada)
- 👍 Refractory schizophrenia (thioridazine – USA)
- 👍 Schizophrenia in patients with depressive symptoms (perphenazine + amitriptyline – USA)
- 👍 Psychotic disorders (chlorpromazine, fluphenazine, haloperidol – Canada and USA; methotrimeprazine, perphenazine, trifluoperazine – Canada; thiothixene – USA)
- 👍 Adjunctive therapy in psychotic patients for control of residual prevailing hostility, impulsiveness, and aggressiveness (periciazine – Canada)
- Psychotic depression (loxapine is metabolized to the antidepressant amoxapine)
- Delusional disorder

Bipolar

- 👍 Manic phase of bipolar disorder/manic syndromes (chlorpromazine – Canada and USA; trifluoperazine – Canada)
- 👍 Manic states: Rapid control of acute manifestations (haloperidol short-acting injection – Canada)
- 👍 Acute agitation associated with bipolar I disorder (loxapine inhalation powder – USA)
- 👍 Psychosis associated with manic-depressive syndromes (haloperidol, methotrimeprazine – Canada)

Acute Agitation and Delirium

- 👍 Chronic brain syndrome and intellectual disability: Management of aggressive and agitated behavior (haloperidol – Canada)
- 👍 Short-term treatment of hyperactive children with excessive motor activity and concomitant conduct disorders such as impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance (haloperidol – USA)

[a] Adult population unless otherwise stated. ‡ Indications listed here do not necessarily apply to all FGAs or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

First-Generation Antipsychotics (FGAs) (cont.)

- Severe behavior problems in children with combative, explosive hyperexcitability that is not accounted for by immediate provocation with failure to respond to non-antipsychotic medication or psychotherapy (haloperidol – USA)
- Anxiety, tension, and agitation
- Delirium (chlorpromazine, haloperidol)

Anxiety

- Generalized anxiety disorder (GAD): Short-term management (trifluoperazine – USA)
- Depression/depressed mood with anxiety in association with chronic physical disease or with moderate–severe anxiety and/or agitation (perphenazine + amitriptyline – USA)
- Conditions associated with anxiety and tension, such as autonomic disturbances, personality disturbances, emotional disturbances secondary to such physical conditions as resistant pruritus (methotrimeprazine, trifluoperazine – Canada)
- Restlessness and apprehension before surgery (chlorpromazine – Canada and USA)

Movement Disorders

- Dyskinesias: Management of various types, including Sydenham's and Huntington's chorea (chlorpromazine, fluphenazine, haloperidol, pimozide)

Mental Health – Other

- Tourette's disorder and tic disorders: Symptomatic control of tics and vocal utterances in adults and children (haloperidol – Canada and USA, pimozide – USA, in those who have failed standard treatment and daily life is severely compromised by motor and phonic tics)
- Severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (chlorpromazine, haloperidol – USA); the potential risks of these agents should be considered
- Insomnia (methotrimeprazine – Canada)
- ADHD: Short-term treatment of hyperactive children who exhibit excessive motor activity that is manifested as impulsive behavior, difficulty sustaining attention, aggression, mood lability, and/or poor frustration tolerance; generally not considered a first-line option
- Trichotillomania

Other

- Analgesia in pain due to cancer, zona (i.e., herpes zoster/shingles), trigeminal neuralgia, and neurocostal neuralgia, and in phantom limb pains and muscular discomforts (methotrimeprazine – Canada)
- Nausea and vomiting: Prevention and control (chlorpromazine, perphenazine – Canada and USA; methotrimeprazine, trifluoperazine – Canada; haloperidol – USA)
- Nausea, vomiting, and restlessness/anxiety associated with attacks of acute intermittent porphyria: Management (chlorpromazine – USA)
- Potentiator of anesthetics; in general anesthesia, can be used as both a pre- and post-sedative and analgesic (methotrimeprazine – Canada)
- Tetanus: Treatment adjunct (chlorpromazine – USA)
- Intractable hiccups (chlorpromazine, haloperidol – USA)

General Comments

- Generally speaking, FGAs, especially high-potency agents, are associated with a higher incidence of EPSE and TD and a lower potential for metabolic adverse events compared to SGAs, but this is not absolute and risk should be considered on an individual medication basis
- There is scant evidence to support the notion that FGAs are inferior to newer antipsychotics with the exception of clozapine in terms of efficacy in psychosis
- Low-potency FGAs are more likely to be associated with anticholinergic effects (e.g., constipation, dry mouth/eyes, blurred vision, urinary retention, confusion/delirium), antihistaminic effects (e.g., sedation, weight gain), and anti-adrenergic effects (e.g., orthostatic hypotension, dizziness, and reflex tachycardia). Cardiac conduction abnormalities and QTc interval prolongation are a significant concern with some FGAs, notably pimozide and thioridazine

Pharmacology

- See p. 153 and p. 217
- All FGAs antagonize postsynaptic D_2 receptors as their main pharmacological activity. They may be further subclassified as low (e.g., chlorpromazine), moderate (e.g., perphenazine, loxapine), or high (e.g., haloperidol, zuclopenthixol) potency agents according to their affinity for the D_2 receptor
- Antagonism of D_2 receptors in the various dopaminergic pathways is thought responsible for the efficacy and also for some of the adverse effects associated with these agents. D_2 receptor antagonism in the mesolimbic pathway relieves positive symptoms of psychosis; D_2 antagonism in the mesocortical pathway may worsen negative symptoms or cognition; D_2 antagonism in the nigrostriatal pathway may result in EPSE (short-term) and TD (long-term); D_2 antagonism in the tuberoinfundibular tract may lead to hyperprolactinemia

- FGAs also have varying abilities to antagonize three other main receptors – α_1-adrenergic, H_1, and M_1 receptors. Generally, their affinities for these three receptors are the inverse of their affinities for the D_2 receptor. For example, haloperidol has high affinity for D_2, but low affinity for α_1, H_1, and M_1. Based on haloperidol's pharmacological profile, it could be predicted that EPSE and hyperprolactinemia would be more common; whereas adverse effects related to α_1 (e.g., postural hypotension), H_1 (e.g., sedation), and M_1 (e.g., constipation) antagonism would be less common

Dosing

- See table pp. 221–223
- Current opinion suggests use of lower doses of FGAs are required; clinical efficacy of FGAs is correlated with D_2 binding above 60%, while hyperprolactinemia and EPSE are associated with D_2 occupancies of 50–75% and 78%, respectively (see p. 162 and p. 163); outcome studies show that most patients respond similarly to low doses as to high doses, with fewer adverse effects
- Patients with acute symptoms may require slightly higher doses than chronic patients; manic patients may need even higher doses; maintenance doses for bipolar patients tend to be about half those used in schizophrenia
- Lower doses are used in first-episode patients, children, and those with compromised liver and/or renal function
- *Renal Impairment*: Chlorpromazine, haloperidol – no dose adjustment required, monitor for hypotension, sedation, and EPSE
- The usefulness of serum levels is still unclear; it is suggested that a curvilinear relationship exists with some antipsychotics, and they may be effective within a narrow plasma level range (therapeutic window, e.g., haloperidol (1–10 ng/mL)[10])

Pharmacokinetics

- See table pp. 221–223 for kinetics of individual agents
- **Hepatic** primary route of metabolism: Chlorpromazine, haloperidol, loxapine, methotrimeprazine, perphenazine, pimozide, trifluoperazine
- **Renal** primary route of excretion: Chlorpromazine, pimozide, trifluoperazine

Oral

- May be taken with or without meals. Take with food or milk to prevent/reduce GI upset – haloperidol
- AVOID grapefruit juice (and related citrus fruits) with pimozide (see Drug Interaction p. 173)
- Peak plasma level of oral doses generally reached 1–4 h after administration
- Highly bound to plasma proteins
- Most phenothiazines and thioxanthenes have active metabolites
- Metabolized extensively by the liver; specific agents inhibit CYP450 metabolizing enzymes (see pp. 221–223)

Short-acting IM

- Generally peak plasma level reached sooner than with oral formulation – watch for orthostatic hypotension
- Bioavailability usually greater than with oral drug (loxapine excepted); dosage should be adjusted accordingly
- Loxapine single IM doses produce lower concentrations of active metabolite for first 12–16 h than oral therapy does – this may result in a different balance between D_2 and 5-HT_2 blockade
- Zuclopenthixol Acuphase: Short/intermediate-acting depot injection (see p. 223); peak plasma level: 24–48 h; duration of action = 48–72 h

Long-acting IM

- See chart on pp. 228–229
- Bioavailability is greater than with oral agents (by a factor of at least 2); eliminates bioavailability problems related to absorption and first-pass metabolism and maintains stable plasma concentrations
- Injections can be painful; highest pain reported 5 min after administration and tends to decrease gradually over 2–10 days
- Presence of "free" fluphenazine in multi-dose vials of fluphenazine decanoate is responsible for high peak plasma level seen within 24 h of injection – monitor for EPSE

Adverse Effects

- See chart on p. 219 for incidence of adverse effects; the incidence may differ between different dosage forms of the same drug (e.g., oral vs. long-acting vs. short-acting injection) or with dosage
- High-potency agents typically cause more D_2-related adverse effects (EPSE and hyperprolactinemia), low-potency agents cause more α_1, H_1, and M_1-related adverse effects (e.g., postural hypotension, sedation, anticholinergic effects), and moderate-potency agents fall somewhere in the middle
- Some adverse effects may be preventable by employing simple strategies (e.g., slow upwards titration or dosing schedule manipulation in order to decrease adverse effects related to higher peak levels)
- Many adverse effects are transient; persistent effects may have a number of therapeutic treatment alternatives including altering the drug administration schedule or dosage, adding a medication or other non-drug therapy to alleviate the side effect, or switching to a different antipsychotic medication with less propensity for causing the particular adverse effect

First-Generation Antipsychotics (FGAs) (cont.)

CNS Effects

- Confusion, disturbed concentration, disorientation (more common with high doses). Concomitant anticholinergic agents may exacerbate this effect
- Extrapyramidal – acute onset: A result of antagonism at dopamine D_2 receptors (extrapyramidal reactions correlated with D_2 binding over 80%)
  - Includes acute dystonias, akathisia, pseudoparkinsonism, Pisa syndrome, rabbit syndrome – see p. 244 for onset, symptoms, and treatment options and pp. 242–262 for detailed treatment options
  - More common with high-potency FGAs vs. moderate- to low-potency agents, also more common with FGAs vs. SGAs/TGAs – see pp. 244–248 to compare incidence of EPSE associated with these agents
  - Most commonly occur within the first days to weeks of treatment and are dose related
- Extrapyramidal – late onset or tardive movement disorders
  - Includes tardive akathisia, tardive dyskinesia, and tardive dystonia – see p. 247 for onset, symptoms, and therapeutic management options
  - Late-onset movement disorders usually develop after months or years of treatment; they may be irreversible so prevention is key – use lowest doses for shortest possible time period and assess for signs of movement disorders regularly. Tardive symptoms may not be alleviated and may be exacerbated by antiparkinsonian medications (e.g., benztropine)
  - Annual risk of TD with FGAs estimated to be 4–5% with a cumulative risk of up to 50%.[11]
- Neuroleptic malignant syndrome (NMS) – rare disorder characterized by autonomic dysfunction (e.g., tachycardia and hypertension), hyperthermia (heat produced by muscle contraction), altered consciousness, and muscle rigidity with an increase in creatine kinase and myoglobinuria. Can occur with any class of antipsychotic agent, at any dose, and at any time (although usually occurs early in the course of treatment). Risk factors may include dehydration, young age, male sex, organic brain syndromes, exhaustion, agitation, and rapid or parenteral antipsychotic administration
- Sedation – common, especially with low-potency agents, following treatment initiation, and with dosage increases. Usually transient, but some individuals may complain of persistent effects. [Management: Prescribe majority of daily dose at bedtime; minimize use of concomitant CNS depressants, if possible]
- Seizures – all FGAs may lower seizure threshold, resulting in seizures ranging from myoclonus to generalized tonic-clonic seizures. At usual dosage ranges, seizure rates are less than 1% for FGAs. Risk appears greater with low-potency agents (e.g., chlorpromazine) and is dose related. May occur if dose increased rapidly or may also be secondary to hyponatremia associated with SIADH. Use with caution in patients with a history of seizures

Anticholinergic Effects

- More common with low-potency FGAs. See p. 219 for a comparison of the anticholinergic effects of FGAs
- Many of these adverse effects are often dose related and may also resolve over time without treatment. Treatment options may include reducing the dose of the FGA or switching to another antipsychotic with less potential to cause anticholinergic effects or employing a specific drug or non-drug strategy to treat the adverse effect (see below for suggestions)
- Blurred vision [Management: Use adequate lighting when reading; pilocarpine 0.5% eye drops]
- Constipation [Management/prevention: Increase dietary fiber and fluid intake, increase exercise, or use a stool softener (e.g., docusate), osmotic laxatives (e.g., PEG 3350), stimulant laxative (e.g., bisacodyl/senna), or lubiprostone]
- Delirium – characterized by agitation, confusion, disorientation, visual hallucinations, tachycardia, etc. May result with use of high doses or combination anticholinergic medication. Drugs with high anticholinergic activity have also been associated with slowed cognition and selective impairments of memory and recall [Management: Discontinuation of offending agent(s)
- Dry eyes (Management: Artificial tears, wetting solutions for contact lens wearers)
- Dry mouth/mucous membranes – if severe or persistent, may predispose patient to yeast infection (oral candidiasis) [Management: Sugar-free gum and candy, oral lubricants (e.g., MoiStir, OraCare D), pilocarpine mouthwash – see p. 105]
- Urinary retention [Management: Bethanechol]

Cardiovascular Effects

- Arrhythmias and ECG changes (see p. 184):
  - Thioridazine has the most compelling evidence regarding QTc prolongation, with numerous reports of torsades de pointes and sudden cardiac death. There also appears to be an association for pimozide at higher doses. There have also been reports of torsades de pointes with haloperidol. A list of drugs associated with QTc prolongation can be found at https://crediblemeds.org
  - Tachycardia may occur as a compensatory mechanism to orthostatic hypotension caused by α_1-adrenergic antagonism (in children, hypotension is less common, but tachycardia more common). Tachycardia due to anticholinergic effects in the absence of above conditions, may be treated with a low-dose peripherally-acting β-blocker

- Orthostatic hypotension/compensatory tachycardia/dizziness/syncope – may occur as a result of α_1-adrenergic antagonism. More likely to occur with low-potency FGAs and those given parenterally. When employing antipsychotics that are potent α_1-adrenergic antagonists, increase doses gradually to minimize hypotension as well as sinus and reflex tachycardia. [Management: Rise slowly, divide the daily dose, consider a switch to another agent, increase fluid and salt intake; treatment with fluid-retaining corticosteroid – fludrocortisone; DO NOT USE NOREPINEPHRINE, as it may lower blood pressure]
- Venous thrombosis – low-potency agents may be a risk factor for venous thrombosis in predisposed individuals, case reports of deep vein thrombosis in patients on chlorpromazine – usually occurs in first 3 months of therapy
- Cardiovascular disease (CVD) is the leading cause of death in individuals with schizophrenia. There may be a number of contributing factors to CVD in this population, including smoking, sedentary lifestyles, poverty, poor nutrition, reduced access to health care, and a number of metabolic abnormalities including weight gain, dyslipidemias, glucose intolerance, and hypertension. Please see Endocrine and Metabolic Effects for more details on these effects and their role in CVD

Endocrine & Metabolic Effects

- Antidiuretic hormone dysfunction:
  - Disturbances in antidiuretic hormone function: PIP (polydipsia, intermittent hyponatremia, and psychosis syndrome); prevalence in schizophrenia estimated at 6–20% (adults), can range from mild cognitive deficits to seizures, coma, and death; increased risk in smokers and patients with alcohol use disorders. Monitor sodium levels in chronically treated patients to help identify risk for seizures [Management: Fluid restriction, demeclocycline up to 1200 mg/day, captopril 12.5 mg/day, propranolol 30–120 mg/day; replace electrolytes]
- Dyslipidemia:
  - See p. 154 for suggested monitoring guidelines
  - The low-potency FGAs carry a higher metabolic liability (weight gain, glucose dysregulation, and lipid abnormalities) than moderate- or high-potency agents
- Glucose intolerance, insulin resistance, hyperglycemia, type 2 diabetes, diabetic ketoacidosis:
  - Schizophrenia is a risk factor for the development of type 2 diabetes mellitus. While the risk appears highest with SGAs (most notably clozapine and olanzapine), there are also reports in the literature of glycosuria, glucose intolerance, hyperglycemia, and diabetes mellitus occurring in association with FGAs. Within FGAs, the risk may be greater with low-potency agents or phenothiazines
  - See p. 154 for suggested monitoring guidelines
  - Treatment options may include lifestyle and dietary modifications; switching to another antipsychotic associated with a lower potential for glucose dysregulation; adding metformin
- Hyperprolactinemia:
  - Prolactin level may be elevated up to 10-fold from baseline. Develops over first week of treatment and usually remains throughout treatment course
  - More common in women than men despite similar doses. Adolescents and children may be at higher risk
  - *Clinical consequences* of elevated prolactin levels: Patients may be asymptomatic or may have short-term symptoms such as galactorrhea, gynecomastia, menstrual irregularities, and sexual dysfunction, or potential long-term risks such as osteoporosis (as a result of decreased bone density secondary to chronic hypogonadism), pituitary tumors, and breast cancer (data conflicting)
  - *Effects in women:* Breast engorgement and lactation (may be more common in women who have previously been pregnant), amenorrhea (with risk of infertility), menstrual irregularities, changes in libido, hirsutism (due to increased testosterone). Bone mineral density loss may be more intense in females than males and may vary by ethnic group; extent of loss may correlate with duration of hyperprolactinemia. Recommended women with hyperprolactinemia or amenorrhea for more than 12 months have a bone mineral density evaluation
  - *Effects in men:* Gynecomastia, rarely galactorrhea, decreased libido, and erectile or ejaculatory dysfunction
  - The 2009 PORT schizophrenia guidelines rank the relative risk for hyperprolactinemia and sexual side effects with antipsychotics as follows: Risperidone = paliperidone > FGAs > olanzapine > ziprasidone > quetiapine ≥ clozapine > aripiprazole
  - See p. 154 for Lab Test/Monitoring Suggestions
  - *Treatment options:* Assuming discontinuation of antipsychotic therapy is not an option, the preferred treatment is to switch to another antipsychotic agent with a reduced risk of hyperprolactinemia – weighing the potential risk for relapse associated with this action. Other treatment options may include lowering the dose or adding a medication to treat the condition. Case reports that addition of low dose aripiprazole (partial dopamine agonist) has been effective in lowering prolactin
- Metabolic syndrome:
  - See p. 186 for details

First-Generation Antipsychotics (FGAs) (cont.)

  - Little is known about the relative risks of FGAs with respect to causing or contributing to metabolic syndrome, as heightened awareness of the relationship between antipsychotics and this condition arose primarily during the era of SGAs. Weight gain, dyslipidemias, and glycemic abnormalities have been noted to occur with low-potency FGAs
- Weight gain:
  - Reported in up to 40% of patients receiving treatment with FGAs. More likely to occur early in treatment (e.g., within first 6 months) and the risk appears greater with low-potency FGAs[13]
  - The 2009 PORT schizophrenia guidelines rank the relative risk for weight gain with antipsychotics as follows: Clozapine = olanzapine > low-potency FGAs > risperidone = paliperidone = quetiapine > moderate-potency FGAs > high-potency FGAs = aripiprazole = ziprasidone
  - The mechanism by which antipsychotics may influence weight gain is unknown, but may be a result of multiple systems including 5-HT_{1B}, 5-HT_{2C}, α_1, and H_1 blockade, prolactinemia, gonadal and adrenal steroid imbalance, and increase in circulating leptin; may also be due to sedation and inactivity, carbohydrate craving, and excessive intake of high-calorie beverages to alleviate drug-induced thirst and dry mouth

GI Effects

- Anorexia, dyspepsia
- Constipation – see Anticholinergic Effects p. 184
- Dysphagia – (difficulty swallowing) and aspiration have been reported with antipsychotic use. Use all agents cautiously in individuals at risk for developing aspiration pneumonia (e.g., developmental delays)
- Dry mouth – see Anticholinergic Effects p. 184
- Pancreatitis – rare reports of pancreatitis with haloperidol
- Peculiar taste, glossitis
- Sialorrhea, difficulty swallowing, gagging [see p. 188 for additional information on management]
- Vomiting common after prolonged treatment, especially in smokers

Urogenital & Sexual Effects

- Sexual effects may result from altered dopaminergic (including hyperprolactinemia – main cause of sexual dysfunction in women), serotonergic, ACh, α_1, or H_1 activity
- An estimated 25–60% of patients on FGAs report sexual dysfunction
- Treatment options may include: 1) dosage reduction, 2) waiting 1–3 months to see if tolerance develops, 3) switching antipsychotics, or 4) adding a medication to treat the problem (see below for treatment suggestions regarding specific types of dysfunction; evidence for their use is based primarily on open-label studies and case reports)
- *Anorgasmia* [Management: Bethanechol (10 mg tid or 10–25 mg prn before intercourse), neostigmine (7.5–15 mg prn), cyproheptadine (4–16 mg/day), amantadine (100–300 mg/day)]
- *Ejaculation dysfunction* (including inhibition of ejaculation, abnormal ejaculation, retrograde ejaculation – especially thioridazine) – reported to be the most common sexual disturbance associated with FGAs [Management suggestions: For retrograde ejaculation – imipramine (25–50 mg at bedtime), or cyproheptadine (4–16 mg/day)]
- *Erectile dysfunction, impotence* – erectile dysfunction is reported to occur in 23–54% of males on FGAs [Management suggestions: Bethanechol (10 mg tid or 10–50 mg prn before intercourse), sildenafil (25–100 mg prn), amantadine (100–300 mg/day)]
- *Libido* – decreased libido [Management: Neostigmine (7.5–15 mg prn) or cyproheptadine (4–16 mg prn 30 min before intercourse)]
- *Priapism* – rare case reports of priapism occurring in patients on FGAs (e.g., chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, thiothixene, and trifluoperazine). Antagonism of α-adrenergic receptors is believed to play a role in this effect
- *Urinary retention* – see Anticholinergic Effects p. 184

Ocular Effects

- Blurred vision/dry eyes – see Anticholingeric Effects p. 184
- Cataracts/lens changes: Association reported between phenothiazine use and cataract formation
- Lenticular pigmentation
  - Related to long-term use of antipsychotics (primarily chlorpromazine)
  - Presents as glare, halos around lights or hazy vision
  - Granular deposits in eye

- Vision is usually not impaired; may be reversible if drug stopped
- Often present in patients with antipsychotic-induced skin pigmentation or photosensitivity reactions

- Pigmentary retinopathy (retinitis pigmentosa)
  - Primarily associated with chronic use/higher doses of the low-potency FGAs thioridazine or chlorpromazine [annual ophthalmological examination recommended]
  - Reduced visual acuity (may occasionally reverse if drug stopped) or blindness can occur
- With chronic use, chlorpromazine can cause pigmentation of the endothelium and Descemet's membrane of the cornea; it may cause a slate-bluish discoloration of the conjunctiva, sclera, and eyelids – may not be reversible when drug stopped

Hematological Effects

- Blood dyscrasias, including those affecting erythropoiesis, granulopoiesis, and thrombopoiesis, have been reported with most antipsychotics
- Clinically significant hematological abnormalities with antipsychotics medication are rare. Accordingly, the development of any blood abnormalities in individuals on antipsychotics, especially other than clozapine, should undergo rigorous medical assessment to determine the underlying cause
- *Aplastic anemia* – reported primarily with chlorpromazine and trifluoperazine. Also noted to have occurred with fluphenazine, flupenthixol, haloperidol, perphenazine, and thioridazine
- *Eosinophilia* – not typically of clinical significance unless severe. Reported with chlorpromazine and trifluoperazine
- *Leukopenia* [defined as WBC less than 4×10^9/L] and *neutropenia/agranulocytosis* [neutropenia (defined as ANC less than 1.5×10^9/L) may be subclassified as mild (ANC = 1–1.5×10^9/L), moderate (ANC = 0.5–1×10^9/L) or severe (also termed agranulocytosis – defined as ANC less than 0.5×10^9/L or sometimes as ANC less than 0.2×10^9/L)]
  - Mild neutropenia may be transient (returning to normal without a change in medication/dose), or progressive (continuing to drop, leading to agranulocytosis)
  - Reported incidence of severe neutropenia in 1 study was 0.02% with phenothiazines and 0.003% with butyrophenones
- *Thrombocytopenia* – reported with a number of FGAs, including chlorpromazine and thioridazine. In most cases withdrawal of the medication was reported to result in normalization of platelet counts

Hepatic Effects

- Cholestatic jaundice
  - Occurs in less than 0.1% of patients within first 4 weeks of treatment, with most antipsychotics
  - Noted to occur in 0.1–0.5% of patients taking chlorpromazine
  - Signs include yellow skin, dark urine, pruritus, may require discontinuation of the offending agent – reversible if drug discontinued
- Transient asymptomatic transaminase elevations (ALT 2–3 times the upper limit of normal) reported with haloperidol (up to 16% of patients)

Hypersensitivity Reactions

- Rarely, asthma, laryngeal, angioneurotic or peripheral edema, and anaphylactic reactions occur
- Loxapine inhalation powder has been associated with bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. This product is only available through a restricted program in the USA – Adasuve Risk Evaluation and Mitigation Strategy (REMS) – in which the health care facility must have immediate access to advanced airway management personnel and equipment
- Photosensitivity and photoallergy reactions including sunburn-like erythematous eruptions that may be accompanied by blistering. Occurs most commonly with low-potency phenothiazines. Patients should be advised to avoid excess exposure to sunlight and wear appropriate clothing/sunscreen
- Hypersensitivity reactions at injection site (especially haloperidol decanoate 100 mg/mL); indurations reported with higher doses (see p. 229)
- Cases of systemic lupus erythematosus reported with chlorpromazine

Temperature Regulation

- Altered ability of body to regulate response to changes in temperature and humidity; may become hyperthermic or hypothermic in temperature extremes due to inhibition of the hypothalamic control area. Patients should be advised to avoid temperature extremes, dress appropriately, and maintain adequate hydration

D/C Discontinuation Syndrome

- Abrupt discontinuation (or in some cases large dose reductions) of an antipsychotic may be associated with a number of potential risks including:

1. Discontinuation syndromes – typically characterized by development of a number of symptoms including nausea, vomiting, diarrhea, diaphoresis, cold sweats, muscles aches and pains, insomnia, anxiety, and confusion. Many are believed to result from cholinergic rebound. Usually appear within days of discontinuation [Management: Mild cases may only require comfort and reassurance; for more severe symptoms consider restarting the antipsychotic followed by slow taper if possible; or, if rebound cholinergic effects present, consider adding an anticholinergic agent short term]

First-Generation Antipsychotics (FGAs) (cont.)

2. Psychosis – exacerbation or precipitation of psychosis including a severe, rapid onset or supersensitivity psychosis, most notable with clozapine and possibly quetiapine vs. FGAs. Most likely to occur within the first 2–3 weeks post discontinuation or sooner [Management: Restart antipsychotic]
3. Movement disorders – withdrawal dyskinesias noted to appear, usually around 2–4 weeks post abrupt withdrawal [Management: Restart antipsychotic and taper slowly]. Rebound dystonia, parkinsonism, and akathisia also reported to occur, usually within days to the first week post discontinuation [Management: Restart antipsychotic and taper slowly or treat with appropriate anti-EPSE medication]

- Abrupt cessation of a long-acting or depot antipsychotic is of less concern as plasma concentrations decline slowly (i.e., drug tapers itself)
- ☞ **AFTER PROLONGED USE, THESE MEDICATIONS SHOULD BE WITHDRAWN GRADUALLY WHERE POSSIBLE.** If switching to another antipsychotic, see pp. 233–234 for specific recommendations
- Readers may find the website https://www.switchrx.com helpful for managing antipsychotic switching

Precautions

- Hypotension occurs most frequently with parenteral use, especially with high doses; the patient should be in supine position during short-acting IM administration and remain supine or seated for at least 30 min; measure BP before and following each IM dose
- IM injections should be administered slowly; the deltoid offers faster absorption as it has better blood perfusion; need to ensure children have adequate muscle mass in deltoid – gluteal or thigh sites may be preferred alternatives
- Use with caution in the presence of cardiovascular disease, chronic respiratory disorder, hypoglycemia or convulsive disorders
- Caution in prescribing to patients with known or suspected hepatic disorder; monitor clinically and measure transaminase level (ALT) periodically
- Should be used very cautiously in patients with narrow-angle glaucoma
- Prior to prescribing thioridazine or pimozide, a baseline ECG and serum electrolytes should be done and monitored periodically during the course of therapy. DO NOT USE these drugs in patients with QTc interval over 450 msec or with significant risk factors for QTc prolongation/development of torsades de pointes (see p. 184)
- Monitor if QTc interval exceeds 420 msec, discontinue drug if 500 msec exceeded; do not exceed daily dosing guidelines for thioridazine or pimozide
- Allergic cross-reactivity (rash) between chlorpromazine and clozapine reported

Toxicity

- In the majority of cases, overdose is associated with a low mortality and morbidity rate as FGAs have a high therapeutic index
- Symptoms may include nausea and vomiting, confusion, hallucinations, agitation, drowsiness progressing to coma, hypotension, respiratory depression, electrolyte imbalances, ECG changes (QTc prolongation) and arrhythmias, and/or EPSE. Convulsions may appear late in course

Management

- See p. 191 for further details on antipsychotic management

Use in Pregnancy◊

- For each individual, consider the risks of not treating/undertreating (e.g., illness relapse, self-harm, poor adherence with prenatal care, poor nutrition, exposure to additional medication or herbal remedies, increased alcohol, tobacco or illicit drug use, deficits in mother-infant bonding) vs. the risks of continuing or starting an antipsychotic
- Pregnancy-related changes (i.e., increased body weight, blood volume, and body fat, altered drug metabolism, and increased drug excretion) may require the use of higher drug doses to maintain efficacy. Postpartum dose tapering may be needed as liver metabolism and fluid volumes return to baseline levels
- Early data suggests *in utero* exposure to FGAs may decrease infant birth weight, increase the risk of small size for gestational age, and slightly increase the risk of preterm birth. However, data is conflicting and complicated by differences in study design, study population (e.g., use of concurrent medications, psychiatric diagnosis), and the inherent difficulties in studying medication use during pregnancy
- Consider the potential effects on delivery (e.g., maternal hypotension with chlorpromazine) and for withdrawal effects in the newborn if used during the third trimester. There are case reports of fetal and neonatal toxicity including NMS, dyskinesia, EPSE (manifested by heightened muscle tone and increased rooting and tendon reflexes persisting for several months), neonatal jaundice, and postnatal intestinal obstruction. In 2011, the US FDA and Health Canada asked manufacturers to update their prescribing information to warn clinicians and patients that third-trimester use of antipsychotics is associated with risk of EPSE and withdrawal symptoms in newborns. Symptoms in the neonate may

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

include: Feeding disorder, hypertonia, hypotonia, tremor, respiratory distress, and agitation. Signs related to atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, abdominal bloating, tachycardia, and feeding disorders in neonates can occur

- Avoid, if possible, FGAs that have no or very limited human pregnancy data (e.g., flupenthixol, loxapine, periciazine, pimozide, pipotiazine, thiothixene, and zuclopenthixol). FGAs with a larger reproductive safety profile include chlorpromazine, fluphenazine, haloperidol, perphenazine, and thioridazine[14]
- High-potency FGAs (e.g., haloperidol) may yield the best therapeutic benefit with the least anticholinergic and sedative effects, however, comparative safety with other FGAs in pregnancy is unavailable
- If an antipsychotic will be used during pregnancy, consider patient enrollment or registration in any relevant studies or pregnancy exposure registries (e.g., in the USA: FDA list of pregnancy registries http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm134848.htm)
- **Chlorpromazine** was initially used for nausea and vomiting during pregnancy. This data suggests it is safe if used in low doses during pregnancy. However, when given near term, particularly in doses of more than 500 mg, it may increase the incidence of respiratory distress in the neonate and has been implicated in producing lethargy and EPSE in the neonate
- **Flupenthixol**: Limited human data. No relevant animal data
- **Fluphenazine**: Limited human data. Human data suggest risk in 3rd trimester. Case reports of withdrawal effects (e.g., EPSE, irritability) that developed up to 6 weeks post delivery with in utero exposure to the long-acting injection formulation
- **Haloperidol**: Limited human data. Animal data suggest moderate risk. Although the rates of major malformations in humans do not appear to be greater than baseline there have been cases of limb defects after first-trimester exposure. If haloperidol is required during pregnancy, ultrasound with particular attention to limb formation should be considered in first-trimester exposures. Two case reports of neonate tardive dyskinesia. Case report of NMS with third-trimester exposure to haloperidol and risperidone
- **Loxapine**: Manufacturer reports outcomes from only 3 pregnancies with loxapine exposure – one child born with achondroplasia, one with multiple unspecified malformations, and one with tremors at 15 weeks of age
- **Methotrimeprazine**: Limited human data; probably compatible. No relevant animal data. Initially used in obstetric analgesia
- **Periciazine**: No published human data. No relevant animal data
- **Perphenazine**: Limited human data. Sporadic cases of both fetal malformations and gestational metabolic complications also emerged from a recent retrospective study investigating the use of perphenazine during pregnancy
- **Pimozide**: Limited human data (fewer than 5 case reports). Animal data suggest low risk
- **Thioridazine**: Limited human data. No relevant animal data
- **Thiothixene**: Limited human data. No teratogenic effects seen in animals
- **Trifluoperazine**: Limited human data. Animal data suggest low risk. Studies indicate no causal relationship between trifluoperazine exposure and congenital malformations
- **Zuclopenthixol**: Published human data (fewer than 10 case reports). Not teratogenic in animals

Breast Milk

- For each individual, consider the benefits of breastfeeding vs. the risks of infant drug exposure via breast milk and possible effects on milk production
- Antipsychotics, like most medications, pass into breast milk, however, antipsychotic amounts found are generally low. Antipsychotics have been detected in breast milk in concentrations of 0.1–11%. Long-term effects on the infant are largely unknown
- If used while breastfeeding, use lowest effective dose and monitor infant's progress
- Very limited data. Single or small numbers of case reports have found no short-term adverse effects of breastfed infants exposed to flupenthixol, perphenazine or zuclopenthixol. One report of drowsiness and lethargy with chlorpromazine. Cases of a decline in mental and psychomotor development at age 12–18 months with higher doses of haloperidol (20–40 mg/day) and chlorpromazine (200–600 mg/day). Long-term effects on neurodevelopment are largely unknown. A 5-year follow-up study of 7 breastfed infants exposed to chlorpromazine found no developmental deficits
- Phenothiazines given directly to infants and children for sedation or cough and cold symptoms have been associated with apnea and sudden infant death syndrome (SIDS); however, phenothiazine exposure via breast milk is significantly lower
- For more detailed information on specific drugs and lactation, refer to the Drugs and Lactation Database (https://www.ncbi.nlm.nih.gov/books/NBK501922/)

First-Generation Antipsychotics (FGAs) (cont.)

Nursing Implications

Oral

- May be taken with or without meals. Take with food or milk to prevent/reduce GI upset (haloperidol)
- AVOID grapefruit juice and related citrus fruits with pimozide (See Drug Interactions p. 173)
- Dilute oral liquid solutions with water or an acidic beverage such as juice; DO NOT mix with tea or coffee
- Avoid skin contact with liquid forms of fluphenazine as it may result in contact dermatitis
- Discard markedly discolored solutions; however, a slight yellowing does not affect potency
- Storage: Protect liquids from light

Short-acting Injections

- Watch for orthostatic hypotension, especially with parenteral administration of chlorpromazine or methotrimeprazine; keep patient supine or seated for 30 min afterwards; monitor BP before and after each injection
- Give IM into upper outer quadrant of buttocks or in the deltoid (deltoid offers faster absorption as it has better blood perfusion, must ensure children have adequate muscle mass for this site); alternate sites, charting (L) or (R); massage slowly after, to prevent sterile abscess formation; tell patient injection may sting
- Prevent contact dermatitis by keeping drug solution off patient's skin and clothing and injectors' hands, AVOID contact with fluphenazine, in particular
- Do not let drug stand in syringe for longer than 15 min as plastic may adsorb drug
- If irritation occurs at the chlorpromazine IM injection site, dilute drug with 0.9% sodium chloride or 2% procaine HCl
- Haloperidol lactate can be administered IM in the same syringe as lorazepam. Compatibility of other medications in syringe is reviewed in [15, 16]
- Storage: Room temperature and protected from light (chlorpromazine HCl, fluphenazine HCl, haloperidol lactate, loxapine HCl, methotrimeprazine HCl)

Long-acting IM

- Strongly recommended to establish tolerability with an oral form prior to initializing a long-acting IM dosage form
- Short-acting formulations may be required for supplementation while dosage titration is taking place
- Use a needle of at least 21 gauge; give deep IM into large muscle (e.g., buttock, using Z-track method); rotate sites and specify in charting
- As with all oily injections, it is important to ensure, by aspiration before injection, that inadvertent intravascular injection does not occur
- Do not let drug stand in syringe for longer than 15 min as plastic may adsorb drug
- DO NOT massage injection site
- Storage: Room temperature and protected from light – haloperidol decanoate, flupenthixol decanoate, fluphenazine decanoate

Intravenous

- Some short-acting injection formulations can be administered IV. Long-acting formulations CANNOT be administered via this route.
- IV administration generally occurs in the intensive care or surgical setting
- Haloperidol administered IV is associated with higher rates of QTc prolongation, torsades de pointes, and sudden death
- Methotrimeprazine injection diluted with 5% dextrose can be given as a slow infusion (20–40 drops/min) to potentiate anesthetics during surgery

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Acetylcholinesterase inhibitor (central)	Donepezil, galantamine, rivastigmine	Interaction not well described in children and adolescents. May enhance neurotoxicity of antipsychotics, presumably due to a relative acetylcholine/dopamine imbalance (i.e., increased acetylcholine in the presence of dopamine receptor blockade) in the CNS. Case reports of severe EPS (e.g., generalized rigidity, shuffling gate, facial grimacing) in elderly patients within a few days of starting an antipsychotic (risperidone or haloperidol) and an acetylcholinesterase inhibitor (donepezil). Symptoms resolved after discontinuing the antipsychotic agent, the acetylcholinesterase inhibitor, or both
Adsorbent	Activated charcoal, attapulgite (kaolin-pectin), cholestyramine	Oral absorption decreased significantly when used simultaneously; give at least 1 h before or 2 h after the antipsychotic
α_1-adrenergic blocker	Doxazosin, prazosin, terazosin	Additive hypotension, particularly with low-potency FGAs like chlorpromazine. Antipsychotics generally cause hypotension via α_1 blockade
Anesthetic	Enflurane	Additive hypotension, particularly with low-potency FGAs such as chlorpromazine
Amylinomimetic	Pramlintide	Pramlintide slows the rate of gastric emptying. Antipsychotics with significant anticholinergic effects can further reduce GI motility. Use drugs with minimal anticholinergic effects at the lowest effective dose. See frequency of adverse effects table p. 219
Antiarrhythmic	General	DO NOT COMBINE with chlorpromazine, fluphenazine, pimozide or thioridazine. NOT recommended with phenothiazines or zuclopenthixol. CAUTION with all other FGAs. Possible additive prolongation of QTc interval and associated life-threatening cardiac arrhythmias. Factors that further increase the risk include uncompensated heart failure, recent acute MI, eating disorders (e.g., anorexia), bradycardia, electrolyte imbalances (e.g., hypokalemia, hypomagnesemia), and a family history of sudden death. Also see FGA Cardiovascular Effects p. 162
	Amiodarone, quinidine	With quinidine, increased peak plasma level and AUC of haloperidol by ~2-fold due to inhibited metabolism via CYP2D6 and/or displacement from tissue binding With amiodarone and quinidine likely to increase chlorpromazine, fluphenazine, pimozide, and thioridazine levels via inhibition of CYP2D6; further increasing risk of QT prolongation
Antibiotic		
Macrolide	Clarithromycin, erythromycin	DO NOT COMBINE with pimozide or thioridazine. NOT recommended with phenothiazines or zuclopenthixol. CAUTION with all other FGAs. Possible additive prolongation of QTc interval and associated life-threatening cardiac arrhythmias. Factors that further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects p. 162 With clarithromycin, decreased clearance of pimozide by 46% due to inhibition of metabolism via CYP3A4. Two reports of deaths occurring within days of adding clarithromycin to pimozide. Azithromycin (which does not inhibit CYP3A4) may have a lower risk when used with pimozide, although all macrolides including azithromycin are specifically listed as contraindicated in the US pimozide product monograph Clarithromycin may decrease clearance of chlorpromazine and haloperidol. Similar interaction with erythromycin likely. Increased antipsychotic adverse effects including prolonged QT interval possible
Quinolone	Ciprofloxacin, levofloxacin, moxifloxacin	DO NOT COMBINE with pimozide or thioridazine. NOT recommended with phenothiazines or zuclopenthixol. CAUTION with all other FGAs. Possible additive prolongation of QTc interval and associated life-threatening cardiac arrhythmias. Factors that further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects p. 162. Ciprofloxacin is thought to have less potential for QTc prolongation but there are isolated cases of increased QTc CAUTION. Potential to exacerbate psychiatric conditions as quinolone-induced psychosis has been reported With ciprofloxacin, may increase plasma level of trifluoperazine due to inhibition of metabolism via CYP1A2. Clinical significance unknown
Anticholinergic	Antidepressants, antihistamines, antiparkinsonian drugs	Increases the risk of anticholinergic adverse effects (e.g., dry mouth, urinary retention, inhibition of sweating, blurred vision, constipation, paralytic ileus, confusion, toxic psychosis)
Anticoagulant	Warfarin	Decreased INR possible with chlorpromazine or haloperidol

First-Generation Antipsychotics (FGAs) (cont.)

Class of Drug	Example	Interaction Effects
Anticonvulsant	General	All FGAs may lower seizure threshold. At usual dosage ranges, seizure rates are less than 1%. Risk greater with low-potency FGAs and is dose related
	Carbamazepine	Decreased antipsychotic plasma level via potent induction of CYP3A4, CYP1A2, CYP2D6, and/or possibly UGT1A4. Note it may take 2–4 weeks to reach maximum induction and an equivalent period to return to baseline after discontinuation of an inducer With haloperidol, decreased plasma level of carbamazepine (40%). Conflicting reports on haloperidol levels likely a result of a dose-dependent interaction (i.e., the interaction is more significant with increasing carbamazepine doses). Carbamazepine 100 mg daily reduced haloperidol levels by 15% while carbamazepine 600 mg daily reduced haloperidol levels by 75%. Adjust dose as needed Likely to decrease levels of chlorpromazine, fluphenazine, flupenthixol, thiothixene, and zuclopenthixol With loxapine, increased plasma level of carbamazepine epoxide metabolite
	Lamotrigine	Chlorpromazine may inhibit metabolism of lamotrigine, resulting in increased lamotrigine level. Clinical significance unknown
	Phenobarbital, phenytoin	Decreased plasma level of antipsychotic due to potent induction of metabolism; for phenytoin via CYP2C9 and CYP3A4; for phenobarbital primarily via CYP1A2, CYP2C9, and CYP3A4 With phenytoin, reduced levels of chlorpromazine, haloperidol, and thioridazine reported. With phenobarbital, reduced levels of chlorpromazine (by 25%) and haloperidol reported. Limited data available; interactions with other FGAs probable. Adjust antipsychotic dose as needed Loxapine decreased phenytoin levels in one case report
	Valproate (divalproex, valproic acid)	Chlorpromazine inhibits the metabolism of valproate, resulting in increased valproate level. Clinical significance unknown
Antidepressant	General	DO NOT COMBINE with pimozide or thioridazine and CAUTION with all other FGAs applies to the majority of antidepressants, due to possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. Factors that further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects p. 162 and Antipsychotic Augmentation Strategies p. 235
SSRI	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Case report of QT prolongation and patient collapsing with concurrent chlorpromazine and fluoxetine Case report of galactorrhea and amenorrhea with loxapine and fluvoxamine possibly via additive increase in prolactin level Increased EPS and akathisia
		Increased plasma level of antipsychotic due to inhibition of metabolism of CYP1A2 (potent – fluvoxamine), 2D6 (potent – fluoxetine and paroxetine), and/or 3A4 (fluvoxamine). Adjust antipsychotic dose as needed
		DO NOT COMBINE with pimozide or thioridazine; CAUTION with all other FGAs due to additive prolongation of QTc interval. A single dose of pimozide added to citalopram did not alter the kinetics of pimozide, but did cause a prolongation of QTc by ~10 ms Pimozide levels: With paroxetine, 151% higher AUC and 62% higher peak level. With sertraline, 40% higher AUC and peak level. Case reports of bradycardia with concurrent use of pimozide and fluoxetine
		Haloperidol level: With fluoxetine, 20–35% higher levels. With fluvoxamine, 23–60% higher. With sertraline, 28% higher
		Phenothiazine level: With fluvoxamine, thioridazine level 3-fold higher. With paroxetine, perphenazine peak level 2- to 13-fold higher
SNRI	Desvenlafaxine, duloxetine, venlafaxine	DO NOT COMBINE with pimozide or thioridazine; CAUTION with all other FGAs; due to additive prolongation of QTc interval. Increased plasma level of thioridazine and other phenothiazines possible due to inhibition of CYP2D6 by duloxetine Venlafaxine increased AUC (70%) and peak plasma level (88%) of haloperidol; case report of urinary retention developing when venlafaxine was added to haloperidol

Class of Drug	Example	Interaction Effects
SARI	Nefazodone	DO NOT COMBINE with pimozide or thioridazine; CAUTION with all other FGAs; due to additive prolongation of QTc interval. Increased plasma level of pimozide possible due to inhibition of CYP3A4 by nefazodone
		Increased AUC (36%) and peak plasma level (13%) of haloperidol. Clinical significance likely minor
	Trazodone	Case reports of hypotension in combination with chlorpromazine or trifluoperazine, and fatal hepatic necrosis via additive hepatotoxicity of trazodone and phenothiazines
SMS	Vortioxetine	Serotonin modulators may enhance the dopamine blockade of antipsychotics and increase the risk of side effects
Cyclic	Amitriptyline, clomipramine, maprotiline, trimipramine	DO NOT COMBINE with pimozide or thioridazine. NOT recommended with phenothiazines or zuclopenthixol. CAUTION with all other FGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias
		Additive sedation, hypotension, and anticholinergic effects
		Haloperidol and phenothiazines may increase the plasma level of cyclic antidepressants (TCAs). TCAs may increase the plasma level of chlorpromazine. Clinical significance unknown
Irreversible MAOI, RIMA	Tranylcypromine, moclobemide	Additive hypotension, particularly with low-potency FGAs such as chlorpromazine
Antifungal	Fluconazole, itraconazole, ketoconazole, voriconazole	DO NOT COMBINE with pimozide or thioridazine. NOT recommended with phenothiazines or zuclopenthixol. CAUTION with all other FGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias
		Increased plasma level of antipsychotics due to inhibition of metabolism via CYP3A4 and possibly P-glycoprotein. Increased plasma level of haloperidol (by 30% with itraconazole)
Antihypertensive	Losartan, metoprolol, ramipril	Additive hypotensive effect particularly with low-potency FGAs such as chlorpromazine. Antipsychotics generally cause hypotension via α_1 blockade (see receptor table p. 217 and frequency of adverse effects table p. 219). Start with a lower dose of antipsychotic, titrate slowly, and monitor for orthostatic hypotension
	β-blocker	See Class of Drug "β-blocker" p. 172
	Calcium channel blocker	See Class of Drug "Calcium channel blocker" p. 173
	Clonidine	Clonidine lowers blood pressure by having agonist effects on presynaptic α_2-adrenergic receptors. FGAs that are potent α_2-adrenergic receptor antagonists can block clonidine's antihypertensive effects (see receptor table p. 217); additive hypotensive effects also possible
	Diuretic	See Class of Drug "Diuretic" p. 173
Antiparkinsonian	Levodopa, pramipexole, ropinirole	Potential for reduced therapeutic effect of antiparkinson agents. Antipsychotics reduce dopamine while antiparkinson agents increase dopamine in the CNS
Antipsychotic combination	General	Increased risk of adverse effects (e.g., EPS, elevated prolactin levels, sedation, hypotension, anticholinergic effects), increased cost, and potential for decreased adherence with use of multiple antipsychotic agents
		CAUTION – possible additive prolongation of QTc interval and associated life-threatening cardiac arrhythmias. DO NOT COMBINE with pimozide or thioridazine. Factors that further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects p. 162
	Haloperidol + aripiprazole	See TGA Drug Interactions, p. 215
	Haloperidol + SGAs	See SGA Drug Interactions, p. 201
	Phenothiazines (e.g., chlorpromazine, thioridazine) + SGAs	Possible additive QT prolongation (see above). DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. See SGA Drug Interactions, p. 201 for further information
	Pimozide + SGAs	Possible additive QT prolongation (see above). DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone
	Thioridazine + SGAs	Possible additive QT prolongation (see above). DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. See SGA Drug Interactions, p. 201 for further information
	Pimozide, thioridazine + FGAs	DO NOT COMBINE. Possible additive QT prolongation (see above)

First-Generation Antipsychotics (FGAs) (cont.)

Class of Drug	Example	Interaction Effects
Antiretroviral		See [17]
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Delavirdine, efavirenz, etravirine, nevirapine	CAUTION. Possible interactions as NNRTIs inhibit and induce CYP enzymes (e.g., delavirdine is a strong inhibitor of 2D6, nevirapine weakly inhibits 2D6. Efavirenz and etravirine induce 3A4 moderately, nevirapine weakly induces it) Delavirdine may increase levels of perphenazine, chlorpromazine, and zuclopenthixol due to CYP2D6 inhibition Efavirenz and etravirine may decrease levels of haloperidol and pimozide due to CYP3A4 induction
Protease inhibitor	Atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, simeprevir telaprevir, tipranavir	CAUTION. Complex interactions likely as various protease inhibitors potently inhibit as well as induce a variety of CYP enzymes (e.g., on CYP3A4, ritonavir is a potent inhibitor; atazanavir, boceprevir, darunavir, saquinavir, and telaprevir are strong inhibitiors; indinavir and fosamprenavir are mild to moderate inhibitors; tipranavir is an inducer. Low boosting doses of ritonavir have little effect on CYP2D6 but higher doses cause inhibition) AVOID with pimozide and thioridazine. Increased plasma level of pimozide/thioridazine possible due to inhibition of metabolism via CYP3A4 or CYP2D6, respectively, which increases the risk of cardiotoxicity (QT prolongation, cardiac arrest) Increased levels of FGAs metabolized by CYP3A4 (i.e., haloperidol, loxapine, phenothiazines, flupenthixol, and zuclopenthixol) possible. Higher doses of ritonavir may cause a significant increase even for FGAs that are weak substrates of CYP3A4 and/or are metabolized by CYP2D6 (e.g., potentially increased chlorpromazine levels with higher doses of ritonavir, but unlikely with lower boosting doses of ritonavir). With unboosted tipranavir, levels of the FGAs may be decreased. Clinical significance unknown. Adjust antipsychotic dose as needed
Antitubercular drug	Isoniazid	Limited data suggests some may experience increased plasma levels of haloperidol. Adjust antipsychotic dose as needed
	Rifabutin, rifampin, rifapentine	Decreased plasma level of haloperidol (by 30–70%) due to induction via CYP3A4 and/or P-glycoprotein with rifampin and accompanying increase in psychiatric symptoms. Adjust antipsychotic dose as needed
Anxiolytic		
Azapirone, benzodiazepines	Buspirone, clonazepam, diazepam, lorazepam	Synergistic effect with antipsychotics; used to calm agitated patients Potential for additive CNS adverse effects (e.g., dizziness, sedation, confusion, respiratory depression) and hypotension May increase extrapyramidal reactions Conflicting information with respect to effects on haloperidol levels from no change to increased levels (by 19%). Likely not clinically significant Haloperidol lactate can be administered IM in the same syringe as lorazepam
Belladonna alkaloid	Atropine, hyoscyamine, scopolamine	Additive anticholinergic effects (e.g., dry mouth, urinary retention, inhibition of sweating, blurred vision, constipation, paralytic ileus, confusion, toxic psychosis)
β-blocker		Also see Class of Drug "Antihypertensive" p. 171
	Pindolol	DO NOT COMBINE with thioridazine. Increased plasma level of thioridazine due to inhibition of metabolism via CYP2D6, thus increasing the risk of cardiotoxicity (QT prolongation, cardiac arrest) and pindolol level may be increased. Pindolol may increase plasma level of other phenothiazines
	Propranolol	DO NOT COMBINE with thioridazine. Increased plasma level of thioridazine (3- to 5-fold) due to inhibition of metabolism via CYP2D6, thus increasing the risk of cardiotoxicity (QT prolongation, cardiac arrest) Increased plasma level of both chlorpromazine (5-fold) and propranolol (decreased clearance by 25–32%). Case report of delirium and seizures. With haloperidol, case report of a severe hypotensive reaction

Class of Drug	Example	Interaction Effects
Betel (areca) nut		Two case reports of severe EPS following a period of heavy betel nut consumption in those who were maintained on a depot FGA (fluphenazine decanoate and flupenthixol, respectively). Symptoms occurred within 2 weeks and resolved 4–7 days after stopping Betel nut. Betel nut's potent cholinergic effects potentially counteracted procyclidine, the anticholinergic agent both patients were taking to control EPS
Calcium channel blocker	Diltiazem, verapamil	Also see Class of Drug "Antihypertensive" p. 171 DO NOT COMBINE with pimozide or thioridazine. Increased risk of cardiotoxicity (QT prolongation, cardiac arrest) due to possible additive calcium-channel blocking effects and increased plasma level of pimozide due to inhibition of metabolism via CYP3A4
Caffeine	Coffee, tea, cola, energy drinks, guarana or mate-containing products	Increased akathisia/agitation/insomnia Haloperidol oral liquid is incompatible with tea or coffee (see Nursing Implications, p. 168)
Cannabis/marijuana		Drugs with anticholinergic and α_1-adrenergic properties (e.g., chlorpromazine) can cause marked hypotension and increased disorientation
CNS depressant	Alcohol, antihistamines, hypnotics, opioids	CAUTION. Increased CNS effects (e.g., sedation, fatigue, impaired cognition). Additive orthostatic hypotension Alcohol may worsen EPS
Diuretic	Furosemide, hydrochlorothiazide	Also see Class of Drug "Antihypertensive" p. 171 above CAUTION with all FGAs. Diuretics can cause electrolyte disturbances resulting in additive QTc interval prolongation and risk of associated life-threatening cardiac arrhythmias. Monitor for dehydration, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects, p. 162
Disulfiram		CAUTION. Case reports of disulfiram-induced psychosis possibly due to blockade of dopamine β-hydroxylase, however, no increased psychotic features seen in small studies of participants with psychotic disorders Case report of decreased plasma level of perphenazine, increased level of its metabolite, and clinical decline; potentially due to inhibition of CYP2E1
Grapefruit juice		AVOID with pimozide. Increased plasma level of pimozide possible due to inhibition of metabolism via CYP3A4, which increases the risk cardiotoxicity (QT prolongation, cardiac arrest) Haloperidol levels not affected by consumption of grapefruit juice 600 mL/day for 7 days
H_2 antagonist	Cimetidine	Both elevated and decreased chlorpromazine plasma level has been reported. Chlorpromazine absorption may be decreased at higher doses of cimetidine, possibly due to increased gastric pH. Chlorpromazine metabolism may be decreased by inhibition of CYP2D6. Case reports of excessive sedation with the addition of cimetidine to chlorpromazine. May interact with other phenothiazines
Hormone	Oral contraceptive	Estrogen potentiates hyperprolactinemic effect of antipsychotics Case report of increased plasma level of chlorpromazine (6-fold) and development of severe tremor and dyskinesias after the addition of an oral contraceptive (ethinyl estradiol [50 micrograms]/norgestrel [0.5 mg]). Mechanism unknown; ethinyl estradiol is known to be an inhibitor of CYP1A2 and CYP2C19 and substrate of CYP3A4
Kava kava		Case report of atrial flutter and hypoxia after administration of IM haloperidol and lorazepam for severe aggression; suggested due to kava inhibition of CYP2D6
Lithium		CAUTION with all FGAs. Avoid toxic lithium plasma level when used concurrently with pimozide or thioridazine, since both pimozide/thioridazine and toxic lithium levels are associated with QT prolongation Although numerous studies indicate lithium and FGAs can be safely used together, there are rare cases of severe neurotoxicity (e.g., delirium, dyskinesias, seizures, encephalopathic syndrome, NMS) and EPS with concurrent lithium and haloperidol and other FGAs (i.e., loxapine, thiothixene or phenothiazines). Factors that may increase the risk of developing neurotoxicity are the presence of acute mania, pre-existing brain damage, infection, fever, dehydration, a history of EPS, and high doses of one or both agents Decreased plasma level of chlorpromazine (by 40%) and both increased and decreased lithium level reported

First-Generation Antipsychotics (FGAs) (cont.)

Class of Drug	Example	Interaction Effects
Opioid		CAUTION. Additive CNS effects. See Class of Drug "CNS depressant" p. 173
	Codeine	Inhibition of conversion of codeine to its active metabolite, morphine, with haloperidol and phenothiazines. Monitor for efficacy of pain control. Switch to an analgesic which doesn't require CYP2D6 conversion if needed
	Methadone	DO NOT COMBINE with pimozide or thioridazine. NOT recommended with phenothiazines or zuclopenthixol. CAUTION with all other FGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. Factors that further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects p. 162
	Tramadol	CAUTION. Tramadol lowers the seizure threshold; potential additive lowering of seizure threshold with FGAs
Prokinetic agent/Antiemetic	Metoclopramide	CAUTION. Metoclopramide is a potent central dopamine receptor antagonist that can cause EPS, hyperprolactinemia, and rarely NMS. Concurrent use with a FGA may increase the risk of these adverse effects
QT-prolonging agent	Antiarrhythmics (e.g., amiodarone, sotalol), antimalarials (e.g., chloroquine, mefloquine), antiprotozoals (e.g., pentamidine), arsenic trioxide, contrast agents (e.g., gadobutrol), dolasetron, droperidol, methadone, pazopanib, ranolazine, tacrolimus	DO NOT COMBINE with pimozide or thioridazine. NOT recommended with phenothiazines or zuclopenthixol. CAUTION with all other FGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. A study suggests ziprasidone causes less QT prolongation than thioridazine but about twice that of quetiapine, risperidone, haloperidol, and olanzapine. Factors that further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects, p. 162
Smoking (tobacco)		Smoking induces CYP1A2; polycyclic aromatic hydrocarbons in tobacco smoke are believed to be responsible for this induction, not nicotine Decreased plasma level of chlorpromazine (by 24%), fluphenazine (by 51%), and thioridazine (by 46%) and increased clearance of haloperidol (by 44–61%), perphenazine (by 33%), and thiothixene (by 36%) due to the induction of CYP1A2. Similar interaction with other phenothiazines possible. Case report of marked worsening of adverse effects and increased chlorpromazine plasma level after abrupt smoking cessation. Discuss with patient the effects of and assess on a regular basis any changes in smoking behavior
Stimulant	Amphetamine, methylphenidate	Antipsychotic agents may impair the stimulatory effect of amphetamines Case reports of worsening of tardive movement disorder and prolongation or exacerbation of withdrawal dyskinesia following antipsychotic discontinuation Concurrent use not recommended
Sympathomimetic	Cocaine	Increased risk of EPS (especially dystonia) with concurrent use, possibly via dopamine depletion from chronic use of cocaine
	Epinephrine/adrenaline, dopamine	AVOID using for the treatment of FGA-induced hypotension. May result in paradoxical fall in blood pressure as antipsychotics block peripheral α_1-adrenergic receptors, thus inhibiting α_1-vasoconstricting effects of epinephrine and leaving β-vasodilator effects relatively unopposed Norepinephrine and phenylephrine are safe substitutes for severe hypotension unresponsive to fluids
Zileuton		AVOID with pimozide. Zileuton is an inhibitor of CYP3A4 and may increase pimozide levels, increasing the risk of QTc interval prolongation and associated life-threatening cardiac arrhythmias. Factors which further increase the risk include anorexia, bradycardia, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects p. 162

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/ Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Asenapine	Dibenzo-oxepinopyrrole	Dopamine, serotonin, norepinephrine/ Antagonist	Saphris	Sublingual tablets: 5 mg, 10 mg	Safety and efficacy not established in children and adolescents under age 10 (manic or mixed episode bipolar disorder – USA only)
			Secuado[B]	Transdermal patch: 3.8 mg/24 h, 5.7 mg/24 h, 7.6 mg/24 h	Safety and efficacy not established in children and adolescents under age 18
Clozapine	Dibenzodiazepine	Dopamine, serotonin, norepinephrine/ Antagonist	Clozaril	Tablets: 25 mg, 50 mg[C], 100 mg, 200 mg[C]	Safety and efficacy not established in children and adolescents under age 18
			FazaClo ODT[B]	Oral disintegrating tablets: 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg	
			Versacloz[B]	Oral suspension: 50 mg/mL	
Iloperidone[B]	Benzisoxazole	Dopamine, serotonin/Antagonist	Fanapt	Tablets: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg	Safety and efficacy not established in children and adolescents under age 18
Lumateperone[B]	Alkyl-phenylketone	Multimodal	Caplyta	Capsules: 42 mg	Safety and efficacy not established in children and adolescents under age 18
Lurasidone	Benzisothiazol	Dopamine, serotonin/Antagonist	Latuda	Tablets: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg	Safety and efficacy not established in children and adolescents under age 13 (schizophrenia) and age 10 (depressive episode associated with bipolar depression)
Olanzapine	Thienobenzo-diazepine	Dopamine, serotonin/Antagonist	Zyprexa	Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg	Safety and efficacy not established in children and adolescents under age 13 (schizophrenia, manic or mixed episode bipolar disorder)
			Zyprexa Zydis	Oral disintegrating tablets: 5 mg, 10 mg, 15 mg, 20 mg	
			Zyprexa IntraMuscular	Short-acting injection (olanzapine tartrate): 10 mg/vial	
			Zyprexa Relprevv[B]	Long-acting injection (olanzapine pamoate): 210 mg/vial, 300 mg/vial, 405 mg/vial	Safety and efficacy not established in children and adolescents under age 18

Second-Generation Antipsychotics (SGAs) (cont.)

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/ Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
			Symbyax[B]	Capsules (fluoxetine/olanzapine): 25 mg/3 mg, 25 mg/6 mg, 25 mg/12 mg, 50 mg/6 mg, 50 mg/12 mg	Safety and efficacy not established in children and adolescents under age 10 (depressive episode associated with bipolar disorder)
			Lybalvi[B]	Tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, 20 mg/10 mg	Safety and efficacy not established in children and adolescents under age 18
Paliperidone	Benzisoxazole	Dopamine, serotonin, norepinephrine/ Antagonist	Invega	Extended-release tablets: 1.5 mg[B], 3 mg, 6 mg, 9 mg	Safety and efficacy not established in children and adolescents under age 12 (schizophrenia)
			Invega Sustenna	Long-acting once-monthly injection (paliperidone palmitate): US labeling indicates amount of paliperidone palmitate – 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL; Canadian labeling indicates amount of paliperidone base (not palmitate) – 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/mL, 150 mg/1.5 mL	Safety and efficacy not established in children and adolescents under age 18
			Invega Trinza	Long-acting once every 3 months injection (paliperidone palmitate): US labeling indicates amount of paliperidone palmitate – 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, 819 mg/2.625 mL; Canadian labeling indicates amount of paliperidone base (not palmitate) – 175 mg/0.875 mL, 263 mg/1.315 mL, 350 mg/1.75 mL, 525 mg/2.625 mL	Safety and efficacy not established in children and adolescents under age 18
			Invega Hafyera[B]	Long-acting once every 6 months injection (paliperidone palmitate): US labeling indicates amount of paliperidone palmitate – 1092 mg/3.5 mL, 1560 mg/5 mL	Safety and efficacy not established in children and adolescents under age 18
Quetiapine	Dibenzothiazepine	Dopamine, serotonin, norepinephrine/ Antagonist	Seroquel	Tablets: 25 mg, 50 mg[B], 100 mg, 150 mg, 200 mg, 300 mg, 400 mg[B]	Safety and efficacy not established in children and adolescents under age 13 (schizophrenia), age 10 (manic episode bipolar disorder)
			Seroquel XR	Extended-release tablets: 50 mg, 150 mg, 200 mg, 300 mg, 400 mg	

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/ Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Risperidone	Benzisoxazole	Dopamine, serotonin, norepinephrine/ Antagonist	Risperdal	Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg Oral solution: 1 mg/mL	Safety and efficacy not established in children and adolescents under age 13 (schizophrenia), age 10 (manic or mixed episode bipolar disorder), age 5 (irritability associated with autism)
			Risperdal M-tab	Oral disintegrating tablets: 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	
			Risperdal Consta	Long-acting injection (risperidone microspheres): 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial	Safety and efficacy not established in children and adolescents under age 18
			Perseris	Long-acting once-monthly subcutaneous injection (risperidone): 90 mg/vial, 120 mg/vial	Safety and efficacy not established in children and adolescents under age 18
Ziprasidone	Benzothiazolyl-piperazine	Dopamine, serotonin/Antagonist	Geodon[B], Zeldox[C]	Capsules: 20 mg, 40 mg, 60 mg, 80 mg Short-acting injection (ziprasidone mesylate)[B]: 20 mg/mL	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- 👍 Acute schizophrenia (lurasidone – Canada (age 15–17) and USA (age 13–17); olanzapine (age 13–17), paliperidone (age 12–17), quetiapine (age 13–17), risperidone (age 13–17) – USA)
- 👍 Acute bipolar I disorder manic episode (asenapine (age 10–17), olanzapine (age 13–17), quetiapine (age 10–17), risperidone (age 10–17) – USA)
- 👍 Acute bipolar I disorder mixed episode (asenapine (age 10–17), olanzapine (age 13–17), risperidone (age 10–17) – USA)
- 👍 Depressive episode associated with bipolar I disorder (fluoxetine/olanzapine (age 10–17) – USA; lurasidone – Canada (age 13–17) and USA (age 10–17))
- 👍 Irritability associated with autism spectrum disorder (risperidone (age 5–16) – USA)
- Early-onset psychosis/schizophrenia (risperidone, quetiapine, olanzapine)
- Treatment-resistant childhood-onset schizophrenia: Clozapine appears effective[18]
- Behavioral disturbance and psychotic symptoms associated with a wide range of childhood psychiatric disorders; efficacy reported in the management of irritability, aggression, stereotypies and explosive behavior in autism spectrum disorder, intellectual disability, oppositional defiant disorder, and conduct disorder
- Used in managing aggression, temper tantrums, psychomotor excitement, stereotypies, and hyperactivity unresponsive to other therapy
- Augmentation in refractory OCD and related disorders – but occasional reports of worsening of OCD symptoms
- Self-mutilation and aggressive behavior in different populations (risperidone, clozapine)
- Tic disorders, Tourette's disorder, and trichotillomania (olanzapine, quetiapine, risperidone, ziprasidone)

‡ Indications listed here do not necessarily apply to all SGAs or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications

Second-Generation Antipsychotics (SGAs) (cont.)

In adults:

Schizophrenia & Psychotic Disorders

Schizophrenia
- 👍 Treatment (asenapine, asenapine transdermal patch, lurasidone, olanzapine, paliperidone, paliperidone long-acting injection, quetiapine, quetiapine XR, risperidone, risperidone long-acting injection, ziprasidone – Canada and USA; iloperidone, lumateperone, olanzapine long-acting injection, olanzapine/samidorphan combination – USA)
- 👍 Acute agitation (olanzapine short-acting IM – Canada and USA; ziprasidone short-acting IM – USA)
- 👍 Treatment resistant (clozapine – Canada and USA)
- 👍 Reduction of recurrent suicidal behavior in those at chronic risk (clozapine – USA)

Schizophrenia-related psychotic disorders
- 👍 Treatment (paliperidone, risperidone long-acting injection, ziprasidone – Canada)
- 👍 Acute agitation (olanzapine short-acting IM – Canada and USA; ziprasidone short-acting IM – USA)

Schizoaffective disorder
- 👍 Monotherapy treatment (paliperidone long-acting injection – Canada and USA; paliperidone – USA)
- 👍 Adjunctive therapy to mood stabilizers and/or antidepressants (paliperidone, paliperidone long-acting injection – USA)
- 👍 Risk reduction of recurrent suicidal behavior in those at chronic risk (clozapine – USA)

Other psychotic disorders
- Psychosis/hallucinations associated with Parkinson's disease (clozapine, quetiapine)
- Drug-induced (e.g., amphetamines) psychosis treatment
- Monotherapy and co-therapy with an antidepressant for psychotic symptoms associated with PTSD
- Postpartum psychosis

Bipolar Disorder

Manic episodes
- 👍 Acute monotherapy treatment (asenapine, olanzapine, quetiapine, quetiapine XR, risperidone, ziprasidone – Canada and USA; olanzapine/samidorphan combination – USA)
- 👍 Acute adjunctive therapy (e.g., with lithium or divalproex/valproate) (asenapine, olanzapine – Canada and USA; olanzapine/samidorphan combination, quetiapine, quetiapine XR, risperidone – USA)
- 👍 Acute agitation (olanzapine short-acting IM – Canada and USA)

Mixed episodes
- 👍 Acute monotherapy treatment (asenapine, olanzapine, ziprasidone – Canada and USA; olanzapine/samidorphan combination, quetiapine, risperidone – USA)
- 👍 Acute adjunctive therapy (e.g., with lithium or divalproex/valproate) (asenapine, olanzapine – Canada and USA; olanzapine/samidorphan combination, quetiapine XR, risperidone – USA)

Depressive episodes
- 👍 Acute monotherapy treatment (lurasidone, quetiapine, quetiapine XR – Canada and USA; fluoxetine/olanzapine combination, lumateperone – USA)
- 👍 Acute adjunctive therapy (e.g., with lithium or divalproex/valproate) (lurasidone – Canada and USA; lumateperone – USA)

Maintenance treatment
- 👍 Monotherapy treatment (olanzapine – Canada, risperidone long-acting injection – Canada and USA; olanzapine/samidorphan combination – USA)
- 👍 Adjunctive therapy (e.g., with lithium or divalproex/valproate) (quetiapine, quetiapine XR, risperidone long-acting injection, ziprasidone – USA)

Other bipolar
- Refractory and rapid-cycling bipolar disorder

Depression

- 👍 Treatment-resistant major depressive disorder (quetiapine XR – Canada; fluoxetine/olanzapine combination – USA)
- 👍 Adjunct to antidepressants (quetiapine XR – USA)
- Adjunct therapy for major depressive disorder (olanzapine, risperidone, ziprasidone)
- Monotherapy for major depressive disorder (olanzapine)
- Monotherapy for combined depression and anxiety (case series: Low-dose quetiapine, low-dose risperidone)

Other Uses

- Substance use disorders (e.g., smoking, alcoholism, drug abuse) in dual diagnosis individuals (clozapine, olanzapine, quetiapine, risperidone)
- Anorexia nervosa (olanzapine, quetiapine, risperidone (all data comes from poor-quality clinical trials))
- Borderline personality disorder (olanzapine, quetiapine, risperidone; limited data)
- Insomnia refractory to other hypnotics/sedatives (quetiapine, olanzapine; limited data)
- Obsessive-compulsive disorder (OCD): Augmentation in treatment-resistant OCD (olanzapine, quetiapine, paliperidone (case report), risperidone, ziprasidone); occasional reports of worsening of OCD symptoms, usually in individuals with primary psychotic disorders
- Posttraumatic stress disorder: Treatment-resistant PTSD; some improvement in flashbacks, hyperarousal, and intrusive symptoms (olanzapine, quetiapine, risperidone)

General Comments

- There remains no significant evidence to favor one class of medications over the other. Consideration of the antipsychotic used should be based on response, tolerability, and cost
- Versus the high-potency FGAs (e.g., haloperidol), SGAs are generally associated with a lower incidence of EPSE and tardive dyskinesia. Of these, risperidone appears to have the highest incidence of EPSE – comparable to a low-potency FGA. With the exception of paliperidone and risperidone, SGAs typically have minimal effects on prolactin elevation
- Unwanted metabolic effects of antipsychotics may include weight gain, dyslipidemias, glucose intolerance, and diabetes. Individuals may also meet the criteria for metabolic syndrome. Children are at greater risk for metabolic effects compared to adults.[19, 20] The risk appears greatest with olanzapine and clozapine, moderate with asenapine, risperidone, paliperidone, and quetiapine, and lowest with aripiprazole, brexpiprazole, asenapine, lurasidone, and ziprasidone

Pharmacology

- There is significant variation in the receptor profiles of antipsychotics. See p. 217 and p. 218 for individual agents' receptor affinities
- SGAs and TGAs are frequently referred to as "atypical" agents because of a lower incidence of EPSE vs. FGAs. Although several mechanisms have been postulated to account for these differences, none are without confounding factors:
  - Unlike FGAs, most SGAs have greater affinity for 5-HT_{2A} vs. D_2 receptors (note: amisulpride, not currently available in Canada or the USA, does not share this feature). Antagonism of 5-HT_{2A} receptors in dopaminergic pathways outside the limbic system is believed to enhance dopaminergic transmission, thereby reducing EPSE and hyperprolactinemia and potentially improving (or not exacerbating) negative, cognitive, and mood symptoms
  - Regionally selective binding to the D_2 receptor in mesolimbic/cortical areas has also been proposed to account for the atypical features of SGAs
  - Variation in receptor specificity (e.g., the relative lower affinity of SGAs for the D_2 receptor) appears to be determined at least in part by their faster rate of dissociation (i.e., unbinding) from the D_2 receptor (speed is determined by the fat solubility of the antipsychotic). Rapid dissociation from the D_2 receptor (aka "fast-off D_2 theory"), allowing the receptor to periodically accommodate endogenous dopamine, has also been postulated as an explanation for why "atypical" agents may be less likely to cause EPSE. However, some SGAs (e.g. asenapine, olanzapine, risperidone, ziprasidone) appear to dissociate more slowly from the D_2 receptor

Dosing

- For dosing of individual oral and short-acting agents for schizophrenia and psychosis, see table pp. 223–226. For long-acting agents, see table pp. 229–233
- For administration details, see the implications for nursing section pp. 194–195
- In general, compared to adults, lower doses are recommended in children and patients with compromised liver or renal function
- Initial doses should be lower, and titration slower in patients prone to hypotension or with developmental delays/intellectual disability
- Dose titration recommended in general to minimize orthostatic hypotension. This is true also for clozapine but minimizes sedation, myocarditis risk, and seizures
- Drug discontinuation is recommended over 1–2 weeks with highly anticholinergic agents (e.g., clozapine, quetiapine). However, if a patient's medical condition requires abrupt discontinuation (e.g., severe leukopenia, cardiovascular toxicity), observe for recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting, and diarrhea
- Prescribing **restrictions apply for clozapine** – dependent on results of WBC and granulocyte/neutrophil counts (see p. 192 for details): Weekly for 6 months, then every other week for 6 months, then monthly indefinitely thereafter

Concomitant Medications

- Antipsychotic metabolism can be affected by CYP inducers or inhibitors. Antipsychotic dose reduction may be needed based on interactions with CYP inhibitors. For specific drug interactions, see pp. 196–205

Second-Generation Antipsychotics (SGAs) (cont.)

- Patients taking a strong CYP3A4 inducer (e.g., carbamazepine, phenytoin): Goal antipsychotic doses may need to be increased using the following correction factors: quetiapine and lurasidone (≥ 5x, do not use antipsychotic), paliperidone (3x), clozapine and olanzapine (1.5–3x), iloperidone and risperidone (2x, not well studied), ziprasidone (1.3x), asenapine (not well studied). Consider alternative therapies or therapeutic drug monitoring as appropriate[21]
- Smokers: Dosage requirements of asenapine, clozapine, and olanzapine may be higher due to hepatic enzyme induction of CYP1A2 by polycyclic hydrocarbons (see p. 205 for interactions of smoking with SGAs)

Pharmacogenetics

- See chapter Pharmacogenetic Information for Common Psychotropic Drugs p. 418
- Pharmacodynamic pathway-related genetic testing (e.g., *DRD2*, *HTR1A*, *MTHFR* etc.) currently does not have sufficient evidence for use in clinical practice
- CYP poor metabolizers may be at increased risk for adverse drug events at usual doses and lower starting doses or avoidance of specific agents may be recommended. CYP intermediate metabolizers have some degree of metabolic activity and are often not described as "clinically important" in regards to drug dosing adjustments. CYP ultra-rapid metabolizers may be at increased risk for therapeutic failures when certain agents are used; avoiding agents which are substrates for certain CYP isoenzymes or using therapeutic drug monitoring is usually warranted.[22] See table pp. 223–226 for metabolic pathways of specific agents. See https://www.pharmgkb.org/ for updated clinical guidelines and dosing recommendations when utilizing pharmacogenetic testing
- A study of 257 children showed that poor or intermediate CYP2D6 metabolizers were more likely to have adverse events to risperidone[23]

Renal Impairment

- Manufacturers do not provide dosing recommendations for pediatric patients with renal impairment, adult dosing information is provided below as a guide
- Mild impairment (i.e., CrCl 50–79 mL/min): Clozapine (starting dose should be 12.5 mg once daily); paliperidone oral (starting dose = 3 mg once daily, maximum dose = 6 mg once daily); paliperidone palmitate 1-monthly IM (Canadian product – day 1 = 100 mg IM, day 8 = 75 mg IM, followed by 50 mg IM q monthly; US product – day 1 = 156 mg IM, day 8 = 117 mg IM, followed by 78 mg IM q monthly); paliperidone palmitate 3-monthly IM (adjust dose and stabilize patient using paliperidone 1-monthly injectable, then transition to an equivalent long-acting 3-monthly dose); risperidone long-acting injection (caution, start with 12.5–25 mg IM q 2 weeks)
- Moderate to severe impairment (i.e., CrCl 10–49 mL/min): Lurasidone (starting dose = 20 mg/day, titrate to a maximum dose of 80 mg/day); paliperidone oral (starting dose = 1.5 mg once daily, maximum dose = 3 mg once daily); paliperidone palmitate 1- and 3-monthly IM not recommended; risperidone oral (if CrCl below 30 mL/min, starting and consecutive doses should be halved with slow titration and BID dosing to a maximum of 1.5 mg BID)
- Severe impairment: Clozapine contraindicated
- No dose adjustment required: Asenapine, iloperidone, olanzapine (however, suggested to start with a lower dose and use a slower titration), quetiapine (however, information with the XR form is limited), ziprasidone (however, ziprasidone short-acting IM contains cyclodextrin, which is renally cleared; caution advised)

Hepatic Impairment

- Manufacturers do not provide dosing recommendations for pediatric patients with hepatic impairment, adult dosing information is provided below as a guide
- Contraindicated: Clozapine (in active liver disease associated with nausea, anorexia or jaundice, progressive liver disease or hepatic failure)
- Not recommended: Asenapine (in severe impairment – Child-Pugh Classification C); iloperidone (primarily hepatic metabolism; not studied in hepatic impairment)
- Caution: Clozapine (can be given to those with pre-existing, stable liver disorders, however, regular monitoring for signs and symptoms of liver dysfunction required); quetiapine (moderate to severe impairment)
- Reduce dose: Lurasidone (starting dose = 20 mg/day, maximum dose in moderate impairment [Child Pugh Score = 7–9] is 80 mg/day and in severe impairment [Child Pugh Score = 10–15] is 40 mg/day); quetiapine (in mild impairment, start with 25 mg/day, increase by 25–50 mg/day as needed); quetiapine XR (in mild impairment, start with 50 mg/day, increase by 50 mg/day as needed) risperidone oral (starting and consecutive dosing should be halved; dose titration slower and use BID dosing); risperidone long-acting injection (caution, start with 12.5 mg or 25 mg IM q2 weeks); ziprasidone (in Child-Pugh Class A and B, start with a lower dose and use a slower titration)
- No dose adjustment required in mild to moderate impairment (i.e., Child-Pugh Classification A and B): Asenapine, olanzapine (however, suggested to start with a lower dose and use a slower titration), paliperidone oral, paliperidone palmitate IM

Pharmacokinetics

- See tables pp. 223–226, p. 232 for kinetics of individual agents
- **Hepatic** primary route of metabolism (i.e., ≥50%): Asenapine, clozapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone
- Hepatic impairment: Asenapine's exposure ~7 times higher in severe impairment; quetiapine's AUC and C_{max} increased by 40%, clearance reduced by 25%, and half-life prolonged by 45% in mild impairment; lurasidone's AUC increased 1.5, 1.7, and 3-fold in mild, moderate, and severe impairment, respectively, with C_{max} 1.3-fold higher in all levels of impairment; risperidone's free fraction in the plasma increased by ~35%; ziprasidone's AUC increased by 19% and 34%, respectively, in mild to moderate impairment – half-life prolonged by ~2.3 h
- **Renal** primary route of excretion (i.e., ≥50%): Asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone
- Renal impairment: Lurasidone's C_{max} increased by 40%, 92%, and 54%, and AUC increased by 53%, 91%, and 2-fold in mild, moderate, and severe impairment, respectively; paliperidone's clearance 32%, 64%, and 71% lower and half-life increased to 24 h, 40 h, and 51 h in mild, moderate, and severe impairment, respectively; risperidone's and metabolite's C_{max} and AUC increased by ~40% and 160%, respectively – half-life prolonged and clearance reduced by 60%
- **Sex**: Differences in plasma concentration between males and females demonstrated with clozapine (18–50% increase in females), lurasidone (18% higher AUC in females), olanzapine (30% increase in females), and paliperidone (19% lower clearance in females). May be related to differences in lean body weight and/or creatinine clearance. Dosage adjustments not routinely needed on the basis of gender alone
- **Race**: Studies suggest pharmacokinetic differences may exist by race. Differences are likely reflective of genotypic differences in metabolizing enzymes
- **Smoking**: Induces CYP1A2, increasing the clearance of asenapine, clozapine, and olanzapine (see p. 205) for interactions of smoking with SGAs

Oral

- Most agents are highly bound to plasma proteins, primarily albumin and/or α_1-acid glycoprotein (except paliperidone)
- The following agents can be taken with or without meals: clozapine, iloperidone, olanzapine, paliperidone, quetiapine, quetiapine XR, risperidone (tablets, M-tabs, and solution)
- Once-daily dosing is appropriate for most drugs because of long elimination half-life; recommended that doses of clozapine above 200–300 mg be divided due to seizure risk; manufacturer recommends asenapine, iloperidone, quetiapine (immediate release), and ziprasidone be given twice daily (due to short half-life)
- Clozapine exhibits considerable variability in plasma level in patients taking similar doses. Differences in plasma concentration between males and females demonstrated with clozapine (40–50% increase in females) and with olanzapine (30% increase in females). There is no difference in dose-normalized plasma concentrations between children and adults
- Lurasidone C_{max} and AUC increased 3- and 2-fold, respectively, when given with food. These increases were independent of meal size (i.e., 350–1000 calories) and meal fat content. Lurasidone plasma exposure in children was similar to that seen in adults after multiple administrations; as expected, higher AUC exposure seen with children vs. adolescents when given the same dose
- Olanzapine pharmacokinetics reported to be similar in children and adolescents (age 10–18) as in nonsmoking adults, but may be as much as 2-fold higher than in adults who smoke
- Paliperidone tablets are formulated using the OROS system, which provides extended release. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the stool as a tablet shell, along with insoluble core components. Administration with high-fat/high-calorie meal increased mean C_{max} and AUC by 60% and 54%, respectively, vs. fasting conditions in adults. Data in children show comparable pharmacokinetic profile as in adults with low peak-trough fluctuations
- Quetiapine pharmacokinetics appear to be similar in children and adults. Quetiapine XR dosed once daily at steady state has comparable bioavailability, C_{max}, and AUC to an equivalent total daily dose of quetiapine regular release tablets administered twice daily. When given with a high-fat meal (~800–1000 calories), it had increases in C_{max} (44–52%) and AUC (20–22%). In comparison, a light meal (~300 calories) had no effect. Suggest taking consistently with respect to food. Quetiapine XR tablet T_{max} is longer (5–6 h) compared to quetiapine IR tablet T_{max} (1–2 h). XR tablets recommended to be administered once daily at 1700h for adults, but this time may need to be earlier in the afternoon for children and adolescents due to their typically earlier bedtimes
- Risperidone pharmacokinetics appear to be similar in children and adults. In extensive CYP2D6 metabolizers, single oral doses were rapidly and dose-proportionally absorbed regardless of food
- Ziprasidone bioavailability increased 2-fold with food. The calorie count, not the fat content, of food influences ziprasidone bioavailability. Optimal bioavailability when given with a meal of 500 or more calories. Preliminary pharmacokinetic data suggests linear pharmacokinetics, similar to adults after single dose exposure

Second-Generation Antipsychotics (SGAs) (cont.)

Disintegrating and Sublingual Tablets

- Useful in children and adolescents who have difficulty swallowing tablets or when medication nonadherence (e.g., "cheeking") is suspected, and help to ensure the patient is receiving the medication
- Asenapine sublingual tablet absolute bioavailability is 35%, however, this is greatly reduced when swallowed (< 2% with sublingual tablet formulation) due to extensive first-pass metabolism. Administration with water or food results in reduced asenapine exposure. Reduced exposure following water administration at 2 min (19% decrease) and 5 min (10% decrease); food consumption immediately prior to or following asenapine decreases exposure by 20% and 4 h after asenapine decreases exposure by ~10%
- Orally disintegrating formulations of olanzapine (Zydis) and risperidone (M-Tab) dissolve in saliva within 15 sec (can be swallowed with or without liquid) – bioequivalent to oral tablet. Time to dissolution may vary by product and also by patient (e.g., dry mouth may impede dissolution times)

Short-acting Intramuscular Injections

- Olanzapine short-acting IM C_{max} occurs in 15–45 min (compared to 5–8 h with oral form) and is 4–5 times higher than for the same oral dose. Half-life for IM and oral forms is similar
- Ziprasidone short-acting IM peak plasma level reached within 60 min and is dose related

Long-acting Injections

- See table on p. 232
- Long-acting (depot) antipsychotics improve medication adherence and reduce consequences of missed doses; depending on the reasons for nonadherence, long-acting antipsychotic formulations may be a viable strategy to reduce relapse rates and progression of illness. No long-acting antipsychotic has been approved for children or adolescents and data supporting use is limited, therefore use should only be considered in adolescents with chronic schizophrenia and poor medication adherence[24]
- Olanzapine pamoate IM is a practically insoluble salt that slowly dissolves after deep IM gluteal injection. If inadvertently injected into vasculature, it will rapidly dissolve in the blood, leading to potentially very high plasma level of olanzapine within minutes to hours and development of a **post-injection delirium sedation syndrome**. Treatment with olanzapine pamoate IM for ~3 months may be required to re-establish steady-state levels when switching from oral olanzapine. Steady-state olanzapine plasma concentrations for doses of 150–405 mg q2–4 weeks are within the range of steady-state concentrations achieved with oral doses of 5–20 mg olanzapine once daily. Apparent half-life for olanzapine pamoate IM is ~30 days vs. ~30 h for oral olanzapine. Exposure to olanzapine pamoate may persist for months after an injection. Typical concentration peak occurs within 1 week after injection
- Paliperidone palmitate has extremely low water solubility, dissolving slowly after IM injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single IM dose of paliperidone palmitate, plasma concentrations gradually rise to reach maximum at a median T_{max} of 13 days. Release of the drug starts as early as day 1 and lasts for as long as 126 days. The median apparent half-life after a single dose increased over the dose range of 39–234 mg of paliperidone palmitate (i.e., 25–150 mg of paliperidone base) from 25–49 days. Paliperidone palmitate C_{max} is 28% higher where administered into the deltoid vs. gluteal muscle (deltoid offers faster absorption as it has better blood perfusion). Two initial deltoid injections on day 1 and day 8 help attain therapeutic concentrations rapidly without the need for oral supplementation. Comparing the 1-month paliperidone injection to the 3-month paliperidone injection, gluteal injections lead to longer apparent half-lives (118–139 days) than do deltoid injections (84–95 days)[25]
- Risperidone long-acting intramuscular injection releases a negligible amount of risperidone (less than 1%, mostly from the surface of the microspheres) immediately after injection. Over several weeks, the microspheres are gradually hydrolyzed and release a steady amount of risperidone, producing therapeutic levels within 3–4 weeks for most patients. Oral antipsychotic supplementation should be given during the first 3 weeks following initiation of risperidone long-acting injection to maintain therapeutic levels until risperidone reaches therapeutic plasma concentration. When administered q 2 weeks, steady-state plasma concentrations are reached after the 4th injection and maintained for 4–6 weeks after the last injection. Complete elimination occurs approximately 7–8 weeks after the last injection. Risperidone microspheres injection into the deltoid and gluteal muscle is bioequivalent
- Risperidone long-acting subcutaneous injection requires no oral overlap. Peak concentrations occur twice, with the first T_{max} at 4–6 h and the second T_{max} occurring at 10–14 days. Bioequivalence of the 90 mg and 120 mg once-monthly subcutaneous injections are equal to a 3 mg and 4 mg oral risperidone daily dose, respectively

Adverse Effects

- See chart on p. 220 for incidence of adverse effects
- Significant variation exists among the SGAs with respect to their adverse effect profiles. They are generally viewed as being less likely to cause EPSE and TD and more likely to result in metabolism-associated adverse effects, but the individual agents vary greatly in their propensity to cause these and other unwanted effects. Some adverse effects may be preventable by employing simple strategies including slow upwards titration and dosing schedule manipulation (e.g., dosing a sedating drug at bedtime or dividing up the daily dose to minimize adverse effects related to higher peak levels)
- Persistent or bothersome adverse effects typically require intervention. Altering the dosage schedule or dose, adding a nonpharmacological or pharmacological treatment for the adverse effect, or switching to a different antipsychotic may be options to consider

CNS Effects

- Activation, insomnia, disturbed sleep, nightmares, vivid dreams – activation reported with lower doses of ziprasidone, may subside with dosage increase. Although complaints of sedation are more common with most SGAs, insomnia has been reported with many agents including asenapine, clozapine (may be more common following withdrawal), olanzapine, paliperidone, risperidone, and ziprasidone. Disturbed sleep, nightmares, or vivid dreams occasionally reported for some of these agents (clozapine, olanzapine, quetiapine, risperidone)
- Confusion, disturbed concentration, disorientation (more common with high doses); toxic delirium reported with clozapine. Concomitant anticholinergic agents may exacerbate
- EPSE – acute onset: A result of antagonism at dopamine D_2 receptors in the nigrostriatal tract (correlate with D_2 binding above 80%). D_2 receptor densities higher in children and adolescents than in adults, therefore increased risk of EPSE
  - Includes acute dystonias, akathisia, pseudoparkinsonism, Pisa syndrome, rabbit syndrome (see pp. 244–248 for onset, symptoms, and treatment options, and pp. 242–262 for detailed treatment options)
  - The 2009 Schizophrenia PORT guidelines rank the relative risk of developing EPSE with antipsychotics as follows: High-potency FGAs > mid-potency FGAs = risperidone > low-potency FGAs > olanzapine = ziprasidone > quetiapine > clozapine
  - Akathisia seems lowest in iloperidone, followed by paliperidone LAI, aripiprazole LAI, brexpiprazole, and asenapine. It is highest in lurasidone, cariprazine, and risperidone. Aripiprazole, ziprasidone, and risperidone LAI fall in between. Akathisia can be misdiagnosed in children as they may not be able to verbalize their symptoms[26]
- EPSE – late onset or tardive movement disorders
  - Includes tardive akathisia, tardive dyskinesia (TD), and tardive dystonia (see p. 248 for onset, symptoms, and therapeutic management options)
  - Late onset movement disorders usually develop after months or years of treatment
  - May be irreversible, so prevention is key – use lowest possible doses and assess for signs of movement disorders regularly. Symptoms may not be alleviated and may be exacerbated by antiparkinsonian medications[11]
  - In adults, annual risk of TD with FGAs estimated to be 4–5%, with a cumulative risk of up to 50%. Risk of TD appears lower with SGAs and TGAs. In children and adolescents, an annualized rate of TD of 0.42% was found during long-term treatment with SGAs of up to 3 years – this review was limited by over-representation of risperidone usage, relatively low doses, and relatively short duration of use[27]
  - Clozapine has lowest TD risk and its use has been associated with a significant reduction in existing TD (especially tardive dystonia), often within 1–4 weeks (sometimes up to 12 weeks)
- Headache – reported with clozapine, olanzapine, paliperidone, quetiapine, risperidone, and asenapine at an incidence of 5–15%
- Neuroleptic malignant syndrome (NMS) – rare disorder characterized by autonomic dysfunction (e.g., tachycardia and hypertension), hyperthermia, altered consciousness, and muscle rigidity with an increase in creatine phosphokinase (CPK) and myoglobinuria. There is a strong overlap in syndrome, etiology, and treatment for NMS, malignant catatonia, and serotonin syndrome. Fatalities from NMS are rare if syndrome identified early
  - A review of case reports showed that, in adolescents, the incidence of symptoms were stiffness (84%), autonomic instability (84%), fever (79%), and CPK elevation and leukocytosis (42%)[28]
  - Can occur with any class of antipsychotic agent, at any dose, and at any time (although usually occurs early in the course of treatment). Risk factors may include dehydration, young age, male sex, organic brain syndromes, exhaustion, agitation, rapid or parenteral antipsychotic administration and concurrent use of multiple antipsychotics
  - NMS is potentially fatal unless recognized early and medication stopped. Supportive therapy (e.g., maintain hydration, correct electrolyte imbalances, control fever) must be instituted as soon as possible. Additional treatment with dopamine agonists (such as amantadine and bromocriptine may be helpful – controversial, may reduce muscle rigidity without an effect on overall outcome). Benzodiazepines have been used in children with NMS, recognizing its strong relationship with malignant catatonia, and ECT has also been used successfully to improve symptoms. Treatment with an antipsychotic agent may recommence several weeks post recovery

Second-Generation Antipsychotics (SGAs) (cont.)

- Paresthesias – or "burning sensations" reported with risperidone. Oral parathesia/hypoesthesia reported to occur in about 5% of patients treated with asenapine. The effect occurs immediately following sublingual administration, affects a coin-size area 15–25 mm in diameter, and lasts approximately 10–30 min. Paresthesias also reported infrequently with iloperidone and lurasidone
- Post-injection delirium sedation syndrome (PDSS) – associated with olanzapine depot injection. CNS symptoms may include sedation (ranging from mild sedation to coma), delirium, dizziness, weakness, dysarthria, and seizures. Injection must be administered in a facility with access to emergency services. Patients should be assessed every 30 min for 3 h post each injection for signs of post-injection syndrome. Reported in 0.07% of injections and approximately 1.4% of patients
- Sedation, somnolence, and fatigue – common, especially following treatment initiation and dosage increase. Usually transient, but some individuals may complain of persistent effects. May be most bothersome with clozapine and, to a lesser extent, with quetiapine and olanzapine. Somnolence and fatigue are among the more frequent adverse effects reported with asenapine, iloperidone and lurasidone. [Management: Evening/bedtime administration; lower the dose if feasible, minimize use of concomitant CNS depressants] Sedation may be less with quetiapine XR compared to quetiapine IR
- Seizures – all antipsychotics may lower seizure threshold, resulting in seizures ranging from myoclonus to generalized tonic-clonic seizures. May occur if dose increased rapidly or may also be secondary to hyponatremia associated with SIADH. Use with caution in patients with a history of seizures or with organic brain disorder

Anticholinergic Effects

- A result of antagonism at muscarinic receptors. Effects are additive if given concurrently with other anticholinergic agents
- Many of these adverse effects are often dose related and may resolve over time without treatment. Treatment options may include reducing the dose of the SGA or switching to another antipsychotic with less potential to cause anticholinergic effects or employing a specific drug or nondrug strategy to treat the adverse effect (see below for suggestions)
- Blurred vision [Management: Use adequate lighting when reading; pilocarpine eye drops]
- Constipation – [Management/prevention: Increase dietary fiber and fluid intake, increase exercise or use a fecal softener (e.g., Docusate) or docusate, osmotic laxative (e.g., PEG 3350), stimulant laxative (e.g., bisacodyl/senna), lubiprostone, or osmotic laxative (e.g., PEG 3350)]. Clozapine has been associated with varying degrees of impairment of peristalsis ranging from constipation to intestinal obstruction, fecal impaction, and paralytic ileus (potentially fatal if undetected)
- Delirium – characterized by agitation, confusion, disorientation, visual hallucinations, tachycardia, etc. May result with use of high doses or combination anticholinergic medication. Drugs with high anticholinergic activity have also been associated with impaired cognition and selective impairments of learning and memory
- Dry eyes [Management: Artificial tears, wetting solutions]
- Dry mouth/mucous membranes – if severe or persistent, may predispose patient to candida infection [Management: Sugar-free gum and candy oral lubricants (e.g., MoiStir, OraCare D), pilocarpine mouthwash – see p. 105]
- Urinary retention [Management: bethanechol]

Cardiovascular Effects

- Many result from antagonism at α_1-adrenergic and muscarinic receptors (see p. 217 to compare relative affinities of SGAs for these receptors)
- Arrhythmias and ECG changes:
  - Bradycardia reported with IM olanzapine, often accompanied by decreased resting BP or an orthostatic drop. Caution in patients who have received other medications associated with hypotensive or bradycardic effects (e.g., IM lorazepam)
  - ECG changes (e.g., T-wave inversion, ST segment depression, QTc prolongation – may increase risk of arrhythmias) reported with many antipsychotic medications, the clinical significance of which is unclear for many. A QTc of more than 500 msec or an increase from baseline of more than 60 msec is associated with an increased risk for torsades de pointes, ventricular fibrillation, and sudden cardiac death. Prominent risk factors for QTc prolongation include congenital long QTc syndrome (ask patients about syncope and a family history of sudden death under age 40 or congenital long QTc syndrome), elderly age, female sex, heart failure, myocardial infarction (MI), and concomitant use of medications that prolong the QTc interval or inhibit the metabolism of a drug known to prolong QTc interval (see Drug Interactions pp. 196–205). Other risk factors may include altered nutritional status (e.g., eating disorders, alcoholism), bradycardia, cerebrovascular disease, diabetes, electrolyte imbalances (e.g., hypokalemia, hypomagnesemia, hypocalcemia), hypertension, hypothyroidism, and obesity. The presence of risk factors for QTc prolongation should be controlled (e.g., electrolyte imbalances corrected, interacting drugs or use of concomitant drugs that prolong QTc

avoided), when possible, before initiation of treatment with a SGA. A list of drugs associated with QTc prolongation can be found at https://crediblemeds.org
  - Current literature does not provide sufficient evidence to stratify antipsychotics for their potential to prolong QTc and cause torsades de pointes. A meta-analysis of 55 studies of 9 antipsychotics used in children and adolescents found ziprasidone (+8.74 msec) and risperidone (+1.68 msec) to be associated with increased QTc interval and limited risk with other medications compared to placebo. Considering these patients were otherwise healthy, potential for reporting bias, individual factors that may contribute to QTc prolongation risk, and the lack of linear relationship between the QTc interval and torsades de pointes, all antipsychotics may pose risk for torsades de pointes[30]
  - A surveillance cohort of 101 children (average age 11.5 years) with an average follow-up of 20 months revealed that only 7% had abnormal changes in QTc, but none had a QTc interval longer than 500 msec.[31] A review of 28 adolescents using clozapine found that 17% developed QTc prolongation longer than 450 msec[32]
  - Tachycardia reported with clozapine, olanzapine, quetiapine, risperidone, paliperidone, and ziprasidone. Tachycardia may occur as a compensatory mechanism to orthostatic hypotension caused by α_1-adrenergic antagonism or may be an anticholinergic effect caused by M_1 receptor antagonism. Persistent tachycardia at rest accompanied by other signs of heart failure requires cardiology consultation
  - Collapse/respiratory/cardiac arrest reported with clozapine alone and in combination with benzodiazepines and other psychotropic agents
- Cardiomyopathy, pericarditis, myocardial effusion, heart failure, myocardial infarction, mitral valve insufficiency, and myocarditis reported with clozapine. Deaths have been reported. The risk of myocarditis appears greatest in the first 4–6 weeks of therapy. DO NOT USE in patients with severe cardiac disease. Investigate patients who develop persistent tachycardia at rest, accompanied by symptoms of heart failure (e.g., chest pain, shortness of breath or arrhythmia), and/or fatigue, flu-like symptoms, hypotension, and unexplained fever. A review of 38 reported cases of clozapine-related myocarditis suggested fever and elevations in C-reactive protein (CRP) may be early indicators and therefore diagnostically useful.[33] Drug should be promptly discontinued and not rechallenged
- Clozapine-induced cardiomyopathy can present much later on during clozapine therapy with most cases occurring between 6 and 9 months of therapy but some reports as late as 4 years. Patients with significant history of heart disease or abnormal cardiac findings on physical exam should be assessed by a physician or cardiologist before starting clozapine therapy. Clinical presentation of cardiomyopathy includes shortness of breath, orthopnea palpitations, cough, fatigue, edema, and chest pain. Patients should be assessed for the presence of these signs and symptoms regularly (e.g., four times per year). Patients with new symptoms consistent with heart failure should receive an ECG, chest x-ray and, where possible, an echocardiogram. There may be a role for routine monitoring of serum B-type brain natriuretic (BNP) or echocardiograms serially for patients on long-term clozapine therapy although this has not been evaluated with controlled studies
- Dyslipidemia (see p. 185)
- Edema – reports of peripheral edema with all antipsychotics. Tongue and facial edema reported with ziprasidone
- Orthostatic hypotension/compensatory tachycardia/dizziness/syncope – may occur as a result of α_1-adrenergic antagonism. Reported with all antipsychotics. May be more common with clozapine, iloperidone, olanzapine, quetiapine, and risperidone. Sitting and standing BP and heart rate assessments should be considered in individuals with or at risk of developing hypotension [Management: Reduce or slow dosage titration, divide the daily dose, increase fluid and salt intake, treatment with fluid-retaining corticosteroid – fludrocortisone]
- Thromboembolism – case reports of pulmonary and/or venous thromboembolism with asenapine, clozapine, lurasidone, olanzapine, and quetiapine in adults

Endocrine & Metabolic Effects

- Antidiuretic hormone dysfunction
- Polydipsia, intermittent hyponatremia, and psychosis syndrome may occur in chronically treated patients. Monitor sodium and utilize fluid restriction, captopril 12.5 mg/day, propranolol 30–120 mg/day, and correct electrolyte imbalances
- Metabolic abnormalities associated with antipsychotics include dyslipidemia, glucose intolerance/diabetes, metabolic syndrome, and weight gain. Clozapine and olanzapine have been associated with the highest overall metabolic liability. The SGAs asenapine, lurasidone, ziprasidone and the TGAs appear to have a lower overall metabolic risk potential
- A study examining pre-antipsychotic lipid profiles in adolescents suggested that some of the metabolic problems predate the use of antipsychotics; this highlights the need for baseline screening knowing that the risk increases[34]
- Dyslipidemia:
  - Lipid abnormalities (increases in fasting total cholesterol, LDL cholesterol, and triglycerides, decreased HDL) have been associated with SGAs. Overall the risk appears greatest with clozapine and olanzapine; moderate with quetiapine, risperidone, and paliperidone, and low with ziprasidone. The limited information that is available for asenapine, iloperidone, and lurasidone suggests they typically do NOT cause significant dyslipidemia

Second-Generation Antipsychotics (SGAs) (cont.)

  - This risk appears to be associated with, but not dependent on, weight gain. Weight gain and obesity, dietary changes, glucose intolerance, and insulin resistance have all been proposed as possible causes/contributors to lipid dysregulation
  - Treatment options may include lifestyle and dietary modifications; switching to another antipsychotic associated with a lower potential for lipid dysregulation; adding cholesterol-lowering medication (e.g., statins, fibrates, fish oil, etc.)
  - Eight of 24 adolescents developed new-onset hypercholesterolemia after one year of antipsychotic use, with a higher frequency in females[35]
- Glucose intolerance/insulin resistance/hyperglycemia/type 2 diabetes mellitus (DM):
  - Treatment with SGAs has been associated with an increased risk for insulin resistance, hyperglycemia, and type 2 diabetes (new onset, exacerbation of existing DM, ketoacidosis). A diagnosis of schizophrenia is also a risk factor for developing diabetes
  - Overall the risk of developing disturbances in glucose metabolism appear greatest with clozapine and olanzapine; moderate with quetiapine, risperidone, and paliperidone, and lowest with ziprasidone. The relative risks for developing glucose dysregulation with asenapine, iloperidone, and lurasidone in comparison to other SGAs is uncertain at this point, but these agents appear to have minimal effect on glucose regulation
  - See p. 154 for suggested monitoring guidelines
  - Treatment options may include lifestyle and dietary modifications; switching to another antipsychotic associated with a lower potential for glucose dysregulation; adding metformin
- Hyperprolactinemia:
  - Prolactin level may be elevated – increases occur several hours after dosing and normalize by 12–24 h with clozapine, olanzapine, quetiapine, and ziprasidone; elevation persists during chronic administration with risperidone (incidence greater than 30% – less with long-acting IM risperidone) and paliperidone; increased plasma prolactin level related to dose of olanzapine (higher if above 20 mg/day)
  - A network meta-analysis showed that the highest increase of prolactin in adolescents occurred in the following order: risperidone > paliperidone > olanzapine = quetiapine. Clozapine and aripiprazole do not demonstrate significant prolactin elevation[37]
  - Increases in prolactin levels reported with asenapine (increase in prolactin appears to be greater than that caused by olanzapine, but less than that with risperidone), iloperidone, and lurasidone but the clinical significance is uncertain. Infrequent reports of clinical effects such as gynecomastia or galactorrhea in short-term clinical trials
  - Effects in women: Breast engorgement and lactation (may be more common in women who have previously been pregnant), amenorrhea (with risk of infertility), menstrual irregularities, changes in libido, hirsutism (due to increased testosterone), and possibly osteoporosis (due to decreased estrogen). Recommended that women with hyperprolactinemia or amenorrhea for over 12 months have a bone mineral density evaluation
  - Effects in men: Gynecomastia, rarely galactorrhea, decreased libido, and erectile or ejaculatory dysfunction
  - Monitoring/investigation: Recent guidelines suggest routine assessments for the presence of symptoms associated with prolactin elevation. If findings are positive, a prolactin level should be ordered and an attempt made to rule out non-pharmacological causes. Fasting morning serum prolactin level recommended as it is least variable and best correlated with disease states. If an antipsychotic medication is strongly suspected as cause, discontinuing the agent (or switching to another with less potential for prolactin elevation) for a short period of time (e.g., 3–4 days), if clinically feasible, and follow-up monitoring to determine whether prolactin levels fall may be a simple means to confirm suspicions and avoid MRI or CT of the hypothalamic/pituitary region
  - Treatment options: Assuming discontinuation of antipsychotic therapy is not an option, the preferred treatment is to switch to another antipsychotic agent with a reduced risk of hyperprolactinemia (aripiprazole, clozapine) – weighing the potential risk for relapse associated with this action. Other treatment options may include lowering the dose or adding a medication to treat the condition[38]
- Metabolic syndrome:
  - Metabolic syndrome is an interrelated cluster of CVD risk factors that include abdominal obesity, dyslipidemia, hypertension, and impaired glucose tolerance
  - Using the International Diabetes Federation (IDF) Consensus definition criteria, children/adolescents must have central obesity, which is defined according to age (only diagnosable over age 10), sex, and ethnicity (e.g., a waist circumference of 90th percentile or greater for age/sex/ethnicity), in addition to at least 2 of the following characteristics:

1. Triglycerides: > 1.7 mmol/L (150 mg/dL)
2. HDL cholesterol: Males < 1.03 mmol/L (40 mg/dL)/Females < 1.3 mmol/L (50 mg/dL)
3. Blood pressure: ≥ 130/> 85 mmHg (or treatment for hypertension)
4. Fasting glucose: > 5.6 mmol/L (100 mg/dL) or known type 2 diabetes mellitus

  - Individuals with metabolic syndrome are 5 times more likely to develop type 2 diabetes mellitus and 2–3 times more likely to experience myocardial infarction or stroke
  - In adults, the risk of developing metabolic syndrome appears to be greater with clozapine and olanzapine, followed by risperidone, asenapine, iloperidone, and quetiapine. Ziprasidone and lurasidone appear to have a lower risk
  - Organizational commitments and environmental supports to screening for metabolic parameters in antipsychotic use have demonstrated modest (up to 35%) increase in screening rates for these problems[40]
- Thyroid hormone effects – dose-dependent decrease in total T_4 and free T_4 concentrations reported with quetiapine. Has also been demonstrated with olanzapine, risperidone, and aripiprazole; other agents not included in the study. Clinical significance unknown[41]
- Weight gain:
  - Approximately 50% of patients gain an average of 20% of their baseline weight (primarily as adipose tissue)
  - The mechanism by which antipsychotics may influence weight gain is unknown (may be a result of multiple systems including 5-HT_{1B}, 5-HT_{2C}, α_1, and H_1 blockade, prolactinemia, gonadal and adrenal steroid imbalance, and increase in circulating leptin; may also be due to sedation and inactivity, carbohydrate craving, and excessive intake of high-calorie beverages to alleviate drug-induced thirst and dry mouth)
  - Overall, clozapine and olanzapine have been associated with the greatest propensity for significant weight gain in adults (≥ 7% from baseline); iloperidone, paliperidone, quetiapine, and risperidone are probably intermediate; asenapine, lumateperone, lurasidone, and ziprasidone appear to be associated with the lowest risk[39, 42]
  - After 12 weeks, drug naïve children and adolescents gained an average of 4–8 kg. Likelihood of weight gain as follows: olanzapine > quetiapine > risperidone > aripiprazole (clozapine and ziprasidone not evaluated in this study)
  - A longitudinal cohort of 290 adolescents showed that weight gain was most pronounced during the first 15 weeks, it then stabilized. A higher BMI z score predicted increases during follow-up, while the use of stimulants predicted decreases[44]
  - See p. 154 for suggested monitoring guidelines
  - Treatment options: Since it is often challenging to lose weight, preventative strategies that focus on healthy lifestyles (e.g., diet and exercise) are recommended. May not be dose dependent, so the efficacy of dosage reduction strategies is uncertain. Treatment options may include healthy lifestyle strategies; switching from an antipsychotic with higher weight gain liability to one of lower liability (may result in significant reductions in body weight)[43]; or use of medications to promote weight loss. Treatment with the following agents has been tried with varying degrees of success based on case reports and RCTs: Amantadine (100–300 mg/day), famotidine (40 mg/day), topiramate (up to 200 mg/day), nizatidine (300 mg bid), orlistat (120 mg tid), and metformin (850–1000 mg bid). The bulk of evidence is in adults using metformin and topiramate, with studies typically reporting a gradual loss of weight up to 5–10 kg over 12–16 weeks. In adolescents, metformin addition appeared beneficial in some open label trials, and a meta-analysis of five trials (205 participants in total) showed a decrease in weight by 1 kg at 4 weeks, and 3.2 kg at 16 weeks, though the quality of evidence was low.[45] The sustained efficacy and optimal duration of treatment with these agents is unknown. Behavioral weight counseling interventions did not mitigate olanzapine-induced weight gain in a long-term adolescent study[46]

GI Effects

- Constipation – see Anticholinergic Effects p. 184. Clozapine and olanzapine have high affinity for M_1 receptors; quetiapine has moderate affinity, the remaining SGAs are categorized as low to negligible affinity for these receptors
- Dysphagia (difficulty swallowing) and aspiration have been reported with antipsychotic use
- Dry mouth – see Anticholinergic Effects, p. 184. Despite a high affinity for M_1 receptors, sialorrhea more commonly reported with clozapine – see below
- GI obstructions – do not administer paliperidone to patients with pre-existing severe GI narrowing (e.g., esophageal motility disorders, small bowel inflammatory disease, short gut syndrome, etc.) due to its OROS formulation. Clozapine associated with varying degrees of impaired intestinal peristalsis, including bowel obstruction, ischemia, perforation, and aspiration; 102 cases of suspected life-threatening hypomotility disorder reviewed, resulting in mortality rate of 27.5% and considerable morbidity, largely due to bowel resection[47] – see Anticholinergic Effects p. 184
- Oral hypoesthesia – decreased oral sensitivity reported with asenapine
- Parotitis reported with clozapine
- Reflux esophagitis (approximately 11% incidence reported with clozapine)

Second-Generation Antipsychotics (SGAs) (cont.)

- Sialorrhea, with difficulty swallowing/gagging that is most profound during sleep; dose related – may lead to aspiration pneumonia. May be due to stimulation of M_4 or α_2 receptors in salivary glands. [Management: Chew sugarless gum, cover pillow with towels, reduce dose. Preliminary evidence suggests benefit with: Amitriptyline (25–100 mg), benztropine (1–4 mg) or trihexyphenidyl (5–15 mg per day) – caution: Additive anticholinergic effects; clonidine (0.05–0.2 mg once daily orally or transdermal patch 0.1–0.2 mg applied weekly) – caution: Additive hypotension; terazosin (2 mg daily), scopolamine patch (1.5 mg/2.5 cm^2 patch applied every 72 h), atropine "eye" drops given sublingually (1 drop 1–2 times a day), ipratropium nasal spray (given as 2 sprays under the tongue tid)]

Urogenital & Sexual Effects

- Sexual effects may result from altered dopamine (D_2), serotonergic, ACh, α_1 or H_1 activity; hyperprolactinemia is the main cause of SGA-induced sexual dysfunction in women. Lower rates of sexual dysfunction reported with quetiapine, ziprasidone, and aripiprazole
- Identify and develop strategies to deal with other co-prescribed medications (e.g., antidepressants (especially TCAs and SSRIs), β-blockers, illicit substances – e.g., cocaine, opioids, etc.) and conditions (e.g., age, excess alcohol, diabetes, hypertension, smoking, etc.) that may be associated with sexual dysfunction
- Treatment options may include: 1) dosage reduction, 2) waiting 1–3 months to see if tolerance develops, 3) switching antipsychotics or 4) adding a medication to treat the problem. (For treatment suggestions regarding specific types of dysfunction, please see [48])
- Priapism – has been reported in patients on most SGAs. Antagonism of α_1-adrenergic receptors is believed to play a role
- Spontaneous ejaculation reported with olanzapine
- Renal dysfunction – rare reports of interstitial nephritis and acute renal failure with clozapine
- Urinary incontinence (overflow incontinence)/enuresis (nocturnal enuresis) reported with clozapine (up to 42%); case reports with olanzapine and risperidone. Appears to be more frequent with clozapine but the relative risks of the various SGAs for causing this effect are unknown. Reported to occur early in treatment and often self-limiting although may persist in some individuals. Etiology is not well understood and a variety of mechanisms implicated. [Management strategies: Dosage reduction; limiting fluid intake in the evening, especially caffeine-containing beverages or alcohol; voiding directly before bed; and setting an alarm to wake up and void during the night. Case reports of successful treatment with a wide array of pharmacological treatments including desmopressin (DDAVP) 0.1–0.4 mg (tablets) or 0.12–0.24 mg (melt tablets), or oxybutynin 5–15 mg/day. (For further treatment suggestions, please see [49, 50, 51])
- Urinary retention – see Anticholinergic Effects p. 184

Ocular Effects

- Blurred vision/dry eyes: see Anticholingeric Effects p. 184
- Esotropia: Case report of esotropia (form of strabismus) with olanzapine
- Oculogyric crisis (sustained fixed upward gaze): Causative reports with olanzapine and risperidone; implicated with others

Hematological Effects

- Blood dyscrasias, including those affecting erythropoesis, granulopoesis, and thrombopoesis, have been reported with most antipsychotics
- Clinically significant hematological abnormalities with antipsychotics are rare. Accordingly, the development of any blood abnormalities in individuals on antipsychotic medication, especially other than clozapine, should undergo rigorous medical assessment to determine the underlying cause
- Risk may increase with concomitant prescribing of antiepileptic drugs that are also associated with blood dyscrasias (e.g., carbamazepine)
- **Aplastic anemia** – reported with risperidone and clozapine
- **Anemia** – reported with asenapine, clozapine, iloperidone, lurasidone, and ziprasidone
- **Eosinophilia** – not typically of clinical significance unless severe. Transient elevations in eosinophil counts without clinical sequelae reported with olanzapine, quetiapine, and ziprasidone. Eosinophilia reported with clozapine frequently between weeks 3 and 5 of treatment; higher incidence in females. Neutropenia can occur concurrently. In most case reports, withdrawal of the drug resulted in normalization of the hematological profile
- **Leukopenia** [defined as WBC under 4×10^9/L] and **neutropenia/agranulocytosis** [neutropenia (defined as ANC under 1.5×10^9/L) may be subclassified as mild (ANC = 1–1.5 $\times 10^9$/L), moderate (ANC = 0.5–1 $\times 10^9$/L) or severe (also termed agranulocytosis – defined as ANC under 0.5×10^9/L or sometimes as ANC under 0.2×10^9/L)]
  - Mild neutropenia may be transient (returning to normal without a change in medication/dose) or progressive (continuing to drop, leading to agranulocytosis)
  - Transient neutropenia occurring only in the morning (with an afternoon ANC count returning to normal) has been reported with clozapine

  - Agranulocytosis can occur with all antipsychotics but is generally rare (incidence less than 0.1%) except with clozapine (occurs in approximately 1% of patients; 0.38% risk with monitoring). The rate of occurrence is highest in the first 26 weeks of clozapine therapy. Fatalities typically resulting from infections due to compromised immune status have been reported. Patients treated with clozapine must consent to routine hematological monitoring (see p. 192 for guidelines)
  - Children are at increased risk of hematological side effects from clozapine. Neutropenia reported in 13% of 172 children and agranulocytosis in 1 child (0.6%) over an 8-month period. Risk factors include female gender and certain ethnic groups (i.e., Ashkenazi Jews). Do not use clozapine in patients with myeloproliferative disorders, granulocytopenia or baseline WBC count under 3.5×10^9/L and/or ANC under 2×10^9/L (exception: benign ethnic neutropenia). Monitor for, and advise patients to immediately report, any signs of infection or flu-like symptoms (e.g., fever, sore throat, chills, malaise, etc.). Individuals on clozapine may develop transient, benign fever, especially during the first few weeks of treatment. Fever due to underlying blood dyscrasia/infection, neuroleptic malignant syndrome or myocarditis must be ruled out. Avoid concomitant use of other medications associated with blood dyscrasias (see Drug Interactions pp. 196–205)
- **Leukocytosis** – 41% risk of transient leukocytosis reported with clozapine. May occur with other agents
- **Pancytopenia** – case reports with quetiapine, olanzapine, and clozapine
- **Thrombocytopenia** – case reports with asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone; cases of thrombocytosis with clozapine. In most cases, withdrawal of the medication resulted in normalization of platelet counts

Hepatic Effects

- Cholestatic jaundice (reversible if drug stopped). Occurs in less than 0.1% of patients on antipsychotics within first 4 weeks of treatment. Signs include yellow skin, dark urine, and pruritus. Reported with clozapine, olanzapine, and ziprasidone
- Hepatomegaly/steatohepatitis – case reports of nonalcoholic steatohepatitis (i.e., fatty liver with inflammation, necrosis, and hepatomegaly, with mild to moderate increase in ALT and/or AST) reported with olanzapine and risperidone; risk factors include weight gain, hyperlipidemia, T2DM, and polypharmacy – usually benign but can progress to cirrhosis. Hepatomegaly and fatty liver deposits also reported with ziprasidone
- Pancreatitis – reports of pancreatitis with risperidone, olanzapine, quetiapine, and clozapine; generally occurred within first 6 months of therapy; hyperamylasemia reported with risperidone
- Transaminase elevations – elevations in ALT, AST and/or GGT have been reported typically within the first 2–6 weeks of treatment. May be asymptomatic and transient in nature with rare/very rare reports of hepatitis/hepatic failure
- See p. 180 for dosing in hepatic impairment and https://livertox.nih.gov for further data regarding individual agents

Hypersensitivity Reactions

- Usually appear within the first few months of therapy (but may occur after the drug is discontinued)
- Photosensitivity and photoallergy reactions including sunburn-like erythematous eruptions which may be accompanied by blistering
- Skin reactions, rashes, and, rarely, abnormal skin pigmentation (risperidone); rash (5%) and urticaria reported with ziprasidone, potentially dose related, improved with antihistamine/steroid administration and/or discontinuation of ziprasidone in most cases
- Rarely, asthma, laryngeal, angioneurotic or peripheral edema, and anaphylactic reactions occur. Serious allergic reactions (Type 1 hypersensitivity) have been reported with asenapine, clozapine, olanzapine, paliperidone, quetiapine, and risperidone. Patients should be informed and advised to seek emergency medical treatment if they develop signs and symptoms of a serious reaction (swelling of face, tongue, or throat, difficulty breathing, feeling lightheaded or faint, itching)

Temperature Regulation

- Altered ability of body to regulate response to changes in temperature and humidity; may become hyperthermic or hypothermic; more likely in temperature extremes due to inhibition of the hypothalamic control area. Patients should be counseled to avoid becoming overheated or dehydrated
- Transient temperature elevation can occur with clozapine in up to 55% of patients, usually within the first 3 weeks of treatment and lasting several days; not correlated with dose; older individuals at higher risk; may be accompanied by respiratory and gastrointestinal symptoms, mild creatine phosphokinase (CPK) elevation, and an elevation in WBC

Other Adverse Effects

- Epistaxis (aripiprazole and risperidone) and gingival bleeding (risperidone)
- Rhinitis (risperidone 15%; olanzapine 12%; also with clozapine) – incidence higher with risperidone in children
- Case reports of exacerbation of bulimia nervosa with risperidone and clozapine
- Flu-like symptoms reported with long-acting IM risperidone
- Somnambulism and sleep-related eating disorder (risperidone)

Second-Generation Antipsychotics (SGAs) (cont.)

D/C Discontinuation Syndrome

- Abrupt discontinuation (or in some cases large dosage reduction) of an antipsychotic may be associated with a number of potential risks. Prolonged antagonism of (dopaminergic, muscarinic, histaminic, α-adrenergic) receptors by the antipsychotic, resulting in a compensatory up-regulation which then produces a rebound-type reaction when the antagonist is removed and the supersensitized receptors are exposed, has been proposed as a pharmacological explanation for these effects
  1. Discontinuation syndromes – typically characterized by development of a number of symptoms including nausea, vomiting, diarrhea, diaphoresis, cold sweats, muscles aches and pains, insomnia, anxiety, and confusion. Usually appear within days of discontinuation [Management: Mild cases may only require comfort and reassurance; for more severe symptoms, consider restarting the antipsychotic, followed by slow taper if possible; or, if rebound cholinergic effects present, consider adding an anticholinergic agent short term]
  2. Psychosis – exacerbation or precipitation of psychosis including a severe, rapid onset or supersensitivity psychosis. Most likely to occur within the first 2–3 weeks of discontinuation or sooner [Management: Restart antipsychotic]
  3. Movement disorders – withdrawal dyskinesias noted to appear usually around 2–4 weeks post abrupt withdrawal [Management: Restart antipsychotic and taper slowly] Rebound dystonia, parkinsonism, and akathisia also reported to occur, usually within days to the first week post discontinuation [Management: Restart antipsychotic and taper or treat with appropriate anti-EPSE medication]
- Abrupt cessation of a long-acting or depot antipsychotic is of less concern, as plasma concentrations decline slowly (i.e., drug tapers itself)
- Clinicians should be cognizant of the potential for withdrawal effects to occur from a discontinued agent when switching to a new antipsychotic in order to avoid misinterpreting them as adverse effects of the new agent and subsequently discontinuing it unnecessarily
- When an antipsychotic is stopped and relapse occurs, there is controversy and challenge to separating relapse of psychosis from discontinuation syndrome, however, a study showed that patients randomized to be switched to placebo vs. continuation of monthly injection antipsychotic mostly experienced symptoms of relapse[52], not discontinuation. Withdrawal psychosis should be rare in the absence of discontinuation syndrome (e.g., elevated blood pressure, heart rate, etc.)
- Note on re-initiating clozapine – if restarting clozapine following 2 or more days post last dose, it is recommended to initiate treatment with 12.5 mg once or twice daily on the first day with potential for more rapid dosage increases thereafter than recommended during initial treatment (see also p. 192 and p. 179)

☞ **AFTER PROLONGED USE, THESE MEDICATIONS SHOULD BE WITHDRAWN GRADUALLY where possible.** If switching to another antipsychotic, see pp. 233–234 for specific recommendations. Readers may find the website https://www.switchrx.com helpful for managing antipsychotic switching

Precautions

- Body temperature regulation dysfunction has been associated with antipsychotic medications. Appropriate precaution is advised for patients undergoing conditions which may elevate core body temperature and/or lead to dehydration. Assess patients routinely for presence of significant risk factors for cardiovascular disease. See sections on Lab Tests/Monitoring on pp. 154 and 191. Control risk factors and consider SGAs with lower metabolic liabilities where possible
- Do not use clozapine in patients with severe cardiac disease; perform a thorough cardiac evaluation prior to starting therapy in all patients. Monitor patients regularly for signs of myocarditis (e.g., shortness of breath, edema, unexplained fever)
- Neuroleptic malignant syndrome: Manage with immediate discontinuation and close monitoring
- Tardive dyskinesia: Discontinue antipsychotic if clinically appropriate, reduce dose, or consider switching agents
- Orthostatic hypotension, syncope, other hemodynamic effects, increased risk of falls, cognitive and/or motor impairment
- Leukopenia, neutropenia, and agranulocytosis reported with antipsychotic medications
- Prolonged QTc interval and risk of arrhythmia and sudden cardiac death exists. Risk may be increased in the presence of other risk factors. See notes on ECG changes in Adverse Effects/Cardiovascular Effects on p. 184 for a more detailed discussion
- Dysphagia and aspiration have been associated with use of antipsychotic medications. These agents should be used cautiously in patients at risk for aspiration pneumonia
- All SGAs may lower the seizure threshold, though mechanisms are not clear. Use with caution in patients with history of seizures, cormorbidities, or concomitant medications that lower seizure threshold. Clozapine has consistently shown a higher risk of seizures, which is clearly dose and titration dependent[53]

- Agents with higher affinities for antagonizing the M_1 receptor (e.g., clozapine, olanzapine, quetiapine) should be used very cautiously in patients with narrow-angle glaucoma or other conditions that may be exacerbated by anticholinergic actions
- Patients at high risk of suicide should be followed closely. Consider clozapine if appropriate (clozapine approved for reduction of risk of suicidal behaviors in schizophrenia or schizoaffective disorder)
- Evaluate clinical status and vital signs prior to IM olanzapine administration and monitor for oversedation and cardiorespiratory depression. DO NOT ADMINISTER together with an IM benzodiazepine (see Interactions p. 202)
- It has been suggested that antipsychotics may be used for sedative and anxiolytic effects to relieve unpleasant effects of drug of abuse[54]

Toxicity

- May occur as a consequence of an acute ingestion, intentional or accidental, or with chronic use. In general, signs and symptoms of toxicity present as exaggerations of known adverse effects within a few hours post ingestion
- Serious toxicity primarily involves the cardiovascular (QTc prolongation, respiratory arrest) and central nervous system (coma, seizures, sedation)
- Dystonic reactions and other EPSE as well as neuroleptic malignant syndrome (NMS) may also occur
- Convulsions occur late, except with clozapine; symptoms may persist as drug elimination may be prolonged following intoxication

Management

- Any patient experiencing signs or symptoms other than mild drowsiness should be transported to an emergency department. Local poison control centers should be contacted
- Gastric lavage and/or activated charcoal may be considered if less than 1 h has elapsed since ingestion and airways are not compromised. Do NOT induce vomiting. Syrup of ipecac should not be administered due to concerns of additive sedation and potential for aspiration pneumonia
- Hemoperfusion/hemodialysis not recommended due to large volumes of distribution and high plasma protein binding profiles of antipsychotics
- No specific antidotes; provide supportive treatment for symptomatic patients – establish/maintain airway, ensure adequate oxygenation/ventilation, monitor vital signs and ECG for at least 6 h and admit the patient for at least 24 h if significant intoxication apparent. Agents with extended-release technologies such as paliperidone may require longer supervision/monitoring
- Hypotension and circulatory collapse treated with IV fluids. IV vasopressors may be considered if there is no response to fluids (caution – use of epinephrine or dopamine or other sympathomimetics with β-agonist activity may worsen hypotension in the presence of antipsychotic-induced α_1 blockade; see Drug Interactions pp. 196–205). Sodium bicarbonate (1–2 meq/kg) should be considered for ventricular dysthymias or QRS prolongation $>$ 0.12 sec
- Correct hypokalemia or hypomagnesemia. Torsades de pointes are treated with IV magnesium sulfate. Avoid co-administration of drugs that produce additive QTc prolongation effects
- Seizures may not require treatment if short lived. Multiple or refractory seizures may be treated with lorazepam or diazepam
- Acute dystonia may be treated with benztropine (1–2 mg IV or IM)
- NMS treatment may include oxygen/ventilation, correction of hyperthermia with cooling blankets, ice-water bath etc., and correction of hypotension (see above)

Lab Tests/Monitoring

- See p. 154
- Monitor weight, fasting blood glucose, and lipid profiles at baseline and periodically during treatment
- Specific monitoring guidelines apply to clozapine (see p. 192)
- Therapeutic drug monitoring (TDM): Threshold plasma level suggested for response to clozapine (range of 350–550 ng/mL or 1050–1650 nmol/L). TDM of other antipsychotics may be utilized when clinically significant CYP inducers or inhibitors are believed to lead to toxicity or therapeutic failure, but TDM has limited evidence in youth for predicting drug response[55]
- On initiation and with dose increases, monitor: Clozapine (for hypotension, sedation, and seizures); iloperidone, risperidone, quetiapine (especially IR formulation) (for orthostatic hypotension)
- Olanzapine injection: Recommend clinical status and vital signs be evaluated prior to and as clinically indicated post olanzapine IM (short-acting or long-acting) administration; monitor for orthostatic hypotension, oversedation, delirium, and cardiorespiratory depression. Olanzapine IM long-acting: Observe for at least 3 h and instruct patient not to drive or operate heavy machinery for remainder of the day
- May result in false-positive methadone or tricyclic antidepressant (quetiapine) or amphetamine (aripiprazole) urine drug screen – consult your laboratory
- Risperidone: Preliminary data has associated iron depletion and deficiency with long-term use, which was inversely related to serum prolactin[56]

Second-Generation Antipsychotics (SGAs) (cont.)

- Ziprasidone: Patients at risk of significant electrolyte disturbances (risk factor for arrhythmias) should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during ziprasidone therapy need periodic monitoring of serum potassium and magnesium
- **Clozapine monitoring:** WBC/ANC monitoring requirements in Canada and the USA. See https://www.clozapinerems.com for registration and more information in the USA

	Hematological Parameters	Monitoring and Treatment Implications
Canada	WBC $\geq$ 3500/mm^3 (3.5 × 10^9/L) and/or ANC $\geq$ 2000/mm^3 (2.0 × 10^9/L)	Continue clozapine and appropriate frequency of monitoring (weekly for 6 months, then every 2 weeks for 6 months, then q4 weeks thereafter)
	2.0 × 10^9/L $\leq$ WBC $<$ 3.5 × 10^9/L, or 1.5 × 10^9/L $\leq$ ANC $<$ 2.0 × 10^9/L, or Single fall or sum of falls in WBC of $\geq$ 3.0 × 10^9/L measured in the last 4 weeks and reaching a value of $<$ 4.0 × 10^9/L, or Single fall or sum of falls in ANC of $\geq$ 1.5 × 10^9/L measured in the last 4 weeks and reaching a value of $<$ 2.5 × 10^9/L, or Flu-like complaints, fever, or other symptoms suggestive of infection	Continue clozapine Monitor twice weekly
	WBC $<$ 2.0 × 10^9/L or ANC $<$ 1.5 × 10^9/L	Hold clozapine and confirm laboratory results within 24 h Stop clozapine if confirmed and do not rechallenge
USA*	Normal range for new patient (ANC $\geq$ 1500/microliter)	Weekly from initiation for 6 months, then every 2 weeks for 6 months, then every 4 weeks thereafter
	Mild neutropenia (ANC 1000–1499/microliter)	Continue treatment Increase monitoring to 3 x/week until ANC $\geq$ 1500/microliter; once $\geq$ 1500/microliter, return to patient's last "normal range" ANC monitoring interval
	Moderate neutropenia (ANC 500–999/microliter)	Recommend hematology consult, interrupt treatment if clozapine-induced neutropenia suspected, resume treatment after ANC $\geq$ 1000/microliter Daily ANC until $\geq$ 1000/microliter, then 3 x/week until $\geq$ 1500/microliter; once $\geq$ 1500/microliter, weekly ANC for 4 weeks, then return to patients last "normal range" ANC monitoring interval
	Severe neutropenia (ANC $<$ 500 microliter)	Recommend hematology consult, interrupt treatment if clozapine-induced neutropenia suspected, do not rechallenge unless benefits outweigh risks Daily ANC until $\geq$ 1000/microliter, then three times weekly until $\geq$ 1500/microliter If rechallenged, resume treatment as if a new patient

* Guidance differs for patients with benign ethnic neutropenia. See https://www.clozapinerems.com for more information

Use in Pregnancy◊

- General:
  - For each individual, consider the risks of not treating/undertreating (e.g., illness relapse, self-harm, poor adherence with prenatal care, poor nutrition, exposure to additional medication or herbal remedies, increased alcohol, tobacco or illicit drug use, deficits in mother-infant bonding) vs. the risks of continuing or starting an antipsychotic
  - A large study of more than 1.3 million pregnancies and more than 700 filled prescriptions for FGAs and more than 9000 filled prescriptions for SGAs found no meaningful increases in congenital malformations.[57] Another study using the National Pregnancy Registry for Atypical Antipsychotics showed no increased risk for major malformations[58]
  - Pregnancy-related changes (i.e., increased body weight, blood volume, and body fat, altered drug metabolism and increased drug excretion) may require the use of higher drug doses to maintain efficacy. Pregnancy induces CYP2D6 and 3A4 enzymes, therefore antipsychotics that are substrates for these metabolic pathways may have reduced concentrations in late pregnancy. Postpartum dose tapering may be needed, as liver metabolism and fluid volumes return to baseline levels. Quetiapine serum concentrations in the third trimester were reduced 76%, olanzapine concentrations appeared unaffected, limited data available with other agents. Monitor for SGA adverse effects and reduce dose as needed
  - Animal data suggest there may be at least a moderate risk with some agents but animal reproduction studies are not always predictive of human response. Greatest risk of fetal malformations associated with use during first trimester
  - There may be increased weight gain and risk of gestational diabetes, with competing systematic reviews of studies looking at this arriving at different conclusions[59, 60] though there may be some signal in clozapine and olanzapine and possibly quetiapine. Close monitoring of weight, glucose, lipids, and blood pressure are warranted. Some suggest a glucose tolerance test be performed early in pregnancy (14–16 weeks' gestation) and a glucose tolerance test (rather than a glucose challenge test) be performed at 28 weeks' gestation. Some suggest high-dose folic acid (i.e., 4 mg/day) for pregnant women taking SGAs, as they may be at a higher risk of neural tube defects due to inadequate folate intake and obesity
  - In 2011, the US FDA and Health Canada asked manufacturers to update their prescribing information to warn clinicians and patients that third trimester use of antipsychotics is associated with risk of EPSE and withdrawal symptoms in newborns. Symptoms in the neonate may include: feeding disorder, hypertonia, hypotonia, tremor, respiratory distress, and agitation
  - A study of more than 300,000 pregnancies revealed that health and lifestyle factors that accompany antipsychotic use were relevant confounders, and controlling for these factors removed the significance of any risk increases[61]
  - If an antipsychotic will be used during pregnancy, consider patient enrollment or registration in any relevant studies or pregnancy exposure registries (e.g., in the USA: FDA list of pregnancy registries http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm134848.htm)
- **Asenapine**: No published human data. Animal data suggest potential for fetal risk (i.e., death and decreased weight)
- **Clozapine**: Limited human data. Animal data suggest low risk and a meta-analysis of 42 articles on clozapine in pregnancy and lactation found that data does not support that clozapine is teratogenic, stillbirth inducing, or increases the risk of delivery complications.[62] Compared to other antipsychotics, clozapine did not show increased signal of safety concerns in an analysis of over 230,000 pregnancies.[63] Possible increased incidence of maternal excessive weight gain and gestational diabetes. A case report suggests the concentration of clozapine in fetus plasma can exceed (2-fold) that in the mother and potential adverse effects have been reported (i.e., floppy infant syndrome, neonatal seizures, and rare cases of congenital malformations). Monitor WBC of newborn infant if mother on clozapine. One case report of delayed peristalsis in a newborn. One case report of delayed speech acquisition after in utero and breast milk exposure to clozapine
- **Iloperidone**: No published human data. Animal data suggest moderate risk (i.e., death and decreased weight)
- **Lumateperone**: Limited human data. May cause EPSE and/or withdrawal symptoms in neonates with third-trimester exposure
- **Lurasidone**: No human data. Potential risk in third trimester due to antipsychotics potential to cause EPSE and withdrawal symptoms in newborn. No adverse developmental or teratogenic effects seen in animals
- **Olanzapine**: Human data suggest low risk from in utero exposure, however, there is potential for excessive weight gain and gestational diabetes. A study comparing 4500 pregnancies with antipsychotic use to 22,500 pregnancies without antipsychotic use found that olanzapine was associated with greater risk of congenital malformations, specifically musculoskeletal malformations.[64] A preliminary study found olanzapine use associated with infants who were large for gestational age, however, there is conflicting data. Another preliminary study found ~72% (CI 47–98%) of human maternal olanzapine levels in umbilical cord blood, however, there was considerable variability in the range (7–167%). In clinical trials, 7 pregnancies occurred, which resulted in 2 normal births, 1 neonatal death due to cardiovascular defect, 3 therapeutic abortions, and 1 spontanous abortion

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Second-Generation Antipsychotics (SGAs) (cont.)

- **Paliperidone**: No published human data. Animal data suggest low risk. A small study of 17 pregnancies in which paliperidone was used revealed no significant safety signals. As paliperidone is the active metabolite of risperidone, also consult risperidone information
- **Quetiapine**: Limited human data. Animal data suggest risk (i.e., delays in skeletal development). However, no pattern of issues in humans seen to date with at least 65 cases of no major malformations with quetiapine exposure, and another study of 152 pregnancies with first-trimester exposure to quetiapine.[66] Potential for excessive weight gain and gestational diabetes. A preliminary study found ~24% (CI 19–30%; range 9–47%) of human maternal quetiapine levels in umbilical cord blood
- **Risperidone**: Limited human data. A slight but significant increase in congenital malformations was found in a study of 1566 risperidone prescriptions during first-trimester pregnancy.[57] Reversible EPSE (e.g., tremor, jitteriness, irritability) seen in neonates with third trimester risperidone exposure. Four retrospective reports of poorly defined developmental syndromes, however, relationship to risperidone use unclear. Case report of maternal NMS with third-trimester exposure to haloperidol and risperidone. Case report of maternal tardive dyskinesia with first trimester exposure to low-dose, short-term risperidone. A preliminary study found ~49% (CI 14–85%) of human maternal risperidone levels in umbilical cord blood, however, there was considerable variability in the range (17–105%)
- **Ziprasidone**: Limited human data. Animal data suggest risk, including possible teratogenic effects at doses similar to human therapeutic doses. One case report of ziprasidone use throughout pregnancy (in combination with citalopram) reports no adverse effects on mother or infant at 6-month follow-up, while another report describes malformations of the face and extremities in an infant

Breast Milk

- For each individual, consider the benefits of breastfeeding (e.g., clinical and psychosocial advantages for mother and infant, cost savings) vs. the risks of infant drug exposure via breast milk and possible effects on milk production
- Antipsychotics, like most medications, pass into breast milk, however, antipsychotic amounts found are generally low. Long-term effects on neurodevelopment are largely unknown. The American Academy of Pediatrics classifies antipsychotics as drugs "whose effect in the nursing infant is unknown but may be of concern"
- If used while breastfeeding, use lowest effective dose and monitor infant's progress
- For more detailed information on specific drugs and lactation, refer to the Drugs and Lactation Database (https://www.ncbi.nlm.nih.gov/books/NBK501922/) or see [48]

Nursing Implications

- See pp. 155–157

Oral

- **With or without food?**
  - Asenapine should be taken without food or drink for at least 10 min post dose
  - Clozapine, iloperidone, olanzapine, paliperidone, and risperidone (tablets, M-tabs, and solution) may be taken with or without meals
  - Lurasidone should be taken with food (at least 350 calories). Food increases lurasidone's bioavailability 2-fold
  - Quetiapine can be taken with or without food, however, high-fat meals (~800–1000 calories) increase quetiapine exposure, which may be clinically relevant for some patients. Suggest taking consistently with respect to food, particularly for once daily dosing
  - Ziprasidone must be taken with food, ideally with a meal of at least 500 calories. Food increases ziprasidone's bioavailability 2-fold
- **Compatibility with beverages**
  - CAUTION: Grapefruit juice and related citrus fruits may increase the levels of clozapine, iloperidone, quetiapine, and ziprasidone (see Drug Interactions p. 203)
  - Risperidone solution is compatible with water, coffee, orange juice, and low-fat milk. It is NOT compatible with caffeine-containing soft drinks or tea
  - Olanzapine Zydis is compatible with water, milk, coffee, orange juice, and apple juice. The mixture should be consumed promptly after mixing
- **Oral formulation considerations – sublingual, oral disintegrating tablets, extended release, suspensions**
  - Asenapine sublingual tablets dissolve in saliva within seconds when placed under the tongue. DO NOT swallow tablets as absorption is significantly reduced. DO NOT push tablet through foil backing as this could damage tablet. Use dry hands to remove tablet and immediately place tablet under the tongue

- Oral disintegrating tablets (ODT) (clozapine ODT, risperidone M-tabs, and olanzapine Zydis) disintegrate rapidly in saliva and can be taken with or without liquid. These products are not absorbed sublingually but swallowed, then absorbed enterally. Because they start to disintegrate upon contact with moisture, ODTs should be handled carefully with dry hands (avoid direct contact with hands as much as possible)
- If half tablets of olanzapine Zydis are required, break tablet carefully and wash hands after the procedure. Avoid exposure to powder as dermatitis, eye irritation, and hypersensitivity reactions reported. Store broken tablet in tight, light-resistant container (tablet discolors) and use within 7 days
- Asenapine, paliperidone, quetiapine XR, and risperidone M-tabs should not be chewed, divided or crushed
- Paliperidone is supplied in a non-absorbable shell that may appear in stool and is not a cause for concern
- Use liquid (risperidone, ziprasidone), ODTs, or asenapine sublingual tablets if patient has difficulty swallowing or is suspected of nonadherence. However, more challenging individuals can cheek ODTs. Time to dissolution may vary by product and by patient (e.g., dry mouth may impede dissolution times)
- Storage: Room temperature, protected from light and moisture – clozapine ODT, olanzapine Zydis, risperidone solution and M-tabs, ziprasidone suspension

Short-acting IM

- Olanzapine
  - Olanzapine IM is reconstituted using the provided 2.1 mL of sterile water for injection to yield a clear, yellow 5 mg/mL solution. Use within 1 h of mixing. Inject slowly, deep into the muscle mass
  - Concomitant administration of olanzapine IM and parenteral benzodiazepine is NOT RECOMMENDED (see Drug Interactions p. 202)
  - Prior to olanzapine IM administration, evaluation of vital signs is recommended. Post-injection monitor for hypotension, oversedation, and cardiorespiratory depression
  - Storage: Room temperature (pre-mixing and reconstituted stable for a maximum of 1 h)
- Ziprasidone
  - Ziprasidone IM is reconstituted into a suspension using the provided 1.2 mL of sterile water for injection. Shake vial vigorously until all of the drug is dissolved. Following reconstitution, any unused portion should be discarded after 24 h, since no preservative or bacteriostatic agent is present in this product
  - Ziprasidone IM may be used with a benzodiazepine but should NOT be mixed in the same syringe
  - Storage: Room temperature (protect from light; pre-mixing and reconstituted stable for a maximum of 24 h)

Long-acting IM

- It is recommended to establish tolerability with an oral form of the medication prior to initializing a long-acting IM dosage form
- Rotate administration sites. Document in charting the muscle and location (e.g., left or right) of each injection
- Storage: Room temperature – olanzapine pamoate (pre-mixing and reconstituted stable for a maximum of 24 h), paliperidone palmitate, risperidone (pre-mixing stable for a maximum of 7 days when stored at room temperature); refrigerate – risperidone (pre-mixing), aripiprazole
- Olanzapine pamoate IM
  - Can cause a **post-injection sedation (including coma)/delirium syndrome**. Administer where emergency services are readily accessible. Observe for at least 3 h. Instruct patient not to drive or operate heavy machinery for remainder of the day. Risk $< 0.1\%$ at each injection
  - **Wear gloves** when reconstituting to prevent skin irritation. Reconstitute with supplied diluent. Inject slowly, deep into the gluteal muscle. Use 1.5-inch 19-gauge needle provided for non-obese patients. In the obese, may use 2-inch 19-gauge or larger needle. To prevent clogging, a 19-gauge or larger needle must be used. If not administered immediately, use within 24 h and **shake** vigorously to resuspend prior to administration. After insertion of the needle into the muscle, **aspirate for several seconds to ensure that no blood appears**. If any blood is drawn into the syringe, discard the syringe and the dose and begin with a new kit
    - The injection should be performed with steady, continuous pressure
    - DO NOT massage injection site
- Paliperidone palmitate 1-, 3-, and 6-month IM
  - Paliperidone palmitate 1-monthly IM is a suspension in a prefilled syringe. **Shake** the syringe vigorously for a minimum of 10 sec to ensure a homogeneous suspension
  - Paliperidone palmitate 1-monthly IM initial dose (day 1) and second dose (day 8) should be administered intramuscularly into the deltoid muscle. These two initial injections help attain therapeutic concentrations rapidly without the need for oral supplementation. Further doses can be administered into the deltoid or upper outer quadrant of the gluteal muscle. (See Pharmacokinetics, p. 182). Inject slowly, deep into the muscle. Alternate injections between arms or buttocks and specify in charting. For the deltoid injection, use 1.5-inch 22-gauge needle for

Second-Generation Antipsychotics (SGAs) (cont.)

patients weighing 90 kg or more (200 lb or more) or 1-inch 23-gauge for patients under 90 kg (under 200 lb). For the gluteal injection, use 1.5-inch 22-gauge needle regardless of patient weight. Use the needles provided in the kit
  - Paliperidone palmitate every 3 months IM (Trinza formulation) and every 6 months IM (Hafyera formulation) have no published reports of use in youth; safety unknown
- Risperidone microspheres IM
  - Dose pack should be allowed to come to room temperature before reconstitution and injection. Reconstitute with diluent provided. Should be used as soon as possible after reconstitution – shelf life is 6 h
  - **Only use needles supplied** with the kit as use of a higher gauge may impede the passage of microspheres. Needle detachments have been reported; to prevent, follow the accompanying instructions and recheck the syringe-needle attachment prior to injection
  - **Shake** the formulation vigorously for at least 10 sec within 2 min before administering; give deep IM into deltoid (1-inch needle) or gluteal (2-inch needle) muscle; alternate injections between arms or buttocks and specify in charting
  - DO NOT massage injection site
- Risperidone extended-release subcutaneous injection
  - Dose pack should be allowed to come to room temperature for at least 15 minutes before reconstitution and injection. After removal from refrigerator, use within 7 days. Reconstitute with diluent provided and mixing syringes. The final suspension should appear cloudy and can vary from white to yellow-green in color. Should be used as soon as possible after reconstitution
  - **Only use needles supplied** with the kit. Needle detachments have been reported; to prevent, follow the accompanying instructions and recheck the syringe-needle attachment prior to injection
  - Pinch abdominal tissue and administer subcutaneously; alternate injections and specify in charting
  - DO NOT massage injection site

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Acetylcholinesterase inhibitor (central)	General	Interaction not well described in children and adolescents
	Donepezil, galantamine, rivastigmine	May enhance neurotoxicity of antipsychotics, presumably due to a relative acetylcholine/dopamine imbalance (i.e., increased acetylcholine in the presence of dopamine receptor blockade) in the CNS. Case reports of severe EPS (e.g., generalized rigidity, shuffling gait, facial grimacing) in elderly patients within a few days of starting an antipsychotic (risperidone or haloperidol) and an acetylcholinesterase inhibitor (donepezil). Symptoms resolved after discontinuing the antipsychotic, the acetylcholinesterase inhibitor or both. Case reports of NMS with concurrent use of olanzapine and an acetylcholinesterase inhibitor (donepezil and rivastigmine).
Adsorbent	Activated charcoal, attapulgite (kaolin-pectin), cholestyramine	Gastrointestinal absorption decreased significantly when used simultaneously; give at least 1 h before or 2 h after the antipsychotic. Charcoal (1 g) reduced the C_{max} and AUC of olanzapine by 50–60%
α_1-adrenergic receptor blocker	Doxazosin, prazosin, terazosin	Additive hypotensive effect possible. Antipsychotics generally cause hypotension via α_1 blockade (see Effects of Antipsychotics on Receptors table p. 217)
Amylinomimetic	Pramlintide	Pramlintide slows the rate of gastric emptying. Antipsychotics with significant anticholinergic effects can further reduce GI motility
Antiarrhythmic	General	Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. CAUTION with all other SGAs. Also see Cardiovascular Effects of SGAs section p. 184
	Amiodarone, quinidine	CYP2D6 is inhibited by amiodarone and potently by quinidine. With amiodarone and quinidine, increased plasma level of asenapine, clozapine (case report with amiodarone), iloperidone, and risperidone likely

Class of Drug	Example	Interaction Effects
Antibiotic		
Quinolone	Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin	DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. CAUTION with all other SGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. Also see Cardiovascular Effects of SGAs section p. 184
		CAUTION. Potential to exacerbate psychiatric conditions, as quinolone-induced psychosis has been reported
		Ciprofloxacin and norfloxacin inhibit CYP1A2. With ciprofloxacin, increased clozapine and norclozapine levels (by 29–100%; case report of a 5-fold increase); increased olanzapine level (by more than 2-fold in a case report). Increased levels of asenapine likely. Case report of sudden-onset dystonia in a patient taking asenapine and ciprofloxacin. Norfloxacin likely to cause similar SGA level increases. Adjust antipsychotic dose as needed
Macrolide	Clarithromycin, erythromycin	DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. CAUTION with all other SGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. See quinolone above p. 197 for further discussion
		CYP3A4 is inhibited potently by clarithromycin and moderately by erythromycin. With erythromycin, decreased clearance of quetiapine (by 52%) and with clarithromycin, a case report of ~7-fold increase in quetiapine levels. Consider reducing quetiapine dose by 50% with concurrent use of strong CYP3A4 inhibitors and by 25% with moderate CYP3A4 inhibitors. Although a pharmacokinetic study suggests no significant interaction between erythromycin and clozapine, there are case reports of increased clozapine levels (by ~2- to 3-fold) and associated symptoms (e.g., disorientation, seizures, neutropenia, somnolence, slurred speech). Reduce iloperidone dose by 50% with concurrent use of strong CYP3A4 inhibitors. Lurasidone should NOT be used concurrently with strong CYP3A4 inhibitors and reduce its dose by 50% in the presence of moderate CYP3A4 inhibitors. Ziprasidone levels increased by ~40% in the presence of strong CYP3A4 inhibitors Adjust antipsychotic dose as needed
Tetracycline	Tetracycline	Case report of increased motor and vocal tics when tetracycline added to risperidone and sertraline; mechanism unknown
Anticholinergic	Antidepressants, antihistamines, antiparkinsonian drugs	Increased risk of anticholinergic adverse effects (e.g., dry mouth, urinary retention, inhibition of sweating, blurred vision, constipation, paralytic ileus, confusion, toxic psychosis)
Anticoagulant	Warfarin	Two case reports of increased INR with the addition of quetiapine to warfarin
Anticonvulsant	General	All SGAs may lower seizure threshold. May occur if dose is increased rapidly or may also be secondary to hyponatremia. Potential additive risk for hyponatremia as both SGAs and carbamazepine/oxcarbazepine can cause low sodium levels. Risk of seizures is greatest with clozapine and is dose related: 1% (doses below 300 mg), 2.7% (300–599 mg), and 4.4% (above 600 mg)
	Carbamazepine	Decreased antipsychotic plasma level via potent induction of CYP3A4, CYP1A2, CYP2D6 and/or possibly UGT1A4. Note it may take 2–4 weeks to reach maximum induction and an equivalent period to return to baseline after discontinuation of an inducer. Adjust antipsychotic dose as needed
		Clozapine levels reduced by 50%. AVOID due to potential additive risk for agranulocytosis. Case report of fatal pancytopenia
		Olanzapine levels reduced by 36–71%.
		Paliperidone's C_{max} level reduced by 37% with 400 mg/day of carbamazepine
		Quetiapine levels reduced by up to 80% with other reports of undetectable levels. Two case reports of 3- to 4-fold increase in the ratio of carbamazepine epoxide/carbamazepine resulting in ataxia and agitation in one case. AVOID combination if possible
		Risperidone and 9-hydroxyrisperidone levels reduced by 50%. Risperidone causes a modest, clinically insignificant increase in carbamazepine level. Two cases in children of hyperammonemia, and one case of catatonia with the addition of valproic acid to risperidone and sertraline. Monitoring of serum ammonia levels may be warranted if new or increased manic behavior occurs
		Ziprasidone AUC reduced by 36% with 400 mg/day of carbamazepine. Higher carbamazepine doses may have a greater effect

Second-Generation Antipsychotics (SGAs) (cont.)

Class of Drug	Example	Interaction Effects
	Lamotrigine	Lamotrigine is a weak UGT inducer. A significant reduction (58%) of quetiapine levels suggested by one study, however, a larger study found a clinically insignificant (17%) reduction. Studies suggest low dose lamotrigine ($\leq$ 200 mg/day) does not significantly affect the levels of clozapine, olanzapine or risperidone. However, case reports of clinically significant increased levels of clozapine and risperidone and a study found an increase in olanzapine levels (35%) in smokers taking lamotrigine. Mechanism unknown. With concurrent clozapine, monitor CBC as both drugs can depress bone marrow function. Case report of fatal agranulocytosis within 6 weeks of starting concurrent quetiapine, lamotrigine, mirtazapine, and venlafaxine. Monitor for reduced antipsychotic efficacy as well as antipsychotic toxicity (e.g., sedation, dizziness), particularly with higher doses of lamotrigine
	Oxcarbazepine	Oxcarbazepine is a weak CYP3A4 inducer and does not appear to significantly affect the levels of clozapine, olanzapine, quetiapine or risperidone, however, consider the potential for additive bone marrow suppression with clozapine and possibility of more significant SGA level reductions with high doses of oxcarbazepine ($\geq$ 1500 mg/day)
	Phenobarbital, phenytoin	Decreased level of SGA due to potent induction of metabolism; for phenytoin via CYP2C9 and CYP3A4; for phenobarbital primarily via CYP1A2, CYP2C9, and CYP3A4. Note it may take 2–4 weeks to reach maximum induction and an equivalent period to return to baseline after discontinuation of an inducer. Adjust antipsychotic dose as needed
		Iloperidone level likely to decrease by 2-fold based on interaction with potent inducers. Iloperidone dose may need to be increased by 50% Lurasidone levels decreased by 5-fold in the presence of other potent CYP3A4 inducers (i.e., rifampin). Recommended to avoid lurasidone with concurrent potent CYP3A4 inducers Paliperidone, risperidone, and ziprasidone levels reduced by other potent CYP3A4 inducers (i.e., carbamazepine); similar interaction anticipated
		With phenytoin, clozapine level decreased by 65–85%, which resulted in re-emergence of psychotic symptoms and a case report of phenytoin intoxication after IV phenytoin loading possibly due to clozapine inhibition of CYP2C9. Quetiapine level decreased by 80% With phenobarbital, clozapine level decreased by 35% Olanzapine level significantly reduced by other potent CYP1A2 inducers (i.e., carbamazepine); similar interactions anticipated
	Topiramate	Topiramate is a weak CYP3A4 inducer and CYP2C19 inhibitor. Modest reduction of risperidone's C_{max} (by 23–29%) with no effect on 9-hydroxyrisperidone. Likely not clinically significant. One study found no significant changes to the levels of clozapine, norclozapine, olanzapine, risperidone, 9-hydryoxyrisperidone or quetiapine. The effects of higher doses of topiramate (more than 400 mg/day) are unknown
	Valproate (divalproex, valproic acid)	Valproate inhibits CYP2C9 and UGT and weakly inhibits CYP1A2, CYP2D6, and CYP2E1. Adjust antipsychotic dose as needed Asenapine: Product monograph states no dose adjustment required based on a single dose of asenapine and 9 days of valproate
		Clozapine: Conflicting information. Both increased and decreased clozapine levels reported. Possibly a clinically significant reduction in clozapine levels in smokers. Case reports of hepatic encephalopathy, onset of seizures in nonepileptic patients, and delirium. Reports suggest a greater risk of agranulocytosis with concurrent valproate and clozapine than with either alone. Concurrent valproate with rapid clozapine dose titration may increase risk of myocarditis
		Olanzapine: Most studies found no clinically significant change in the levels of either medication. However, reduced olanzapine levels found in one study (by ~20%) and seen in case reports (by ~50%). Incidence of hepatic enzyme elevations may increase the risk of hepatic adverse effects
		Paliperidone: C_{max} of a single dose of paliperidone increased by 50% with no effect on valproate level. Consider reduction of paliperidone dose

Class of Drug	Example	Interaction Effects
		Quetiapine: Case reports of adverse effects possibly due to increased quetiapine levels. Case report of severe cervical dystonia with the addition of valproic acid. Case report of drug-induced parkinsonism and cognitive decline with concurrent use of quetiapine (800 mg/day) and valproic acid (1500 mg/day). Two case reports of delirium in patients with mild renal impairment after the addition of valproate to quetiapine. A case report of severe hypertriglyceridemia in the absence of weight gain with the addition of valproate to quetiapine that resolved on valproate discontinuation. Cases of hyperammonemia induced by interaction with valproate and quetiapine reported. Four case reports of neutropenia with concurrent quetiapine and valproate, with one also having thrombocytopenia. Monitor CBC at baseline, in 1–2 weeks, and after any dose increases
		Risperidone: No effect on risperidone levels with a modest (20%) increase in valproate levels. A case report of elevated and another of reduced valproate levels. Two case reports of generalized edema. Case report of neutropenia resolving after valproic acid stopped. Two cases in children of hyperammonemia, and one case of catatonia with the addition of valproic acid to risperidone and sertraline. Monitoring of serum ammonia levels may be warranted if new or increased manic behavior occurs
Antidepressant	General	Case reports of serotonin syndrome with concurrent use of antidepressants that increase serotonin and SGAs
SSRI	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	CAUTION with paliperidone, quetiapine, and ziprasidone; possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias
		Increased plasma level of antipsychotic possible due to inhibition of CYP1A2 (potent – fluvoxamine), 2D6 (potent – fluoxetine and paroxetine) and/or 3A4 (fluvoxamine). Adjust antipsychotic dose as needed
		Asenapine's C_{max} (+ 13%) and AUC (+ 29%) increased by fluvoxamine based on an asenapine single-dose study. Asenapine (a weak inhibitor of CYP2D6) increased exposure to a single dose of paroxetine by ~2-fold
		Clozapine level: With citalopram, no change to increased. With fluoxetine, 41–76% higher levels plus 38–45% higher norclozapine levels; one fatality reported; case report of acute myocarditis after addition of clozapine to fluoxetine and lithium. With fluvoxamine, 3–11-fold higher level. With paroxetine, no change to 41% increase plus 45% norclozapine increase. With sertraline, 41-76% increase plus 45% norclozapine increase; one fatal arrhythmia reported but causality unclear
		Iloperidone's AUC increased by ~1.6- to 3-fold in the presence of fluoxetine or paroxetine. Reduce iloperidone dose by 50% if fluoxetine or paroxetine added
		Olanzapine level: With fluoxetine, 16% increase in C_{max}; not clinically significant. With fluvoxamine, 2.3- to 4-fold increase in olanzapine levels. Case reports of fatal hyponatremia, marked hyperglycemia, and acute pancreatitis with long-term use of paroxetine + fluphenazine + haloperidol + olanzapine
		Quetiapine level: With fluvoxamine, may be increased by up to 159%. Case reports of NMS/serotonin syndrome with quetiapine and SSRIs (i.e., citalopram, fluvoxamine). Monitor for symptoms (e.g., fever, myoclonus, and tremor)
		Risperidone level: With fluoxetine, 2.5- to 8-fold increased levels and case report of tardive dyskinesia. With paroxetine, 3- to 9-fold higher levels and cases of serotonin syndrome. Case reports of serotonin syndrome and/or NMS with fluvoxamine and trazodone + sertraline Case of gynecomastia and galactorrhea without elevated prolactin level in a male taking risperidone and fluvoxamine
		Ziprasidone: Case report of serotonin syndrome with ziprasidone and citalopram
NDRI	Bupropion	Risperidone: Potential for additive seizure risk due to increased plasma level of risperidone due to competitive inhibition of CYP2D6
SNRI	Venlafaxine	Clozapine: Increased levels of both clozapine and venlafaxine possible due to competitive inhibition of CYP2D6 and/or CYP3A4. A study with venlafaxine doses of 150 mg/day or less suggests no clinically significant interaction. Case report of NMS/serotonin syndrome Quetiapine: Case report of fatal agranulocytosis within 6 weeks of starting concurrent quetiapine, lamotrigine, mirtazapine, and venlafaxine

Second-Generation Antipsychotics (SGAs) (cont.)

Class of Drug	Example	Interaction Effects
SARI	Nefazodone, trazodone	Potential for additive adverse effects (e.g., sedation, orthostatic hypotension). Nefazodone is a potent CYP3A4 inhibitor Increased plasma level of clozapine (case report) and quetiapine (*in vitro* data) possibly due to inhibited metabolism via CYP3A4 and associated adverse effects (e.g., dizziness, hypotension) Lurasidone is contraindicated with concomitant use of potent CYP3A4 inhibitors Case report of NMS with nefazodone and olanzapine. Case report of serotonin syndrome with trazodone, sertraline, and risperidone
SMS	Vortioxetine	Serotonin modulators may enhance the dopamine blockade of antipsychotics and increase the risk of side effects. Antipsychotics may enhance the serotonergic effects of serotonin modulators and increase the risk of serotonin syndrome
NaSSA	Mirtazapine	Potential for additive metabolic adverse effects (e.g., increased cholesterol, weight), and increased appetite and sedation. Case report of status epilepticus with mirtazapine and olanzapine. Case report of serotonin syndrome with mirtazapine, tramadol, and olanzapine and another within 7 weeks of adding quetiapine and mirtazapine to venlafaxine and donepezil. Case report of fatal agranulocytosis within 6 weeks of starting concurrent quetiapine, lamotrigine, mirtazapine, and venlafaxine
Cyclic	Amitriptyline, clomipramine, maprotiline, trimipramine	Additive sedation, hypotension, and anticholinergic effects. Potential for additive seizure risk DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. CAUTION with all other SGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias Potential for increased SGA levels as CYP2D6 is moderately inhibited by amitriptyline, clomipramine, desipramine, and imipramine Asenapine: Imipramine caused modest (17%) increase in C_{max} of a single dose of asenapine. No adjustment of asenapine dose required Clozapine: Case report of serotonin syndrome after withdrawal of clozapine in a patient taking clomipramine. Case report of 2-fold increase in nortriptyline level after the addition of clozapine. Patient developed delirium, which was preceded by extreme fatigue and slurred speech. Case report of increased clomipramine levels and myoclonic jerks followed by seizures, possibly due to competitive inhibition for CYP1A2 and/or CYP2D6 Olanzapine: Case report of NMS/serotonin syndrome with clomipramine. Suggest using lowest doses possible if olanzapine and clomipramine used concurrently Quetiapine: Case report of 17-fold increase in quetiapine level with concurrent doxepin and pantoprazole; mechanism unknown Risperidone: Case reports of increased maprotiline level (40–60%) and anticholinergic effects with risperidone, possibly due to competitive inhibition of CYP2D6
Irreversible MAOI, RIMA	Moclobemide, phenelzine, tranylcypromine	Additive hypotension Case report of serotonin syndrome with quetiapine and phenelzine and another with ziprasidone and tranylcypromine
Antidiarrheal	Loperamide	Case report of fatal gastroenteritis with clozapine. Potentially anticholinergic effects of clozapine added to antimotility effects of loperamide lead to toxic megacolon
Antifungal	Fluconazole, itraconazole, ketoconazole, voriconazole	Ketoconazole and itraconazole are potent, while fluconazole and voriconazole are moderate CYP34A inhibitors. Increased iloperidone (level by 57% with ketoconazole), lurasidone (C_{max} 6- to 9-fold and AUC 9-fold), 9-hydroxyrisperidone (level by 70% in a study of risperidone with itraconazole), quetiapine (C_{max} by 335% with ketoconazole), risperidone (level by ~80% with itraconazole), and ziprasidone (AUC and C_{max} by 35–40% with ketoconazole). Adjust antipsychotic dose as needed. Recommended to AVOID concurrent use of lurasidone and ketoconazole or itraconazole CAUTION – possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias with antipsychotics
	Terbinafine	Increased plasma level of iloperidone and risperidone possible due to inhibited metabolism via CYP2D6. Any interaction will be prolonged (up to 3 months) due to terbinafine's long half-life (200–400 h)
Antihistamine	Diphenhydramine, hydroxyzine	See Class of Drug "Anticholinergic" above (p. 197) and "CNS depressant" below (p. 203)

Class of Drug	Example	Interaction Effects
Antihypertensive		Additive hypotensive effect possible. Antipsychotics generally cause hypotension via α_1 blockade (see receptor table p. 217 and frequency of adverse effects table pp. 219–219). Start with a lower dose of antipsychotic, titrate slowly, and monitor for orthostatic hypotension
	Calcium channel blockers	Also see Class of Drug "calcium channel blocker" p. 202
	Clonidine	SGAs that are potent α_2-adrenergic receptor antagonists may block clonidine's antihypertensive effects via α_2-adrenergic receptor agonism (see receptor table p. 217). Additive hypotensive effects also possible
	Diuretic	Also see Class of Drug "diuretic" p. 203
	Lisinopril	Case report of significantly increased plasma level of clozapine and norclozapine. Case report of pancreatitis 3 months after lisinopril added to olanzapine
Antiparkinsonian agent	Levodopa, pramipexole, ropinirole	Potential for reduced therapeutic effect of antiparkinson drugs. Antipsychotics reduce dopaminergic activity while antiparkinson agents increase dopamine in the CNS. If a SGA is necessary, consider using clozapine or quetiapine, which have been reported to be less likely to cause worsening control of movement disorders than other antipsychotics
Antipsychotic combination	General	Increased risk of adverse effects (e.g., EPS elevated prolactin levels, sedation hypotension, and anticholinergic effects), increased cost, and potential for decreased adherence with use of multiple antipsychotic agents
	Aripiprazole + SGAs	See p. 215 in TGA interaction section
	Clozapine + olanzapine	Case reports of NMS. Potential for additive metabolic effects and weight gain Case report of delayed recovery of clozapine-induced agranulocytosis when given olanzapine
	Clozapine + quetiapine	Clozapine increased serum concentration of quetiapine by 82% (unknown mechanism but suggested to be clinically significant); consider starting at a lower than usual dose of quetiapine
	Clozapine + risperidone	Isolated case reports suggest increased clozapine and risperidone level with concurrent use. However, kinetic studies found no effects on levels. Discrepancy potentially due to genetic variability in metabolism. Chronic concurrent administration may increase risperidone levels. Most common adverse effects with concurrent use are EPS (e.g., akathisia), higher fasting glucose, sedation, hyperprolactinemia and hypersalivation. Case reports of NMS
	Haloperidol + SGAs	With clozapine, a case of significantly elevated haloperidol decanoate level and cases of NMS; including one after a single IM dose of haloperidol following abrupt clozapine discontinuation, another after abrupt discontinuation of both medications
		With olanzapine, a case of extreme parkinsonism potentially due to competitive inhibition of CYP2D6 and/or additive adverse effects Case report of fatal hyponatremia, marked hyperglycemia, and acute pancreatitis with long-term use of paroxetine + fluphenazine + haloperidol + olanzapine
	Phenothiazines (e.g., chlorpromazine) + SGAs	Possible additive QT prolongation (see Cardiovascular Effects p. 184). DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone Case reports of NMS including with olanzapine + fluphenazine; olanzapine + chlorpromazine; after several years of olanzapine + clozapine + fluphenazine. Case report of fatal hyponatremia, marked hyperglycemia, and acute pancreatitis with long-term use of paroxetine + fluphenazine + haloperidol + olanzapine
	Pimozide + SGAs	Possible additive QT prolongation (see above). DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone
	Thioridazine + SGAs	Possible additive QT prolongation (see above). DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone
		Increased clearance (i.e., decreased plasma level) of quetiapine (by 65%). Increased plasma level of risperidone (by ~5-fold) with reduced 9-hydroxyrisperidone level due to inhibition of metabolism via CYP2D6. Increased levels of other SGAs (e.g., iloperidone, clozapine) possible. Increased SGA level have the potential to further increase the risk of QT prolongation
	Quetiapine + ziprasidone	Case report of increased QTc prolongation with cardiac arrhythmia, possibly due to increased plasma level of either drug as a result of competitive inhibition via CYP3A4

Second-Generation Antipsychotics (SGAs) (cont.)

Class of Drug	Example	Interaction Effects
Antiretroviral		See [68] for additional information
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Delavirdine, efavirenz, etravirine, nevirapine	CAUTION. Possible interactions as NNRTIs inhibit and induce CYP enzymes (e.g., delavirdine is a strong inhibitor of 2D6, nevirapine weakly inhibits 2D6. Efavirenz and etravirine induce 3A4 moderately, nevirapine weakly induces it) Delavirdine may increase levels of risperidone and iloperidone due to CYP2D6 inhibition Efavirenz and etravirine may decrease levels of quetiapine and lurasidone due to CYP3A4 induction
Protease inhibitor	Atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, simeprevir, telaprevir, tipranavir	CAUTION. Complex interactions likely as various protease inhibitors (PI) potently inhibit as well as induce a variety of CYP enzymes (e.g., on CYP3A4, ritonavir is a potent inhibitor; atazanavir, boceprevir, darunavir, saquinavir, and telaprevir are strong inhibitiors; fosamprenavir and indinavir are mild to moderate inhibitors; tipranavir is an inducer. Low boosting doses of ritonavir have little effect on CYP2D6 but higher doses cause inhibition) Increased plasma level of clozapine possible due to inhibition of CYP3A4, however, ritonavir may also decrease levels via induction of CYP1A2. Net effect of ritonavir difficult to predict.[17] AVOID if possible due to potential for clozapine toxicity and additive effects on cardiac conduction. Consider monitoring clozapine levels if used concurrently
Antitubercular drug	Rifabutin, rifampin, rifapentine	Decreased clozapine (plasma level by 6-fold), lurasidone (C_{max} by 86% and AUC by 80%), risperidone (C_{max} by up to 50%), and 9-hydroxyrisperidone (i.e., paliperidone; C_{max} by 46%) due to induction via CYP3A4, CYP2C and/or P-glycoprotein with rifampin. Coadministration of lurasidone and rifampin NOT recommended. Reduced levels of iloperidone and quetiapine likely
Anxiolytic		
Benzodiazepines	Clonazepam, diazepam, flurazepam, lorazepam, midazolam	Synergistic effect with antipsychotics; used to calm agitated patients Potential for additive CNS adverse effects (e.g., dizziness, sedation, confusion, respiratory depression) and hypotension Increased incidence of dizziness, hypotension, sedation, excessive salivation, and ataxia when combined with clozapine; cases of ECG changes, delirium, cardiovascular or respiratory arrest and deaths reported – more likely to occur early in treatment when clozapine added to benzodiazepine regimen Lurasidone (120 mg/day) slightly increased level of midazolam (C_{max} by 21% and AUC by 44%). May not be clinically significant Concomitant administration of short-acting IM olanzapine and parenteral benzodiazepine and/or other drugs with CNS depressant activity has been associated with serious adverse events (e.g., hypotension, bradycardia, respiratory or CNS depression), including fatalities; thus it is NOT RECOMMENDED
	Buspirone	Case report of GI bleeding and hyperglycemia with clozapine
Aprepitant		Case report of 11-fold increase in quetiapine level with accompanying somnolence. Quetiapine dose reduced by 50% with subsequent aprepitant courses and somnolence did not occur
Belladonna alkaloid	Atropine, hyoscyamine, scopolamine	Additive anticholinergic effects (e.g., dry mouth, urinary retention, inhibition of sweating, blurred vision, constipation, paralytic ileus, confusion, toxic psychosis). The elderly are particularly vulnerable to these effects. See frequency of adverse reactions table p. 220 Caution is advised
Calcium channel blocker	Diltiazem, verapamil	Increased lurasidone (C_{max} 2.1-fold and AUC 2.2-fold) with diltiazem. If coadministered, maximum dose of lurasidone should be 40 mg/day Increased risperidone (C_{max} 1.8-fold), and 9-hydroxyrisperidone (i.e., paliperidone; slight increase) with verapamil. Interactions likely due to diltiazem's/verapamil's ability to inhibit metabolism via CYP3A4 and/or to increase intestinal absorption via inhibition of P-glycoprotein. Increased quetiapine possible

Class of Drug	Example	Interaction Effects
Caffeine	Coffee, tea, cola, energy drinks, guarana or mate containing products	Increased akathisia/agitation/insomnia Increased plasma levels of clozapine due to competition for metabolism via CYP1A2. Clozapine and norclozapine levels decreased by a mean of 47% and 31% following a 5-day caffeine-free period More likely to be clinically relevant in those who are nonsmokers or consuming more than 400 mg of caffeine/day (e.g., more than 4 cups of caffeinated coffee/day). Variations in caffeine intake should be considered when clozapine concentrations fluctuate Risperidone solution is incompatible with cola or tea, but it is compatible with coffee
CNS depressant	Alcohol, antihistamines, hypnotics, opioids	CAUTION. Increased CNS effects (e.g., sedation, fatigue, impaired cognition) and orthostatic hypotension. Alcohol may worsen EPS. Monitor for adverse effects when starting a SGA or increasing the dose; recommended to avoid alcohol during these times
Disulfiram		CAUTION. Case reports of disulfiram-induced psychosis, possibly due to blockade of dopamine β-hydroxylase, however, no increased psychotic features seen in small studies of participants with psychotic disorders. Decreased metabolism and increased plasma level of clozapine possible due to inhibition of CYP2E1
Diuretic	General Furosemide	CAUTION. Diuretics can cause electrolyte disturbances resulting in additive QT interval prolongation and risk of associated life-threatening cardiac arrhythmias. Monitor for dehydration, hypokalemia, and hypomagnesemia. Also see Cardiovascular Effects p. 184 In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%) when compared to patients treated with risperidone alone (3.1%), furosemide alone (4.1%) or placebo without furosemide (2.9%). The increase in mortality with furosemide plus risperidone was observed in two of four clinical trials. No pathophysiological mechanism has been identified to explain this finding and no consistent pattern for cause of death observed
Ginkgo biloba		Case report of priapism with recent addition of ginkgo to long-standing risperidone. Mechanism unclear; potentially due to additive vessel-dilating properties. In theory, reduction of clozapine levels may occur via induction of CYP2E1
Glucocorticoid	Betamethasone, hydrocortisone, prednisone	CAUTION. Potential to exacerbate psychiatric conditions as glucocorticoid-induced psychiatric disorders such as psychosis can occur. Glucocorticoids can induce metabolism via CYP3A4. Higher doses of antipsychotics metabolized via CYP3A4 (e.g., clozapine, iloperidone, lurasidone, quetiapine or ziprasidone) may be needed
Grapefruit		CAUTION. Increased plasma level of clozapine, iloperidone, lurasidone, quetiapine, and ziprasidone possible due to inhibition of metabolism via intestinal CYP3A4 and possibly inhibition of intestinal transporters such as P-glycoprotein. Grapefruit's inhibitory effects may be prolonged (i.e., 24–48 h). Data with clozapine suggests 500 mL or less of grapefruit juice daily may not result in clinical changes Pertinent to avoid or minimize grapefruit and grapefruit juice until more information is available
H_2 antagonist	Cimetidine Nizatidine Ranitidine	Increased plasma level of clozapine (case reports), possibly due to inhibited metabolism via CYP1A2, 2D6, and/or 3A4. Effect on quetiapine and ziprasidone not clinically significant. Increased bioavailability of risperidone (by 64%), however, no effect on AUC, therefore unlikely to be clinically significant Case report of higher doses (600 mg/day) of nizatidine in combination with quetiapine and paroxetine resulting in akathisia, bradykinesia, mild rigidity, and bilateral tremor in upper extremities Increased bioavailability of risperidone (26%) and AUC of risperidone plus 9-hydroxyrisperidone (20%). Not clinically significant
Hormone	Oral contraceptive, ethinyl estradiol	Estrogen potentiates hyperprolactinemic effect of antipsychotics Ethinyl estradiol is an inhibitor of CYP1A2 and CYP2C19 and substrate of CYP3A4, which are the main enzymes that metabolize clozapine. Case report of ~2-fold increase in clozapine levels and marked drowsiness, anergy, and dizziness with the addition of an ethinyl estradiol-containing oral contraceptive (OC). Another report of increased plasma level of clozapine with an OC (ethinyl estradiol [35 micrograms]/norethindrone [0.5 mg]). Case report of seizures with addition of lithium 900 mg/day to clozapine 300–600 mg/day and an OC (ethinyl estradiol [35 micrograms]/norethindrone [0.5/0.75/1 mg])
Lithium		CAUTION. Monitor plasma level of lithium closely when it is used concurrently with SGAs, since both SGAs (in particular ziprasidone) and high lithium level are associated with QT prolongation. Also see Cardiovascular Effects p. 184

Second-Generation Antipsychotics (SGAs) (cont.)

Class of Drug	Example	Interaction Effects
		Although studies indicate lithium and SGAs can be safely used together, there are cases of severe adverse effects. Factors that may increase the risk of developing neurotoxicity are the presence of acute mania, pre-existing brain damage, infection, fever, dehydration, a history of EPS, and high doses of one or both agents With clozapine: Asterixis (+ zuclopenthixol), diabetic ketoacidosis (no history of hyperglycemia and no signs of lithium toxicity), acute myocarditis (+ fluoxetine), rhabdomyolysis, and seizures (one case also taking an oral contraceptive and exhibiting mild jerking of the arms 2 days prior to the seizure) With olanzapine: Encephalopathy, NMS, nonketotic hyperosmolar syndrome (+ valproic acid), priapism, and somnambulism (+ valproic acid) With quetiapine: Delirium and tonic-clonic seizure With risperidone: Diabetic ketoacidosis + NMS + MI, encephalopathy, EPS (acute rabbit syndrome), NMS, and priapism Potential for additive adverse effects (e.g., weight gain) Monitor patients closely, especially during the first 3 weeks and after dose increases. In particular, monitor for EPS, NMS, and hyperglycemia. Monitor lithium level, however, note that in the case reports of severe adverse effects listed above, lithium level was within therapeutic range Case reports of adding lithium in those who developed neutropenia with clozapine or olanzapine. Lithium resulted in normalization of WBC (via its ability to induce leukocytosis) and permitted continued use of clozapine or olanzapine
Opioid	General	CAUTION. Additive CNS effects
	Methadone	DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. CAUTION with all other SGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. Also see Cardiovascular Effects p. 184 Quetiapine modestly increased methadone levels (7–30%), possibly via inhibition of CYP2D6 and/or P-glycoprotein; this may be clinically significant for some patients. Quetiapine may result in a false-positive methadone urine drug screen.
	Tramadol	CAUTION. Tramadol lowers the seizure threshold; potential additive lowering of seizure threshold with SGAs (in particular clozapine); case report of a fatal seizure in a complicated patient who was taking tramadol and clozapine. Tramadol blocks reuptake of serotonin; potential additive increase in serotonin with SGAs, which could result in serotonin syndrome; case report with mirtazapine, tramadol, and olanzapine
Prokinetic agent/antiemetic	Metoclopramide	CAUTION. Metoclopramide is a potent central dopamine receptor antagonist that can cause EPS, hyperprolactinemia, and rarely NMS. Concurrent use with a SGA may increase the risk of these adverse effects. Case report of Pisa syndrome after addition of metoclopramide to clozapine
Proton pump inhibitor	Esomeprazole, omeprazole	Case reports of decreased plasma level of clozapine (by ~40%) likely due to induction of metabolism via CYP1A2 and/or CYP3A4 with omeprazole. Similar interaction likely with the S-isomer of omeprazole (i.e., esomeprazole). Increase clozapine dose as needed or use an alternative proton pump inhibitor. The interaction may be more clinically relevant in nonsmokers. Decreased levels of asenapine and olanzapine possible
QT-prolonging agent	Antiarrhythmics (e.g., amiodarone, sotalol), antimalarials (e.g., chloroquine, mefloquine), antiprotozoals (e.g., pentamidine), arsenic trioxide, contrast agents (e.g., gadobutrol), dolasetron, droperidol, methadone, pazopanib, ranolazine, tacrolimus	DO NOT COMBINE with asenapine, iloperidone, paliperidone or ziprasidone. CAUTION with all other SGAs. Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias

Class of Drug	Example	Interaction Effects
Smoking (tobacco)		Smoking induces CYP1A2; polycyclic aromatic hydrocarbons in tobacco smoke are believed to be responsible for this induction, not nicotine. Decreased plasma level of clozapine/norclozapine and olanzapine due to induction of metabolism via CYP1A2. Dosage modifications not routinely recommended, however, some patients, in particular males who are heavy smokers, may require higher doses of clozapine for efficacy. Caution when patient stops smoking as level of antipsychotic will increase; case reports suggest after smoking cessation symptoms from increased antipsychotic levels emerge after 4–10 days with olanzapine and 2–4 weeks with clozapine. Case reports of serious clozapine toxicity and EPS with olanzapine following smoking cessation; serum clozapine increases of 72–261% reported. Smoking induces olanzapine clearance by ~55%.
Statin	Lovastatin	Case report of prolonged QTc interval with quetiapine, possibly due to competitive inhibition of CYP3A4
	Simvastatin	Case report of rhabdomyolysis with quetiapine, however, an interaction between simvastatin and clarithromycin may have been the cause Three case reports of rhabdomyolysis with simvastatin plus risperidone; possibly due to competitive inhibition of CYP3A4; in one case, cyclosporine may also have contributed to the event
Stimulant	Amphetamine, methylphenidate	Antipsychotic agents may impair the stimulatory effect of amphetamines. Concurrent use not recommended Case reports of acute EPS, agitation, irritability, worsening of tardive movement disorder, and prolongation or exacerbation of withdrawal dyskinesia following the abrupt discontinuation of risperidone with the concurrent start of methylphenidate Case reports of rebound dystonia when a stimulant medication was withdrawn from patients taking risperidone. These reactions may be due to supersensitivity of dopamine receptors Two case reports of priapism with concurrent use of stimulants and SGAs (quetiapine, olanzapine)
	Armodafinil	Decreased C_{max} and AUC of quetiapine by 45% and 42% respectively
	Modafinil	CAUTION. Potential to exacerbate psychosis. Case report of re-emergence of psychotic symptoms after the addition of modafinil to clozapine Case report of an almost 2-fold increase in clozapine levels and related toxicity (dizziness, gait disturbance, tachycardia, and hypoxia). Modafinil may inhibit clozapine metabolism via inhibition of CYP2C19
St. John's wort		Potential for additive increase in serotonin resulting in serotonin syndrome St. John's wort induces P-glycoprotein, CYP1A2; to a lesser extend CYP3A4 and possibly CYP2C19. Decreased plasma level of SGAs (in particular asenapine, clozapine, quetiapine, risperidone, and olanzapine) reported (mechanism unclear)
Sympathomimetic	Epinephrine/adrenaline, dopamine	AVOID using for the treatment of SGA-induced hypotension. May result in paradoxical fall in blood pressure, as antipsychotics block peripheral α_1-adrenergic receptors, thus inhibiting α-vasoconstricting effects of epinephrine and leaving β-vasodilator effects relatively unopposed
	Cocaine	Case reports of EPS, particularly dystonia, with concurrent use of ziprasidone and risperidone, possibly via dopamine depletion from chronic use of cocaine; case report of clozapine causing a dose-dependent increase in plasma concentration of intranasal cocaine dose, though the positive effects of cocaine were reduced Case reports of severe hypotension in those with quetiapine overdose who were given IV epinephrine. Substitution with norepinephrine resolved the problem. Case report of severe hypotension with olanzapine and venlafaxine overdose unresponsive to IV dopamine but responsive to norepinephrine Norepinephrine and phenylephrine are safe substitutes for severe hypotension unresponsive to fluids Benefits may outweigh risk in anaphylaxis

Third-Generation Antipsychotics (TGAs)

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/ Mode of Action)	Trade Name	Dosage Forms and Strengths	Monograph Statement
Aripiprazole	Phenylpiperazine	Dopamine, serotonin/ Partial agonist and antagonist	Abilify	Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg Oral solution[B]: 1 mg/mL	Approved for some indications and age ranges – see Indications
			Abilify Discmelt[B]	Orally disintegrating tablets (ODT): 10 mg, 15 mg	
			Abilify Maintena	Prolonged-release injectable suspension: 300 mg/vial and 400 mg/vial of lyophilized powder for reconstitution	Safety and efficacy not established in children and adolescents under age 18
Aripiprazole lauroxil	Phenylpiperazine	Dopamine, serotonin/ Partial agonist and antagonist	Aristada[B]	Prolonged-release injectable suspension, prefilled syringe: 441 mg/1.6 mL, 662 mg/2.4 mL, 882 mg/3.2 mL, 1064 mg/3.9 mL	Safety and efficacy not established in children and adolescents under age 18
Brexpiprazole	N-arylpiperazine	Dopamine, serotonin/ Partial agonist and antagonist	Rexulti	Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg,	Approved for some indications and age ranges in USA – see Indications
Cariprazine	Phenylpiperazine	Dopamine, serotonin/ Partial agonist and antagonist	Vraylar[B]	Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [B] Not marketed in Canada

Indications[ab‡] (👍 approved)

In children and adolescents:

- 👍 Schizophrenia in adolescents (aripiprazole (age 13–17) – USA; (age 15–17) – Canada; brexpiprazole – USA)
- 👍 Bipolar disorder in adolescents (aripiprazole (age 10–17) – USA; (age 13–17) – Canada)
- 👍 Irritability associated with autism spectrum disorder (aripiprazole (age 6–17) – USA)
- 👍 Tourette's disorder (aripiprazole (age 6–18) – USA)
- ADHD (no comorbidities) – low-quality evidence supports use
- ADHD (in ASD) – open label study of aripiprazole showed tolerability and efficacy[70]
- Disruptive mood dysregulation disorder and ADHD - open label study showed tolerability and efficacy of aripiprazole/methylphenidate combination[71]

In adults:

Schizophrenia & Psychotic Disorders

- 👍 Schizophrenia:
  - Treatment in adults (aripiprazole, aripiprazole long-acting injection, brexpiprazole – Canada and USA; cariprazine – USA)
- Schizoaffective disorder (subpopulation in RCTs[72]) – aripiprazole

[a] Adult population unless otherwise stated [b] Canadian approved indications unless otherwise stated ‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Bipolar Disorder

- Acute manic/mixed episodes (aripiprazole as monotherapy or in combination with lithium or valproate – Canada and USA; cariprazine as monotherapy – USA)
- Acute depressive episodes associated with bipolar 1 disorder (brexpiprazole – USA)
- Maintenance treatment (aripiprazole, aripiprazole long-acting injection as adjunctive therapy with lithium or valproate – Canada and USA; aripiprazole, aripiprazole long-acting injection as monotherapy – USA)

Depression

- Adjunctive treatment to antidepressants (aripiprazole, brexpiprazole – Canada and USA)

Other

- Delirium
- Tourette's disorder: Decrease in motor and vocal tic frequency (two meta-analyses[74, 75], 11 studies for efficacy and 50 studies for tolerability) showed moderate evidence in support of use in tic and Tourette's disorder
- Addiction: Alcohol, amphetamines, cocaine (limited studies, some suggest a lack of efficacy and potential for increased drug abuse)
- Anxiety disorders (small, open studies in a variety of anxiety disorders suggesting benefit)
- Obsessive-compulsive disorder: aripiprazole augmentation with SSRI
- Personality disorders (low or very low evidence)
- Agitation in dementia (low or very low evidence)

General Comments

- TGAs are sometimes referred to as second-generation antipsychotics due to their dopamine antagonism and serotonergic antagonism, although they have distinct pharmacological profiles with dopamine partial agonism
- TGAs have comparable efficacy to other antipsychotic agents in the treatment of positive symptoms of schizophrenia
- TGAs are associated with a lower overall risk of:
  - Metabolic adverse effects (weight gain, dyslipidemias, and glucose intolerance/diabetes mellitus – monitoring for such effects is still advised
  - Hyperprolactinemia (conversely, hypoprolactinemia may occur)
  - Sedation and anticholinergic effects
- Most notable adverse effects of TGAs:
  - Insomnia, activation, akathisia
  - Dizziness and/or orthostatic hypotension during initiation or dosage increase
- TGAs have long elimination half-lives – see Pharmacokinetics p. 208 and p. 227, Dosing with concomitant medications p. 208 and Drug Interactions pp. 213–216

Pharmacology

- TGAs act as partial agonists with high affinity at pre- and post-synaptic dopamine (D_2) receptors and serotonin ($5\text{-}HT_{1A}$) receptors, and as an antagonist at $5\text{-}HT_{2A}$ receptors
- Aripiprazole exhibits high affinity for D_2 and D_3, $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, receptors and moderate affinity for D_4, $5\text{-}HT_{2C}$, $5\text{-}HT_7$, α_{1A}, and histamine (H_1) receptors as well as serotonin reuptake site. It has no appreciable affinity for cholinergic muscarinic (M) receptors
- Brexpiprazole acts as a partial agonist at $5\text{-}HT_{1A}$, D_2 (high affinity), D_3 (high affinity) receptors and as an antagonist at $5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$, $5\text{-}HT_7$, α_{1A}, α_{1B}, α_{1D}, and α_{2C}, receptors. It also exhibits affinity for H_1 and M_1 receptors
- Cariprazine acts as a partial agonist at D_2 and D_3 receptors with high affinity at $5\text{-}HT_{1A}$ receptors. It acts as an antagonist at $5\text{-}HT_{2A}$ (moderate affinity) and $5\text{-}HT_{2B}$ (high affinity) receptors as well as binding to H_1 receptors. It shows lower binding affinity to $5\text{-}HT_{2C}$ and α_{1A} receptors and has no appreciable affinity for cholinergic muscarinic (M) receptors
- As partial dopamine agonists, the intensity of interaction with the dopamine receptor is less than that of endogenous dopamine (intrinsic activity = 100%). Accordingly, the net effect of dopamine partial agonism depends on whether a hypo- or hyperdopaminergic state exists. In areas of hypodopaminergic activity, partial D_2 agonism results in an increase in overall dopaminergic function (postulated as an explanation for benefit in negative symptoms and affective symptoms, and less EPSE). Conversely, in areas of hyperdopaminergic activity, partial D_2 agonism results in a net decrease in dopaminergic function (postulated as explanation for improvement of positive symptoms)

Dosing

- See table p. 226 for more information on dosing for schizophrenia and psychosis
- No pediatric studies exist for cariprazine
- For administration details, see Nursing Implications p. 212

Third-Generation Antipsychotics (TGAs) (cont.)

Aripiprazole Dosing

- General: After initial target doses are achieved, further dose increases can occur at 5 mg/day increments at one-week intervals
- Schizophrenia: In adolescents, begin with 2 mg/day for 2 days, then increase to 5 mg/day for 2 days, then increase to 10 mg/day. Further dose adjustments should be done gradually to a maximum of 30 mg/day, if needed (not shown to be more efficacious than 10 mg/day in adolescent schizophrenia trial)
- Bipolar disorder (acute and maintenance treatment): Begin with 2 mg/day for 2 days, then increase to 5 mg/day for 2 days, then increase to 10 mg/day. Further dose adjustments should be done gradually to a maximum of 30 mg/day, if needed (not shown to be more efficacious than 10 mg/day in pediatric bipolar trial)
- Irritability associated with autistic disorder (age 6–17): Begin at 2 mg orally once daily, then increase to 5 mg/day. Further dose adjustments should be done gradually to a maximum of 10 or 15 mg/day, if needed
- Tourette's disorder (age 6–18): $<$ 50 kg: Begin at 2 mg orally once daily, then a target dose of 5 mg/day after 2 days. Dose can be increased to 10 mg/day; $\geq$50 kg: Begin at 2 mg orally once daily for 2 days, then 5 mg/day for 5 days, then a target dose of 10 mg/day. Further dose adjustments should be done gradually to a maximum of 20 mg/day, if needed
- Major depression (adjunctive treatment) in adults: Begin at 2 or 5 mg orally once daily; usual treatment range = 2–15 mg/day
- Oral solution can be substituted for tablets on a mg-per-mg basis up to the 25 mg dose level. Patients receiving 30 mg tablets should receive 25 mg of the solution as plasma level achieved with solution are slightly higher than with the tablet formulation
- Dose adjustment NOT required in smokers or those with renal or hepatic impairment. However, renal and hepatic impairment dosing recommendation is only based on a single-dose study

Brexpiprazole Dosing

- General: After initial target doses are achieved, further dose increases can occur at 1 mg/day increments at one-week intervals
- Schizophrenia: In adolescents, begin with 0.5 mg/day for 4 days, then increase to 1 mg/day for 3 days, then increase to 2 mg/day based on tolerability and efficacy. Further dose adjustments should be done gradually to a maximum of 4 mg/day, if needed

Concomitant Medications

- TGA metabolism can be affected by inducers or inhibitors of CYP2D6 (no known inducers) and 3A4. For specific drug interactions, see pp. 213–216
- Taking strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine): Goal TGA dose 50% of usual
- Taking strong CYP3A4 inhibitor (e.g., clarithromycin): Goal TGA dose 50% of usual
- Taking strong CYP2D6 and 3A4 inhibitor: Goal TGA dose 25% of usual
- Taking strong CYP3A4 inducer (e.g., carbamazepine, phenytoin): Goal dose of aripiprazole and brexpiprazole 200% of usual; cariprazine not recommended. Consider therapeutic drug monitoring if available

Pharmacogenetics

- Pharmacodynamic pathway-related genetic testing (e.g., *DRD2*, *HTR1A*, *MTHFR* etc.) currently does not have sufficient evidence for use in clinical practice
- CYP poor metabolizers may be at increased risk for adverse drug events at usual doses and lower starting doses or avoidance of specific agents may be recommended. CYP intermediate metabolizers have some degree of metabolic activity and are often not described as "clinically important" in regards to drug dosing adjustments. CYP ultra-rapid metabolizers may be at increased risk for therapeutic failures when certain agents are used; avoiding agents which are substrates for certain CYP isoenzymes or using therapeutic drug monitoring is usually warranted. See table p. 226. See https://www.pharmgkb.org/ for updated clinical guidelines and dosing recommendations when utilizing pharmacogenetic testing

Pharmacokinetics

- Also see table p. 227

Absorption

- Oral:
  - All TGAs may be taken with or without food
  - Aripiprazole: Bioavailability of tablet is 87%. At equivalent doses, peak plasma concentrations from the oral solution are higher (~22%) than from the tablet. Time to peak plasma concentration (T_{max}) is 3–5 h when taken on an empty stomach, and up to 6 h if taken with a high-fat meal
  - Brexpiprazole: Bioavailability of tablet is 95%. After single dose administration, peak plasma concentrations occurred within 4 h. Absorption not affected when taken with high-fat meal

- Cariprazine: Bioavailability is high. Peak plasma concentrations occurred in approximately 3–6 h. Absorption not affected when taken with high-fat meal
- Aripiprazole disintegrating tablets: Bioequivalent to oral tablets. Dissolve in saliva within 15 sec. Recommended to be taken without liquid, but can be given with liquid if needed

Distribution

- Aripiprazole: Protein binding of aripiprazole and dehydro-aripiprazole (major, active metabolite) is > 99% (primarily to albumin). Volume of distribution at steady state is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution
- Brexpiprazole: Protein binding is > 99% to serum albumin and α_1-acid glycoprotein, and is not affected by renal or hepatic impairment. Volume of distribution following intravenous administration is high (1.56 ± 0.42 L/kg), indicating extravascular distribution
- Cariprazine: Parent compound and major active metabolites are highly protein bound (91–97%) to plasma proteins

Metabolism and Elimination

- Aripiprazole:
  - Hepatic metabolism, primarily via CYP2D6 (dehydrogenation, hydroxylation) and CYP3A4 (dehydrogenation, hydroxylation, *N*-dealkylation)
  - Dehydro-aripiprazole is the major metabolite. It is active, represents 40% of parent drug exposure in plasma, and has similar affinity for D_2 receptors
  - Mean half-lives are about 75 h and 94 h for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days for both active moieties when taken orally and 3–4 months when administered via long-acting injectable
  - Half-life and aripiprazole exposure are influenced by capacity to metabolize CYP2D6 and 3A4 substrates. Ariprazole exposure increases by about 80% and dehydro-aripiprazole exposure decreases by about 30% in poor CYP2D6 metabolizers. In extensive CYP2D6 metabolizers, aripiprazole half-life = 75 h vs. poor metabolizers = 146 h. Steady-state concentrations may take 28 days to be attained in poor metabolizers
  - Excretion of an oral dose is via feces (55%, with ~18% as unchanged aripiprazole) and urine (25%, with < 1% as unchanged aripiprazole)
- Brexpiprazole:
  - Hepatic metabolism, primarily via CYP2D6 and 3A4
  - Its major metabolite is not considered to contribute to the therapeutic effects of brexpiprazole
  - Half-life and brexpiprazole exposure are influenced by capacity to metabolize CYP2D6 and 3A4 substrates
- Cariprazine:
  - Extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to two major active metabolites: desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). DCAR is further metabolized into DDCAR by CYP3A4 and CYP2D6. DDCAR is then metabolized by CYP3A4 to a hydroxylated metabolite
  - DCAR and DDCAR are pharmacologically equipotent to cariprazine
  - Half-lives based on time to reach concentration steady state, estimated from the mean concentration-time curves, are 2–4 days for cariprazine and approximately 1–3 weeks for DDCAR
  - CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR
- Approximately 8–12% of Caucasians, 3–20% of African Americans, 3–20% of Hispanics, 2–6% of Native Americans, and 0.3–20% East Asians are intermediate-to-poor CYP2D6 metabolizers

Adverse Effects

- See General Comments p. 207 and the Frequency of Adverse Reactions table p. 220 for a quick summary
- Adverse events may first appear several weeks after the initiation of TGA treatment, probably due to plasma level of TGAs and major metabolites accumulating over time. As a result, the incidence of adverse reactions in short-term trials may not reflect the rates after long-term exposure

CNS Effects

- Aripiprazole commonly reported adverse effects include: Headache (> 20%, may respond to over-the-counter analgesics), agitation (> 15%), anxiety (> 25%), insomnia (> 15%), nervousness, lightheadedness, and dizziness (> 10%), somnolence (> 10%), akathisia, and asthenia. Many of these develop during the first week of treatment and resolve over time. A lower starting dose of 2–5 mg/day may minimize these adverse effects
- Based on pooled data from short-term trials, brexpiprazole and cariprazine seem to cause less agitation, insomnia, and sedation (> 10%)
- EPSE – acute onset
  - Includes acute dystonias, akathisia, pseudoparkinsonism, Pisa syndrome, rabbit syndrome (see pp. 242–246 for onset, symptoms, and treatment options, and pp. 242–262 for detailed treatment options)
  - Aripiprazole has a favorable EPSE profile, though dystonia, akathisia reported; tremor (mostly described as mild intensity, limited duration) reported (> 2%); case report of exacerbation of Parkinson's disease and case reports of rabbit syndrome

Third-Generation Antipsychotics (TGAs) (cont.)

- EPSE – late onset or tardive movement disorders (TD): Risk of TD appears highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether TGA drugs differ in their potential to cause TD is unknown. Case reports of TD associated with aripiprazole are available
- Headache commonly reported in clinical trials. May respond to treatment with over-the-counter analgesics
- Neuroleptic malignant syndrome and rhabdomyolysis reported to occur with aripiprazole
- Seizures (0.2–0.3%) – use cautiously in individuals with a history of seizures, poorly controlled seizures, or medications and/or conditions known to lower the seizure threshold

Cardiovascular Effects

- Arrhythmias and ECG changes
  - ECG changes (e.g., T-wave inversion, ST segment depression, QTc lengthening – may increase risk of arrhythmias) reported with many antipsychotic medications, the clinical significance of which is unclear for many. See p. 184
  - No clinically significant increases in QTc interval noted with aripiprazole in clinical trials; some youth had a shortened QTc interval. Alternatively, one case of torsades de pointes reported with aripiprazole
- Cardiomyopathy – 1 case report noting eosinophilic myocarditis and elevated levels of aripiprazole found on autopsy of a 36-year-old male with schizophrenia
- Dyslipidemias – see Endocrine & Metabolic Effects
- Orthostatic hypotension/compensatory tachycardia/dizziness/syncope – likely due to antagonism of α_1-adrenergic receptors. Incidence low when recommended dosing titration guidelines for pediatric patients followed

Endocrine & Metabolic Effects

- Antidiuretic hormone dysfunction – a few cases of hyponatremia/SIADH in adults documenting resolution within 7–10 days of aripiprazole discontinuation have been reported
- Dyslipidemias – risk appears lower than with many SGAs; baseline and periodic metabolic monitoring still recommended – see p. 154 for guidelines
- Glucose dysregulation, ketoacidosis, type 2 diabetes mellitus; risk appears lower than with many SGAs; case reports of hyperglycemia and of diabetic ketoacidosis, so monitoring still recommended – see p. 154 for suggested guidelines
- Prolactin abnormalities – hyperprolactinemia appears to be rare and hypoprolactinemia has been reported. For more information on hyperprolactinemia symptoms, monitoring, and treatment options see p. 186
- Weight gain – may still be evident in children and adolescents but possibly to a lesser degree than with most SGAs

GI Effects

- Constipation reported to be more than 10% for aripiprazole; 2–3% for brexpiprazole and 6% for cariprazine in short-duration studies
- Urinary retention – case reports with aripiprazole
- Dysphagia and aspiration reported with antipsychotic use
- Nausea and vomiting more than 10% for aripiprazole, may dissipate over the first week of therapy; less than 10% for brexpiprazole and more than 10% for cariprazine in short-duration studies

Urogenital and Sexual Effects

- Priapism – case report of recurrent priapism starting 6 h after the first dose of aripiprazole
- Based on its pharmacological profile (D_2 partial agonist in tuberoinfundibular tract translating into less hyperprolactinemia and low affinity for cholinergic receptors), it appears unlikely that aripiprazole would cause sexual dysfunction. Alternatively, hypoprolactinemia can occur, which reduces sperm motility and count, results in abnormal sperm morphology in men and failure to lactate after delivery when used during pregnancy
- The 2009 PORT treatment recommendations for schizophrenia rank the relative risk for prolactin elevation and sexual side effects with antipsychotics as follows: Risperidone = paliperidone > FGA medications > olanzapine > ziprasidone > quetiapine = clozapine > aripiprazole

Hematological Effects

- Leukopenia – a few case reports which suggest a possible association of aripiprazole and the development of leukopenia and/or neutropenia, and thrombocytopenia
- Stop TGA treatment if neutrophil count drops below 1.0×10^9/L ($1000/mm^3$)

Hepatic Effects

- Elevations in liver function tests (ALT, AST) reported infrequently

Hypersensitivity Reactions

- Rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm) reported

Other Adverse Effects

- Acneiform eruption – case report of acneiform eruptions which resolved upon discontinuation of aripiprazole
- Raynaud's phenomenon, epistaxis, gingival bleeding (rare) with aripiprazole
- Hiccups
- Blurred vision (2.5%)
- Rhinitis and pharyngitis

D/C Discontinuation Syndrome

- Withdrawal symptoms reported similar to those seen with other classes of antipsychotics. However, due to the long elimination-half lives of TGAs, these medications may self-taper with little withdrawal symptoms if promptly discontinued. See Discontinuation Syndrome p. 190 for a general discussion.
- Since aripiprazole and cariprazine have minimal affinity for cholinergic receptors, abrupt switch from an agent with high affinity for these receptors to aripiprazole or cariprazine could result in cholinergic rebound symptoms upon withdrawal of the initial antipsychotic[76]
- Utilizing the delayed withdrawal method when switching from an SGA/FGA to a TGA may be advisable. Theoretically, an abrupt switch from a D_2 antagonist (FGA or SGA) to a D_2 partial agonist (TGAs) could result in a temporary surge of dopamine agonist activity as a result of unmasking upregulated D_2 receptors. In the mesolimbic tract, this could translate into a temporary exacerbation of positive symptoms. The same actions in the nigrostriatal tract could result in the onset of withdrawal dyskinesias
- Readers may find the website https://www.switchrx.com helpful for managing antipsychotic switching

Precautions

- Caution in patients with known cardiovascular disease, cerebrovascular disease, seizure disorders or conditions that predispose patients to hypotension or aspiration pneumonia
- Increased risk of suicidal thinking in children, adolescents, and young adults; occurrence of pathological gambling or other impulsive activities (aripiprazole, possibly others), neuroleptic malignant syndrome, tardive dyskinesia, cognitive and motor impairment, risk of falling, metabolic changes, leukopenia, neutropenia, and agranulocytosis

Toxicity

- Aripiprazole:
  - A retrospective study of 286 cases of isolated aripiprazole overdose/exposures found 55% of patients reported symptoms – somnolence (56%), sinus tachycardia (20%), nausea/vomiting (18%), dystonia (13%), tremor (6%), agitation, dizziness (2%), paresthesias, headache (1%). There were no reports of death, respiratory depression, or ECG abnormalities including clinically significant QTc prolongation. Symptoms were more likely to occur with doses above 90 mg in adults (lower in pediatrics)
  - A 2009 review of atypical antipsychotic overdoses suggested cardiovascular toxicity with aripiprazole ingestion was minimal[77]
  - Acute ingestion of up to 1080 mg aripiprazole reported with no fatalities
  - Vomiting and lethargy reported lasting 30 h in 2-year-old boy following ingestion of 40 mg; a 6-year-old boy experienced lethargy, drooling, and flaccid facial muscles after 2 doses of aripiprazole
  - Toxic dose in children under age 6 reported as 3 mg/kg
- There is limited clinical experience with brexpiprazole and cariprazine overdose

Management

- No specific antidote is available. Close medical supervision, monitoring of vital signs and functions including cardiac function, and supportive therapy to maintain airways and oxygenation and manage symptoms is required. Early administration of charcoal may help in partially preventing absorption. Hemodialysis is not deemed likely to be of benefit due to aripiprazole high plasma protein binding. Consult a certified poison control center for up-to-date guidance and advice
- In a retrospective study of aripiprazole overdose, no treatment was required for 62% of patients; 38% of patients received treatment, 43% of whom received activated charcoal

Lab Tests/Monitoring

- See p. 191
- Consensus guidelines suggest aripiprazole concentrations between 150–350 ng/mL to be therapeutic reference range[10]
- Case report of false-positive for pheochromocytoma with concurrent aripiprazole and lamotrigine. Urine and plasma normetanephrines were elevated but returned to normal on discontinuation of lamotrigine and aripiprazole

Third-Generation Antipsychotics (TGAs) (cont.)

Use in Pregnancy◊

- Aripiprazole:
  - Pregnancy alters the pharmacokinetic profile of aripiprazole, a 52% decrease of serum aripiprazole concentrations was observed in the third trimester. Pregnancy induces CYP2D6 and 3A4 enzymes, therefore TGAs, which are substrates for these metabolic pathways, may have reduced concentrations in late pregnancy. Consider therapeutic drug monitoring, if indicated
  - Aripiprazole is considered a drug with "Limited human data – Animal data suggest risk"
  - Chemical properties (e.g., small molecular weight) and measurement of umbilical cord blood levels of aripiprazole and dehydro-aripiprazole at delivery in case reports indicate aripiprazole and dehydro-aripiprazole cross the human placenta
  - In a study of 158 women with first-trimester exposure to aripiprazole, the odds ratio for malformations was 1.4, suggesting no increased risk in the first trimester
  - A study in Japan using an adverse drug event database showed a safety signal (reporting ratio 2.76) for aripiprazole compared to other antipsychotics for occurrence of miscarriage during pregnancy (based on 18 reports in the database)
  - The following adverse events have been reported with third-trimester exposure to aripiprazole: Fetal distress (i.e., tachycardia) during labor with subsequent failure to establish lactation, mild respiratory distress 10 min post-delivery, and no spontaneous breath with poor muscle tone just after birth requiring short-term (1 min) resuscitation
- Brexpiprazole: Adequate and well-controlled studies have not been conducted in pregnant women to inform drug-associated risks. In animal reproduction studies, no teratogenicity was observed with oral administration of brexpiprazole to pregnant rats during organogenesis, however, when administered during organogenesis through lactation, the number of deaths increased when administered 73 times the maximum human recommended dose
- Cariprazine: Adequate and well-controlled studies have not been conducted in pregnant women to inform drug-associated risks. Based on animal data, cariprazine may cause fetal harm. Animal exposure during organogenesis caused malformation, lower survival, and developmental delays at drug exposure 0.2–3.5 times the maximum recommended human dose
- If an antipsychotic will be used during pregnancy, consider patient enrollment or registration in any relevant studies or pregnancy exposure registries (e.g., in the USA: FDA list of pregnancy registries http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm134848.htm)

Breast Milk

- Aripiprazole: Two case reports found the concentration of aripiprazole in human breast milk to be ~20% of the maternal plasma level while one case report found undetectable aripiprazole levels in breast milk. Possibility of somnolence in breastfed infants
- Brexpiprazole and cariprazine: Lactation studies have not been conducted to assess the presence in human milk, or the effects on the breasted infant, or the effects on milk production
- The development and health benefits of breastfeeding should be considered along with the mother's clinical need for TGAs and any potential adverse effects on the breastfed infant from the medication or from the underlying maternal condition. Refer to the Drugs and Lactation Database (https://www.ncbi.nlm.nih.gov/books/NBK501922/) for more information

Nursing Implications

Oral

- TGAs can be taken with or without food
- AVOID grapefruit juice (see Drug Interactions p. 216)
- Aripiprazole disintegrating tablets:
  - Dissolve rapidly in saliva; recommended to be taken WITHOUT liquid, however, if needed can be taken with liquid
  - Break easily. Do NOT push the tablet through the foil backing as this could damage the tablet. Use dry hands to remove the tablet and immediately place tablet on the tongue
  - Contain phenylalanine (a component of aspartame) – contraindicated in phenylketonuria

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

- Aripiprazole oral solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle. Store at room temperature; each mL of oral solution contains 400 mg of sucrose and 200 mg of fructose

Long-acting IM

- Aripiprazole monohydrate (polymorphic form)
  - Aripiprazole monohydrate is an extended-release injectable suspension in prefilled dual chamber syringes or vials, at 300 mg or 400 mg strengths
  - Aripiprazole monohydrate must be stored below 30° C (syringe) or 25° C (vial) and should be protected from light
  - Shake the vial or syringe for 30 or 20 sec, respectively, until the reconstituted suspension appears uniform
  - For deltoid administration, use a 23-gauge 25 mm hypodermic safety needle for non-obese patients, or a 22-gauge 38 mm hypodermic safety needle for obese patients
  - For gluteal administration, use a 22-gauge 38 mm hypodermic safety needle for non-obese patients, or a 21-gauge 51 mm hypodermic safety needle for obese patients
  - Inject slowly into the deltoid or gluteal muscle. Do not massage the injection site
- Aripiprazole lauroxil
  - Aripiprazole lauroxil is an extended-release suspension available in the following strengths: 441 mg (1.6 mL), 662 mg (2.4 mL), 882 mg (3.2 mL), and 1064 mg (3.9 mL)
  - Aripiprazol lauroxil should be stored at room temperature (20–25° C) with excursions permitted between 15° C and 30° C
  - Tap vigorously 10 times then vigorously shake for 30 sec, until the reconstituted suspension appears uniform. If unused within 15 min, shake again
  - For deltoid administration, use a 21-gauge 25 mm hypodermic safety needle or a 20-gauge 38 mm hypodermic safety needle
  - For gluteal administration, use a 20-gauge 38 mm hypodermic safety needle or a 20-gauge 51 mm hypodermic safety needle
  - Inject rapidly and continuously into the deltoid or gluteal muscle. Do not hesitate or inject slowly

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Acetylcholinesterase inhibitor (central)	Donepezil, galantamine, rivastigmine	May enhance neurotoxicity of antipsychotics, presumably due to a relative acetylcholine/dopamine imbalance (i.e., increased acetylcholine in the presence of dopamine receptor blockade) in the CNS
Antiarrhythmic	General	Possible additive prolongation of QT interval and associated life-threatening cardiac arrhythmias. However, aripiprazole, brexpiprazole, and cariprazine appear to have a low potential to prolong the QT interval compared to other antipsychotics. Also see TGA Cardiovascular Effects p. 210
	Quinidine	Quinidine is a potent CYP2D6 inhibitor resulting in an increased AUC of aripiprazole by 107–112% (i.e., doubled). AUC of active metabolite decreased by 32–35%. Due to aripiprazole's long half-life, interaction effects may be delayed for up to 10–14 days. Brexpiprazole AUC was approximately 2-fold higher with concurrent use of quinidine (brexpiprazole's major metabolite is inactive). Cariprazine is not metabolized extensively by CYP2D6, consequently the interaction with quinidine might not be clinically significant
	Amiodarone	Amiodarone is a CYP2D6 inhibitor. Increased plasma level of aripiprazole and brexpiprazole possible
Antibiotic	Clarithromycin, erythromycin	CYP3A4 is inhibited potently by clarithromycin and moderately by erythromycin. Increased plasma level of aripiprazole, brexpiprazole, and cariprazine likely to occur. Effects may be delayed due to the their long half-life

Third-Generation Antipsychotics (TGAs) (cont.)

Class of Drug	Example	Interaction Effects
Anticonvulsant	General	As with other antipsychotics, aripiprazole, brexpiprazole, and cariprazine may lower seizure threshold. Monitor for increased seizure frequency and increase anticonvulsant medication as needed. See also Antipsychotic Augmentation Strategies p. 235
	Carbamazepine, oxcarbazepine	CYP3A4 is induced potently by carbamazepine and weakly by oxcarbazepine Carbamazepine reduces C_{max} and AUC of aripiprazole and its active metabolite by about 70% with concurrent use and one week after discontinuing carbamazepine. Brexpiprazole prescribing information recommends increase in dose when used concomitantly with strong CYP3A4 inducer. Cariprazine prescribing information recommends concomitant use to be avoided Note it may take 2–4 weeks to reach maximum induction and an equivalent period to return to baseline after discontinuation of an inducer. Oxcarbazepine at higher dose (i.e., $\geq$ 1500 mg/day) may result in a clinically relevant induction of aripiprazole
	Clobazam	Clobazam may cause potent CYP2D6 inhibition and weak CYP3A4 induction
	Lamotrigine	No clinically significant pharmacokinetic changes. Case reports of adverse effects with concurrent use: Three cases of Stevens-Johnson syndrome within 2–4 weeks after adding lamotrigine to aripiprazole; one case of disabling intention tremor 2 months after the addition of aripiprazole to lamotrigine which resolved on lamotrigine discontinuation; one case of false-positive diagnosis of pheochromocytoma
	Phenobarbital, phenytoin	Phenobarbital and phenytoin are potent CYP3A4 inducers. Degree of induction likely similar to the interaction between aripiprazole, brexpiprazole, and cariprazine and carbamazepine Case report of leucopenia and thrombocytopenia with addition of aripiprazole (10 mg/day) to phenytoin (300 mg/day)
	Valproate (divalproex, valproic acid)	Mild reductions of aripiprazole's C_{max} and AUC (by up to 25%). Not clinically significant. No dose adjustment required. Approved for concurrent use in the management of bipolar disorder. Adverse effects reported with concurrent use include: More frequent – akathisia, increased triglyceride levels, tiredness, tremor, weight gain; serious – one case of severe abdominal pain
Antidepressant	General	Increased rates of akathisia and fatigue with concurrent antidepressant use Serotonin syndrome theoretically possible with antidepressants that increase serotonin (e.g., SNRIs, SSRIs)
SSRI	Citalopram, escitalopram, sertraline	No clinically significant pharmacokinetic changes to escitalopram, sertraline or aripiprazole. Adverse effect case reports with citalopram and aripiprazole include one of urinary obstruction and one of EPS. Adverse effect case reports with sertraline (at 200 mg/day) and aripiprazole include one each of severe akathisia, acute dystonia, and myxedema coma
	Fluoxetine, paroxetine	Fluoxetine and paroxetine are significant CYP2D6 inhibitors. Increased aripiprazole levels (30–70%) reported. Effects may be delayed due to the antipsychotic's long half-life. Small changes in fluoxetine (18% increase), norfluoxetine (36% increase), and paroxetine (27% decrease) levels reported. Case reports with fluoxetine and aripiprazole of: NMS 2 weeks after starting the combination; leucopenia that resolved on aripiprazole discontinuation and reoccurred on rechallenge Secondary to strong inhibition of CYP2D6, dosage decrease has been recommended for brexpiprazole
	Fluvoxamine	Fluvoxamine is a weak CYP2D6 and CYP3A4 inhibitor. Clearance of aripiprazole may be reduced by 40%. Clinical significance unknown
NDRI	Bupropion	CAUTION. Potential for additive risk of seizures. No published reports of seizures with concurrent use, however, data limited to six patients. Bupropion is an inhibitor of CYP2D6, which could increase aripiprazole and brexpiprazole levels. No published reports of aripiprazole levels with concurrent bupropion. In the six cases of concurrent use, akathisia and/or insomnia occurred in at least three cases (50%)

Class of Drug	Example	Interaction Effects
SNRI	Duloxetine	Duloxetine is a moderate CYP2D6 inhibitor, however, a study found no significant change in aripiprazole levels. Case report of high aripiprazole levels, confusion, and loss of coordination in a patient taking high-dose aripiprazole (50 mg/day) with darunavir and ritonavir (modest CYP2D6 and potent CYP3A4 inhibitors) and duloxetine. Case report of hypertensive crisis within 2 weeks of adding aripiprazole to duloxetine; blood pressure decreased on aripiprazole dose reduction
	Venlafaxine	No clinically significant pharmacokinetic changes. Case report of hypertensive crisis with confusion and agitation 2 days after adding aripiprazole to venlafaxine which resolved on aripiprazole discontinuation. Two case report of parkinsonism with concurrent use of venlafaxine and aripiprazole
Antifungal	Fluconazole, itraconazole, ketoconazole, voriconazole	Ketoconazole and itraconazole are potent, while fluconazole and voriconazole are moderate CYP3A4 inhibitors. AUC of aripiprazole and metabolite increased by 63% and 77% with ketoconazole and 48% and 39% with itraconazole, respectively AUC of brexpiprazole approximately 2-fold higher with concurrent administration of ketoconazole. Refer to dosing recommendations for concurrent administration of strong CYP3A4 inhibitors AUC of cariprazine on average 4-fold higher with concurrent administration of ketoconazole. Refer to dosing recommendations for concurrent administration of strong CYP3A4 inhibitors
	Terbinafine	Increased plasma level of aripiprazole and brexpiprazole possible due to inhibited metabolism via CYP2D6. Any interaction will be prolonged (up to 3 months) due to terbinafine's long half-life (200–400 h)
Antihistamine	Trimeprazine (aka alimemazine)	Increased serum level of aripiprazole (by 56%) but not of dehydro-aripiprazole found in a pharmacokinetic study. Mechanism and clinical significance unknown
Antiparkinsonian agent	Levodopa, pramipexole, ropinirole	Worsening of motor symptoms reported in some patients with Parkinson's disease. Antipsychotics reduce dopaminergic activity while antiparkinson agents increase dopamine in the CNS. If an antipsychotic is necessary, consider using clozapine or quetiapine, which have been reported to be less likely to cause worsening control of movement disorders than other antipsychotics. Note: A pilot study of very low-dose aripiprazole (0.625 mg/day) found improvement in levodopa-induced dyskinesias. Case report of hypoglycemia 10 days after adding aripiprazole to levodopa
Antipsychotic combination	General	When combining antipsychotics, consider the risks (e.g., additive adverse effects, cost, increased pill burden) vs. potential and evidence for efficacy
	Clozapine	Preliminary data on adding aripiprazole to clozapine to improve efficacy and/or mitigate adverse effects of clozapine (e.g., weight gain, enuresis)
	Haloperidol	Resolution of haloperidol-induced hyperprolactinemia with addition of aripiprazole (15–30 mg/day) in a small RCT. No significant change in serum haloperidol levels. Case report of asymptomatic QTc prolongation (by 75 ms) when haloperidol (5 mg/day) added to aripiprazole (30 mg/day)
	Olanzapine	Case report of NMS with the addition of aripiprazole (10 mg/day) to olanzapine (10 mg/day). Case reports of worsening hallucinations, paranoia, and delusions with addition of aripiprazole (10–30 mg/day)
	Quetiapine	Case report of worsening irritation, grandiosity, and hallucinations with the addition of aripiprazole (15–30 mg/day) to quetiapine (800 mg/day)
	Paliperidone, risperidone	Preliminary data on adding aripiprazole to resolve risperidone- or paliperidone-induced hyperprolactinemia. Case report of improvement in tardive dyskinesia with addition of aripiprazole (15 mg/day)
	Ziprasidone	Case report of worsening psychosis with addition of aripiprazole (30 mg/day)

Third-Generation Antipsychotics (TGAs) (cont.)

Class of Drug	Example	Interaction Effects
Antiretroviral		See [68] for additional information
Protease inhibitor	Atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, simeprevir telaprevir, tipranavir	CAUTION. Complex interactions likely as various protease inhibitors potently inhibit as well as induce a variety of CYP enzymes (e.g., on CYP3A4 ritonavir is a potent inhibitor; atazanavir, boceprevir, darunavir, saquinavir, and telaprevir are strong inhibitiors; indinavir and fosamprenavir are mild to moderate inhibitors; tipranavir is an inducer. Low boosting doses of ritonavir have little effect on CYP2D6 but higher doses cause inhibition) Increased levels of TGAs possible with enzyme-inhibiting protease inhibitors (e.g., ritonavir, indinavir). Decreased levels possible with unboosted tipranavir Case report of high aripiprazole levels, confusion, and loss of coordination in a patient taking high-dose aripiprazole (50 mg/day) with darunavir and ritonavir (modest CYP2D6 and potent CYP3A4 inhibitors) and duloxetine
Antitubercular	Rifampin	Decreased brexpiprazole AUC (70%) and C_{max} (20%) via CYP3A4 induction
Benzodiazepine	Lorazepam	Increased incidence of sedation and orthostatic hypotension
β-blocker	Metoprolol, propranolol	Increased serum levels of aripiprazole and dehydro-aripiprazole found in one study, possibly due to inhibition of metabolism via CYP2D6 Metoprolol may increase serum levels of brexpiprazole
Cardiac	Ranolazine	CAUTION. In theory, increased plasma level of aripiprazole and brexpiprazole possible due to inhibited metabolism via CYP2D6
CNS depressant	General (e. g., alcohol, hypnotics, opioids)	CAUTION. Potentiation of CNS effects (e.g., sedation, hypotension, respiratory depression)
	Alcohol	May worsen EPS
Glucocorticoid	Betamethasone, methylprednisolone, hydrocortisone, prednisone	CAUTION. Potential to exacerbate psychiatric conditions, as glucocorticoid-induced psychiatric disorders such as psychosis can occur Glucocorticoids can induce metabolism via CYP3A4. In theory, higher TGA doses may be needed
Grapefruit		Grapefruit juice is a moderate CYP3A4 inhibitor. In theory, increased plasma level of TGAs possible
H_2 antagonist	Famotidine	Decreased rate (C_{max}) by 37% and 21%, and extent of absorption (AUC) by 13% and 15% of aripiprazole and its active metabolite, respectively. Of low clinical significance; no dose adjustment required
	Cimetidine	Cimetidine is a moderate CYP2D6 and CYP3A4 inhibitor. In theory, increased plasma level of TGAs possible
Lithium		Increased rates of akathisia and tremor generally occur within 6 weeks and resolve with continued use. Adverse effect case reports with concurrent use include one each of NMS, Pisa syndrome, and tardive dyskinesia
Metoclopramide		CAUTION. Metoclopramide is a potent central dopamine receptor antagonist that can cause EPS, hyperprolactinemia, and rarely NMS. Concurrent use with an antipsychotic may increase the risk of these adverse effects
Opioid	Methadone	Methadone is a moderate CYP2D6 inhibitor and weak CYP3A4 inhibitor. Potential for increased aripiprazole and brexpiprazole levels
Stimulant	Amphetamine, methylphenidate	CAUTION. Potential to exacerbate psychiatric conditions as stimulant-induced psychosis can occur Antipsychotics can counteract many signs of stimulant toxicity (e.g., anxiety, aggression, visual or auditory hallucinations, psychosis), may impair the stimulatory effect of amphetamines, and have additive adverse effects (e.g., insomnia, restlessness, tremor) Case report of acute dystonia on abrupt discontinuation of methylphenidate. Case report of acute dystonia with recreational amphetamine use

Effects of Antipsychotics on Neurotransmitters/Receptors*

	FIRST-GENERATION AGENTS (FGAs)												
	Chlorpromazine	Fluphenthixol	Fluphenazine	Haloperidol	Loxapine	Methotrimeprazine	Periciazine	Perphenazine	Pimozide	Thioridazine	Thiothixene	Trifluoperazine	Zuclopenthixol
D_2 blockade	++++	+++++	+++++	+++++	++++	+++	++++	+++++	++++	++++	+++++	++++	+++++
H_1 blockade	+++	+++	+++	+	+++	+++++	?	++++	+	+++	+++	++	+++
M_1 blockade	+++	+++	+	+	++	?	?	+	+	++++	+	+	++
M_3 blockade	+++	?	+	+	++	?	?	+	?	+++	?	?	?
α_1 blockade	++++	+++	+++	+++	+++	?	?	+++	+++	++++	++	+++	++++
α_2 blockade	++	++	+	+	+	?	+	++	++	+	++	+	++
5-HT_{1A} blockade	+	?	++	+	+	?	?	++	++	++	++	++	?
5-HT_{2A} blockade	++++	++++	++++	+++	++++	++++	?	++++	+++	++++	+++	++++	++++
5-HT_{2C} blockade	+++	?	++	+	+++	?	?	++	+	+++	+	++	?
5-HT_7 blockade	+++	?	++++	++	+++	?	?	+++	+++++	+++	+++	++	?

	SECOND-GENERATION AGENTS (SGAs)										THIRD-GENERATION AGENTS (TGAs)		
	Asenapine	Clozapine	Iloperidone	Lumateperone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone	Aripiprazole	Brexpiprazole	Cariprazine
D_2 blockade	++++	++	+++	+++	++++	+++	++++	++	++++	++++	+++++[a]	+++++[a]	+++++[a]
H_1 blockade	++++	++++	++	—	+	++++	+++	+++	+++	+++	+++	+++	+++
M_1 blockade	+	+++[a]	+	—	+	++++	—	++	—	—	—	+	—
M_3 blockade	?	+++	+	—	?	+++	—	+	+	+	+	?	—
α_1 blockade	++++	++++	++++	+++	+++	+++	++++	+++	++++	+++	+++	+++	++
α_2 blockade	++++	++	++	+++	+++	++	+++	+++	++	++	+++	+++	?
5-HT_{1A} blockade	++++	++[a]	++[a]	—	++++[a]	+	++	++[a]	++	+++[a]	++++[a]	+++++[a]	++++[a]
5-HT_{2A} blockade	+++++	+++	+++++	+++++	+++++	++++	+++++	+++	+++++	++++	++++	+++++	+++
5-HT_{2C} blockade	+++++	+++	+++	++	++	++++	+++	+	+++	+++	+++	?	++
5-HT_7 blockade	+++++	+++	++	—	+++++	++	+++	++	++++	++++	++++	++++	++

[a] Partial agonist Key: K_i (nM) > 10,000 = –; 1000–10,000 = +; 100–1000 = ++; 10–100 = +++; 1–10 = ++++; 0.1–1 = +++++; ? = unknown

See p. 218 for Pharmacological Effects on Neurotransmitters.

Adapted from: [36, 78, 79, 80, 81, 82, 83]. See also the National Institute of Mental Health's Psychoactive Drug Screening Program. Available at http://pdsp.med.unc.edu

* The ratio of K_i values (inhibition constant) between various neurotransmitters/receptors determines the pharmacological profile for any one drug

Pharmacological Effects of Antipsychotics on Neurotransmitters/Receptor Subtypes

D_2	• Antagonism of postsynaptic D_2 receptors: – In mesolimbic tract – reduction in positive symptoms (partial agonism of this receptor may also reduce positive symptoms; partial agonist behaves like an antagonist in cases where a hyperdopaminergic state exists) – In mesocortical tract – may exacerbate negative symptoms – In nigrostriatal tract – EPSE (e.g., dystonias, pseudoparkinsonism, akathisia, tardive movement disorders, etc.) – In tuberoinfundibular tract – prolactin elevation (e.g., galactorrhea, sexual dysfunction, etc.). TGAs (partial agonists) may cause hypoprolactinemia related adverse effects (reduces sperm motility, count, and abnormal sperm morphology in men and failure to lactate after delivery in women)
H_1	• Antagonism of H_1 receptors: – Anti-emetic effect, anxiolytic effects – Sedation, drowsiness, appetite increase, weight gain
M_1	• Antagonism of M_1 receptors: – Mitigation of extrapyramidal adverse effects – Dry mouth, blurred vision, constipation, urinary retention and incontinence, sinus tachycardia, QRS changes, memory disturbances, sedation – Potentiation of effects of drugs with anticholinergic properties
M_3	• Antagonism of M_3 receptors: – Beta cell failure, reduced insulin release, glucose intolerance, type 2 diabetes mellitus
α_1	• Antagonism of α_1 adrenergic receptors: – Postural hypotension, dizziness, reflex tachycardia, sedation
α_2	• Antagonism of α_2-adrenergic receptors: – May improve cognitive deficits and have antidepressant activity; enhance serotonergic and noradrenergic transmission (presynaptic receptor antagonism) • Agonism of α_2-adrenergic receptors (i.e., clonidine) may result in: – Improvement in cognitive performance
5-HT_{1A}	• Antagonism/partial agonism of 5-HT_{1A} serotonergic receptors: – Postulated to be associated with procognitive, anxiolytic, and antidepressant effects
5-HT_{2A}	• Antagonism of 5-HT_{2A} serotonergic receptors: – Sedation, prodopaminergic actions may ameliorate EPSE, and postulated to improve (not worsen) negative, cognitive, and mood symptoms
5-HT_{2C}	• Antagonism of 5-HT_{2C} serotonergic receptors: – Increased appetite, weight gain – Postulated to be associated with procognitive and antidepressant effects
5-HT_7	• Antagonism of 5-HT_7 serotonergic receptors: – Postulated to be associated with procognitive, anxiolytic, and antidepressant effects

Frequency (%) of Adverse Reactions to Antipsychotics at Therapeutic Doses

Reaction	FIRST-GENERATION AGENTS (FGAs)												
	Chlorpromazine	Fluspenthixol	Fluphenazine	Haloperidol	Loxapine	Methotrimeprazine	Periciazine	Perphenazine	Pimozide	Thioridazine	Thiothixene	Trifluoperazine	Zuclopenthixol
CNS Effects													
Drowsiness, sedation	> 30	> 2	> 2	> 2[o]	> 30	> 30	> 30	> 10	> 10	> 30	> 10	> 2	> 30
Insomnia, agitation	< 2	< 2	> 2	> 10	< 2	< 2	< 2	> 10	> 2	< 2	> 10	> 2	> 10
Extrapyramidal Effects													
Parkinsonism	> 10	> 30	> 30	> 30[p]	> 30	> 10	> 2	> 10	> 30	> 2	> 30	> 30	> 30
Akathisia	> 2	> 30	> 30	> 30	> 30	> 2	> 2	> 10	> 10	> 2	> 30	> 30	> 10
Dystonic reactions	> 2	> 10	> 10	> 30[p]	> 10	< 2	< 2	> 10	> 2	< 2	> 2	> 10	> 10[p]
Anticholinergic Effects	> 30	> 10	> 2	> 2	> 10	> 30	> 30	> 10	> 2	> 30	> 2	> 2	> 10[k]
Cardiovascular Effects													
Orthostatic hypotension	> 30[o]	> 2	> 2	> 2	> 10	> 30[o][a]	> 10	> 10	> 2	> 30	> 2	> 10	> 2
Tachycardia	> 10	> 2	> 10	< 2	> 10	> 10	> 10	> 10	> 2	< 2	> 2	< 2	> 2
ECG abnormalities[b]	> 30[c]	> 2	< 2	< 2	< 2	> 10	< 2	> 2	> 2[q]	> 30[c]	< 2	< 2	< 2
QTc prolongation (> 450 msec)	> 2[c]	< 2	> 2[c]	> 2[c]	–	> 2	> 2	< 2	> 2[q]	> 10[c]	< 2	> 2	< 2
Endocrine Effects													
Sexual dysfunction[d]	> 30[e]	> 30[e]	> 30[e]	> 30[e]	> 2	> 2[e]	> 10[e]	> 10[e]	> 30	> 30[e]	> 2[e]	> 30[e]	> 30[e]
Galactorrhea	> 30	–	> 10	< 2	> 2	> 30	> 10	> 10	< 2	> 30	< 2	> 10	–
Weight gain	> 30	> 10	> 30	> 10	< 2[f]	> 10	> 10	> 10	> 2[f]	> 30	> 10	> 10	> 10
Hyperglycemia	> 30	> 10	> 10	> 10	> 2[r]	> 2[r]	> 2[r]	> 10	> 2	> 2[r]	> 2[r]	> 2	> 2[r]
Hyperlipidemia	> 30	?	?	> 2	> 10	?	?	> 2[r]	?	> 30	?	?	?
Ocular Effects [s]													
Lenticular pigmentation	> 2	< 2	< 2	< 2	< 2	> 2	> 2	< 2	< 2	> 2	< 2	< 2	< 2
Pigmentary retinopathy	> 2[s]	< 2	–	–	< 2	> 2[s]	–	< 2	–	> 10[s]	< 2	< 2	–
Blood dyscrasias	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2
Hepatic disorder	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2
Seizures[h]	< 2[o]	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2	< 2
Skin Reactions													
Photosensitivity	> 10	< 2	< 2	< 2	< 2	> 10	> 2	< 2	–	> 10[c]	< 2	< 2	< 2
Rashes	> 10	> 2	< 2	< 2	> 2	> 2	> 2	< 2	> 2	> 10	< 2	< 2	< 2
Pigmentation[s]	> 30[c]	–	–	< 2	–	< 2	–	–	–	> 2	> 2	–	< 2

Data are pooled from separate studies and are not necessarily comparable; the figures in the table cannot be used to predict the incidence of side effects in the course of usual medical practice, where patient characteristics and other factors differ from those in the clinical trials.

– = None reported in literature perused

[a] May be higher at start of therapy or with rapid dose increase, [b] = ECG abnormalities usually without cardiac injury including ST segment depression, flattened T waves, and increased U wave amplitude, [c] Higher doses pose greater risk, [d] Includes impotence, inhibition of ejaculation, anorgasmia, [e] Priapism reported, [f] Weight loss reported, [h] In nonepileptic patients, [k] Sialorrhea reported, [o] More frequent with rapid dose increase, [p] Lower incidence with depot formulation, [q] Pimozide above 20 mg daily poses greater risk, [r] Reported to occur, but no definitive data published as to incidence, [s] Usually seen after prolonged use

Frequency (%) of Adverse Reactions to Antipsychotics at Therapeutic Doses (cont.)

Reaction	SECOND-GENERATION AGENTS (SGAs)										THIRD-GENERATION AGENTS (TGAs)		
	Asenapine	Clozapine	Iloperidone	Lumateperone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone	Aripiprazole	Brexpiprazole	Cariprazine
CNS Effects													
Drowsiness, sedation	> 30	> 30	> 10	> 10	> 30	> 30	> 2	> 30	> 10[a]	> 30	> 10	> 2	> 2
Insomnia, agitation	> 2	> 2	> 10	< 2	> 2	> 10	> 10	> 10	> 10	> 10	> 10	> 2	> 2
Extrapyramidal Effects													
Parkinsonism	> 2	> 2	< 2	< 2	< 2	> 2	> 2	> 2	> 10[i]	> 2	> 2	> 2	> 2
Akathisia	> 2	> 10	> 2	> 2	> 10	> 10	> 2	> 2	> 10[i]	> 2	> 10	> 2	> 2
Dystonic reactions	> 2	< 2	< 2	< 2	> 2	< 2	< 2	< 2	< 2[i]	> 2	< 2	> 2	< 2
Anticholinergic Effects	> 2	> 30[k]	> 2	> 2	> 2	> 10	> 2	> 30	> 2	> 10	> 2	> 2	< 2
Cardiovascular Effects													
Orthostatic hypotension	> 10	> 10–30[a]	> 10	< 2	> 2	> 2	> 2	> 10	> 10[a]	> 10	> 2	> 2	> 2
Tachycardia	< 2	> 10[a]	> 10	< 2	—	> 10[l]	> 2	> 10	< 2	< 2	> 2	< 2	< 2
ECG abnormalities[b]	< 2	> 30[c]	< 2	< 2	< 2	< 2	< 2	< 2	> 2	> 2[c]	< 2	< 2	< 2
QTc prolongation (> 450 msec)	9	< 2[c]	< 2	< 2	–	< 2	> 2	< 2	< 2	< 2[c]	–	–	–
Endocrine Effects													
Sexual dysfunction[d]	?	< 2[e]	> 2	< 2	< 2	> 30[e]	< 2	> 30[e]	> 30[e]	< 2[e]	< 2[e]	< 2[e]	< 2[e]
Galactorrhea	?	< 2	< 2	< 2	< 2	> 2	< 2	–	> 10	> 2	< 2	< 2	< 2
Weight gain	> 10	> 30	> 10	< 2	< 2	> 30	> 10	> 10	> 10	> 2	> 2[f]	> 2[f]	< 2[f]
Hyperglycemia	> 10	> 30	?	< 2	< 2	> 30	?	> 30	> 10	> 2	< 2	< 2	< 2
Hyperlipidemia	> 10	> 30	?	> 2	< 2	> 30	?	> 10	> 10	< 2	< 2	< 2	< 2
Ocular Effects[s]													
Lenticular pigmentation	?	–	?	> 2	–	–	?	< 2	–	–	–	–	–
Pigmentary retinopathy	?	–	?	–	–	–	–	–	–	–	–	–	–
Blood dyscrasias	< 2	< 2[m]	?	< 2	< 2	< 2	?	–	< 2	< 2	< 2	< 2	< 2
Hepatic disorder	> 2	> 2	< 2	< 2	—	> 2	?	> 2	< 2	–	< 2	< 2	< 2
Seizures[h]	< 2	> 2[n]	< 2	< 2	< 2	< 2	< 2	< 2	< 2	–	< 2	< 2	< 2
Skin Reactions													
Photosensitivity	?	> 2	?	< 2	–	–	?	–	> 2	–	< 2	< 2	< 2
Rashes	?	> 2	?	< 2	< 2	< 2	?	< 2	< 2	> 2	> 2	< 2	< 2
Pigmentation[s]	?	–	?	< 2	–	–	?	–	< 2	–	–	–	–

Data are pooled from separate studies and are not necessarily comparable; the figures in the table cannot be used to predict the incidence of side effects in the course of usual medical practice, where patient characteristics and other factors differ from those in the clinical trials.

– = None reported in literature perused

[a] May be higher at start of therapy or with rapid dose increase, [b] = ECG abnormalities usually without cardiac injury including ST segment depression, flattened T waves, and increased U wave amplitude, [c] Higher doses pose greater risk, [d] Includes impotence, inhibition of ejaculation, anorgasmia, [e] Priapism reported, [f] Weight loss reported, [g] Usually seen after prolonged use, [h] In nonepileptic patients, [i] Increased risk with oral doses above 10 mg daily, [k] Sialorrhea reported, [l] Bradycardia frequent with IM olanzapine; often accompanied by hypotension, [m] Risk < 2% with strict monitoring (legal requirement in North America), [n] Risk increased with doses above 300 mg

Antipsychotic Doses and Pharmacokinetics (Oral and Short-Acting Injections)

FIRST-GENERATION AGENTS (FGAs)											
Drug	**CPE (mg)**	**OLE in Schizophrenia**	**Monograph Doses for Psychosis**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[1] / Transporters (CYP450; other)**	**Enzyme Inhibition[2] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[3] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
Chlorpromazine (Largactil[C], Thorazine[B])	100	600	Age 6–12: Oral: 0.5 mg/kg q4–6 h Rectal: 1 mg/kg q 6–8 h Suggested daily dose ranges: Children: 150–200 mg Adolescents: 225–375 mg	Oral: 25–65%	95–99% (to albumin)	Oral: 0.51	Oral: 16–30	1A2[w], **2D6**[p], 3A4[w]; UGT1A4	1A2, **2D6**[p], 3A4[w], 2C9[w], 2C19, 2E1; P-gp	78–80% (100–200 mg; 10 nmol/L)	?
Flupenthixol[C] (Fluanxol)	2–5	10	Children: 0.4–2 mg/day Adolescents: up to 3 mg/day as maintenance dose, up to 12 mg/day used in some patients	30–70%	99%	3–8	26–36	?	2D6[w]	70–74% (5–10 mg; 2–5 nmol/L)	?
Fluphenazine HCl (Moditen[C], Prolixin[B])	2	12	Children: 1.5–5 mg Adolescents: 2.5–10 mg; 0.04 mg/kg/day or 0.5–10 mg/day	1–50%	90–99%	Oral: 0.5 Short-acting IM: 1.5–2	Oral and short-acting IM: 13–58	1A2, 2D6; P-gp	1A2, **2D6**[p], 3A4[w], 2E1 2C8/9; P-gp	?	?
Haloperidol (Haldol)	2	10	Age 3–12 (weight: 15–40 kg): 0.5 mg to start; can increase by 0.5 mg q5–7 days (given bid or tid) Psychotic Disorders: 0.05–0.15 mg/kg/day Suggested daily dose ranges: Children: 1–4 mg Adolescents: 2–10 mg Nonpsychotic Disorders: 0.05–0.075 mg/kg/day Doses above 10 mg/day not recommended	40–80%	92% (to α_1-AGP)	0.5–3 Short-acting IM (lactate): 10–20 min	12–36	1A2[w], 2D6[w], **3A4**[p]	**2D6**, 3A4; P-gp[w]	75–89% (4–6 mg; 6–13 nmol/L)	?
Loxapine (Adasuve[B], Loxapac[C], Loxitane[B], Xylac[C])	10	60	Initial dose: 5–10 mg/day (in divided doses) and increase gradually by 5–10 mg/day Usual dose: 50–100 mg/day (in divided doses) Oral inhalation: 2.5–5 mg (<50 kg) or 5–10 mg (> 50 kg) via single-use inhaler Short-acting IM: 5–25 mg (0.1–0.2 mg/kg/dose, maximum 25 mg) q4–6 h prn	33%	97%	Oral = 1–2 Oral inhalation = 2–5 min Short-acting IM = 2–5	Oral = 3 (range 1–14); 5–19 (metabolites) Short-acting IM = 12 h (range 8–23); 8–30 (metabolites)	1A2, 2D6, 3A4; UGT1A4	P-gp	60–80% (15–30 mg)	58–75% (10–30 mg) 75–90% metabolite (> 30 mg)

Antipsychotic Doses and Pharmacokinetics (Oral and Short-Acting Injections) (cont.)

FIRST-GENERATION AGENTS (FGAs)											
Drug	**CPE (mg)**	**OLE in Schizophrenia**	**Monograph Doses for Psychosis**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[1] / Transporters (CYP450; other)**	**Enzyme Inhibition[2] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[3] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
Methotrimeprazine/ Levomepromazine[C] (Nozinan)	70	300; rarely used	Initial dose: 0.25 mg/kg/day in 2–3 divided doses; increase gradually to effective dose Under age 5: Maximum 40 mg/day, age 5–12: Maximum 75 mg/day, over age 12: May require 200 mg/day or higher	Oral: 21–50%	?	Oral: 1–3 Short-acting IM: 30–90 min	Oral: 16–78	1A2, 2D6, 3A4; P-gp	**2D6**[p]; P-gp	?	?
Periciazine[C] (Neuleptil)	15–24	50; not used	Over age 5: 2.5–10 mg am and 5–30 mg at bedtime (approx. 1–3 mg/year of age/day)	?	?	2	~12	2D6, 3A4	P-gp	?	?
Perphenazine (Trilafon)	10	30	Suggested daily dose ranges: Children: 6–12 mg Adolescents: 12–22 mg	25%	91–92%	1–4	9–21	1A2, **2D6**[p], 3A4, 2C9, 2C19	1A2[w], **2D6**[p], 3A4, 2C9, 2C19; P-gp	79% (4–8 mg)	?
Pimozide (Orap)	2	8	Initial dose: 0.05 mg/kg at bedtime; may increase every 3 days to a maximum of 0.2 mg/kg (10 mg/day) Usual dose: 1–5 mg/day	15–50%	97%	6–8 (range 4–12)	29–55[y]	1A2[w], **3A4**[p]	**2D6**[p], 3A4; P-gp[p]	77–79% (4–8 mg)	?
Thioridazine[B][x] (Mellaril)	100	500; not recommended	Not recommended in children and adolescents Previous dosing guidelines in children and adolescents: Age 1–5: 1 mg/kg/day Over age 5: 75–150 mg/day Usual daily dose range: Children: 100–250 mg Adolescents: 225–325 mg	10–60%	97–99%	1–4	9–30	1A2[w], 2D6[w], 2C19[w]	1A2, **2D6**[p], 2C8/9, 2E1; P-gp; Inducer of 3A4	74–81% (100–400 mg; 620–900 nmol/L)	?

FIRST-GENERATION AGENTS (FGAs)											
Drug	**CPE (mg)**	**OLE in Schizophrenia**	**Monograph Doses for Psychosis**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[1] / Transporters (CYP450; other)**	**Enzyme Inhibition[2] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[3] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
Thiothixene[B] (Navane)	5	30	0.25 mg/kg/day Suggested daily dose ranges: Children: 4–7 mg Adolescents: 4–20 mg	50%	90–99%	1–3	34	**1A2**[p]	2D6[w]	?	?
Trifluoperazine (Stelazine)	5	20	Age 6–12: Start at 1 mg once daily or bid, increase gradually to a maximum of 10 mg/day Usual daily dose ranges: Children: 2–10 mg Adolescents: 6–15 mg/day	?	95–99%	2–4	7–18	1A2; P-gp; UGT1A4	P-gp	75–80% (5–10 mg)	?
Zuclopenthixol[C] (Clopixol)	12	50	10–25 mg to start; increase by 10–20 mg every 2—3 days Usual daily dose: 10–60 mg; doses above 100 mg/day not recommended	44%	98%	2–4	12–28	**2D6**[p]	2D6	> 70%	?
Zuclopenthixol acetate[C] (Clopixol acuphase)	30 mg q2–3 days	–	Usual dose: 25–100 mg IM and repeat every 2–3 days as needed to a maximum of 4 injections (a second injection may need to be given 1–2 days after the first in some patients)	–	98%	24–48	48–72	**2D6**[p]	2D6	> 70%	?

Antipsychotic Doses and Pharmacokinetics (Oral and Short-Acting Injections) (cont.)

SECOND-GENERATION AGENTS (SGAs)											
Drug	**CPE (mg)**	**OLE in Schizophrenia**	**Suggested Doses for Psychosis in Children and Adolescents**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[1] / Transporters (CYP450; other)**	**Enzyme Inhibition[2] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[3] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
Asenapine (Saphris)	5	25	Adolescents: Oral: 2.5–5 mg sublingually bid initially, may increase to maximum of 10 mg bid if tolerated after 7 days	35% (< 2% if swallowed; reduced if food/drink taken within 10 min)	95% (including albumin and α_1-AGP)	0.5–3	16–25	**1A2**[(p)], 2D6[(w)], 3A4[(w)]; **UGT1A4**[(p)]	2D6[(w)]	79% (4.8 mg sublingual)	?
Clozapine (Clozaril, FazaClo ODT[(B)], Versacloz[(B)])	50	400	12.5 mg once daily to bid on day 1, then increase as tolerated by 12.5–25 mg increments every 2–5 days, to a target dose of 125–475 mg/day (in divided doses) Suggested clozapine trough concentration > 300 ng/mL in youth Prescribing restrictions: First 6 months: Max. 1-week prescription Months 7–12: If approved, max. 2-week prescription 1 year onward: If approved, max. 4-week prescription (other countries may have less stringent regulations)	90–95% (40–60% after 1st pass metabolism)	95–97% (to α_1-AGP)	1–6 (mean 2.5)	6–33 (mean 12; parent) 11–105 (active metabolite) Reduced in smokers (20–40% shorter)	**1A2**[(p)], 2D6[(w)], 3A4[(m)], 2C9[(w)], 2C19[(m)], 2E1[(w)]; FMO; UGT1A4; P-gp[(w)]	1A2[(w)], 2D6[(w)], 3A4, 2C9[(w)], 2C19, 2E1[(w)]	38–68% (300–900 mg; 600–2500 nmol/L)[(G)]	85–94% (> 125 mg)
Iloperidone[(B)] (Fanapt)	6	20	No pediatric studies. Adults: 1 mg bid initially and increase daily for 7 days to a target dose of 6 mg bid	96%	~95%	2–4	18[(E)]–33[(D)] (parent) 26[(E)]–37[(D)] and 23[(E)]–31[(D)] (active metabolites)	**2D6**[(p)], **3A4**[(p)]	3A4[(m)]	?	?
Lumateperone (Caplyta)	10	42	No pediatric studies Adults: single dose of 42 mg, with no titration required	Absolute bioavailability is about 4.4%	97.4%	1–2 h	19	UDP: 1A1, 1A4, 2B15 AKR: 1B10, 1C1, 1C4 CYP: 1A2, 2C8, 3A4	Little to none	? Ki = 32nM	? Ki = 0.57 nM

SECOND-GENERATION AGENTS (SGAs)											
Drug	**CPE (mg)**	**OLE in Schizophrenia**	**Suggested Doses for Psychosis in Children and Adolescents**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[1] / Transporters (CYP450; other)**	**Enzyme Inhibition[2] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[3] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
Lurasidone (Latuda)	20	100	20–40 mg once daily to start Maximum: 80 mg once daily	9—19%	> 99.8% (to albumin and α_1-AGP)	1.6—2.3	18—37 (parent) 7.5—10 (active metabolite)	**3A4**$^{(p)}$	–	63—79% (40—80 mg)	?
Olanzapine (Zyprexa, Zyprexa Zydis)	5	20	Oral: 2.5–5 mg once daily to start, adjust in increments of 2.5–5 mg/day to a target dose of 10 mg/day Maximum: 20 mg/day	Oral: 57–80%	93% (to albumin and α_1-AGP)	Oral: 5–8	21–54 (30 mean) No change in hepatic disease (only based on single-dose study) or renal disease. Prolonged in females (30% longer – clinical significance unclear) Reduced in smokers (40% shorter)	1A2$^{(p)}$, 2D6$^{(w)}$; FMO; UGT1A4$^{(p)}$	1A2$^{(w)}$, 2D6$^{(w)}$, 3A4$^{(w)}$, 2C9$^{(w)}$, 2C19$^{(w)}$	55–80% (5–20 mg; 59–187 nmol/L) 83–88% (30–40 mg)	80–90% (5–20 mg)
(Zyprexa IntraMuscular)			No pediatric studies Adults: Short-acting IM: 10 mg to start If needed, give 2nd dose of 5–10 mg 2 h after 1st; if 3rd dose needed, give ≥ 4 h after 2nd dose Maximum: 30 mg/day (high rate of orthostatic hypotension) with no more than 3 injections in 24 h			Short-acting IM: 15–45 min (C_{max} 4—5 fold greater than same oral dose)					
Paliperidone (active metabolite of risperidone; Invega)	1.5	8	Adolescents: 3–6 mg once daily (preferably in AM) If needed, increase by 3 mg q5 days to a maximum of 6 mg/day (< 51 kg) or 12 mg/day (> 51 kg)	28%	74% (to albumin and α_1-AGP)	24	23 In mild, moderate, and severe renal impairment: 24, 40, and 51, respectively	2D6$^{(w)}$, 3A4$^{(w)}$, P-gp (minimally metabolized, < 7%)	P-gp$^{(w)}$ (at high doses *in vitro*)	66% (6 mg) 70—80% predicted for 4.5—9 mg	?
Quetiapine (Seroquel)	75	750	Oral: 25 mg bid on day 1, 50 mg bid on day 2, then increase by 100 mg/day (in divided doses) to maximum of 800 mg/day	~73% (relative bioavailability; absolute unknown)	83%	Oral: 0.5–3	~6–7 (parent) ~12 (active metabolite) Prolonged in hepatic disease (45% longer; based on a low-, single-dose study in those with mild disease), renal disease (25% longer; based on a low-, single-dose study in those with severe disease)	**3A4**$^{(p)}$, 2D6$^{(w)}$; P-gp	1A2$^{(w)}$, 2D6$^{(w)}$, 3A4$^{(w)}$, 2C9$^{(w)}$, 2C19$^{(w)}$	20–44% (300–700 mg) 13–41% (150–750 mg)	21–80% (150–600 mg) 38–74% (150–750 mg)

Antipsychotic Doses and Pharmacokinetics (Oral and Short-Acting Injections) (cont.)

SECOND-GENERATION AGENTS (SGAs)											
Drug	**CPE (mg)**	**OLE in Schizophrenia**	**Suggested Doses for Psychosis in Children and Adolescents**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[1] / Transporters (CYP450; other)**	**Enzyme Inhibition[2] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[3] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
(Seroquel XR)			Oral (XR): 50 mg/day on day 1, 100 mg/day on day 2, then increase by 100 mg/day to a maximum of 800 mg/day			Oral (XR): ~6 (give in late afternoon/evening, to peak at bedtime)					
Risperidone (Risperdal, Risperdal M-tab)	2	6	0.25 mg bid to start and increase gradually Suggested daily dose ranges: Children: 1–2 mg Adolescents: 2.5–4 mg	70%	88–90% (parent; to albumin and α_1-AGP) 77% (active metabolite) Reduced in hepatic disease	1–1.5 (parent) 3[(E)]–17[(D)] (active metabolite)	3[(E)]–20[(D)] (parent) 21[(E)]–30[(D)] (active metabolite) Increased by ~60% in moderate to severe renal disease	**2D6**[(p)], 3A4[(m)], P-gp	2D6, 3A4[(w)]	60–75% (2–4 mg) 63–85% (2–6 mg; 36–252 nmol/L)	60–90% (1–4 mg)
Ziprasidone (Geodon[(B)], Zeldox[(C)])	60	160	Children and adolescents: 10–20 mg bid to start. If needed, increase ≥ q2 days Maximum: 80 mg/day (< 45 kg), 160 mg/day (> 45 kg) Adults: 20–40 mg bid[(F)] to start. If needed, increase ≥ q2 days. Doses above 80 mg bid generally not recommended	Oral: 30% (60% with food)	over 99% (to albumin and α_1-AGP)	Oral: 6–8 (C_{max} increased 32–72% in mild renal impairment)	Oral: 4–10 dose-dependent (6.6 mean) No change in renal disease Prolonged in hepatic disease (mean in hepatic disease = 7.1 vs. 4.8 in control group)	**3A4**[(m)], 1A2[(w)], 2D6, 3C18/19; Aldehyde oxidase[(w)]	2D6[(w)], 3A4[(w)]	45–75% (40–80 mg)	80–90% (40–80 mg)
Ziprasidone mesylate[(B)]			No pediatric studies Adults: Short-acting IM: 10 mg q 2 h or 20 mg q 4 h to a maximum of 40 mg/24 h for up to 3 days	Short-acting IM: 100%		Short-acting IM: ~60 min	Short-acting IM: 2–5 h (Caution in renal disease due to excipient – cyclodextrin)				

THIRD-GENERATION AGENTS (TGAs)											
Drug	**CPE (mg)**	**OLE in Schizophrenia**	**Monograph Doses for Psychosis**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[1] / Transporters (CYP450; other)**	**Enzyme Inhibition[2] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[3] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
Aripiprazole (Abilify)	7.5	30	Oral: 2 mg/day for 2 days, then 5 mg/day for 2 days, then 10 mg/day. Further dose increases in 5 mg increments, up to a maximum of 30 mg/day. Doses above 10 mg not shown to be more effective	87% (tablet; slightly higher with oral solution form) Short-acting IM: 100%	> 99% (primarily to albumin)	Oral: 3–5 Short-acting IM: 1–3	75—146[D] (active metabolite = 94) No change in renal or hepatic impairment	2D6[p], 3A4[p] (Reduce dose by 50% in poor metabolizers of 2D6. Dose changes required with concurrent use of 2D6 and/or 3A4 inducers or inhibitors)	–	40–95% (0.5–30 mg)	54—60% (10—30 mg)
Brexpiprazole (Rexulti)	?	?	Children and adolescents (USA): 0.5 mg once daily on days 1–4. Titrate to 1 mg once daily on days 5–7, then 2 mg on day 8 depending on response and tolerability. Recommended target dose is 2–4 mg once daily	95%	> 99%	4	91 (major metabolite = 86)	2D6[p], 3A4[p] (Reduce dose by 50% in poor metabolizers of 2D6. Dose changes required with concurrent use of 2D6 and/or 3A4 inducers or inhibitors	–	?	?
Cariprazine[B] (Vraylar)	?	?	No pediatric studies Adults: Starting dose 1.5 mg once daily; can be increased to 3 mg on day 2. Depending on tolerability, further dose adjustments can be made in 1.5 or 3 mg increments. Recommended dose range is 1.5–6 mg once daily	High	19–97%	3–6	2–5 days (active metabolite = 2–3 weeks)	2D6[w], 3A4[p] (Reduce dose by 50% in patients initiating a strong 3A4 inhibitor)	–	?	?

[1] CYP450 isoenzymes involved in drug metabolism, [2] CYP450 isoenzymes inhibited by drug, [3] D_2 receptor occupancy correlates better to plasma level than to dose, and appears to relate to clinical efficacy in controlling positive symptoms of schizophrenia as well as risk of extrapyramidal adverse effects (if over 80%), [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Poor metabolizers of CYP2D6, [E] Extensive metabolizers of CYP2D6, [F] One RCT supports once daily dosing, [G] Occasionally higher doses (i.e., 950–1400 mg/day) may be required to reach therapeutic levels, in particular in males who are heavy smokers. In such cases, monitor clozapine levels and for any signs/symptoms of toxicity[84], [m] Moderate activity, [p] Potent activity, [w] Weak activity, [x] Monitor cardiac function in doses above 15 mg/day, [y] Half-life longer (mean 66–111 h) in children and adults with Tourette's disorder

NOTES:

- Comparable doses are only approximations. Generally, doses used are higher in the acute stage of the illness than in maintenance. Each patient's medication dosage must be individualized
- Plasma levels are available for some antipsychotics but their clinical usefulness is limited
- For CYP activity data, see: [85, 86, 87, 88]; product monographs as of July 2017; [*Note: data regarding CYP450 profiles may not be consistent among references*]
- Abbreviations: α_1-AGP = α_1-acid glycoprotein; bid = twice daily; CPE = chlorpromazine equivalents [*the approximate dose of comparator antipsychotic that would be equivalent to oral chlorpromazine 100 mg with respect to D_2 receptor affinity*]; FMO = flavin monooxygenase enzyme involved in *N*-oxidation reactions; OLE = olanzapine equivalents [the approximate dose of comparator antipsychotic that would be equivalent to oral olanzapine 20 mg/day with respect to clinical efficacy[89, 90] – based on expert opinion]; P-gp = p-glycoprotein [*a transporter of hydrophobic substances in or out of specific body organs (e.g., block absorption in the gut)*]; qid = four times daily; tid = three times daily; UGT = uridine diphosphate glucuronosyl transferase [*involved in Phase II reactions (conjugation)*]

Comparison of Long-Acting IM Antipsychotics*

	FIRST-GENERATION AGENTS (FGAs)			
	Flupenthixol decanoate (Fluanxol)	Fluphenazine decanoate (Modecate; Prolixin)	Haloperidol decanoate (Haldol LA)	Zuclopenthixol decanoate[C] (Clopixol Depot)
Chemical class	Thioxanthene	Piperazine phenothiazine	Butyrophenone	Thioxanthene
Form	Esterified with decanoic acid (a 10-carbon chain fatty acid) and dissolved in vegetable oil; must be hydrolyzed to free flupenthixol; metabolites inactive	Esterified with decanoic acid and dissolved in sesame oil; must be hydrolyzed to free fluphenazine	Esterified with decanoic acid and dissolved in sesame oil; must be hydrolyzed to free haloperidol	Esterified with decanoic acid in coconut oil; must be hydrolyzed to free zuclopenthixol
Strength supplied	(2%) – 20 mg/mL (10%) – 100 mg/mL	25 mg/mL 100 mg/mL[C]	50 mg/mL 100 mg/mL	200 mg/mL[C]
Administration	Gluteal muscle Deep IM injection	Gluteal muscle (IM)	Gluteal muscle Deep IM injection	Gluteal muscle Deep IM injection
Overlap with oral formulation	1 week	1 week	None to 4 weeks	2 weeks
Suggested daily dose ranges	Limited data in youth Long-acting IM naive: Test dose of 5–20 mg; assess over next 5–10 days Adolescents: 20–40 mg q2–3 weeks, up to 60 mg/injection	Limited data in youth Children: 6.25–12.5 mg q2–3 weeks Adolescents: 12.5–25 mg q2–3 weeks	Limited data in youth Children: 15–50 mg q4 weeks Adolescents: 50–150 mg q4 weeks	Limited data in youth Adolescents: 100–250 mg q2 weeks
Usual duration of action	2–4 weeks	2–5 weeks	4 weeks	2–4 weeks
Pharmacokinetics				
Time to peak plasma level[G]	3–7 days	First peak in 8–10 h (due to presence of hydrolyzed "free" fluphenazine); level drops, then peaks again in 8–12 days	3–9 days	3–7 days
Elimination half-life[H]	8 days (after single injection), 17 days (multiple dosing)	6.8–9.6 days (single injection), up to 102 days (multiple dosing)	18–21 days	19 days
Time to steady state	2 months	2 months	2–3 months	2 months

* No long-acting IM antipsychotics have been adequately evaluated in children and adolescents. The dosing requirements and safety profile of these medications in this population is unknown.

	FIRST-GENERATION AGENTS (FGAs)			
	Flupenthixol decanoate (Fluanxol)	Fluphenazine decanoate (Modecate; Prolixin)	Haloperidol decanoate (Haldol LA)	Zuclopenthixol decanoate[C] (Clopixol Depot)
Adverse effects: Generally similar to oral drugs in same class	Flupenthixol (see p. 219)	Fluphenazine (see p. 219)	Haloperidol (see p. 219)	Zuclopenthixol (see p. 219)
Skin and local reactions	Indurations rarely seen (at high doses) Photosensitivity and hyperpigmentation very rare; dermatological reactions seen Pain at injection site	One case of induration seen at a high dose; dermatological reactions have been reported Pain at injection site	Local dermatological reactions; Inflammation and nodules at injection site (may be more common with 100 mg/mL formulation or with higher volumes); less common if deltoid used One case of photosensitization reported; "tracking" reported Pain at injection site can continue for 2 days after administration	No indurations but local dermatological reactions reported Pain at injection site

[C] = Not marketed in the USA, [G] Important as indicator when maximum adverse effects will occur, [H] Useful for determining dosing interval; steady state will be reached in approximately 5 half-lives

Note: qX weeks = every X weeks

	SECOND-GENERATION AGENTS (SGAs)**						THIRD-GENERATION AGENTS (TGAs)	
	Olanzapine pamoate[B] (Zyprexa Relprevv)	Paliperidone palmitate 1-monthly (Invega Sustenna)	Paliperidone palmitate 3-monthly (Invega Trinza)	Paliperidone palmitate 6-monthly (Invega Hafyera[B])	Risperidone (Risperdal Consta)	Risperidone RBP-7000 (Perseris)	Aripiprazole (Abilify Maintena)	Aripiprazole lauroxil[B] (Aristada)
Chemical class	Thieobenzodiazepine	Benzisoxazole	Benzisoxazole	Benzisoxazole	Benzisoxazole	Benzisoxazole	Phenylpiperazine	Phenylpiperazine
Form	Yellow solid of olanzapine pamoate monohydrate crystals forming a yellow, opaque suspension on reconstitution with provided aqueous diluent	White to off-white sterile aqueous extended-release suspension in prefilled syringes	White to off-white sterile aqueous extended-release suspension in prefilled syringes	White to off-white sterile, aqueous, extended-release suspension in prefilled syringes	White to off-white free-flowing powder with risperidone encapsulated in a polymer as extended-release microspheres. Must be reconstituted with provided aqueous base just prior to use	White to off-white powder, to be mixed with colorless to yellow solution. Forms viscous suspension white to yellow-green once reconstituted	White to off-white lyophilized powder forming an opaque milky-white suspension on reconstitution with provided sterile water for injection	White to off-white sterile aqueous extended-release suspension in prefilled syringe, supplied as a kit with safety needles

Comparison of Long-Acting IM Antipsychotics* (cont.)

	SECOND-GENERATION AGENTS (SGAs)**						THIRD-GENERATION AGENTS (TGAs)	
	Olanzapine pamoate[B] (Zyprexa Relprevv)	Paliperidone palmitate 1-monthly (Invega Sustenna)	Paliperidone palmitate 3-monthly (Invega Trinza)	Paliperidone palmitate 6-monthly (Invega Hafyera[B])	Risperidone (Risperdal Consta)	Risperidone RBP-7000 (Perseris)	Aripiprazole (Abilify Maintena)	Aripiprazole lauroxil[B] (Aristada)
Strength supplied	210 mg/vial, 300 mg/vial, 405 mg/vial	Strengths vary in different countries, e.g., US labeling indicates amount of paliperone palmitate: 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL Canadian labeling indicates only the amount of paliperidone (base): 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/mL, 150 mg/1.5 mL	Strengths vary in different countries, e.g., US labeling indicates amount of paliperone palmitate: 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, 819 mg/2.625 mL Canadian labeling indicates only the amount of paliperidone (base): 175 mg/0.875 mL, 263 mg/1.315 mL, 350 mg/1.75 mL, 525 mg/2.625 mL	US labeling indicates amount of paliperone palmitate: 1,092 mg/3.5 mL and 1,560 mg/5 mL	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial	90 mg/0.6 mL syringe, 120 mg/0.8 mL syringe	300 mg/vial, 400 mg/vial	441 mg, 662 mg, 882 mg, 1064 mg prefilled syringe
Administration	Gluteal muscle Deep IM injection	Deltoid muscle for days 1 and 8 Deltoid or gluteal muscle thereafter Deep IM injection	Deltoid or gluteal muscle Single, deep IM injection (not divided)	Gluteal muscle Single, deep IM injection (not divided)	Deltoid or gluteal muscle Deep IM injection	Abdominal subcutaneous injection	Gluteal muscle Deep IM injection	Deltoid (441 mg dose only) or gluteal muscle (all strengths) Deep IM injection
Overlap with oral formulation	None	None	None	None	3 weeks	None		3 weeks

	SECOND-GENERATION AGENTS (SGAs)**						THIRD-GENERATION AGENTS (TGAs)	
	Olanzapine pamoate[B] (Zyprexa Relprevv)	Paliperidone palmitate 1-monthly (Invega Sustenna)	Paliperidone palmitate 3-monthly (Invega Trinza)	Paliperidone palmitate 6-monthly (Invega Hafyera[B])	Risperidone (Risperdal Consta)	Risperidone RBP-7000 (Perseris)	Aripiprazole (Abilify Maintena)	Aripiprazole lauroxil[B] (Aristada)
Starting dose[1]	No pediatric studies Adults: For first 8 weeks: If previously on 10 mg/day oral = 210 mg IM q2 weeks or 405 mg q 4 weeks; 15–20 mg/day oral = 300 mg q2 weeks	No pediatric studies Adults: Day 1: 234 mg of paliperidone palmitate (150 mg of paliperidone (base)), Day 8: 156 mg of paliperidone palmitate (100 mg of paliperidone (base))	No pediatric studies Only to be used after treatment with paliperidone 1-monthly IM has been established as an adequate treatment for at least 4 months. Initiate paliperidone 3-monthly IM when the next paliperidone 1-monthly IM dose is due (+/- 7 days), using a 3.5-fold higher dose than that of the previous 1-monthly formulation injection	Only to be used after treatment with paliperidone 1-monthly IM has been established as an adequate treatment for at least 4 months OR after treatment with paliperidone 3-monthly IM has been established as an adequate treatment for at least 3 months Initiate paliperidone 6-monthly IM when the next paliperidone 1- or 3-monthly IM dose is due (+/- 7 days) Use the following conversions: PP1M 156 mg → PP6M 1092 mg PP1M 234 mg → PP6M 1560 mg PP3M 546 mg → PP6M 1092 mg PP3M 819 mg → PP6M 1560 mg	Adolescents: 25 mg q2 weeks	Depending on patient's needs: 90 mg corresponds to 3 mg/day of oral risperidone; 120 mg corresponds to 4 mg/day of oral risperidone	No pediatric studies Adults: 400 mg	No pediatric studies Adults: 10 mg/day oral = 441 mg IM q4 weeks; 15 mg/day oral = 662 mg IM q4 weeks; ≥20 mg/day oral = 882 mg IM q4 weeks
Usual dose range[1]	After first 8 weeks: If previously on 10 mg/day oral = 150 mg IM q2 weeks or 300 mg q4 weeks; 15 mg/day oral = 210 mg q2 weeks or 405 mg q4 weeks; 20 mg/day oral = 300 mg q2 weeks	117 mg of paliperidone palmitate (75 mg paliperidone (base)) q4 weeks 3 mg/day oral = 39–78 mg/month IM; 6 mg/day oral = 117 mg/month IM; 12 mg/day oral = 234 mg/month IM	273–819 mg paliperidone palmitate (175–525 mg paliperidone (base)) q3 months. Dose can be adjusted within the range every 3 months based on tolerability and/or efficacy	1092–1560 mg paliperidone palmitate q6 months. Dose can be adjusted within the range every 6 months based on tolerability and/or efficacy	25 mg q2 weeks 12.5 mg q2 weeks in patients with renal or hepatic impairment	90–120 mg q4 weeks Patients on stable oral risperidone doses < 3 mg/day or > 4 mg/day may not be candidates for injectable	160–400 mg q4 weeks (dose varies if known CYP2D6 poor metabolizer, or if taking strong 2D6 or 3A4 inhibitors – see monograph)	441–882 mg q4 weeks (dose varies if known CYP2D6 poor metabolizer, or if taking strong 2D6 or 3A4 inhibitors – see monograph)

Comparison of Long-Acting IM Antipsychotics* (cont.)

	SECOND-GENERATION AGENTS (SGAs)**						THIRD-GENERATION AGENTS (TGAs)	
	Olanzapine pamoate[B] (Zyprexa Relprevv)	Paliperidone palmitate 1-monthly (Invega Sustenna)	Paliperidone palmitate 3-monthly (Invega Trinza)	Paliperidone palmitate 6-monthly (Invega Hafyera[B])	Risperidone (Risperdal Consta)	Risperidone RBP-7000 (Perseris)	Aripiprazole (Abilify Maintena)	Aripiprazole lauroxil[B] (Aristada)
Maximum dose[I],[D]	300 mg q2 weeks; 405 mg q4 weeks	234 mg of paliperidone palmitate (150 mg paliperidone (base)) q4 weeks	819 mg paliperidone palmitate (525 mg paliperidone (base)) q3 months	1560 mg paliperidone palmitate q6 months	50 mg q2 weeks[E]	120 mg q4 weeks	400 mg q4 weeks	882 mg q4 weeks
Usual duration of action	2–4 weeks	4 weeks	3 months	6 months	2 weeks[F]	4 weeks	4 weeks	441 mg, 662 mg q4 weeks; 882 mg q4–6 weeks; 1064 mg q8 weeks
Pharmacokinetics								
Time to peak plasma level[G]	2–4 days	13 days	Median: 30–33 days	Median: 29–32 days	30 days	First peak: 4–6 h Second peak: 10–14 days	5–7 days	Not in monograph. Reaches systemic circulation after 5–6 days
Elimination half-life[H]	~30 days	25–49 days Increased in renal disease	Median: 84–95 days following deltoid injection, 118–139 days following gluteal injection	Median: 148–159 days	3–6 days Elimination complete by 7–8 weeks Increased in hepatic or renal disease	9–11 days	30 days (300 mg), 47 days (400 mg)	54–57 days
Time to steady state	2–3 months	2–3 months	?	?	2 months	By end of second injection	3–4 months	4 months
Adverse effects[I]: Generally similar to oral drugs in same class	Olanzapine (see p. 220)	Paliperidone (see p. 220)	As per paliperidone 1-monthly IM, except where noted	As per paliperidone 1- and 3-monthly IM, except where noted	Risperidone (see p. 220)	Risperidone (see p. 220)	Aripiprazole (see p. 220)	Aripiprazole (see p. 220)

	SECOND-GENERATION AGENTS (SGAs)**						THIRD-GENERATION AGENTS (TGAs)	
	Olanzapine pamoate[B] (Zyprexa Relprevv)	Paliperidone palmitate 1-monthly (Invega Sustenna)	Paliperidone palmitate 3-monthly (Invega Trinza)	Paliperidone palmitate 6-monthly (Invega Hafyera[B])	Risperidone (Risperdal Consta)	Risperidone RBP-7000 (Perseris)	Aripiprazole (Abilify Maintena)	Aripiprazole lauroxil[B] (Aristada)
Skin and local reactions	At injection site: Pain, induration or site mass $\leq$ 3.6%; dorsal trunk rash reported in one adolescent who continued olanzapine after brief steroid therapy with no reoccurence	At injection site: Pain, redness, swelling or induration $\leq$ 10% (more common with 1st injection; reduced incidence with subsequent injections)	At injection site: Pain, redness, and swelling 2%	At injection site: Pain, redness, and swelling 11%, worse at the first one	At injection site: Pain, redness, swelling or induration over 10% [ensure solution is at room temperature and inject into alternate buttocks]	At injection site: Erythema (5,2%), pain (19%) (decreased frequency and intensity with subsequent injections)	At injection site: Pain, redness, swelling, or induration: 6.3% (decreased frequency and intensity with subsequent injections)	At injection site: Pain (2–4%), induration $\leq$ 1%

** See the relevant sections in "Second-Generation Antipsychotics/SGAs" (pp. 175—192) for further information [1] For schizophrenia and related psychotic disorders. See Dosing section p. 180 for dosing in renal and hepatic impairment, [B] Not marketed in Canada, [D] Typical maximal doses based on product monographs. Some clinicians may use higher doses if they are effective with minimal adverse effects, [E] Maximum dose suggested by manufacturer. Increase in adverse effects without any increase in efficacy reported with 75 mg q2 weeks, [F] Primary data on 50 mg q4 weeks dosing,[91, 92] [G] Important as indicator when maximum adverse effects will occur, [H] Useful for determining dosing interval; steady state will be reached in approximately 5 half-lives, [I] Incidences are not from head to head trials of agents thus incidences may not be comparable

Note: qX weeks = every X weeks

Switching Antipsychotics

Switching Antipsychotics*

Reasons for Considering a Switch

- A switch may be considered in cases of nonresponse, partial or less than optimal response, or relapse despite adherence. Motivating factors may include:
  - Persistent positive symptoms (consider a FGA or a SGA; switching to clozapine may offer additional response in up to a further 50% of patients)
  - Persistent negative symptoms (consider alternate SGA or TGA, lower dose)
  - Persistent cognitive or affective symptoms (consider SGA)
  - Persistent suicidal ideation or behaviors (consider clozapine)
  - A request for change from patient or family member
  - A change in patient's medical or psychiatric condition warranting a change in treatment
- To relieve or decrease a bothersome adverse effect (e.g., sexual dysfunction, sedation, EPSE) or one that may be associated with short- or long-term morbidity (e.g., TD, metabolic effects). These are often major contributors to nonadherence and eventual treatment failure

When Switching Therapies:

- Reaffirm diagnosis and rationale for switching makes sense
- Address any confounding or complicating factors. For example:
  - Attempt to rule out partial adherence or nonadherence. If present, identify and address barriers to adherence if possible (e.g., some adverse effects may be resolved by lowering the dose, changing the administration schedule or waiting for tolerance to develop)
  - Ensure adequate trial period was employed – adequate dose for adequate duration [at least 4–6 weeks at maximally tolerated dose (longer for clozapine)]
  - Determine if any drug interactions may be impacting efficacy or adverse effects
  - Determine if substance use disorder or psychosocial stressors may be confounding response

* Canadian healthcare professionals may find the website https://www.switchrx.com helpful.

Switching Antipsychotics (cont.)

  - Give thoughtful consideration to the pros and cons of making a change
  - Establish a thorough plan including how to make the switch and what to expect. How long will it take to work? What unwanted effects might occur and how to monitor for them
  - Confirm the patient is agreeable to the change and discuss the switching plan with them
- Potential problems that may be anticipated during a switch are:
  - Withdrawal effects related to discontinuation of the initial antipsychotic
  - Adverse effects that result from the addition of a new agent
- These, coupled with a time lag to response, may discourage the patient and negatively impact on adherence unless the patient is educated as to what to expect

Withdrawal Effects

- Abrupt withdrawal of an antagonist medication leads to sensitized receptors, leaving them potentially vulnerable to excessive stimulation. This may result in:
  - Dopaminergic rebound – if a high D_2 affinity medication (e.g., risperidone) is abrupty replaced with a low D_2 affinity medication or a rapid on/off fast-dissociating antipsychotic (e.g., quetiapine) or a partial D_2 agonist (e.g., aripiprazole), dopaminergic rebound may result. In the mesolimbic tract, this could lead to supersensitivity psychosis; in the nigrostriatal tract, treatment-emergent EPSE and TD may materialize
  - Cholinergic rebound – if a high-affinity cholinergic antagonist (e.g., olanzapine) is abruptly replaced by an antipsychotic with little affinity for blocking cholinergic receptors, cholinergic rebound may ensue, causing the patient to complain of flu-like symptoms such as nausea, vomiting, diarrhea, diaphoresis, and insomnia
  - Histaminic rebound – abrupt replacement of a high-affinity histamine blocker (e.g., clozapine) with a low-affinity agent (e.g., aripiprazole) may see improvement in several metabolic parameters such as weight gain, glucose intolerance, and dyslipidemias. Sedation may also improve, but some individuals may experience distressing rebound insomnia which may be interpreted as a sign of relapse
  - Serotonergic rebound – it has been suggested that abrupt discontinuation of a high-affinity serotonin 5-HT_{2A} antagonist may result in serotonin syndrome (agitation, diaphoresis, fever, tremor, confusion, etc.) or NMS-like symptoms
  - In the absence of any strong scientific evidence, empirical recommendations favor a slow cross-taper method to minimize rebound and the addition/continuation of adjunctive treatments (e.g., anticholinergics for cholinergic rebound or benzodiazepines for insomnia) when necessary

Switching Methods

- Four options (no clear evidence to support one method over another)
  1. Washout/start:
     - Withdraw the first drug gradually and begin the second drug following a suitable washout period. May minimize withdrawal-emergent reactions. Not clinically practical when patient is symptomatic. May increase the risk of relapse
  2. Stop/start:
     - Abruptly discontinue the first drug, then start the second drug at its usual initial dose; increase the dose to a therapeutic range accordingly. This technique is often used when the patient has a significant/serious adverse reaction to the initial drug (e.g., agranulocytosis, NMS, ketoacidosis). Potential drawbacks include an increased risk of relapse and withdrawal-emergent reactions
  3. Cross-taper:
     - Taper the dose of the first medication while simultaneously increasing the dose of the second drug. Commonly used when stable patients are experiencing bothersome adverse effects and require a medication change. The duration of the cross-titration is usually between 1 and 4 weeks. Generally the most well accepted or preferred strategy, thought to minimize the potential for withdrawal-emergent effects and relapse. Drawbacks of this strategy include an increased risk of relapse should the patient spend time with subtherapeutic doses of both antipsychotics, an increased risk of polypharmacy should the patient improve during the switch and the practitioner become reluctant to make further changes, and an increased risk of additive or synergistic effects from both drugs
  4. Delayed withdrawal:
     - Establishing the patient on a therapeutic dose of the second drug before reducing the existing medication. The strategy may be preferred in situations for which relapse is a significant concern. There is an increased risk for polypharmacy with this method if the changeover is not completed. There is also an increased risk of additive or synergistic effects from both drugs during the procedure
- Rate of switching/cross-tapering should be slow in young patients

Antipsychotic Augmentation Strategies

Augmentation Strategies

- The addition of another pharmacological agent or treatment to an antipsychotic in an attempt to augment or improve the response to the initial antipsychotic
- The ultimate goal is to combine different mechanisms of action to create a synergistic effect that will enhance efficacy while minimizing the potential for increased adverse effects and drug interactions
- A recent meta-analysis in schizophrenia showed that adding a second antipsychotic resulted in a moderate effect size for overall symptom reduction[93]
- Most of the literature on augmentation strategies evaluates augmentation of clozapine therapy, the assumption being that monotherapy with clozapine would often be attempted first before less well-studied alternatives such as augmentation strategies with other antipsychotics would be employed. There are still circumstances in which augmentation of other antipsychotics may be considered before a clozapine trial. In many of these cases, the target symptom is something other than residual psychotic symptoms – e.g., benzodiazepines for agitation and hostility, antidepressants for depressive symptomatology, mood stabilizers for affective lability
- An estimated one third of individuals with schizophrenia do not achieve an adequate response to antipsychotic treatment. The superiority of clozapine in treatment-resistant schizophrenia is well established. Approximately 30–60% of individuals with treatment-resistant schizophrenia will respond to clozapine. A number of strategies have been proposed to augment clozapine in treatment-resistant schizophrenia. There is currently insufficient evidence (small number of studies; study design issues - few RCTs, small sample sizes, industry sponsors; conflicting outcomes; etc.) to endorse any of these
- Before concluding that a trial of clozapine monotherapy has been unsuccessful, the following considerations are suggested:
  - An adequate trial has been employed for at least 3 months
  - Obtain clozapine plasma concentration larger than 350 ng/mL (do not exceed 1000 ng/mL)
  - Rule out contributions from CYP1A2 mediated drug–drug interactions (e.g., omeprazole, carbamazepine, smoking)
  - Rule out nonadherence (including partial adherence) to clozapine
  - Rule out substance use disorder as a contributing factor
  - Rule out presence of an untreated depression
  - Rule out inadequate dosing
- Should a decision to employ an augmentation strategy be made, a detailed plan should be documented that clearly states the agent to be used, the planned dosage strategy, the target symptoms to be evaluated, and the anticipated time to see effect/trial period (e.g., 3–4 months), and how and when to monitor for efficacy and safety. The plan should also include a strategy for discontinuing the augmenting agent should it prove to be ineffective. An adequate trial period of at least 10 weeks has been suggested when augmenting clozapine with a second antipsychotic
- An overview of augmentation strategies is presented below
- In addition to the information provided below, refer to the corresponding drug interaction section

Anticonvulsants

Carbamazepine

- The available evidence does not support the routine use of carbamazepine for augmentation of antipsychotic treatment of schizophrenia. Carbamazepine augmentation was shown inferior to monotherapy in schizophrenia[94]
- In particular, carbamazepine may decrease antipsychotic concentrations through CYP1A2, 2D6, 3A4, and UGT induction and may increase risk for agranulocytosis[95] (see Drug Interactions p. 197)

Lamotrigine

- A meta-analysis of five RCTs reported modest benefit in 20–30% of clozapine-resistant patients following augmentation with lamotrigine versus placebo
- A review from the Cochrane Collaboration concluded that there was evidence of a marginal beneficial effect on some psychotic symptoms with the addition of lamotrigine, but that the current evidence was not sufficient to recommend the routine addition of lamotrigine in treatment-resistant schizophrenia
- Caution – one case report of a tripling in the clozapine level with the addition of lamotrigine, the mechanism of this potential drug interaction is unknown
- Caution – both lamotrigine and clozapine have the potential to depress bone marrow function

Antipsychotic Augmentation Strategies (cont.)

Topiramate

- No data in antipsychotic augmentation in children or adolescents
- A meta-analysis of topiramate co-treatment showed that it outperformed comparators with a moderate effect size. Subgroup analysis showed that nonblinded studies, studies involving combination with a non-clozapine antipsychotic, co-starting with the antipsychotic, trial duration of more than 12 weeks, mixed in-/outpatient populations, Asian trial site, and lower-dose topiramate were associated with higher responses[96]

Valproic acid

- There is conflicting evidence regarding the use of valproic acid as augmentation agent. Case reports suggest benefit in refractory patients on clozapine. A meta-analysis of five RCTs examining valproate as an add-on to various antipsychotics did not report beneficial results
- Caution – there are conflicting reports that valproic acid may increase serum clozapine levels as well as risk of myocarditis and worsen the severity of weight gain (see Drug Interactions p. 198)

Antidepressants

- TCAs, SSRIs, mirtazapine, and MAOIs reported to decrease negative symptoms, poor social or work functioning in some patients. Benefits may be due to improvements in secondary (vs. primary) negative symptoms
- A recent meta-analysis showed that antidepressant augmentation compared to placebo resulted in a decrease in total symptoms of schizophrenia, mainly driven through negative symptomatology. The effect size was small[97]

Benzodiazepines

- Used primarily to calm acutely agitated patients early in treatment
- A review from the Cochrane Collaboration concluded that there was no evidence to support a beneficial effect of benzodiazepines as adjunctive therapy to antipsychotics to alleviate positive symptoms of schizophrenia. The only significant effect noted was short-term sedation
- Caution – reports of cardiorespiratory collapse, delirium, loss of consciousness, and death with the combination of benzodiazepines and clozapine. In many cases, the incidences occurred shortly after the addition of clozapine to existing benzodiazepine treatment. Also, reports of cardiorespiratory depression with the combination of parenteral benzodiazepines and olanzapine IM (see Drug Interactions p. 202).

Combination Antipsychotics

- While mostly supported by open-label but not double-blinded trials, polypharmacy with antipsychotics may be necessary. An evidence-supported algorithm in the treatment of schizophrenia that involves combination antipsychotics would be (assuming inefficacy, not intolerance)[98]:
  1. initiate monotherapy with a non-clozapine antipsychotic
  2. switch to another non-clozapine antipsychotic
  3. switch to clozapine monotherapy
  4. augment with partial dopamine agonist
  5. switch partial dopamine agonist augmentor for a dopamine antagonist augmentor
  6. consider non-clozapine antipsychotic polypharmacy or switching back to monotherapy
- A 2017 Cochrane review from mostly short-term trials found very low evidence that combination of antipsychotics may improve clinical response in schizophrenia, prevent relapse, or cause more serious adverse events than monotherapy
- Decreasing the dose of clozapine and adding quetiapine has also been reported to decrease weight and improve glucose regulation

Electroconvulsive Therapy

- A retrospective review of 28 adolescents taking clozapine (n = 12) or another antipsychotics or benzodiazepine (n = 16) demonstrated similar response rates (67% and 69%, respectively) when combined with ECT. Rehospitalization rates were lower in clozapine-treated group after one-year follow-up. Charges needed to induce seizures were similar between groups[99]
- A long-term effectiveness study of adolescents (n = 21) with schizophrenia spectrum disorder who were either resistant to antipsychotics or had catatonia initiated ECT. These patients were matched against patients with schizophrenia who did not undergo ECT. Positive, negative, and clinical impression was not found to be different between groups[100]
- Benefits may not be sustained upon discontinuation of ECT and the risk-to-benefit ratio of maintenance ECT in this population is unknown

Ethyl Eicosapentaenoic Acid (E-EPA) or Omega-3 Fatty Acids

- Suggested to exert augmenting effect by inhibiting phospholipase-A_2, an enzyme found to be overactive in patients with schizophrenia (see p. 414)
- Two small studies evaluating the benefit of 3 g/day E-EPA on adults with schizophrenia/schizoaffective disorder with residual symptoms despite antipsychotic treatment yielded mixed results
- May have a beneficial effect on elevated triglyceride levels
- The purity and consistency among products may not be reliable

Lithium

- Caution – reports of increased potential for neurotoxic reactions (e.g., NMS-like syndrome) with the combination of lithium and mainly haloperidol – controversial (see Drug Interactions p. 203 and p. 173)
- There are case reports of beneficial effects from a combination of lithium and clozapine in patients with schizophrenia and schizoaffective disorder. A double-blind study reported that the combination of lithium and clozapine was effective in patients with schizoaffective disorder but not in those with schizophrenia
- A 2015 Cochrane meta-analysis showed only low-quality evidence that lithium is effective as an augmentation agent; these effects were dependent on open-label studies
- Mild leukocytosis caused by lithium may allow some patients taking clozapine with borderline hematological counts to remain on clozapine

Memantine

- No data in antipsychotic augmentation in children or adolescents
- Various meta-analyses in adult populations suggest adjunctive memantine (NMDA antagonist) to be beneficial for positive, negative, and neurocognitive symptoms

Selegiline

- No data in antipsychotic augmentation in children or adolescents
- A case report and a number of small open-label trials reported improvement in negative symptoms of schizophrenia following the augmentation of antipsychotic therapy with selegiline
- These findings were not supported by two controlled trials that showed either no benefit or benefit that was not deemed clinically significant. Currently low-dose selegiline cannot be recommended as augmentation treatment for negative symptoms

Stimulants

- E.g., dextroamphetamine, methylphenidate, modafinil
- Transient improvement in negative symptoms and cognitive function reported; effect size is small
- Exacerbation of positive symptoms can occur

Further Reading

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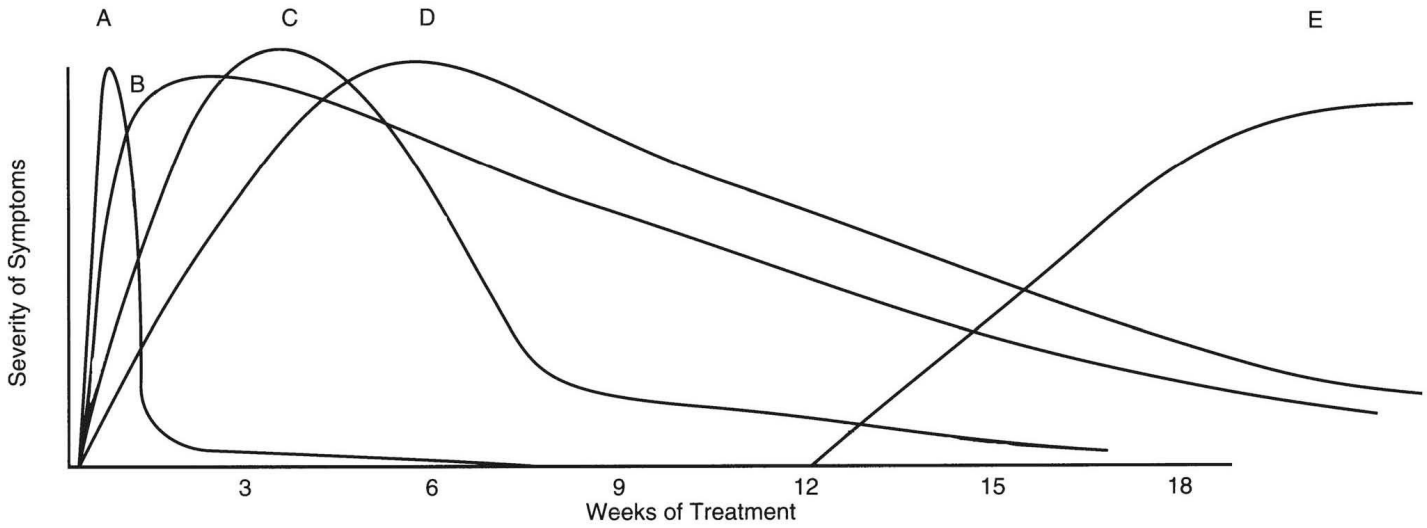
ANTIPSYCHOTIC-INDUCED EXTRAPYRAMIDAL SIDE EFFECTS (EPSE) AND THEIR MANAGEMENT

Extrapyramidal Side Effects of Antipsychotics

	Acute Extrapyramidal Side Effects	Tardive Syndromes
Onset	• Acute or insidious (within hours to 1 month (50–75%) or within 3 months (90%) of initiation or dosage increase of antipsychotic)	• After 3 months or years of treatment, especially if drug dose decreased or discontinued • Tend to persist for years or decades
Proposed mechanism	• Most EPSE are due to dopamine (D_2) blockade (if > 80%); decreased dopamine concentrations in the nigrostriatal pathway of the striatum • Acute dystonia due to cholinergic overactivity suggested by response to anticholinergics • Pisa syndrome due to cholinergic-dopaminergic imbalance • Akathisia due to dopaminergic-serotonergic/noradrenergic imbalance	• Precise pathophysiology remains unclear • Dopamine receptor hypersensitivity likely a main mechanism; upregulation and supersensitivity of postsynaptic dopamine receptors induced by long-term blockade • Neurotoxic effects of free radicals produced by the metabolism of excessive compensatory dopamine release, coupled with impairment of the antioxidant system • Glutamate-associated excitotoxicity • GABA dysfunction in the globus pallidus/substantia nigra • Multiple genetic associations related to schizophrenia, the dopamine system, metabolism of antipsychotics and free radicals (Nur77 deletion, ICOMT, DRD2, CYP1A2, IP5K2A gene polymorphisms) • Cholinergic deficiency
Treatment	• Discontinue offending antipsychotic • If discontinuation is not possible, lower antipsychotic dose • Change antipsychotic to SGA with lower risk (e.g., quetiapine, clozapine) • Taper concurrent medications that can induce pseudoparkinsonism (e.g., valproic acid, lithium) or akathisia (e.g., SSRI) • Anticholinergic drugs (e.g., benztropine, trihexyphenidyl): FDA and Health Canada approved • Amantadine: FDA and Health Canada approved; similar benefit as benztropine, and trihexyphenidyl in small, adult RCTs. May be preferred in patients with comorbid TD (does not worsen TD) • See p. 249 • There is insufficient evidence in pediatric patients to support the long-term use of anticholinergics for antipsychotic-induced EPSE • Akathisia may be mediated by different mechanisms and therefore more responsive to other treatments (e.g., benzodiazepines, β-blockers – see p. 255).	• No agents or strategies with proven efficacy in the treatment of tardive syndromes in children or adolescents • Consider the severity of tardive dyskinesia (TD), the degree of distress, and potential risks and benefits of any treatment strategy before taking action • Early recognition and discontinuation of the offending antipsychotic is the best approach where feasible. If discontinuation is not possible, lower antipsychotic dose • However, the success of dosage reduction or cessation has not been proven and must be weighed against the risk of relapse[1] • Switching to clozapine has also been recommended • Antipsychotic discontinuation can worsen TD (for weeks or months) in patients with long-standing tardive dyskinesia; antipsychotic dosage increase can suppress TD in the short term • Discontinue anticholinergic drug if taking concurrently • The waxing/waning nature of TD over time may bias placebo-controlled studies examining the effectiveness of antipsychotics in treating TD in favor of the antipsychotic and make interpretation of the results difficult

	Acute Extrapyramidal Side Effects	Tardive Syndromes
		• Best evidence for TD efficacy in adults for vesicular monoamine transporter type 2 (VMAT2) inhibitors: – Deutetrabenazine: FDA approved in 2017 for treatment of tardive dyskinesia in adults – Valbenazine: FDA approved in 2017 for treatment of tardive dyskinesia in adults[2] • Lower evidence for efficacy in adults (in alphabetical order): • Amantadine: weak evidence – two small RCTs in adults showed TD symptom improvement • Anticholinergic agents: no benefit and may worsen TD. May benefit tardive dystonia • Benzodiazepines: conflicting results from a few small trials; poorly reported and very low quality • β-blockers: insufficient evidence regarding efficacy in tardive akathisia • Botulinum toxin: limited studies with conflicting results – botulinum toxin has been shown to benefit patients with focal symptoms – cervical dystonia and involuntary tongue protrusion in case reports. A small single-blinded study failed to show benefit in orofacial TD overall but showed benefit in patients with no change in their antipsychotic • Branched-chain amino acids: limited evidence demonstrating potential benefit in children and adolescents, and in adult males • Clonidine: insufficient evidence – few studies, small number of patients, poor methodology • Electroconvulsive therapy (ECT): newer case reports and a retrospective study showed improvement in TD but older case reports show conflicting results – worsening TD, emergence of TD, or no change in TD • Fluvoxamine: case reports for TD and tardive akathisia • GABA agonists (baclofen, sodium valproate): no strong evidence to support use. Adverse effects likely outweigh any possible benefits • Ginkgo biloba: one randomized DBPC study (157 patients) showed significant improvement in TD in adults with dose of 240 mg/day • Levetiracetam: one small RCT (50 patients) showed significant improvement in TD in adults with dose of 500–3000 mg/day; however, high dropout rate due to psychiatric disorientation, non-adherence, etc. • Melatonin: two small RCTs showed significant improvement in TD in a few adults with doses of 10 and 20 mg/day • Pallidal deep brain stimulation: open-label trials; reserved for severe, disabling, refractory cases • Pyridoxine (vitamin B_6): low-quality evidence – 1 small (15 patients) DBPC crossover study reported benefit. A more recent larger 26-week RCT (50 patients) in adults reported a reduction in TD with 1200 mg/day • Tetrabenazine: a number of small trials with design issues suggesting potential benefit in adults. Duration of treatment and significant adverse effect profile are concerns. TD relapsed in most patients once drug withdrawn. Inconvenient three times daily dosing vs. deutetrabenazine (twice daily) and valbenazine (once daily) • Vitamin E: most studied antioxidant for TD. No evidence of improving TD; limited and contradictory evidence that it may protect against further deterioration. Patients with TD for less than 5 years may respond better • Zolpidem: three case reports in adults • See p. 247 for additional information on potential treatments

Extrapyramidal Side Effects of Antipsychotics (cont.)



A: Dystonic reactions: uncoordinated spastic movements of muscle groups (e.g., trunk, tongue, face)
B: Akathisia: restlessness, pacing (may result in insomnia)
C: Bradykinesia: decreased muscular movements
Rigidity: coarse muscular movement; loss of facial expression
D: Tremors: fine movement (shaking) of the extremities ("pill-rolling")
Rabbit syndrome: involuntary movements around the lips
Pisa syndrome: can either be acute or tardive in nature (rare; occurs more commonly in people with brain damage/abnormality)
E: Tardive syndromes: Symptoms of movement disorders that start about 3 months (or later) after therapy is initiated

Type	Physical (Motor) Symptoms	Psychological Symptoms	Onset	Possible Risk Factors	Clinical Course	Treatment Options	Differential Diagnosis
Acute akathisia	Motor restlessness, fidgeting, pacing, marching in place, shaking or rocking of legs and trunk, repeatedly crossing and uncrossing legs, inability to sit or lie still, shifting from foot to foot, rubbing face or moaning to relieve discomfort Respiratory symptoms: dyspnea or breathing discomfort	Restlessness, intense urge to move, irritability, agitation, violent outbursts, dysphoria, feeling "wound-up" or "antsy"; sensation of bugs crawling on/under skin Mental unease	Acute to insidious (within hours to days); 90% occur within first 6 weeks of treatment; sometimes only with higher doses or following rapid dose increase	Young adults High caffeine intake High-potency FGAs, TGAs; lower risk with SGAs Antipsychotic-naïve Rapid antipsychotic dose increase Antipsychotic polypharmacy Genetic predisposition Anxiety Comorbid mood disorder Microcytic anemia Low serum ferritin Concurrent use of SSRI (mostly at initiation of SSRI)	May continue through entire treatment if no drug changes made With discontinuation or lowered dose of offending drug, or treatment, will usually improve in days to weeks Increases risk of TD May contribute to risk of suicide and/or violence	Reduce dose of antipsychotic Stop antipsychotic polypharmacy Change antipsychotic (e.g., clozapine, olanzapine, quetiapine) Anticholinergic drugs: inconsistent evidence; do not use Treatment suggestions include: Benzodiazepines (e.g., clonazepam, diazepam, or lorazepam), β-blockers (e.g., propranolol), mirtazapine, cyproheptadine (preliminary reports), Vitamin B_6 Insufficient evidence: amantadine, apomorphine, clonidine, gabapentin, pregabalin, zolmitriptan Benzodiazepines may have a disinhibiting effect on some children	Psychotic agitation/decompensation Severe agitation Anxiety Substance intoxication Drug-seeking behavior/withdrawal Excess caffeine intake Restless legs syndrome
Acute dystonias	Torsions and spasms of muscle groups; muscle spasms, e.g., oculogyric crisis, trismus, laryngospasm, torti/retro/antero-collis tortipelvis, opisthotonus, blepharospasm	Anxiety, fear, panic, dysphoria, repetitive meaningless thoughts	Acute (usually within 12–48 h after the first dose); 90% occur within 3–5 days of treatment	Young males, large muscle mass, children Antipsychotic naïve High potency FGAs (2–60%) (e.g., haloperidol); lower risk (2–3%) with SGAs and TGAs Injectable antipsychotic Rapid dose increase Lack/rapid withdrawal of prophylactic anticholinergic medication Previous dystonic reaction Hypocalcemia, hyperthyroidism, hypoparathyroidism Recent cocaine use Family history of dystonia	With discontinuation of offending drug and treatment, dystonia will usually improve within minutes to hours and remit completely within hours to days Acute, painful, spasmodic; oculogyria may be recurrent Acute laryngeal/pharyngeal dystonia may be potentially life threatening	IM/PO diphenhydramine or IM/PO benztropine; repeat doses if no response within 30 min Sublingual lorazepam IV diazepam To prevent recurrence: treatment for 2–5 days, prophylactic co-administration of antipsychotic with anticholinergic drug, reduce dose or change antipsychotic to a low-potency SGA/TGA less likely to induce EPSE. Note: Pediatric patients may be more sensitive to antidyskinetic agents than adults	Seizures Catatonia Somatic symptom disorder Factitious disorder Hypocalcemia Primary genetic disorders Neurodegenerative disorders

Extrapyramidal Side Effects of Antipsychotics (cont.)

Type	Physical (Motor) Symptoms	Psychological Symptoms	Onset	Possible Risk Factors	Clinical Course	Treatment Options	Differential Diagnosis
Acute pseudo-parkinsonism	Stiffness, shuffling, mask-like face, "pill-rolling"-type tremor (4–8 cycles per second or hertz (Hz); greater at rest and bilateral), cogwheel rigidity, stooped posture, postural instability, micrographia, bradykinesia, drooling, loss of arm swing, unilateral symptoms	Slowed thinking Fatigue, anergia Cognitive impairment Depression	Acute to insidious (within 30 days) 90% occur within first 3 months of treatment	Female Older age High-potency FGAs; lower risk with SGAs and TGAs Higher doses (dose-dependent) Previous EPS caused by antipsychotics Longer duration of antipsychotic (36% for more than 6 months) Concurrent neurological disorder Adding second antipsychotic Discontinuation of anticholinergic drug HIV infection Concurrent drugs that may induce parkinsonism (e.g., lithium, metoclopramide, valproic acid, verapamil)	May continue through entire treatment if no drug changes made With discontinuation or lowered dose of offending drug, or treatment, will usually improve in days to weeks	Reduce dose or discontinue offending antipsychotic (can take months to resolve after discontinuation) Change antipsychotic (e.g., clozapine, quetiapine) Anticholinergic drug (e.g., benztropine, trihexyphenidyl) or amantadine Taper concurrent drugs (e.g., lithium, valproic acid) if antipsychotic must be continued	Mask-like face: negative symptoms of schizophrenia or depression Essential tremor Non-antipsychotic drug (e.g., lithium or valproic acid) induced tremor Parkinson's disease (elderly)
Pisa syndrome	Abnormally sustained leaning of the body and head to one side and slight axial rotation of the trunk; mild lateral curvature of the spine	Often ignored by patients	Can be acute or tardive	Female Older age Compromised brain function, dementia Past treatment with FGA Longer duration of antipsychotic Antipsychotic polypharmacy Parenteral antipsychotic Discontinuation of antipsychotic	With discontinuation or lowered dose of offending drug, or treatment, will usually improve in days to weeks	Reduce dose or discontinue offending antipsychotic Anticholinergic drug (higher doses)	Catatonia Conversion disorder Congenital scoliosis Neurological disease (e.g., Alzheimer's disease, multisystem atrophy)
Rabbit syndrome	Rhythmic, fine, rapid, and vertical-only tremor of the mouth/lips, resembling the chewing motion of a rabbit	Distress and embarrassment	After months of treatment	High-potency FGAs (e.g., haloperidol), SGAs (most commonly with risperidone), and TGAs	With discontinuation or lowered dose of offending drug, or treatment, will usually improve in days to weeks	Reduce dose or discontinue offending antipsychotic Change to SGA with stronger anticholinergic properties (e.g., clozapine, olanzapine, quetiapine) Anticholinergic drug Fluvoxamine (case report)	Organic disease (e.g., dopaminergic denervation of basal ganglia) Functional movement disorder Tardive dyskinesia (slow and arrhythmic; may involve tongue) Parkinsonism

Type	Physical (Motor) Symptoms	Psychological Symptoms	Onset	Possible Risk Factors	Clinical Course	Treatment Options	Differential Diagnosis
Tardive akathisia	Subtype of tardive dyskinesia Persistent (at least 1 month) symptoms of akathisia	As for akathisia, subjective sense of restlessness may be less intense	After months of antipsychotic (constant dose); after drug withdrawal	As for akathisia Coexisting tardive dyskinesia, dystonia, and iron deficiency	Persistent; early tapering and discontinuation of antipsychotic increases chance of remission. Fluctuating course	Discontinuation of antipsychotic (slow tapering); if discontinuation not possible, reduce dose Potential treatments (insufficient evidence for efficacy) include: switch to clozapine, anticholinergics, benzodiazepines, β-blockers (propranolol), fluvoxamine (case reports), zolpidem (case reports)	See akathisia
Tardive dyskinesia	Involuntary abnormal, repetitive, arrhythmic movements of: face (e.g., tics, frowning, grimacing), lips (pursing, puckering, smacking), jaw (chewing, clenching), tongue ("fly-catcher", rolling, dysarthria), eyelids (blinking, blepharospasm), limbs (tapping, twitching, "piano-playing" fingers or toes), trunk (rocking, twisting), neck (nodding), respiratory (dyspnea, gasping, sighing, grunting, forceful breathing, alternating hyperventilation and hypoventilation) Often coexists with parkinsonism and akathisia. Abnormal movements disappear during sleep. Can be suppressed on request; dyskinesias cease when patient speaks or brings food to the mouth	Cognitive impairment, distress (talking, swallowing, eating) and embarrassment	After 3 or more months of treatment in adults Common early sign is rapid flicking movement of the tongue ("fly-catcher tongue")	Female Older age Increased antipsychotic exposure (particularly FGA) Duration of antipsychotic Dose of antipsychotic History of severe or persistent EPSE early in treatment African American (confounded by receiving higher doses of antipsychotics than Caucasians) Intellectual disability, developmental delay/autism Lithium use, chronic use of high doses of anticholinergic drugs Affective disorder (especially depression) Diabetes Cognitive impairment/brain damage Alcohol/drug abuse may predispose to buccolingual masticatory symptoms HIV infection May be associated with genetic variation of the D_2 and D_3 receptor gene High homocysteine levels as seen in smokers	Persistent; early tapering and discontinuation of antipsychotic increases chance of remission (for long-standing TD, tapering or discontinuation of antipsychotic may worsen TD temporarily for weeks or months) Spontaneous remission in 14–24% after 5 years In children, great prognosis for spontaneous remission	Discontinuation of antipsychotic (slow tapering); if discontinuation not possible, reduce dose Discontinue anticholinergic drug if taking concurrently Switch to clozapine Treatment suggestions include (best evidence in adults): Valbenazine or deutetrabenazine Other treatment suggestions (low evidence in adults): Pyridoxine (vitamin B_6) 300–1200 mg/day Clonazepam 0.5–6 mg/day Tetrabenazine 50–150 mg/day Branched-chain amino acids (Tarvil, 222 mg/kg tid) Vitamin E 1200–1600 units/day	Spontaneous or withdrawal dyskinesia Stereotypic behavior Tourette's disorder Huntington's Chorea or other neurological conditions Movement disorder secondary to co-prescribed drug Systemic lupus erythematosus and other neuroimmune diseases Teeth, gum, tongue, mouth disorders (loose dentures) Drug toxicity (e.g., lithium, phenytoin)

Extrapyramidal Side Effects of Antipsychotics (cont.)

Type	Physical (Motor) Symptoms	Psychological Symptoms	Onset	Possible Risk Factors	Clinical Course	Treatment Options	Differential Diagnosis
Tardive dystonia	Subtype of tardive dyskinesia Sustained muscle contractions of face, eyes, neck, limbs, back, or trunk (craniocervical area involved most frequently), e.g., blepharospasm, laryngeal dystonia, dysarthria, retroflexed hands	Anxiety, fear, panic, dysphoria, repetitive meaningless thoughts	After months or years of treatment	Male Younger age Genetic predisposition Neurological disorder, intellectual disability Coexisting tardive dyskinesia Akathisia	Persistent; early tapering and discontinuation of antipsychotic increases chance of remission	Discontinuation of antipsychotic (slow tapering); if discontinuation not possible, reduce dose Switch to clozapine Treatment suggestions include: Higher doses of anticholinergics (e.g., trihexyphenidyl 40 mg/day); Tetrabenazine 50–150 mg/day; Botulinum toxin 25–50 units/site (multiple sites used); Baclofen For refractory tardive dystonia: bilateral pallidal deep brain stimulation	Myoclonus Motor tics Idiopathic dystonia Meige syndrome
Withdrawal emergent dyskinesia (withdrawal emergent syndrome)	Subtype of tardive dyskinesia Choreiform movements in limbs, trunk, and neck, resembling Sydenham's chorea Brief, abnormal movements flow from one muscle group to another in a random pattern	–	Abrupt antipsychotic discontinuation, dose reduction, or medication change	See tardive dyskinesia	Duration less than 4–8 weeks Disappears spontaneously	Self-limited (90% of cases) If movements are impairing, discontinued antipsychotic can be restarted and tapered over a longer period	See tardive dyskinesia

Monitoring Scales

- Akathisia: Barnes Akathisia Rating Scale (BARS), Extrapyramidal Symptom Rating Scale (ESRS)
- Dystonia: Extrapyramidal Symptom Rating Scale (ESRS)
- Pseudoparkinsonism: Simpson-Angus Extrapyramidal Side Effect Scale, Extrapyramidal Symptom Rating Scale (ESRS). American Psychiatric Association (APA) recommends monitoring weekly initially and until stable for 2 weeks, then at every follow-up visit
- Tardive dyskinesia: Abnormal Involuntary Movement Scale (AIMS), Extrapyramidal Symptom Rating Scale (ESRS). APA recommends monitoring every 3–12 months, depending on the patient's risk factors; usually every 6 months for FGA and every 12 months for SGA
- None of the scales are validated for pediatric use; nevertheless, they are useful in the pediatric population. Selection of the scale depends on physician preference. Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) recommends the use of ESRS since it assesses for all types of drug-induced movement disorders[3]

Treatment Options for Extrapyramidal Side Effects

Product Availability*

Generic Name	Chemical Class	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Amantadine	Dopamine agonist, NMDA receptor antagonist	Gocovri[B]	Extended-release capsules: 68.5 mg, 137 mg	Dosage recommendations available for children over age 1
		Osmolex ER[B]	Extended-release tablets: 129 mg, 193 mg	
		Symmetrel	Capsules/Tablets[B]: 100 mg Syrup: 50 mg/5 mL	
Benztropine	Anticholinergic	Cogentin	Tablets: 0.5 mg[B], 1 mg, 2 mg[B] Injection: 1 mg/mL	Contraindicated in children under age 3; use cautiously in older children
Clonazepam	Benzodiazepine	Klonopin[B], Rivotril[C]	Oral disintegrating tablets: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg	Dosage recommendations available for infants and children
Cyproheptadine	Antihistamine	Periactin	Tablets: 4 mg Syrup[B]: 2 mg/5 mL	Dosage recommendations available for children over age 2
Deutetrabenazine[B]	VMAT2 inhibitor	Austedo	Tablets: 6 mg, 9 mg, 12 mg	Safety and efficacy not established in children
Diazepam	Benzodiazepine	Diastat, Diastat Acudial[B]	Rectal gel: 5 mg/mL	Dosage recommendations available for infants and children
		Diazepam Intensol[B]	Oral concentrate: 5 mg/mL	
		Valium	Tablets: 2 mg, 5 mg, 10 mg Injection: 5 mg/mL Oral solution[B]: 1 mg/mL	
		Valtoco[B]	Nasal spray: 5 mg/spray, 7.5 mg/spray, 10 mg/spray	
Diphenhydramine	Antihistamine	Benadryl	Caplets/Capsules/Liquigels/Tablets[C]: 25 mg, 50 mg Chewable tablets[C]: 12.5 mg Elixir[C]: 12.5 mg/5 mL Oral liquid[C]: 6.25 mg/5 mL, 12.5 mg/5 mL, 50 mg/30 mL Injection: 50 mg/mL Injection (preservative-free): 50 mg/mL	Dosage recommendations available for infants and children
Ethopropazine[C]	Anticholinergic	Parsitan	Tablets: 50 mg	Safety and efficacy not established in children
Lorazepam	Benzodiazepine	Ativan	Tablets: 0.5 mg, 1 mg, 2 mg Sublingual tablets[C]: 0.5 mg, 1 mg, 2 mg	Oral: efficacy not established in children under age 12
			Injection: 2 mg/mL, 4 mg/mL	Injection: not recommended in children under age 18
		Lorazepam Intensol[B]	Oral concentrate: 2 mg/mL	Efficacy not established in children under age 12
		Loreev XR[B]	Extended-release capsules: 1 mg, 2 mg, 3 mg	Safety and efficacy not established in children
Orphenadrine	Antihistamine	Norflex	Extended-release tablets: 100 mg Injection[B]: 30 mg/mL	Safety and efficacy not established in children

Treatment Options for Extrapyramidal Side Effects (cont.)

Generic Name	Chemical Class	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Propranolol	β-blocker	Inderal	Tablets: 10 mg, 20 mg, 40 mg, 60 mg[B], 80 mg Oral solution[B]: 20 mg/5 ml, 40 mg/5 mL Injection: 1 mg/mL	Dosage recommendations available for children
		Inderal LA	Extended-release capsules: 60 mg, 80 mg, 120 mg, 160 mg	LA formulation: experience limited in children under age 12
		InnoPran XL[B]	Extended-release capsules: 80 mg, 120 mg	Safety and efficacy not established in children
Tetrabenazine	VMAT2 inhibitor	Nitoman[C], Xenazine[B]	Tablets: 12.5 mg[B], 25 mg	Safety and efficacy not established in children
Trihexyphenidyl	Anticholinergic	Artane	Tablets: 2 mg, 5 mg Elixir[B]: 2 mg/5 mL	Safety and efficacy not established in children
Valbenazine[B]	VMAT2 inhibitor	Ingrezza	Capsules: 40 mg, 60 mg, 80 mg	Safety and efficacy not established in children

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications related to EPSE for these agents

In adults:

To relieve the neurological (muscular) side effects induced by antipsychotics (see p. 255 for comparison of drugs):

- 👍 Pseudoparkinsonian effects (tremor, rigidity, shuffling) (benztropine, trihexyphenidyl – Canada and USA; amantadine, diphenhydramine injection – USA)
- 👍 Drug-induced extrapyramidal reactions (amantadine, benztropine, trihexyphenidyl – Canada and USA)
- 👍 Essential tremor (propranolol – USA)
- 👍 Tardive dyskinesia (deutetrabenazine, valbenazine – USA; tetrabenazine – Canada)
- 👍 Musculoskeletal conditions – acute, painful (orphenadrine – Canada and USA)

General Comments

- Because of the acute onset and distressing nature of acute dystonic reactions, IM benztropine or diphenhydramine is typically the preferred treatment and usually brings relief within 15 min
- Anticholinergic agents can impair cognition when used in children and adolescents during school and periods of learning
- Controversy exists whether anticholinergic agents should be given prophylactically to patients at risk of developing EPSE with FGA drugs, or whether they should only be started when EPSE develop. The decision to initiate preventative agents should be made on an individual basis with consideration given to a number of factors including patient preference, history of EPSE, potential of the particular antipsychotic to induce EPSE, presence of comorbidities or concomitant medications, which may be exacerbated by anticholinergic effects
- There is a wide variance (e.g., 2–50%) in the reported incidence of antipsychotic-induced parkinsonian effects. Rates are higher in females and are dose related
- Consider dosage reduction or discontinuation of the offending antipsychotic agent (if appropriate) or switching to a newer generation antipsychotic as potential treatment option
- Doses up to 80 mg trihexyphenidyl have been employed in the treatment of hereditary dystonias in children; these were well tolerated with few side effects
- Preliminary evidence: mirtazapine (15 mg/day) has been studied in an RCT in adult patients with antipsychotic-induced akathisia and found to be similar in effect to propranolol (80 mg/day). Specifically, 43% of patients assigned to mirtazapine vs. 30% of those taking propranolol and 7% in the placebo group were considered to have responded by the investigators[4]

‡ Indications listed here do not necessarily apply to all agents for treating extrapyramidal side effects for all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Pharmacology

- Centrally-active anticholinergic drugs cross the blood-brain barrier, block excitatory muscarinic pathways in the basal ganglia, and restore the dopamine/acetylcholine balance disrupted by neuroleptic drugs, thus treating EPSE
- Five subtypes of muscarinic receptors have been determined; the M_1 and M_2 subtypes are the best characterized; the M_1 subtype is found centrally and peripherally, whereas the M_2 subtype is located in the heart
- Agents in order from highest to lowest affinity for the M_1 receptor as follows: Benztropine (0.2 nM), trihexyphenidyl (1.6 nM) [values in parentheses are K_i values as determined using cloned human receptors][5]
- Agents in order from highest to lowest affinity for the M_2 receptor as follows: Benztropine (1.4 nM), trihexyphenidyl (7 nM) [values in parentheses are K_i values as determined using cloned human receptors][5]
- Anticholinergic drugs also block presynaptic reuptake of dopamine (primarily benztropine), norepinephrine (primarily diphenhydramine), and serotonin (diphenhydramine, weakly)
- Amantadine has moderate NMDA (n-methyl-D-aspartate) receptor blocking properties; it may exert its anti-EPSE activity by increasing dopaminergic activity at postsynaptic receptors (facilitates presynaptic release and inhibits reuptake)
- Mirtazapine blocks 5-HT_{2A}, which may have beneficial effect on antipsychotic-induced akathisia but its α_2 blockade may cause akathisia
- Reversible vesicular monoamine transporter 2 (VMAT2) inhibitors reduce presynaptic storage and release of monoamines, particularly dopamine, which then are degraded by monoamine oxidase in cytoplasm, resulting in presynaptic dopamine depletion
- Agents in order from highest to lowest affinity for the VMAT2 receptor as follows: valbenazine (150 nM), tetrabenazine (100 nM)
- Deutetrabenazine is a deuterated form (substitution of deuterium for hydrogen) of tetrabenazine which allows for a longer half-life and less frequent daily dosing

Dosing

- See chart pp. 258–261
- Dosage increases must be balanced against the risk of evoking anticholinergic adverse effects
- Plasma level monitoring is not currently advocated
- Consider dosage reduction in CYP2D6 poor metabolizers or when given in combination with potent CYP2D6 and/or CYP3A4 inhibitors (valbenazine) or CYP2D6 inhibitors (deutetrabenazine)

Adverse Effects of Anticholi

- See chart pp. 256–258 for adverse effects of other agents for treating acute extrapyramidal side effects

CNS

- CNS effects: stimulation, disorientation, confusion, hallucinations, restlessness, weakness, incoherence, headache; cognitive impairment including decreased memory and distractibility
- Excess use/abuse may lead to an anticholinergic (toxic) psychosis with symptoms of disorientation, confusion, euphoria (see Toxicity p. 252), in addition to physical signs such as dry mouth, blurred vision, dilated pupils, dry flushed skin

Peripheral

- Related to anticholinergic potency (i.e., M_1 antagonism): Benztropine > trihexyphenidyl > diphenhydramine
- Common: Dry mouth, blurred vision, decreased bronchial secretions, constipation, dry eyes, flushed skin
- Occasional: Delayed micturition, urinary retention, sexual dysfunction
- Excess doses can suppress sweating, resulting in hyperthermia

Cardiovascular Effects

- Palpitations, tachycardia, and high doses can cause arrhythmias

GI Effects

- Nausea, vomiting, gastroesophageal reflux disease, paralytic ileus

Precautions

- Use anticholinergics cautiously in patients with conditions in which excess anticholinergic activity could be harmful (e.g., prostatic hypertrophy, urinary retention, narrow-angle glaucoma, myasthenia gravis, GI obstruction, arrhythmias)
- Anticholinergics may decrease sweating; educate and monitor patients taking these medications in hot weather to prevent hyperthermia. Monitor breathing patterns in patients with respiratory difficulties since anticholinergic medications can dry bronchial secretions and make breathing difficult
- If withdrawn abruptly, anticholinergic drugs may cause a cholinergic rebound: symptoms include restlessness, anxiety, dyskinesia, dysphoria, sweating, and diarrhea
- Euphorigenic and hallucinogenic properties may lead to abuse of anticholinergic agents

Treatment Options for Extrapyramidal Side Effects (cont.)

- Use of anticholinergic agents in patients with existing TD can exacerbate the movement disorder and may unmask latent TD
- Benztropine is contraindicated in children under the age of 3 years due to atropine-like adverse effects
- Amantadine should be used cautiously in patients with peripheral edema or history of congestive heart failure (there are patients who developed congestive heart failure while receiving amantadine); the clearance of amantadine is significantly reduced in patients with renal insufficiency
- VMAT2 inhibitors have precautions for QT interval prolongation, neuroleptic malignant syndrome, akathisia/agitation/restlessness, parkinsonism, hyperprolactinemia, sedation, and binding to melanin-containing tissues
- Tetrabenazine and deutetrabenazine are contraindicated in patients with suicidal ideation or inadequately treated depression (boxed warning). Tetrabenazine is contraindicated in patients with hepatic impairment

Toxicity

- Can occur following excessive doses, with combination therapy, in the elderly, or with drug abuse
- Symptoms of anticholinergic toxicity include:
  - Blind as a bat (mydriasis, blurred vision)
  - Dry as a bone (dry skin and mucous membranes, no sweating, urinary retention)
  - Hot as a stove (hyperthermia)
  - Mad as a hatter (confusion, delirium, hallucinations)
  - Red as a beet (flushed skin)
  - Sinus tachycardia, hypertension, decreased bowel sounds, muscle twitching, seizures, and coma may also occur

Management

- General guidelines:
  - Absorption may be delayed because of the pharmacological effects of anticholinergics on gastrointestinal motility. Effects of benztropine intoxication can persist for 2–3 days
  - Maintain an open airway and assist ventilation if required; cardiac and pulse oximetry monitoring
  - Decontamination with single-dose activated charcoal may be administered under appropriate conditions – delayed gut emptying and reduced peristalsis caused by anticholinergics may permit use of activated charcoal even when patients present hours post ingestion. Hemodialysis, hemoperfusion, and peritoneal dialysis are not effective in removing these agents
  - Following GI decontamination, many cases can be managed well with supportive care – e.g., control agitation (benzodiazepines); fever (fluids, antipyretics, active cooling measures); seizures (benzodiazepines); urinary retention (bladder catheterization); manage cardiac conduction disturbances

Use in Pregnancy◊

- Greatest risk of malformation during first trimester use
- Consider potential for withdrawal or other effects (e.g., metabolism) in newborn and effects on delivery during third trimester
- Limited human data with many of these agents
- See chart pp. 256–258

Breast Milk

- See chart pp. 256–258

Nursing Implications

- These drugs should be given only to relieve EPSE of antipsychotics; excess use or abuse can precipitate a toxic psychosis
- Akathisia usually does not respond to standard anticholinergic agents; propranolol, lorazepam, clonazepam, or mirtazapine can be tried
- Some adverse effects of anticholinergics are additive to those of some antipsychotics; observe patient for signs of side effects or toxicity
- Monitor patient's intake and output. Urinary retention can occur; bethanechol (Urecholine) can be used to reverse this effect if continued anticholinergic treatment is necessary
- To help prevent gastric irritation, administer drug after meals
- Relieve dry mouth by giving patient cool drinks, ice chips, sugarless chewing gum, or hard, (preferably sugar-free) sour candy. Suggest frequent rinsing of the mouth, and teeth should be brushed regularly. Patients should avoid calorie-laden beverages and sweet candy as they increase the likelihood of dental caries and promote weight gain. Products that promote or replace salivation (e.g., Biotene, MoiStir, Saliment) may be of benefit

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

- Blurring of near vision is due to paresis of the ciliary muscle. This can be helped by wearing suitable glasses, reading by a bright light, or, if severe, by the use of pilocarpine eye drops
- Dry eyes may be of particular difficulty to those wearing contact lenses. Contact lens wetting solutions may be of benefit in dealing with this problem
- Anticholinergics reduce peristalsis and decrease intestinal secretions, leading to constipation. Increasing fluids and bulk (e.g., bran, salads) as well as fruit in the diet is beneficial. If necessary, laxatives (e.g., psyllium, senna, or PEG 3350) can be used; PEG 3350 or lactulose may be used for chronic constipation
- Warn the patient not to drive a car or operate machinery until response to the drug has been determined
- Appropriate patient education regarding medication and side effects is necessary prior to discharge

Patient Instructions

- For detailed patient instructions on anticholinergic agents for treating extrapyramidal side effects, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Only clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent
- For drug interactions associated with benzodiazepines, please see p. 270

Class of Drug	Example	Interaction Effects
Adsorbent	Activated charcoal, antacids, cholestyramine, kaolin-pectin (attapulgite)	Oral absorption decreased when used simultaneously
Antiarrhythmic	Digoxin	Valbenazine: Concomitant use increased digoxin levels due to inhibition of intestinal P-glycoprotein
Anticholinergic	Antidepressants, antihistamines, FGAs (low potency)	Anticholinergic agents: Increased atropine-like effects causing dry mouth, blurred vision, constipation, etc. May produce inhibition of sweating and may lead to paralytic ileus, urinary retention High doses can bring on a toxic psychosis
Anticonvulsant	Carbamazepine, phenytoin	Valbenazine: Decreased exposure to valbenazine and its active metabolite due to CYP3A4 induction; may reduce efficacy
	Divalproex, valproic acid	Trihexyphenidyl: Case report of decreased valproic acid level to below therapeutic range causing increased seizures
	Topiramate	Anticholinergic agents: May potentiate the risk of oligohidrosis and hyperthermia in children
Antidepressant		
SSRI	Fluoxetine, paroxetine	Case reports of reversal of antidepressant and antibulimic effects of fluoxetine and paroxetine with cyproheptadine (a serotonin receptor antagonist, used in serotonin syndrome treatment protocols) Increased plasma level of procyclidine (by 40%) with paroxetine Valbenazine and deutetrabenazine: Increased exposure to the active metabolites due to CYP2D6 inhibition
NDRI	Bupropion	Case reports of neurotoxicity in combination with amantadine (in elderly patients; no information in children and adolescents) Valbenazine and deutetrabenazine: Increased exposure to the active metabolites due to CYP2D6 inhibition
Tricyclic	Desipramine	Tetrabenazine: Central excitation and possibly hypertension
MAOI	Isocarboxazid, phenelzine, selegiline	Deutetrabenazine, tetrabenazine: Central excitation and possibly hypertension. Wait at least 14 days in between use due to risk of hypertensive crisis Valbenazine: Concomitant use may increase the concentration of monoamine neurotransmitters in synapses, potentially increasing risk of serotonin syndrome, or attenuating treatment effect of valbenazine
Antihypertensive	Hydrochlorothiazide, triamterene	Reduced renal clearance of amantadine resulting in drug accumulation and possible toxicity

Treatment Options for Extrapyramidal Side Effects (cont.)

Class of Drug	Example	Interaction Effects
Antipsychotic	Aripiprazole, clozapine, haloperidol, olanzapine, trifluoperazine, etc.	Anticholinergic drugs may aggravate tardive dyskinesia or unmask latent TD Additive anticholinergic effects may occur, resulting in paralytic ileus, hyperthermia, heat stroke, and anticholinergic intoxication syndrome Tetrabenazine: May increase risk of NMS and extrapyramidal disorder
	Thioridazine	Propranolol may significantly increase thioridazine levels or cause arrhythmias Potential for additive hypotensive effects with propranolol
Caffeine		May offset beneficial effects of anti-EPSE treatment by increasing tremor and akathisia
Cholinesterase inhibitor	Donepezil, rivastigmine	Benztropine, diphenhydramine: Antagonism of effects
Herbal preparation	Hawthorn, kava kava, Siberian ginseng, valerian	Diphenhydramine: May increase effects of diphenhydramine. May enhance CNS depression
	Henbane	Diphenhydramine: Increased anticholinergic effects with combination
Nonselective VMAT inhibitor	Reserpine	Tetrabenazine: Contraindicated. Reserpine binds irreversibly to VMAT2 and duration of effects is several days
Opioid	Codeine, methadone, tramadol	Anticholinergic agents: Additive CNS effects including cognitive and psychomotor impairment Diphenhydramine: May interfere with analgesic effect of codeine due to reduced conversion of codeine to morphine via CYP2D6 inhibition
	Methadone, tramadol	Diphenhydramine: Additive respiratory depressant effects
QTc prolonging medications	Antipsychotics (chlorpromazine, haloperidol, ziprasidone), antibiotics (moxifloxacin), Class 1A (quinidine, procainamide), and Class III antiarrhythmic medications (amiodarone, sotalol)	Tetrabenazine: Possible additive QTc prolongation Deutetrabenazine, valbenazine: Possible additive QTc prolongation at higher doses

Effects on Extrapyramidal Side Effects

Agent	Tremor	Rigidity	Dystonia	Akinesia	Akathisia
Amantadine (Gocovri[B], Osmolex ER[B], Symmetrel)	++	++	+	+++	++
Benztropine (Cogentin)	++	+++	+++	++	++
β-blockers (e.g., Propranolol)	++	–	–	–	+++
Clonazepam (Klonopin[B], Rivotril[C])	–	+	+	–	+++
Cyproheptadine (Periactin)	–	–	–	–	+++
Diazepam (Diastat[B], Diazepam Intensol[B], Valium, Valtoco[B])	+	++	+++	+	+++
Diphenhydramine (e.g., Benadryl)	++	+	++	–	+++
Lorazepam (Ativan, Lorazepam Intensol[B], Loreev XR[B])	+	+	+++	–	+++
Trihexyphenidyl (Artane)	+	++	++	+++	++

[B] Not marketed in Canada, [C] Not marketed in the USA

Based on adult literature and clinical observations: – effect not established, + some effect (20% response), ++ moderate effect (20–50% response), +++ good effect (over 50% response)

Comparison of Agents for Treating Acute Extrapyramidal Side Effects

Agent	Therapeutic Effects	Adverse Effects	Pregnancy	Breast Milk
Amantadine (Gocovri[B], Osmolex ER[B], Symmetrel)	May improve akathisia, akinesia, rigidity, acute dystonia, parkinsonism, and tardive dyskinesia; may enhance the effects of other antiparkinsonian agents Tolerance to fixed dose may develop after 1–8 weeks May be useful in levodopa-induced movement disorder	1–10%: Anorexia, nausea, orthostatic hypotension, peripheral edema, agitation, anxiety, ataxia, confusion, dizziness, fatigue, insomnia, psychosis (hallucinations, delusions, paranoia), livedo reticularis (mottled skin discoloration). Many are dose related and disappear on drug withdrawal < 1%: NMS, seizures, coma, increased LFTs, respiratory failure, suicidal ideation The elderly and those with diminished renal function may be more vulnerable to CNS effects Less anticholinergic than other agents Withdrawal syndrome reported – taper dose upon discontinuation	Limited human data but suggested possible association with cardiovascular and limb reduction defects in first-trimester exposure, but number of exposures too small to draw conclusion; avoid in first trimester if possible	Excreted into breast milk in small amounts; should be used with caution because of potential adverse effects in nursing infants such as vomiting, skin rash, and urinary retention. Can reduce milk production via reduction in prolactin level
ANTICHOLINERGICS		All anticholinergic treatments listed below share common adverse effect profiles (see p. 251)		
Benztropine (Cogentin)	Beneficial effect on rigidity, acute dystonia, parkinsonism, akathisia Relieves sialorrhea and drooling Powerful muscle relaxant; sedative action Cumulative and long-acting; once-daily dosing (preferably in the morning) can be used IM/IV route: Rapid/dramatic effect on dystonic symptoms Does not relieve tardive dyskinesia – use not recommended	Dry mouth, dry eyes, blurred vision, urinary retention, constipation, nausea, GERD, paralytic ileus, tachycardia, decreased cognition, hallucinations, delirium, convulsions, heat stroke, hyperthermia Increases intraocular pressure Toxic psychosis when abused or overused	Limited human data. Probably compatible. Possible association with cardiovascular defects in first trimester exposure; reported small left colon syndrome in newborns exposed to the drug *in utero* at term, manifested as decreased intestinal motility, vomiting, abdominal distention, and inability to pass meconium	Unknown excretion into breast milk; may inhibit lactation via reduction in prolactin level
Trihexyphenidyl (Artane)	Mild to moderate effect against rigidity and spasm (occasionally dramatic results) Tremor alleviated to a lesser degree; as a result of relaxing muscle spasm, more tremor activity may be noted Stimulating – can be used during the day for sluggish, lethargic, and akinetic patients	See benztropine for general adverse effects profile and conditions to avoid use in	Limited data	No human data. Unknown excretion into breast milk. May inhibit lactation via reduction in prolactin level
ANTIHISTAMINES				
Cyproheptadine (Periactin)	Moderate effect on akathisia Sedative and anticholinergic effects Has been used to increase appetite	Drowsiness, weight gain, anticholinergic effects (dry eyes, confusion, constipation, urinary retention, etc.). May potentiate the effects of other CNS depressants	Limited data. Possible association with hypospadias and oral clefts in first-trimester exposure. Possible association with preterm delivery	Limited data. As it can reduce prolactin levels, milk production may be reduced. Potential for irritability and drowsiness in the infant

Agent	Therapeutic Effects	Adverse Effects	Pregnancy	Breast Milk
Diphenhydramine (Benadryl)	Has effect on tremor, dystonia, and akathisia Sedative effect may benefit tension and excitation; may enhance the effects of other anticholinergic agents Some effect on rigidity	Somnolence, confusion, and dizziness; delirium, disinhibition, aggression reported	Compatible. Use near delivery can cause neonatal withdrawal effects	Excreted into breast milk. Limited data but probably compatible. High doses or chronic use may reduce prolactin levels and milk production. Potential for irritability and drowsiness in the infant
β-BLOCKERS				
Propranolol (Inderal)	Beneficial effect on akathisia and tremor	Monitor pulse and blood pressure; do not stop high dose abruptly due to rebound tachycardia	Potential for growth restriction and reduced placental weight with use in second and third trimesters. Potential for β-blockade in newborn if used near delivery. Monitor for fetal bradycardia, respiratory depression, and hypoglycemia	Excreted into breast milk; compatible with breastfeeding. Monitor for symptoms of β-blockade in infant
BENZODIAZEPINES				
Clonazepam (Klonopin[B], Rivotril[C])	Useful for akathisia, tardive dyskinesia	Drowsiness, lethargy, disinhibition, aggression (see p. 267)	Benzodiazepines cross placenta. Potential for increased risk of congenital anomalies when used in first trimester, however, conflicting data. Potential for newborn withdrawal symptoms and floppy baby syndrome if used close to delivery	Benzodiazepines are excreted into breast milk. Potential to cause sedation, feeding difficulties, and weight loss in infants. Potential for prolonged effects with diazepam due to long half-life. Short-acting agents (e.g., lorazepam) preferred
Diazepam (Diastat[B], Diazepam Intensol[B], Valium, Valtoco[B])	Beneficial effect on akathisia and acute dystonia Muscle relaxant	Drowsiness, lethargy, disinhibition, aggression (see p. 267)		
Lorazepam (Ativan, Lorazepam Intensol[B], Loreev XR[B])	Beneficial effect on akathisia Excellent for acute dyskinesia (fastest onset with sublingual formulation)	Drowsiness, lethargy, disinhibition, aggression (see p. 267)		
VMAT2 INHIBITORS				
Deutetrabenazine[B] (Austedo)	Beneficial effect on tardive dyskinesia	Sedation, insomnia (similar to placebo); nasopharyngitis, depression, depression, akathisia, parkinsonism, QT prolongation at higher concentrations, binds to melanin-containing tissues and may cause long-term ophthalmic complications	No human data. Animal data suggests no clear effect on embryofetal development, however increased stillbirths and postnatal offspring mortality. May cause fetal harm	No human data. Increased postnatal offspring mortality in exposed rats
Tetrabenazine (Nitoman[C], Xenazine[B])	Beneficial effect on tardive akathisia, tardive dyskinesia, tardive dystonia	Sedation (dose-limiting) most common. Headache, fatigue, dry mouth, vomiting, akathisia, depression, parkinsonism, QTc prolongation (by ~8 msec), binds to melanin-containing tissues and may cause long-term ophthalmic complications	No human data. Animal data suggests no clear effect on embryofetal development, however increased stillbirths and postnatal offspring mortality. May cause fetal harm	Excreted into breast milk. Avoid use

Comparison of Agents for Treating Acute Extrapyramidal Side Effects (cont.)

Agent	Therapeutic Effects	Adverse Effects	Pregnancy	Breast Milk
Valbenazine[B] (Ingrezza)	Beneficial effect on tardive dyskinesia	Sedation, headache, fatigue; 2–5% anticholinergic adverse effects (see benztropine), balance disorders, akathisia, parkinsonism, QT prolongation at higher concentrations, binds to melanin-containing tissues and may cause long-term ophthalmic complications	No human data. Animal data suggests no clear effect on embryofetal development, however increased stillbirths and postnatal offspring mortality. May cause fetal harm	No human data. Detected in rat milk. Increased postnatal offspring mortality in exposed rats. Avoid use

[B] Not marketed in Canada, [C] Not marketed in the USA

Doses and Pharmacokinetics of Agents for Treating Acute Extrapyramidal Side Effects

Agent	Suggested Pediatric Dose	Onset of Action[1]	Time to Peak Plasma Level (T_{max})[1]	Bio-availability[1]	Protein Binding[1]	Elimination Half-life ($T_{1/2}$)[1]	Excretion[1]	Metabolizing Enzymes (CYP450 and/or UGT)[2]	Enzyme Inhibition (CYP450)[3]
Amantadine (Gocovri[B], Osmolex ER[B], Symmetrel)	Oral: Initial: 50 mg/day; increase weekly to 50 mg 2–3 times/day Renal impairment: lower doses; contraindicated with severe impairment Hepatic impairment: no dosage adjustment available, use with caution	Within 48 h	2–4 h	86–90%	67% (normal renal function); 59% (hemodialysis)	9–31 h (normal renal function); 7–10 days (end-stage renal disease)	Urine (80–94% unchanged by glomerular filtration and tubular secretion)	Minimal metabolism	–
ANTICHOLINERGICS									
Benztropine (Cogentin)	Oral/IM: 0.02–0.05 mg/kg/dose 1–2 times/day; usual dose 0.5–2 mg two times/day Acute dystonia: IM/IV: 1–2 mg; may repeat once in 30 min in adolescents Use in age < 3 years should be limited to life-threatening emergencies Hepatic and renal impairment: no dosage adjustment available	Oral: within 1 h IM/IV: few minutes	7 h	29%	95%	7 h (nonlinear relationship between dose and serum levels) Duration of action approx. 24 h	Urine	2D6[m]	–
Trihexyphenidyl (Artane)	Oral: 0.5–1 mg/day, increase by 1 mg every 3–5 days; usual dose 6–60 mg/day in 2–3 divided doses Hepatic and renal impairment: no dosage adjustment available – use caution	1 h	1–1.5 h	?	?	5–10 h; newer studies report 33 h	Primarily urine	?	?

Agent	Suggested Pediatric Dose	Onset of Action[1]	Time to Peak Plasma Level (T_{max})[1]	Bio-availability[1]	Protein Binding[1]	Elimination Half-life ($T_{1/2}$)[1]	Excretion[1]	Metabolizing Enzymes (CYP450 and/or UGT)[2]	Enzyme Inhibition (CYP450)[3]
ANTIHISTAMINES									
Cyproheptadine (Periactin)	Initial: 2–4 mg tid, up to 16 mg/day in children or 32 mg/day in adolescents Hepatic and renal impairment: no dosage adjustment available – use caution	?	6–9 h	?	96–99%	8.6 h Metabolites: 16 h	Urine (~40%, primarily as metabolites); feces (2–20%)	**3A4**[(p)]	?
Diphenhydramine (Benadryl)	IM/IV: 12.5–50 mg for dystonia Oral: Age 2–5: 6.25 mg up to qid; age 6–12: 12.5–25 mg up to qid; over age 12: 25–50 mg up to qid Renal and hepatic impairment: no dosage adjustment available – use caution	Oral: 1–3 h IM/IV: few minutes	~2 h	42–62%	98.5%	Children: 5 h Adults: 9 h	Urine (as metabolites and unchanged drug)	**2D6**[(p)], 1A2[(m)], 2C9[(m)], 2C19[(m)]; UGT1A3	2D6
β-BLOCKERS									
Propranolol (Inderal)	Oral: 1–4 mg/kg/day or 10 mg tid, may increase up to 60 mg/day Renal and hepatic impairment: increases systemic exposure; caution advised	1–2 h	1–4 h (immediate release); 6–14 h (sustained release)	25% (high first-pass metabolism); protein-rich foods increase bioavailability by 50%	90%	3–6 h (immediate release); 8–10 h (sustained release)	Less than 1% excreted in urine as unchanged drug; metabolites are excreted primarily in urine (96–99%)	**1A2**[(p)], **2D6**[(p)], 2C19[(m)], 3A4[(m)]	1A2[(w)], 2D6[(w)]
BENZODIAZEPINES									
Clonazepam (Klonopin[(B)], Rivotril[(C)])	Oral: Children under 30 kg: 0.01–0.03 mg/kg/day given bid–tid, increase up to 0.1–0.2 mg/kg/day divided bid to tid; children over 30 kg: 0.5–3 mg/day in divided doses Renal and hepatic impairment: metabolites may accumulate; use with caution Contraindicated in severe impairment	15–30 min	1–3 h	90%	86%	Children: 22–33 h Adults: 17–60 h	Urine (less than 2% as unchanged drug)	**3A4** [(p)]	–

Doses and Pharmacokinetics of Agents for Treating Acute Extrapyramidal Side Effects (cont.)

Agent	Suggested Pediatric Dose	Onset of Action[1]	Time to Peak Plasma Level (T_{max})[1]	Bio-availability[1]	Protein Binding[1]	Elimination Half-life ($T_{1/2}$)[1]	Excretion[1]	Metabolizing Enzymes (CYP450 and/or UGT)[2]	Enzyme Inhibition (CYP450)[3]
Diazepam (Diastat[B], Diazepam Intensol[B], Valium, Valtoco[B])	Oral: age 6 months to 12 years: 0.12–0.8 mg/kg/day divided, up to 5 mg qid; age over 12: 2–10 mg up to qid IV: 0.1–0.2 mg/kg/day for acute dystonia by slow direct IV push (rate of 5 mg (1 mL)/min) Renal impairment: no dosage adjustment recommended; decrease dose (e.g., by 30–50%) if prescribed for extended periods as metabolite accumulates with chronic use Hepatic impairment: caution in moderate impairment, reducing dose by 50% recommended; Oral: contraindicated in severe impairment	Oral: rapid (15 min or less) IV: immediate	Oral: 15 min–2 h	93%	98%	50 h; 50–100 h for active major metabolite (desmethyldiazepam); increased half-life in those with severe hepatic disorders	Urine (very little as unchanged drug)	**2C19**[p], **3A4**[p], 1A2[m], 2B6[m], 2C9[m]	2C19[w], 3A4[w], UGT
Lorazepam (Ativan, Lorazepam Intensol[B], Loreev XR[B])	Oral/SL: 0.02–0.09 mg/kg/day given in divided doses up to q 4 h IM: 0.025–0.05 mg/kg/dose q 4 h PRN for acute dystonia; maximum single dose: 2 mg in children under age 12 or 4 mg in adolescents up to usual daily maximum of 8 mg (Higher doses up to 18 mg/day may be used in treatment of catatonia) Renal impairment: Oral: no adjustment; IV: repeated doses may increase risk of propylene glycol toxicity Hepatic impairment: mild to moderate – no adjustment; severe – use caution	Oral: 15–30 min IM/IV: few minutes	Oral: 2 h Sublingual: 1 h IM: < 3 h	90%	88–92%	10–20 h; 32–70 h (end-stage renal disease)	Urine (88% as inactive metabolites); feces (7%)	UGT2B7, UGT2B15	–

Agent	Suggested Pediatric Dose	Onset of Action[1]	Time to Peak Plasma Level (T_{max})[1]	Bio-availability[1]	Protein Binding[1]	Elimination Half-life ($T_{1/2}$)[1]	Excretion[1]	Metabolizing Enzymes (CYP450 and/or UGT)[2]	Enzyme Inhibition (CYP450)[3]
VMAT2 INHIBITORS									
Deutetrabenazine[B] (Austedo)	Safety and effectiveness in pediatric patients have not been established	2 weeks	3–4 h; C_{max} increased with food by ~50%; C_{max} is up to 190-fold higher in hepatic impairment	≥80%	Metabolites: α-dihydro-tetrabenazine (α-HTBZ): 60–68% and β-dihydro-tetrabenazine (β-HTBZ): 59–63%	Total α-HTBZ and β-HTBZ: 9–10 h	Urine (75–86%); feces (8–11%)	2D6[p], 1A2[m], 3A4[m], 3A5[m]	–
Tetrabenazine (Nitoman[C], Xenazine[B])	Limited data in children; Oral: Initial: 12.5 mg daily; increase by 12.5 mg/day every 3–4 days; usual dose 50 mg/day (divided into 3 doses); maximum 200 mg/day Renal impairment: not studied Hepatic impairment: contraindicated	Within 7 days of maximal tolerated dose	1–1.5 h; C_{max} is 7- to 190-fold higher in hepatic impairment	4.9%; erratic	82–85%	5–7 h; 10 h (hepatic impairment)	Urine (75% as metabolites); feces (7–16%)	2D6[p], 1A2[m] Single doses above 50 mg should not be given without CYP2D6 genotyping	–
Valbenazine[B] (Ingrezza)	Safety and effectiveness in pediatric patients have not been established	2 weeks	0.5–1 h; C_{max} decreased by high-fat meals by 47%	~49%	> 99%; metabolite: [+]-α-dihydro-tetrabenazine ([+]-α-HTBZ): 64%	15–22 h	Urine (60% as inactive metabolites); feces (30%)	2D6[p], 3A4[p], 3A5[m]	–

[1] Most of the data available is based on adult population, [2] Cytochrome P450 isoenzymes involved in Phase I metabolism (data not consistent among references), UGT: UDP-glucuronosyltransferase is the most important Phase II (conjugative) enzyme, [3] CYP450 isoenzymes inhibited by drug, [B] Not marketed in Canada, [C] Not marketed in the USA, [p] Primary route of metabolism, [m] Minor route of metabolism, [w] Weak inhibitor/inducer of CYP450

Extrapyramidal Side Effects of Antipsychotics (cont.)

Further Reading

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ANXIOLYTIC (ANTIANXIETY) AGENTS

Classification

- Anxiolytic agents can be classified as follows:

Chemical Class	Agent	Page
Antidepressants		
SSRI (1st line)	Examples: Fluoxetine, sertraline, escitalopram	See p. 53
SNRI (2nd line)	Example: Venlafaxine, duloxetine	See p. 73
SARI (2nd line)	Example: Trazodone	See p. 81
NaSSA (2nd line)	Example: Mirtazapine	See p. 97
TCA (2nd line)	Example: Clomipramine	See p. 102
Antihistamines	Example: Hydroxyzine[+]	See p. 282
Azaspirone (1st line for GAD only)	Example: Buspirone	See p. 277
Benzodiazepines (1st line)	Examples: Clonazepam, lorazepam	See p. 263 below
Anticonvulsants		
GABA analogs	Example: Gabapentin	See p. 305
α_2 agonists	Example: Guanfacine	See p. 46

[+] Used primarily for pruritus of psychogenic origin (dose: 10–400 mg/day). Tolerance to sedative effects will develop over several weeks. Has been used in children as anxiolytic, but clinical efficacy not substantiated and adverse effects may be troublesome (including drowsiness, affective and cognitive symptoms). Double-blind studies suggest benefit for GAD in adults (dose: 50 mg/day)

Benzodiazepines

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[(A)]	Dosage Forms and Strengths	Monograph Statement
Alprazolam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Alprazolam Intensol[(B)]	Oral concentrate: 1 mg/mL	Safety and efficacy not established in children and adolescents under age 18
			Xanax	Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg	
			Xanax TS[(C)]	Triscored tablets (TS): 2 mg	
			Xanax XR[(B)]	Extended-release tablets: 0.5 mg, 1 mg, 2 mg, 3 mg	
Bromazepam[(C)]	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Lectopam	Tablets: 1.5 mg 3 mg, 6 mg	Safety and efficacy not established in children and adolescents under age 18
Chlordiazepoxide	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Librium	Capsules: 5 mg, 10 mg, 25 mg	Not recommended for children under age 6

Benzodiazepines (cont.)

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Clonazepam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Klonopin[B], Rivotril[C]	Tablets: 0.25 mg[C], 0.5 mg, 1 mg, 2 mg Oral disintegrating tablets[B]: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg	Not studied in psychiatric disorders in children and adolescents under age 18; dosage recommendations available for seizure disorders
Clorazepate	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Tranxene	Tablets: 3.75 mg, 7.5 mg, 15 mg	Not recommended for children under age 9; dosage recommendations available for seizure disorders
Diazepam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Diastat, Diastat Acudial[B]	Rectal gel: 5 mg/mL	Safety not established for infants under 6 months
			Diazepam Intensol[B]	Oral concentrate: 5 mg/mL	Dosage recommendations available for infants and children
			Valium	Tablets: 2 mg, 5 mg, 10 mg Oral solution[B]: 5 mg/5 mL Injection: 5 mg/mL	
			Valtoco[B]	Nasal spray: 5 mg/spray, 7.5 mg/spray, 10 mg/spray	Not recommended for children under age 6
Estazolam[B]	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	ProSom	Tablets: 1 mg, 2 mg	Safety and efficacy not established in children and adolescents under age 18
Flurazepam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Dalmane	Capsules: 15 mg, 30 mg	Safety and efficacy not established in children and adolescents under age 15
Lorazepam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Ativan	Tablets: 0.5 mg, 1 mg, 2 mg Sublingual tablets[C]: 0.5 mg, 1 mg, 2 mg Injection: 2 mg/mL, 4 mg/mL	Oral: Safety and efficacy not established in children under age 12 Injection: Not recommended in children and adolescents under age 18
			Lorazepam Intensol[B]	Oral concentrate: 2 mg/mL	
			Loreev XR[B]	Extended-release capsules: 1 mg, 2 mg, 3 mg	Safety and efficacy not established in children and adolescents under age 18
Nitrazepam[C]	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Mogadon	Tablets: 5 mg, 10 mg	Not studied in psychiatric disorders in children and adolescents under age 18; dosage recommendations available for seizure disorders
Oxazepam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Serax	Tablets[C]: 10 mg, 15 mg, 30 mg Capsules[B]: 10 mg, 15 mg, 30 mg	Safety and efficacy not established in children under age 6
Temazepam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Restoril	Capsules: 7.5 mg[B], 15 mg, 22.5 mg[B], 30 mg	Safety and efficacy not established in children and adolescents under age 18
Triazolam	Benzodiazepine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Halcion	Tablets: 0.125 mg[B], 0.25 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Approved Indications‡
(👍 approved)

	Drug	Anxiety Disorders	Panic Disorder	Insomnia	Perioperative Sedation	Seizure Disorders	Skeletal Muscle Spasticity	Alcohol Withdrawal
Short-acting	Alprazolam (Xanax)	👍 (adult)	👍 (adult)					
	Triazolam (Halcion)			👍 (adult)				
Intermediate	Bromazepam (Lectopam)[C]	👍 (adult)						
	Estazolam (ProSom)[B]			👍 (adult)				
	Lorazepam (Ativan)	👍 (adult) (pediatric, US)		👍 (adult)	👍 (adult)	👍 (adult – injection)		
	Oxazepam (Serax)	👍 (adult & pediatric)						👍 (adult)
	Temazepam (Restoril)			👍 (adult)				
Long-acting	Chlordiazepoxide (Librium)	👍 (adult & pediatric)			👍 (adult)			👍 (adult)
	Clonazepam (Klonopin[B], Rivotril[C])		👍 (adult, US)			👍 (adult & pediatric)		
	Clorazepate (Tranxene)	👍 (adult)				👍 (adult & pediatric)		👍 (adult)
	Diazepam (Valium)	👍 (adult & pediatric)			👍 (adult)	👍 (adult)	👍 (adult & pediatric)	👍 (adult & pediatric)
	Flurazepam (Dalmane)			👍 (adult)				
	Nitrazepam (Mogadon)[C]			👍 (adult)		👍 (pediatric)		

[B] Not marketed in Canada, [C] Not marketed in the USA

Other Indications in Children & Adolescents

- Akathisia secondary to antipsychotic agents
- Abnormal movements associated with tardive dyskinesia (clonazepam)
- Mania: Often used short-term with an antipsychotic or lithium to control agitation
- Schizophrenia: Used with antipsychotics to control agitation; may potentiate their effect and decrease dosage requirements
- Anxiety disorders: High-potency benzodiazepines (clonazepam) useful for panic disorder/agoraphobia, social anxiety disorder, and separation anxiety disorder
- Catatonia (parenteral or sublingual lorazepam, diazepam, clonazepam)
- Myoclonus, restless legs syndrome, Tourette's disorder, neuralgia (clonazepam)
- Acute dystonia (sublingual or intramuscular lorazepam)
- Premenstrual dysphoric disorder (alprazolam)
- Night terrors, somnambulism
- Nocturnal enuresis (clonazepam; case report)
- Violent behavior: Control of violent outbursts, assaultive behavior (clonazepam, lorazepam); reduce agitation and behavioral problems associated with severe overarousal or anxiety; also used in combination with mood stabilizers, antipsychotics, or β-blockers
- Benzodiazepine use disorder (diazepam; case report), methamphetamine poisoning (lorazepam, clonazepam)
- Status epilepticus (lorazepam, diazepam)
- Chemotherapy-induced nausea/vomiting (lorazepam)

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Benzodiazepines (cont.)

General Comments

- The potency of a benzodiazepine is the affinity of the parent drug, or its active metabolites, for "benzodiazepine"-$GABA_A$ receptors *in vivo*. Potency does not necessarily correlate with onset of action
- Benzodiazepines are suggested to relieve behavioral and somatic manifestations of anxiety, but have little effect on psychic or cognitive symptoms (e.g., worry, anger, interpersonal sensitivity, and obsessionality); may be most helpful during the beginning phase of treatment; not recommended long term (exception: treatment of refractory catatonia). Concerns of dependence and abuse limit their usefulness
- A multimodal treatment approach including medication, psychosocial therapy, and environmental interventions has shown to confer greater improvement in symptoms, as compared to the use of drug alone[1]
- Controlled trials do not support the use of benzodiazepines for the treatment of anxiety in children[2], yet open-label studies indicate symptomatic benefit[1]. Currently the most effective treatments for childhood-onset anxiety disorders are cognitive-behavioral therapy (CBT), behavior therapy (BT), and SSRIs[3]
- Benzodiazepines are considered adjunctive agents, mostly for short-term use in children and adolescents (exception: treatment of refractory catatonia)
- Benzodiazepines should be used with caution in children with aggressive, impulsive tendencies, as their disinhibitory effects can aggravate these conditions. In general, they should be used in children and adolescents without comorbid substance use disorder or major depression who require relief from moderate to severe anxiety or manic symptoms
- Chronic use in children should be carefully evaluated to prevent possible adverse effects on physical and mental development (cognition)

Pharmacology

- Benzodiazepines are positive allosteric modulators of the $GABA_A$-chloride receptor complex. Binding of benzodiazepines to the "benzodiazepine"-$GABA_A$ receptor complex increases the frequency of opening of the chloride channels, facilitating inhibition of neuronal firing at the level of the limbic system, the brain stem reticular formation, and the cortex. Intensity of action depends on degree of receptor occupancy
- Benzodiazepines bind non-selectively to various subtypes of "benzodiazepine"-$GABA_A$ receptor complexes. $GABA_A$ receptor subtypes containing an α_1 subunit are associated with sedation, ataxia, and amnesia; $GABA_A$ receptor subtypes containing α_2 and/or α_3 subunits generally have greater anxiolytic activity
- In children, the GABA receptor also has an excitatory role; this may explain the disinhibiting effects of benzodiazepines in young children and those who have organic brain syndromes
- As the dose of a benzodiazepine is increased (i.e., increased receptor occupancy), the anxiolytic effects are noticed first, followed by anticonvulsant effects, a reduction in muscle tone, and finally sedation and hypnosis
- In addition to its activity at the "benzodiazepine"-$GABA_A$ receptor complex, clonazepam decreases the utilization of serotonin by neurons

Dosing

- See pp. 272–276 for individual agents
- Benzodiazepines are metabolized faster in children than in adults; children may require smaller divided doses to maintain adequate blood levels
- Although the majority of indications for benzodiazepines are for short-term (less than 2 months) treatment, some patients are prescribed these agents for extended periods of time (more than 3 months). Clinicians should discuss the risks and benefits of long-term use with patients early on in therapy
- Following IV administration of diazepam, local pain and thrombophlebitis may occur due to precipitation of the drug, or due to an irritant effect of propylene glycol (a saline flush following the diazepam reduces the incidence)
- IM diazepam use is discouraged as absorption is slow, erratic, and possibly incomplete depending on the muscle mass used (when injected into deltoid muscle, absorption is usually rapid and complete); local pain often occurs. IM lorazepam is adequately absorbed
- When switching from immediate-release (divided dose) to extended-release (XR) (single dose), alprazolam 0.5 mg tid = alprazolam XR 1.5 mg daily. Slower absorption rate results in a relatively constant concentration that is maintained for 5–11 h after dosing. Dose reductions should be in decrements of 0.5 mg every 3 days, or slower
- Alprazolam XR should be administered at a consistent time once daily (preferably in the morning); a high-fat meal given up to 2 h prior to administration of Alprazolam XR can increase the mean C_{max} by about 25%, however, the extent of exposure (AUC) and elimination half-life ($T_{1/2}$) are not affected by eating
- Alprazolam XR should be swallowed whole and should not be broken, crushed, or chewed

Pharmacokinetics

- See pp. 272–276 for individual agents
- Marked interindividual variation (up to 10-fold) is found in all pharmacokinetic parameters. Age, liver disease, physical disorders, and concurrent use of other drugs may influence parameters by changing the volume of distribution, metabolism, and elimination half-life of these drugs
- Well absorbed from GI tract after oral administration; food can delay the rate but not the extent of absorption; onset of action is determined by rate of absorption and lipid solubility
- Lipid solubility positively correlates with enhancing benzodiazepine (a) affinity for peripheral adipose tissue (children typically have little adipose tissue), resulting in redistribution from the vascular compartment (this increases volume of distribution), and (b) passage across the blood/brain barrier, facilitating its CNS activity. Benzodiazepines have a high volume of distribution (i.e., the tissue drug concentration is much higher than the blood drug concentration)
- Elimination half-life is a contributor to, but not the sole determinant of, duration of action. The duration of action is dependent on the size of the dose, the rate of absorption, the rate and extent of drug distribution, and the rate of elimination. A benzodiazepine with a long half-life (e.g., diazepam) may have a short duration of action if the dose is small or if it undergoes rapid and extensive distribution. Conversely, a short half-life benzodiazepine (e.g., lorazepam) may have a long duration of action if the dose is large or if the drug has limited peripheral distribution
- Benzodiazepines are generally equivalent aside from pharmacokinetics (half-life and onset/duration of action); understanding this is important when choosing, switching or discontinuing benzodiazepines. Generally, short-acting benzodiazepines can be used as hypnotics and for acute problems relating to anxiety, while long-acting agents can be used for chronic conditions where a continuous drug effect is needed
- The longer the half-life of a benzodiazepine, the greater the likelihood that the compound will have an adverse effect on daytime functioning (e.g., hangover effect). Conversely, shorter half-life benzodiazepines are more often associated with (a) inter-dose withdrawal, (b) rebound anxiety between doses, and (c) anterograde amnesia
- The major pathway of metabolism is Phase I (i.e., hepatic microsomal oxidation and demethylation). Phase II metabolism (i.e., conjugation) produces more polar (water-soluble) by-products, allowing for easier renal excretion. Phase I metabolism (e.g., oxidation) can be compromised by disease states (e.g., hepatic cirrhosis), age or drugs that inhibit various CYP enzymes. Drugs that only undergo Phase II metabolism (i.e., conjugation) are not affected to the same degree (e.g., lorazepam, oxazepam, temazepam)
- Renal impairment may increase the free unbound plasma concentration of some benzodiazepines and reduce clearance. Reduce dose by 25–50% in patients with CrCl below 10 mL/min

Adverse Effects

CNS Effects

- Most common are extensions of the generalized sedative effect (e.g., fatigue, drowsiness); alprazolam XR may prolong daytime sedation
- Impaired mental speed, central cognitive processing ability, memory, and perceptomotor performance (related to dose, high lipid solubility – see table pp. 272–276, and to peak plasma level of benzodiazepine) have been observed in adults; limited data in pediatric patients
- Tolerance to acute short-term memory impairment does not develop with time
- Anterograde amnesia (more likely with high-potency agents or higher doses); sexual dysmnesia (e.g., IV diazepam)
- Chronic use: Impaired visuospatial and visuomotor abilities (e.g., decreased motor coordination, psychomotor speed and response time, decreased concentration, speed of information processing and verbal learning); patients may underestimate their memory deficits
- Behavior dyscontrol with irritability and impulsivity; paradoxical agitation in children – especially with organic brain disorder, brain injury, autism spectrum disorder, aggressive/impulsive tendencies, or intellectual disability; this can be manifested in the form of irritability, tantrums, aggression, insomnia, nightmares, rage spells, overexcitability, hyperactivity, hallucinations, or oppositional behavior. Another risk factor is presence of borderline personality disorder. The incidence of paradoxical reaction varies: less than 1% in general population, and patients under age 18: 17% in patients with behavioral or psychiatric conditions, 13% in patients with intellectual disability
- Case reports of psychotic symptoms in children given low doses
- Confusion and disorientation – rare in children and adolescents. Periods of blackouts or amnesia have been reported
- Treatment-emergent depression
- Excessive doses can result in respiratory depression and apnea, especially when co-administered with opioids, alcohol, or other sedative agents
- Hypersalivation (clonazepam)
- Dysarthria, muscle weakness, incoordination, ataxia, nystagmus
- Headache

Benzodiazepines (cont.)

Other Adverse Effects

- Anticholinergic effects (e.g., blurred vision, dry mouth)
- Dizziness (up to 12% with higher doses of clonazepam)
- Sexual dysfunction including decreased libido, erectile dysfunction, anorgasmia, ejaculatory disturbance, and gynecomastia
- Increased salivation (clonazepam); troublesome hypersecretion in children with chronic respiratory disease
- Rare reports of purpura and thrombocytopenia with diazepam
- Few documented allergies to benzodiazepines; rarely reported skin reactions include rashes, angioedema[4], photosensitivity reactions, pigmentation, fixed drug eruption, alopecia, bullous reactions, exfoliative dermatitis, vasculitis, and erythema nodosum

D/C Discontinuation Syndrome

- Benzodiazepines present different risks of physiological dependence at therapeutic doses, depending on the individual as well as the drug's potency and its elimination half-life. Up to 30% of patients are suggested to experience withdrawal after 8 weeks of benzodiazepine treatment; very little data on the development of tolerance or dependence in children
- Abrupt discontinuation of a benzodiazepine can produce:
  - Withdrawal: Occurs in 1–2 days (with short-acting agents) to 5–10 days (with long-acting agents) following drug discontinuation. Common symptoms include insomnia, agitation, anxiety, perceptual changes, dysphoria, headache, muscle aches, twitches, tremors, loss of appetite, diaphoresis, tachycardia, and GI distress. Catatonia and depression have also been reported. Severe reactions can occur such as generalized tonic-clonic or absence seizures, delirium, depersonalization, psychotic states, and coma
  - Rebound: Occurs hours to days after drug discontinuation; symptoms (of anxiety) are similar but more intense than those reported originally
  - Relapse: Occurs weeks to months after drug discontinuation; symptoms are similar to original symptoms of anxiety, and get progressively worse until treated
- Pseudo-withdrawal is a psychological withdrawal as a result of the patient's apprehension about discontinuing the drug – consists of anxiety symptoms unaccompanied by true withdrawal symptoms; as with all medications, there is a placebo component and this is best dealt with by slow withdrawal and reassurance

Management

- Dose tapering rates vary based on dosage and duration of use – may need to taper more slowly following long-term use, or at the end of the tapering period
- To withdraw a patient from a benzodiazepine, an equivalent dose of diazepam can be substituted (see pp. 272–276). If insomnia is a major problem, then most of the diazepam should be given at bedtime. Withdrawal schedules will be dependent on patient history and psychological issues regarding benzodiazepine use
  - A conservative schedule would be to reduce the current dose of diazepam by 10–20% every 1–2 weeks depending on patient's symptoms

☞ **The withdrawal schedule for alprazolam should be no faster than 0.25 mg every week; quicker withdrawal may result in delirium and seizures**

☞ **The above withdrawal schedule is only intended as a general guide. The rate of tapering should be flexible, depending on the patient's individual symptoms**

Precautions

- Contraindicated in patients with significant liver disease, acute narrow-angle glaucoma
- Administer with caution in patients with sleep apnea, severe respiratory insufficiency and myasthenia gravis (Canadian labelling: some benzodiazepines contraindicated with these conditions)
- Administer with caution in patients performing hazardous tasks requiring mental alertness or physical coordination
- Administer with caution in children under age 12 or with neurodevelopmental disorder (e.g., autism spectrum disorder, ADHD, intellectual disability); monitor for paradoxical reaction
- Benzodiazepines may diminish therapeutic efficacy of electroconvulsive therapy (ECT) by raising seizure threshold (management for catatonic patients requiring benzodiazepine treatment and ECT: Consider holding benzodiazepine dose on mornings of, and possibly evenings prior to, ECT)
- Anxiolytics lower the tolerance to alcohol, and high doses may produce mental confusion similar to alcohol intoxication
- Can cause physical and psychological dependence, tolerance, and withdrawal symptoms – correlates to dose and duration of use
- Benzodiazepines are at risk of being abused by susceptible individuals (e.g., habitual polysubstance users); agents with rapid peak drug effects (e.g., diazepam, lorazepam, alprazolam) are more likely to be abused

- Users of opioids may use benzodiazepines to self-medicate symptoms of withdrawal; benzodiazepines may contribute to deaths from methadone toxicity by increasing upper airways obstruction
- Withdrawal symptoms resemble those of alcohol and barbiturates (e.g., tremor, agitation, headache, nausea, delirium, hallucinations, metallic taste). Abrupt withdrawal following prolonged use of high doses can produce generalized tonic-clonic seizures (especially with alprazolam)

Toxicity

- Rarely if ever fatal when taken alone; may be lethal when taken in combination with other drugs, such as alcohol, barbiturates or opioids
- Parenteral benzodiazepine administration is not recommended within 1 h of IM olanzapine administration (fatalities have occurred)
- Symptoms of overdose include hypotension, respiratory depression, and coma

Management

- Flumazenil injection (a benzodiazepine antagonist) reverses the hypnotic-sedative and respiratory depressant effects of benzodiazepines. Repeated flumazenil doses may be required due to a short half-life (children without hepatic impairment: 20–75 min) and duration of action (19–50 min)

Use in Pregnancy◊

- Benzodiazepines and metabolites freely cross the placenta and accumulate in fetal circulation
- Benzodiazepines in general are associated with increased risk of congenital anomalies if used in the first trimester and with neonatal withdrawal if used in third trimester
- Use of a benzodiazepine in the last weeks of pregnancy may cause neonatal CNS depression, poor feeding, hypothermia, flaccidity, and respiratory depression

Breast Milk

- Benzodiazepines are excreted into breast milk in levels sufficient to produce effects in the newborn, including sedation, poor feeding, weight loss, lethargy, and poor temperature regulation (e.g., infant can receive up to 13% of maternal dose of diazepam and 7% of lorazepam dose)
- Metabolism of benzodiazepines in infants is slower, especially during the first 6 weeks; long-acting agents can accumulate
- For breastfeeding women who require benzodiazepine treatment, choose a short-acting agent with no active metabolites (e.g., lorazepam). Monitor newborn for poor feeding and sedation

Nursing Implications

- Assess the anxiety level of patients taking these drugs to determine if anxiety control has been accomplished and if oversedation has occurred
- The dose should be maintained as prescribed; caution patient not to increase or decrease the dose without consulting their physician. Direct discussion of medication use with the patient is likely to improve drug adherence irrespective of age[1]
- Sublingual tablet (lorazepam) will dissolve in approximately 20 sec; patient should not swallow for at least 2 min to allow sufficient time for absorption
- Inform patients that activities requiring mental alertness should not be performed after taking these medications (e.g., driving or operating machinery); advise the patient to report any memory lapses or amnesia to their physician immediately
- Caution patients not to use other CNS depressant drugs, including over-the-counter drugs (e.g., antihistamines or alcohol), without consulting their physician
- Excessive consumption of caffeinated beverages can counteract the effects of anxiolytics
- Tolerance and physical dependence can occur; caution patient that withdrawal symptoms can occur with abrupt discontinuation after prolonged use
- Caution patients that introducing grapefruit or pomegranate juice (CYP3A4 inhibitors) into their diet while taking certain benzodiazepines (i.e., alprazolam, clonazepam, diazepam, estazolam, and triazolam) can result in increased blood levels, resulting in more pronounced effects (including side effects)
- Antacids delay the rate of absorption of benzodiazepines from the intestine. Separate the administration of antacids and benzodiazepines to prevent this interaction
- Watch for signs of behavioral disinhibition or paradoxical reactions; may need to discontinue the benzodiazepine
- Alprazolam XR should be administered at a consistent time once daily (preferably in the morning); a high-fat meal prior to administration can affect the plasma level of this drug. Alprazolam XR tablets should be swallowed whole and not be broken, crushed or chewed

Patient Instructions

- For detailed patient instructions on anxiolytic drugs, see the Patient and Caregiver Information Sheet (details p. 429)

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Benzodiazepines (cont.)

Drug Interactions

- Many interactions; only clinically significant ones are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Anesthetics	Ketamine	Prolonged recovery with diazepam due to decreased metabolism Benzodiazepines (higher doses) may reduce delayed antidepressant effects of ketamine in the treatment of depression
	Volatile (e.g., halothane)	Decreased protein binding of diazepam resulting in increased pharmacological effects
Antiarrhythmic	Amiodarone	Case of benzodiazepine toxicity with clonazepam
Antibiotic	Clarithromycin, erythromycin	Decreased metabolism and increased plasma levels of benzodiazepines metabolized by CYP3A4, including triazolam (by 52%), alprazolam (by 60%), estazolam, and diazepam; no interaction with azithromycin
	Quinolones: Ciprofloxacin	Decreased metabolism of diazepam via inhibition of CYP1A2 and 3A4
	Quinupristin/dalfopristin	Decreased metabolism of diazepam via inhibition of CYP3A4
Anticonvulsant	Barbiturates, carbamazepine	Increased metabolism and decreased plasma level of benzodiazepines metabolized by CYP3A4 and 2C19, including alprazolam (over 50%), clonazepam (19–37%), and diazepam; additive CNS effects
	Divalproex, valproic acid	Displacement of diazepam from protein binding sites, resulting in increased plasma level Decreased glucuronide metabolism of lorazepam (by 30–58%) and reduced clearance of lorazepam (by 20–40%) Increased clearance of clonazepam (by 14%) and decreased clearance of valproic acid (by 18%); cases of absence status epilepticus, prolonged sedation, and myotoxicity with comedication
	Phenytoin	Both increases and decreases in phenytoin plasma levels reported. The exact mechanism of the interaction is unknown Increased phenytoin level and toxicity reported with diazepam, chlordiazepoxide, and clonazepam Increased metabolism and decreased plasma level of benzodiazepines metabolized by CYP3A4
Antidepressant		
SSRI	Fluoxetine, fluvoxamine, sertraline	Decreased metabolism and increased plasma level of benzodiazepines metabolized by CYP3A4, including alprazolam (by 100% with fluvoxamine and 46% with fluoxetine) and diazepam (13% with sertraline) Increased AUC of diazepam with CYP2C19 inhibitors: 2.8 fold with fluvoxamine, 1.5 fold with fluoxetine
SARI	Nefazodone	Increased plasma levels of alprazolam (by 200%) and triazolam (by 500%) due to inhibited metabolism via CYP3A4
Cyclic	Desipramine, imipramine	Increased plasma levels of desipramine and imipramine with alprazolam (by 20% and 31%, respectively) Desipramine and triazolam: Report of hypothermia (neither drug causes this effect alone); triazolam potentiates anorexic effect of desipramine
Antifungal	Fluconazole, itraconazole, ketoconazole	Decreased metabolism and increased half-life of chlordiazepoxide; decreased metabolism of triazolam (6–7 fold) – reduce dose by 50–75%; AUC of alprazolam increased up to 4 fold
Antipsychotic	Clozapine	Cases of marked sedation, increased salivation, hypotension (collapse), delirium, and respiratory depression/arrest reported; more likely to occur early in treatment when clozapine is added to benzodiazepine regimen
	Olanzapine	Synergistic increase in somnolence when lorazepam given with IM olanzapine. AVOID IM olanzapine with parenteral benzodiazepines as this combination can potentiate hypotension, bradycardia, and respiratory or CNS depression, and fatalities have been reported. If concurrent administration is absolutely essential, separate parenteral benzodiazepine administration from IM olanzapine dose by at least 1 h, following careful evaluation of clinical status, and monitoring for excessive sedation and respiratory depression

Class of Drug	Example	Interaction Effects
Antituberculosis therapy	Isoniazid Rifampin	Decreased metabolism of benzodiazepines that are metabolized by oxidation (CYP3A4) (triazolam clearance decreased by 75%) Increased clearance of benzodiazepines that are metabolized by oxidation (e.g., clonazepam by 46–58%, diazepam by 4 fold, and alprazolam by 5.6 fold); rifampin is an inducer of multiple CYP enzymes
Anxiolytic	Buspirone	Recent discontinuation (within 4 weeks) of benzodiazepine treatment for generalized anxiety disorder may reduce response to buspirone
β-blocker	Propranolol	Increased half-life and decreased clearance of diazepam and bromazepam (no interaction with alprazolam, lorazepam, or oxazepam)
Caffeine		May counteract sedation and anxiolytic effects, and increase insomnia
Calcium channel blocker	Diltiazem	Decreased metabolism and increased plasma level of drugs metabolized by CYP3A4, including triazolam (by 100%)
Cardiac glycoside	Digoxin	Alprazolam may increase serum levels of digoxin; mechanism unknown but may be related to reduced protein binding
CNS depressant	Alcohol Antihistamines, barbiturates	Alprazolam reported to increase aggression in moderate alcohol drinkers Brain concentrations of various benzodiazepines altered by ethanol: Triazolam and estazolam concentrations decreased, diazepam concentration increased, no change with chlordiazepoxide Increased CNS depression; with high doses coma and respiratory depression can occur Barbiturates are inducers of multiple CYP enzymes and thus may induce the metabolism of benzodiazepines that undergo CYP metabolism
Disulfiram		Decreased plasma clearance of chlordiazepoxide (by 54%) and diazepam (by 41%); no effect reported for oxazepam
Grapefruit juice		Decreased metabolism of alprazolam, clonazepam, diazepam, estazolam, and triazolam via inhibition of CYP3A4 in the gut, resulting in increased absorption/peak concentration
H_2 antagonist	Cimetidine	Decreased metabolism of benzodiazepines that are metabolized by oxidation via CYP1A2, 2C19, 2D6, and/or 3A4; (no effect with ranitidine, famotidine or nizatidine); peak plasma concentration of alprazolam increased by 86%
Hormone	Estrogen, oral contraceptives	Decreased metabolism of benzodiazepines that are metabolized by oxidation (e.g., diazepam, chlordiazepoxide, nitrazepam) Increased half-life of alprazolam by 29% Clearance of combined oral contraceptives may be reduced with diazepam due to inhibited metabolism
Kava kava		May potentiate CNS effects, causing increased side effects and toxicity
Lithium		Increased incidence of sexual dysfunction (up to 49%) when combined with clonazepam
L-dopa		Benzodiazepines can reduce the efficacy of L-dopa secondary to the GABA agonist effect
Opioid	Buprenorphine, methadone, morphine	Increased risk of severe adverse effects such as respiratory depression, coma, or death when combined with benzodiazepines
Pomegranate juice		Decreased metabolism of alprazolam, diazepam, and triazolam via inhibition of CYP3A4 in the gut by pomegranate juice, resulting in increased absorption/peak concentrations
Probenecid		Decreased clearance of lorazepam (by 50%)
Protease inhibitor	Indinavir, ritonavir	Increased plasma level of benzodiazepines that are metabolized by oxidation via CYP3A4 (e.g., triazolam, alprazolam)
Proton pump inhibitor	Omeprazole	Increased ataxia and sedation due to decreased metabolism of benzodiazepines metabolized by oxidation (no effect with lansoprazole)
Smoking (cigarettes)		Decreased alprazolam concentration up to 50% Increased clearance of alprazolam (up to 99%) and lorazepam (by 29% in heavy smokers); theoretically estazolam (CYP3A4); conflicting data for diazepam (possibly increased in young individuals); chlordiazepoxide, triazolam not affected
St. John's wort		Decreased AUC of alprazolam (by 40%) and half-life (by 24%) due to induced metabolism via CYP3A4

Comparison of the Benzodiazepines

Drug	Suggested Pediatric Dose	Comparative Adult Dose[1]	Time to Peak Plasma Level PO (T_{max})	Lipid Solubility[2]	Onset of Action	Protein Binding (PB) Volume of Distribution (Vd)	Elimination Half-life (Parent and Active Metabolite)	Metabolic Pathway Active Metabolite(s)	Comments
Alprazolam	Dosing not well established in children *Anxiety* (≥7 years): Initial: 0.125 mg tid, increase gradually Up to 3.5 mg/day has been used in studies Maximum: 0.06 mg/kg/day	0.25 mg Potency: high	Oral tablet = 1–2 h XR tablet = ~9 h (high-fat meal increases C_{max} by 25% and decreases T_{max} by 33%) Asians reported to reach 15% higher C_{max}	Moderate	15–30 min	PB: 80% Vd: 0.84–1.42 L/kg	Parent: 12–15 h Half-life increased in obese patients (22 h), in Asians (25% higher), and in hepatic insufficiency Plasma level decreased in smokers by up to 50%; half-life reduced; clearance increased by 24%	Oxidation (CYP3A4) Active metabolites: Yes	Rapidly and completely absorbed; absorption rate increased and T_{max} decreased by 1 h when dosed at night as opposed to in the morning for XR formulation Renal impairment: Increased plasma level of free (unbound) alprazolam and possible decreased clearance Hepatic impairment: Start 0.25 mg and increase gradually
Bromazepam[(C)]	Dosing not well established in children *Night terrors*[5]: 1.5 mg 30 min before bedtime	2.5–3 mg Potency: high	1–4 h	Low	15–30 min	PB: 70% Vd: 0.9 L/kg	Parent: 8–30 h Metabolite: 8–30 h	Conjugation (glucuronidation) Active metabolite(s): Yes Does not accumulate on chronic dosing	Metabolite reported to have anxiolytic activity Renal impairment: No dosage adjustment necessary; however, since active metabolites may accumulate, dosage should be reduced during long-term administration Hepatic impairment: Contraindicated with severe impairment
Chlordiazepoxide	*Anxiety* (≥6 years): 5 mg 2–4 times/day; may be increased up to 10 mg 2–3 times/day, or 0.5 mg/kg/day	12.5 mg Potency: low (parent compound less potent than metabolites)	0.5–4 h	Moderate	15–30 min	PB: 96% Vd: 3.3 L/kg	Parent: 6.6–28 h Metabolite: 24–96 h	Oxidation (CYP1A2) Active metabolite(s): Yes Metabolites accumulate on chronic dosing	Renal impairment: Decrease dose by 50% in patients with CrCl below 10 mL/min Hepatic impairment: Caution advised (half-life increased 2–3 fold in patients with cirrhosis)

Drug	Suggested Pediatric Dose	Comparative Adult Dose[1]	Time to Peak Plasma Level PO (T_{max})	Lipid Solubility[2]	Onset of Action	Protein Binding (PB) Volume of Distribution (Vd)	Elimination Half-life (Parent and Active Metabolite)	Metabolic Pathway Active Metabolite(s)	Comments
Clonazepam	Dosing not well established in children *Anxiety:* Children: Initial: 0.25 mg; 0.5–2 mg/day given in 2–3 divided doses Adolescents: Initial: 0.5 mg; 1–3 mg/days given in 2–3 divided doses	0.25 mg Potency: high	1–4 h Quickly and completely absorbed	Low	20–40 min	PB: ~85% Vd: 1.5–3 L/kg (children)	Children: 22–33 h Adults: usual = 30–40 h (range = 17–60 h) Increase in free (unbound) clonazepam in patients with cirrhosis	Oxidation (CYP3A4); reduction Active metabolite(s): No	Duration of action: Young children = 6–8 h, adults = up to 12 h Renal impairment: Use with caution. Metabolites may accumulate Hepatic impairment: Contraindicated in patients with significant impairment
Clorazepate	Dosing not well established in children *Anxiety:* Age 9–18: Start at 3.75–7.5 mg bid; may increase by 3.75–7.5 mg weekly as needed Maximum: 60 mg/day (children) and 90 mg/day (adolescents) Usual dose: 0.5–1 mg/kg/day	7.5 mg Potency: medium	0.5–2 h Rate of hydrolysis to active metabolite depends on gastric acidity, therefore absorption is unreliable (one study disputes this)	High	15 min or less	PB: 97–98% Vd: 0.7–2.2 L/kg (metabolite)	Metabolites: Nordiazepam 20–160 h, oxazepam 6–24 h	Oxidation (CYP2C19, 3A4) Active metabolite(s): Yes (rapidly decarboxylated to nordiazepam in stomach acid prior to absorption; nordiazepam metabolized to oxazepam) Metabolite accumulates on chronic dosing	Renal impairment: Clearance of metabolite impaired Hepatic impairment: No information

Comparison of the Benzodiazepines (cont.)

Drug	Suggested Pediatric Dose	Comparative Adult Dose[1]	Time to Peak Plasma Level PO (T_{max})	Lipid Solubility[2]	Onset of Action	Protein Binding (PB) Volume of Distribution (Vd)	Elimination Half-life (Parent and Active Metabolite)	Metabolic Pathway Active Metabolite(s)	Comments
Diazepam	*Anxiety:* Up to age 12: 0.12–0.8 mg/kg/day divided q 6–8 h; IM/IV: 0.04–0.3 mg/kg/dose q 2–4 h to a maximum 0.6 mg/kg/8 h Age over 12: 2–10 mg 2–4 times/day *Preoperative sedation:* Children: 0.2–0.5 mg/kg 45–60 min before procedure; Maximum 10 mg/dose; IV: 0.05–0.1 mg/kg/dose, titrate slowly to effect; Maximum total dose 0.25 mg/kg Adolescents: 0.2 mg–0.3 mg/kg 45–60 min before procedure; Maximum 10 mg/dose; IV: 5 mg; may repeat with 2.5 mg if needed	5 mg Potency: medium	0.25–2.5 h (food delays T_{max})	High	15 min or less; rapid onset of action followed by redistribution into adipose tissue; IM drug erratically absorbed, if not given in deltoid muscle	PB: 98% Vd: 0.6–1.8 L/kg	Parent: 44–48 h Metabolite: ~100 h Children age 3–8: 18 h Males have a shorter half-life and higher clearance rate than females; half-life increased (2–3 fold) in patients with cirrhosis; smoking associated with higher diazepam clearance, especially in the young	Oxidation (CYP1A2, 2B6, 2C19, 2C9, 3A4) Active metabolite(s): Yes Accumulation on chronic dosing	Renal impairment: Decreased clearance Hepatic impairment: Caution advised in patients with mild–moderate impairment. Contraindicated in patients with severe impairment
Estazolam[B]	Dosing not established in children and adolescents under age 18	0.5–1 mg Potency: high	~2 h (range: 0.5–6 h)	Low	30–60 min	PB: 93% Vd: 0.64 L/kg	Parent: 10–24 h	Oxidation (CYP3A4) Active metabolite(s): No	Renal impairment: No dosage adjustment necessary Hepatic impairment: Metabolism impaired in hepatic disease

Drug	Suggested Pediatric Dose	Comparative Adult Dose[1]	Time to Peak Plasma Level PO (T_{max})	Lipid Solubility[2]	Onset of Action	Protein Binding (PB) Volume of Distribution (Vd)	Elimination Half-life (Parent and Active Metabolite)	Metabolic Pathway Active Metabolite(s)	Comments
Flurazepam	*Insomnia:* Adolescents ≥15 years: 15 mg at bedtime	7.5–15 mg Potency: low	0.5–1 h	High	15 min or less	PB: ~97% Vd: 3.4 L/kg	Parent: Not significant Metabolite: 40–100 h; Multiple doses: 111–113 h	Oxidation (CYP2C9 and 3A4) Active metabolite(s): Yes Rapidly metabolized to active metabolite	Renal impairment: No dosage adjustment necessary Hepatic impairment: Caution advised
Lorazepam	*Anxiety, acute:* Children: Oral, IV: 0.02–1 mg/kg/dose q 4–8 h; maximum 2 mg/dose Adolescents: Oral: 0.25–2 mg/dose 2–3 times daily; maximum 2 mg/dose *Sedative/Preoperative:* Oral: 0.02–0.09 mg/kg/dose (maximum 4 mg/dose) given q 6–8 h *Catatonia:* IV (preferred)/oral/sublingual/IM: Start with 1–2 mg q 4–12 h, titrate by 1 mg q 3–5 days as needed up to 15 mg/day; Maximum 24 mg/day[6]	0.5–1 mg Potency: high	Oral: 2–4 h IM: 45–75 min IV: 5–10 min SL[(C)]: 1 h Well absorbed sublingually	Moderate	15–30 min	PB: 85–91% Vd: 1.3 L/kg	Children: ~17 h Adolescents and adults: 10–20 h; longer elimination half-life in females; half-life and Vd doubled in patients with cirrhosis	Conjugation (glucuronidation) Active metabolite(s): No	Renal impairment: Half-life of metabolite increased; IV: may increase risk of propylene glycol toxicity Hepatic impairment: Caution in hepatic insufficiency
Nitrazepam[(C)]	Not studied in psychiatric disorders in children under age 18; dosage recommendations available for seizure disorders	5 mg Potency: medium	~3 h	Low	20–50 min	PB: 87% Vd: 2.4 L/kg	Parent: 30 h (18–57 h)	Nitroreduction (CYP2E1) Active metabolite(s): No Excreted as amino and acetamide analogs; accumulates with chronic use	Renal impairment: Avoid in patients with severe renal failure Hepatic impairment: No information

Comparison of the Benzodiazepines (cont.)

Drug	Suggested Pediatric Dose	Comparative Adult Dose[1]	Time to Peak Plasma Level PO (T_{max})	Lipid Solubility[2]	Onset of Action	Protein Binding (PB) Volume of Distribution (Vd)	Elimination Half-life (Parent and Active Metabolite)	Metabolic Pathway Active Metabolite(s)	Comments
Oxazepam	Dosing not established in children up to age 12 *Anxiety (mild–moderate):* Adolescents: 10–15 mg 3–4 times/day *Anxiety (severe or with depression):* Adolescents: 15–30 mg 3–4 times/day	10 mg Potency: low	~3 h	Low	30–60 min	PB: 96–98% Vd: 0.6–2 L/kg	Parent: ~8 h (6–11 h); longer half-life in females (~10 h); half-life and plasma clearance not affected by age	Conjugation (glucuronidation) Active metabolite(s): No	Renal impairment: Prolonged half-life Hepatic impairment: No information
Temazepam	Dosing not well established in children under age 18 *Preoperative:* Children: 0.5 mg/kg/dose; Maximum 15 mg/dose	10 mg Potency: low	1.2–1.6 h Variable rate of absorption depending on formulation	Moderate	30–60 min	PB: 96% Vd: 1.4 L/kg	Parent: 3.5–18.4 h; longer elimination half-life in females	Conjugation (glucuronidation) Active metabolite(s): No 5% excreted as oxazepam in urine; plasma concentration too low to detect; no accumulation with chronic use	Renal impairment: No dosage adjustment necessary Hepatic impairment: No information
Triazolam	Dosing not well established in children under age 18 Adolescents (age ≥18): 0.125–0.25 mg at bedtime to maximum of 0.5 mg/day	0.25 mg Potency: high	1–2 h Well absorbed sublingually	Moderate	15–30 min	PB: 89% Vd: 0.6–1.7 L/kg	Parent: 1.5–5.5 h Although half-life is short, clinical effects have been observed up to 16 h after a single dose	Oxidation (CYP3A4) then conjugation (glucuronidation) Active metabolite(s): Yes	Renal impairment: No dosage adjustment necessary Hepatic impairment: Reduced clearance; reduce initial dose by 50%

[1] Based on Dr. Heather Ashton's "benzodiazepine equivalency table," which provides the approximate equivalent dose to 10 mg of diazepam see https://www.benzo.org.uk/bzequiv.htm; the site states that "these equivalents do not agree with those used by some authors. They are firmly based on clinical experience during switch-over to diazepam at start of withdrawal programs but may vary between individuals", [2] Lipid solubility positively correlates with enhancing benzodiazepines' (1) affinity for peripheral adipose tissue, resulting in redistribution from the vascular compartment (this increases volume of distribution), and (2) passage across the blood/brain barrier, facilitating their CNS activity. The higher the lipid solubility the more rapid the onset of activity and the greater the risk of memory impairment. [(B)] Not marketed in Canada, [(C)] Not marketed in the USA

Buspirone

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Buspirone	Azaspirone	Serotonin/Partial agonist	Buspar	Tablets: 5 mg[B], 7.5 mg[B], 10 mg, 15 mg[B], 30 mg[B]	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information * Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications in children and adolescents
- Generalized anxiety disorder (GAD) – not superior to placebo (high placebo response) in underpowered RCTs; positive case reports in patients (including those with Williams syndrome and Down syndrome)
- Anxiety disorder not otherwise specified – positive retrospective chart review for patients with high functioning autism spectrum disorder
- Avoidant/restrictive food intake disorder (ARFID) – positive case report
- Autism spectrum disorder – not superior to placebo for overall autism symptoms; superior for restricted and repetitive behaviors
- Irritability of autism spectrum disorder – risperidone plus buspirone more effective than risperidone plus placebo
- ADHD – inconsistent findings compared to methylphenidate
- Childhood functional abdominal pain – may improve pain and associated psychological symptoms but not superior to placebo

In adults:

- 👍 Generalized anxiety disorder (GAD): Short-term symptomatic relief of excessive anxiety
- As an alternative to benzodiazepines in situations where sedation or psychomotor impairment may be dangerous
- Depression — to augment effect of antidepressants
- Obsessive-compulsive disorder (OCD) – may potentiate effects of SSRIs or clomipramine on obsessions
- Posttraumatic stress disorder (PTSD): Preliminary reports show some efficacy in reducing anxiety, flashbacks, and insomnia
- Body dysmorphic disorder: Preliminary reports show some efficacy in treatment
- Separation anxiety unresponsive to other treatments
- Panic disorder with or without agoraphobia – low-quality evidence
- Social anxiety disorder – contradictory evidence as to efficacy; may be useful as an augmenting agent in partial responders to SSRIs
- Autism spectrum disorder and ADHD: Open studies suggest efficacy in the treatment of anxiety, hyperactivity, aggression, and irritability in these disorders
- Premenstrual syndrome – may help reduce premenstrual irritability
- Bruxism caused by SSRI antidepressants – may be useful in alleviation (case reports)
- Smoking cessation – negative trial; positive results when combined with sertraline and CBT
- Tardive dyskinesia – open-label study
- History of substance use disorder or alcohol abuse, and not recommended to take alternate anxiolytics (e.g., benzodiazepines)
- Sexual impulsivity and inhibition in cocaine users – conflicting results
- Female sexual interest/arousal disorder (FSIAD) – in phase II clinical trials; buspirone/testosterone combination tablet under development
- Central apnea, non-REM parasomnia (case report)
- GI disorders: GERD, esophageal hypomotility, rapid gastric emptying (case report), refractory irritable bowel syndrome (case report)

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Buspirone (cont.)

General Comments

- Buspirone is a selective anxiolytic of the azaspirone class; unlike the benzodiazepines, it has no anticonvulsant or muscle-relaxant properties
- Originally developed as an antipsychotic but was found ineffective for psychosis and had useful anxiolytic features instead
- In children and adolescents with generalized anxiety disorder (GAD), buspirone was not superior to placebo in two underpowered RCTs; studies had high placebo response[7]
- Tolerance to effects of buspirone has not been reported
- Has a low potential for abuse or addiction
- Lack of effect on respiration may make it useful in patients with pulmonary disease or sleep apnea; may actually stimulate respiration
- Minimal effect on cognition, memory or driving performance
- May have a preferential effect for symptoms of anxiety, irritability, and aggression, with little effect on behavioral manifestations
- Eight 3-way (buspirone, diazepam, placebo) controlled trials have been conducted in adults, evaluating buspirone as an anxiolytic agent. Buspirone was significantly better than placebo in 4 trials, not better than placebo in the other 4 trials
- Recent discontinuation (within 4 weeks) of benzodiazepine treatment for generalized anxiety disorder (GAD) may reduce response to buspirone (adults)

Pharmacology

- Unlike the benzodiazepines, buspirone does not bind to the "benzodiazepine"-$GABA_A$ receptor complex
- Buspirone pharmacology is not fully understood; it has affinity for central D_2 receptors (antagonist and agonist) and 5-HT_{1A} receptors (partial agonist)
- Buspirone does not block transporters of monoamines
- Major metabolite, 1-pyrimidinylpiperazine (1-PP), is an α_2-adrenergic receptor antagonist, thus enhancing norepinephrine release

Dosing

- Anxiety (age ≥6): Start with 7.5 mg daily for 4 days, increase to 15 mg per day; may continue or increase weekly by 7.5–15 mg to a maximum of 60 mg/day; usual range 7.5–30 mg twice daily[7]
- Slow onset of action, may take as long as 2–4 weeks for anxiolytic effect to occur
- Decrease dose by 25–50% in patients with CrCl under 10 mL/min
- Do not use with severe hepatic impairment

☞ **Not effective when taken on a prn basis**

Pharmacokinetics

- Absorption is virtually complete; first-pass effect reduces bioavailability to ~4%; buspirone is rapidly absorbed and eliminated in young children, with extensive metabolism to 1-pyrimidinylpiperazine (1-PP)[8]
- Food may reduce rate of absorption (95%), decrease extent of first-pass effect, and therefore increase oral bioavailability; C_{max} increased up to 116%
- Highly bound to plasma proteins (86%)
- T_{max}: 0.7–1.5 h; C_{max} and AUC of drug and active metabolite in children and adolescents are equal to or higher than in adults; girls have higher peak concentrations for buspirone, and a lower peak 1-PP/buspirone concentration ratio[8]
- Plasma concentrations in children aged 4–6 years given doses of 2.5–5 mg were similar to those observed in older children receiving 7.5–15 mg dose[8]
- Elimination half-life: 2–3 h. Parent drug metabolized by CYP3A4; 1-PP metabolite is active and metabolized by CYP2D6
- Clearance reduced in renal (AUC increased 4-fold) and hepatic impairment (AUC increased 13-fold)

Adverse Effects

- Drowsiness more common in children than in adults
- Behavior activation, euphoria, increased aggression, and psychosis reported in children
- Lightheadedness most common adverse effect (10%); headache (9%), nausea (5%), dyspepsia (4%), drowsiness (4%), asthenia (3%), vomiting (2%), and accidental injury (2%) seen in less than 10% of children and adolescents

- Multiple case reports of (in descending order of frequency) dyskinesia, akathisia, myoclonus, pseudoparkinsonism, tics, and dystonia in patients with anxiety disorder, mean age 45 (range 15–74) and 61% male. Possibly mechanism related to norepinephrine, dopamine, and serotonin activity of buspirone
- Dose-dependent increase in prolactin and growth hormone levels reported
- Cases of priapism and somnambulism

D/C Discontinuation Syndrome

- Withdrawal effects have not been reported

Precautions

- Contraindicated in patients taking MAOIs (or discontinued MAOIs within 14 days) or reversible MAOIs (e.g., linezolid and IV methylene blue) due to increased risk of serotonin syndrome
- Use with caution in patients with severe hepatic or renal impairment (contraindicated in Canada)
- Has no cross-tolerance with benzodiazepines and will not alleviate benzodiazepine withdrawal; when switching, taper benzodiazepine dose while adding buspirone to the regimen
- Buspirone does not have anticonvulsant activity and has not been evaluated in patients with a history of seizures; not recommended for patients with seizures
- Use with caution in patients with history of substance abuse or incarceration; case reports of misuse of buspirone by nasal insufflation for sedative and relaxing effect

Toxicity

- No deaths reported
- Excessive doses produce extension of pharmacological effects including dizziness, nausea, and vomiting
- Management:
  - Immediate gastric lavage
  - Symptomatic and supportive therapy
  - Monitor respiration, BP, and pulse

Use in Pregnancy◊

- Limited human data, safety in pregnancy has not yet been determined; no fetal adverse effects reported in animal studies
- Unknown whether buspirone crosses human placenta; molecular weight (~422) suggests that buspirone will cross to embryo and fetus[9]
- In a surveillance study with 42 newborns exposed to buspirone during first trimester, one (2.4%) major birth defect was observed[9]
- In an observational study, buspirone was taken during the first trimester in 16 pregnancies; outcomes included 1 intrauterine death (cause unknown), 12 normal term babies, 1 newborn with a genetic defect (cystic fibrosis), and 2 elective abortions[10]
- In a review of antidepressant use in pregnancy, buspirone was included amongst the "other antidepressant group", which as a whole did not have an association with increased fetal malformations[11]

Breast Milk

- In animals, buspirone is excreted into milk; unknown excretion into human milk; unknown effects on nursing infants
- Potential of CNS impairment in a nursing infant[9]
- In a case report, buspirone was not detected in breast milk of a mother taking 15 mg three times daily (also was on fluoxetine 20 mg/day and carbamazepine 600 mg/day) during pregnancy and postpartum. However, timing of the sample in relation to the mother's ingestion of buspirone and test sensitivity were not specified[9]

Nursing Implications

- Administer consistently with or without food
- The onset of effect of buspirone is gradual; improvement may be seen within 7–10 days (but may take as long as 2–4 weeks) after starting therapy
- When switching from a benzodiazepine to buspirone, it is important to gradually taper the benzodiazepine to avoid precipitating a withdrawal reaction
- Buspirone should be taken consistently, not on an as needed basis

Patient Instructions

- For detailed patient instructions on buspirone, see the Patient and Caregiver Information Sheet (details p. 429)

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Buspirone (cont.)

Drug Interactions

- Clinically significant interactions are listed below

Class of Drug	Example	Interaction Effect
Antibiotic	Clarithromycin, erythromycin	Increased peak plasma level of buspirone (5-fold) and AUC (6-fold) due to inhibited metabolism via CYP3A4 with erythromycin
	Linezolid	Linezolid has reversible MAOI activity. MAOIs may potentiate the activity of serotonergic agents like buspirone via inhibition of serotonin metabolism. The result is an increased risk of serotonin syndrome
Antidepressant		
SSRI	Fluoxetine, fluvoxamine	Concomitant use of serotonergic agents increases the risk of serotonin syndrome Increased plasma level of buspirone (2.4-fold increase in AUC) with fluvoxamine Case reports of serotonin syndrome, euphoria, seizures or dystonia with combination
SARI	Trazodone	Concomitant use of serotonergic agents increases the risk of serotonin syndrome
TCA	Amitriptyline, clomipramine	Concomitant use of serotonergic agents increases the risk of serotonin syndrome
Irreversible MAOI	Phenelzine, tranylcypromine	MAOIs may potentiate the activity of serotonergic agents like buspirone via inhibition of serotonin metabolism. The result is an increased risk of serotonin syndrome
Reversible MAOI	IV methylene blue	Concomitant use of serotonergic agents increases the risk of serotonin syndrome
Antifungal	Itraconazole, ketoconazole	Increased plasma level and/or effect of buspirone due to inhibited metabolism via CYP3A4 with itraconazole (10.5- to 13-fold increase in C_{max})
Antipsychotic	Clozapine	Case report of GI bleeding and hyperglycemia
	Haloperidol	Increased plasma level of haloperidol (by 26%) perhaps due to competitive metabolism via CYP3A4
Antitubercular drug	Rifampin	Decreased peak plasma concentration (by 85%) and half-life of buspirone due to induced metabolism via CYP3A4
Benzodiazepine	Diazepam	Increased metabolite nordiazepam (by 15%) and adverse effects (dizziness, headache, and nausea) with diazepam Recent discontinuation (within 4 weeks) of benzodiazepine treatment for generalized anxiety disorder (GAD) may reduce response to buspirone
Calcium channel blocker	Diltiazem, verapamil	Increased peak plasma level of buspirone with verapamil and diltiazem (3.4- and 5.5-fold increase in C_{max}, respectively) due to inhibited metabolism via CYP3A4
Grapefruit juice		Increased peak plasma level of buspirone (up to 15-fold), AUC (up to 20-fold), and half-life (1.5-fold) due to inhibition of intestinal CYP3A4 metabolism
Immunosuppressant	Cyclosporine	Increased serum level of cyclosporine with possible renal adverse effects
Protease inhibitor	Indinavir, ritonavir	Case report of Parkinson-like symptoms (ataxia, cogwheel rigidity, and tremors) with indinavir/ritonavir
St. John's wort		Concomitant use of serotonergic agents increases the risk of serotonin syndrome Case reports of serotonin syndrome with combination May decrease buspirone level due to induction of CYP3A4

Further Reading

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HYPNOTICS/SEDATIVES

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
	Benzodiazepines	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)		See pp. 263–271	Dosage recommendations provided for children
Chloral hydrate	Chloral derivate	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Aquachloral[B]	Oral solution: 100 mg/mL	Dosage recommendations provided for children
Clonidine	α_2 agonist	Norepinephrine/Agonist	Catapres, Dixarit[C]	See pp. 46–49	Dosage recommendations provided for children
Daridorexant[B]	Orexin receptor antagonist	Orexin/Antagonist	Quviviq	Tablets: 25 mg, 50 mg	
Diphenhydramine	Antihistamine	Histamine/Antagonist	Benadryl, Nytol, Simply Sleep, Sominex[B], Unisom, ZzzQuil[C]	Tablets: 12.5 mg, 25 mg, 50 mg Caplets: 25 mg, 50 mg Capsules: 25 mg, 50 mg Chewable tablets: 25 mg Oral solution: 6.25 mg/5 mL, 10 mg/5 mL[B], 12.5 mg/5 mL Injection: 10 mg/mL[B], 25 mg/mL[B], 50 mg/mL	Dosage recommendations provided for children
Doxylamine[B]	Antihistamine	Histamine/Antagonist	NyQuil, Sleep Aid, Unisom Sleeptabs	Tablets: 25 mg	Dosage recommendation provided for children over age 12
Eszopiclone[D]	Cyclopyrrolone	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Lunesta	Tablets: 1 mg, 2 mg, 3 mg	Safety and efficacy not established in children
Hydroxyzine	Antihistamine	Histamine/Antagonist	Atarax[C], Vistaril[B]	Tablets[B]: 10 mg, 25 mg, 50 mg, 100 mg Capsules: 10 mg[C], 25 mg, 50 mg, 100 mg[B] Oral syrup: 10 mg/5 mL Injection: 25 mg/mL[B], 50 mg/mL	Dosage recommendations provided for children
Lemborexant[B]	Orexin receptor antagonist	Orexin/Antagonist	Dayvigo	Tablets: 5 mg, 10 mg	Safety and efficacy not established in children
Melatonin	Hormone analogue	Melatonin/Agonist		Multiple strengths/dosage forms available	See pp. 408–409
Mirtazapine	Antidepressant	Norepinephrine, serotonin/Multimodal	Remeron, Remeron RD[C], Remeron Soltab[B]	See pp. 97–101	Safety and efficacy not established in children
Pentobarbital**,[B]	Barbiturate	$GABA_A$ receptor positive allosteric modulator	Nembutal	Injection: 50 mg/mL	Dosage recommendations provided for children
Phenobarbital**,[B]	Barbiturate	$GABA_A$ receptor positive allosteric modulator		Tablets: 15 mg, 16.2 mg[B], 30 mg[C], 60 mg[C], 100 mg Elixir: 20 mg/5 mL[B], 5 mg/mL[C] Liquid[B]: 20 mg/5 mL Injection: 30 mg/mL[C], 65 mg/mL[B], 120 mg/mL[C], 130 mg/mL[B]	Dosage recommendations provided for children

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Promethazine	Antihistamine	Histamine, dopamine/Antagonist	Phenergan[B], Histanil[C]	Tablets: 12.5 mg[B], 25 mg[B], 50 mg Oral Solution[B]: 6.25 mg/5mL Suppositories[B]: 12.5 mg, 25 mg, 50 mg Injection[B]: 25 mg/mL, 50 mg/mL	Dosage recommendations provided for children over age 2
Ramelteon[B]	Selective melatonin agonist	Melatonin/Agonist	Rozerem	Tablets: 8 mg (see pp. 408–409)	Safety and efficacy not established in children
Suvorexant[B]	Orexin receptor antagonist	Orexin/Antagonist	Belsomra	Tablets: 5 mg, 10 mg, 15 mg, 20 mg	Safety and efficacy not established in children
Tasimelteon[B]	Selective melatonin agonist	Melatonin/Agonist	Hetlioz, Hetlioz LQ	Capsules: 20 mg Suspension: 4 mg/mL	Safety and efficacy not established in children
Trazodone	Antidepressant	Serotonin/Multimodal	Desyrel	See pp. 81–87	Dosage recommendations provided for children over age 6
Zaleplon[B]	Pyrazolopyrimidine	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Sonata	Capsules: 5 mg, 10 mg	Safety and efficacy not established in children
Zolpidem	Imidazopyridine derivative	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Ambien[B] Ambien CR[B] Edluar[B], Sublinox[C] Zolpimist[B]	Tablets: 5 mg, 10 mg Tablets: 6.25 mg, 12.5 mg Sublingual tablets: 1.75 mg[B], 3.5 mg[B], 5 mg, 10 mg Metered oral spray: 5 mg/spray	Safety and efficacy not established in children
Zopiclone[C]	Cyclopyrrolone	GABA/Benzodiazepine receptor agonist ($GABA_A$ receptor positive allosteric modulator)	Imovane	Tablets: 5 mg, 7.5 mg	Safety and efficacy not established in children

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. * Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com).
** Barbiturate drugs are not recommended for use as hypnotics/sedatives because they are habit forming, causing physical dependence and relatively more adverse effects than other options. Furthermore, they can have severe withdrawal symptoms; tolerance develops quickly, requiring increased dosage; they have a low margin of safety (therapeutic dose close to toxic dose); they are involved in many drug interactions (induce metabolizing enzymes); they can evoke behavioral complications including hyperactivity and conduct disorders in children and depression in adults. [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] S-isomer of zopiclone

Indications‡ (approved)

In children and adolescents:

- Anxiety (hydroxyzine)
- Sedation (promethazine, phenobarbital; chloral hydrate – Canada)
- Procedural sedation (barbiturates)
- Allergies/pruritus (antihistamines)
- Nausea/motion sickness (promethazine)
- Intractable partial arousal parasomnias (e.g., sleep terrors) (benzodiazepines)
- Sedation for diagnostic (e.g., EEG, CT scan) or dental procedures (chloral hydrate)
- Sleep-onset delay and ADHD: clonidine widely used in children[1]

In adults:

- Nocturnal sedation; short-term management of insomnia
- Preoperative sedation
- Chronic insomnia management (ramelteon, eszopiclone – USA)
- Non-24-hour sleep-wake disorders (tasimelteon – USA)

‡ Indications listed here do not necessarily apply to all hypnotics/sedatives or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications

Hypnotics/Sedatives (cont.)

General Comments

- Insomnia is common in children and adolescents who have comorbid medical, psychiatric, and/or neurodevelopmental disorders
- There are currently no medications approved for use as hypnotics in children and there is limited evidence as to the efficacy and safety of these agents in children[2]
- Medication should be used for the shortest period of time, in combination with nonpharmacological strategies; several behavioral interventions have been found to be effective.[1] These are typically referred to as "sleep hygiene strategies" and are available through a number of resources (e.g., https://caringforkids.cps.ca/handouts/healthy-living/teens_and_sleep, https://www.sleepfoundation.org/children-and-sleep/sleep-strategies-kids, https://www.anxietycanada.com/sites/default/files/SleepHygiene.pdf)
- Prior to treatment of insomnia, determine if sleep disturbance is secondary to:
  - Psychiatric disorder (e.g., depression, mania, anxiety, psychosis, ADHD, ASD)
  - Medical disorder (e.g., thyroid, peptic ulcer, pain)
  - Drug-induced (e.g., some antidepressants, corticosteroids, decongestants, sympathomimetics, theophylline, etc.)
  - Breathing disorders during sleep (e.g., sleep apnea, sleep-related asthma, hypoventilation)
  - Lifestyle (e.g., poor sleep hygiene)
  - Use/abuse of psychotropic drugs (e.g., caffeine, alcohol, nicotine, cocaine, stimulants)
  - Other sleep disorders (e.g., periodic limb movement disorder, Willis-Ekbom disease/restless legs syndrome, circadian rhythm disorders, narcolepsy)
- Treat the underlying cause of insomnia whenever possible
- Hypnotic use recommended for limited time period; long-term, continuous treatment is not recommended (though may be required in some cases)
- The goals of pharmacologic therapy are: (a) prevent progression from transient to chronic insomnia, (b) reverse sleep disruption to prevent deterioration of daytime performance, (c) resolve or mitigate underlying conditions that may be contributing to insomnia to promote a sound and satisfying sleep (sleep initiation, quality, quantity, and continuity), (d) prevent dependence on drug therapy, and (e) reinstate a normal sleep pattern without the need for medication
- Diphenhydramine showed no benefit in reducing nighttime awakenings or improving sleep quality in one RCT
- Eszopiclone[3] and zolpidem[4] showed no benefit in reducing sleep latency in children with ADHD
- Recommend that stringent sedation guidelines be adhered to (e.g., as formulated by the American Academy of Pediatrics[5]), to ensure patient safety; sedation prior to diagnostic or dental procedures should minimize physical discomfort or pain, as well as negative psychological response to treatment, and maximize amnesia

Pharmacology

- Antihistamines antagonize H_1 receptors in the brain and disrupt cortical neurotransmission associated with the arousal action of histamine
- Benzodiazepines bind non-selectively to various subtypes of “benzodiazepine”-$GABA_A$-chloride ionotropic receptors in the brain; $GABA_A$ receptor subtypes containing an α_1 subunit are associated with sedation, ataxia, and amnesia; $GABA_A$ receptor subtypes containing α_2 and/or α_3 subunits generally have greater anxiolytic activity
- Daridorexant, lemborexant, and suvorexant are dual orexin receptor antagonists that block both OX_{1R} and OX_{2R}. They block binding of orexin A and B, which are neuropeptides that promote wakefulness
- Ramelteon has high binding affinity for MT_1 and MT_2 melatonin receptors (in the suprachiasmatic nucleus) and enhances the effect of endogenous melatonin; it is not a CNS depressant, has no anxiolytic or muscle relaxant properties, and has no tolerance or abuse potential
- Tasimelteon is an agonist for MT_1 and MT_2 melatonin receptors (greater affinity to MT_2 than MT_1 receptor)
- Barbiturates, eszopiclone, zaleplon, zolpidem, and zopiclone are positive allosteric modulators of $GABA_A$ receptors with predominance to α_1 subunits

Dosing

- See pp. 289–291 for individual agents
- Dosage may need to be adjusted in patients with hepatic impairment

Pharmacokinetics

- See pp. 289–291
- Eszopiclone: T_{max} delayed after high-fat meal; AUC increased 2-fold in moderate to severe hepatic impairment
- Melatonin: Large variability in bioavailability amongst manufacturers[6]; bioavailability is greater in females than in males; C_{max} is higher in younger individuals
- Daridorexant: High-fat and high-calorie meal delays T_{max} by 1.3 h and decreases C_{max} by 16%
- Lemborexant: High-fat, high-calorie meal delays T_{max} by approximately 2 h and decreases C_{max} by 23%
- Suvorexant: Food delays T_{max} by approximately 90 min. Women attain higher serum suvorexant concentrations than men. Obese females attain higher serum suvorexant concentrations compared to non-obese females
- Ramelteon: High inter-patient variability in C_{max} and AUC; high-fat meal delays T_{max} and increases AUC by 31%. Drug exposure increased 4-fold in mild hepatic impairment; 4 active metabolites; 84% of drug is eliminated in urine
- Tasimelteon: High-fat meal delays T_{max} by 1.75 h and decreases C_{max} by 44%; smokers have 40% decrease in tasimelteon exposure
- Zaleplon: Absorption and peak plasma level may decrease with high-fat meal (C_{max} and T_{max} decreased by 35%). In one study, Japanese patients showed increased C_{max} and AUC by 37% and 64%, respectively; differences in body weight or hepatic enzyme activity may explain this difference
- Zolpidem: CR formulation is formulated with an immediate-release layer and a slow-release layer; C_{max} occurs later and is higher than with immediate-release product. Children metabolize zolpidem more quickly than adults and clearance is 3 times higher[1]. Women attain significantly higher serum zolpidem concentrations than men. Due to high protein binding, patients with low serum albumin attain higher levels of free zolpidem
- Zopiclone: Half-life can double in patients with hepatic impairment

Onset & Duration of Action

- See pp. 289–291
- Tolerance to effects of many hypnotics may occur after 2 weeks of continuous use
- Tolerance does not appear to occur with dual orexin antagonists[7]

Adverse Effects

- See chart pp. 291–294
- Children may metabolize some drugs more quickly than adults (e.g., zolpidem), resulting in underdosing and subsequent behavioral disinhibition[1]
- Some drugs may precipitate or exacerbate coexisting sleep problems (e.g., complex sleep-related behaviors, daytime drowsiness)[1]
- Daytime sedation and impairment: Dependent on drug dosage, half-life, and patient tolerance
- Antihistamines, benzodiazepines, chloral hydrate: paradoxical CNS excitation may occur
- Barbiturates, benzodiazepines: Anterograde amnesia is dependent on drug potency and dose. Rebound insomnia is dependent on drug dose, half-life, and duration of use
- Benzodiazepines: High doses may result in respiratory depression and reduced blood pressure
- Ramelteon and melatonin have been associated with decreased testosterone and increased prolactin in adults; results controversial and long-term effects unknown
- Priapism reported with trazodone and hydroxyzine (rare); the metabolite of hydroxyzine (norchlorcyclizine) has structural and conformational similarities to trazodone's metabolite (m-chlorophenylpiperazine (mCPP)) and may suggest a common underlying pharmacologic mechanism
- An association between lower antidepressant response rates when combining trazodone with fluoxetine or paroxetine in a non-randomized trial exists[8]; possibly due to CYP2D6 inhibition and an increase in trazodone's metabolite (mCPP)

D/C Discontinuation Syndrome

- Can occur with chronic use of all hypnotics (exceptions: melatonin receptor agonists and dual orexin antagonists)
- Discontinuation of hypnotics can produce:
  - Withdrawal: Occurs within 1–2 days (with short-acting agents) to 3–7 days (with long-acting agents) following discontinuation of regular use of most hypnotics (for more than 2 weeks); suggested to occur less frequently with zopiclone and zolpidem. Common symptoms include insomnia, agitation, dizziness, nausea/vomiting, anxiety, perceptual disturbances (e.g., photophobia), malaise, and anorexia. Abrupt withdrawal of high doses may result in twitching, hyperthermia, tremors, seizures and/or psychosis, and possibly death
  - Rebound: Occurs hours to days after drug withdrawal; described as worsening of insomnia beyond pretreatment levels, nightmares (due to REM rebound). More likely to occur with short-acting agents
  - Relapse: Recurrence of the insomnia, to pre-treatment levels, when the hypnotic is discontinued

Hypnotics/Sedatives (cont.)

Management

- Withdrawal of a hypnotic (after chronic use) should be tailored to each patient; consider switching medications (if on a short-acting agent) to a comparable dose of a long-acting agent and gradually tapering the dose over several weeks. For benzodiazepine examples, see p. 268

Precautions

- Abrupt withdrawal of hypnotics (excluding melatonin receptor agonists and dual orexin antagonists) may produce a significant discontinuation syndrome.
  See preceding section for symptoms and consequences of abrupt discontinuation
- Hypnotic use use may lead to hypotension or increase daytime sedation and risk of falls
- Long-term use (for years) of hypnotics may occur for patients reporting unsuccessful efforts to decrease use (due to withdrawal effects)
- Recreational abuse of hypnotics can occur (especially with benzodiazepines) to achieve a "high"; avoid use in addiction-prone individuals (no abuse potential with clonidine, melatonin receptor agonists, or trazodone); abuse may result in clouding of consciousness and visual hallucinations
- Use with caution in individuals with untreated sleep apnea
- Zolpidem and related hypnotics reported to cause complex sleep-related behaviors, including sleepwalking, driving, food binging, and sexual activity while "asleep"
- Melatonin has been suggested to have negative and positive consequences in people with autoimmune disorders. The literature on this is mixed and difficult to interpret at this time[9]

Toxicity

- Symptoms of overdose include: Excitement, restlessness, delirium, nystagmus, ataxia, and stupor (less likely with melatonin receptor agonists)
- Lethal dose of chloral hydrate is approximately 10 times the therapeutic dose (5–10 g)
- Onset of CNS symptoms occurs rapidly with zolpidem following overdose, may follow zero-order kinetics, and may be responsive to flumazenil

Use in Pregnancy◊

- See pp. 291–294 for individual agents. For benzodiazepines, see p. 269

Breast Milk

- The American Academy of Pediatrics considers many hypnotics/sedatives compatible with breastfeeding – see table pp. 291–294

Nursing Implications

- Assess personal sleep habits and underlying factors that may be contributing to insomnia (e.g., medical disorders, use/abuse of psychotropic drugs, lifestyle, etc.); use of recreational drugs may have synergistic clinical effects/drug interactions when combined with sedative/hypnotics[1]
- Suggest alternative and complementary methods of treating insomnia (e.g., cognitive-behavioral therapy, relaxation techniques, regular sleep/wake cycle 7 days/week, general sleep hygiene such as avoiding daytime naps and caffeine)
- Counsel patient regarding chronic use of hypnotic and loss of efficacy of drug over time (tolerance) (exceptions include: lemborexant, melatonin, ramelteon, suvorexant, and perhaps eszopiclone, zopiclone, and zolpidem); increasing the dose may not increase efficacy and may result in adverse or toxic effects
- Monitor children with hyperactivity or ASD taking antihistamines, benzodiazepines, or chloral hydrate for paradoxical excitation
- Chloral hydrate solution should be well diluted with water, fruit juice, or ginger ale to minimize gastric irritation
- Moisten suppositories slightly prior to insertion
- Food may delay the effects of hypnotic medications (see Comparison of Hypnotics/Sedatives pp. 291–294)
- Abrupt withdrawal after chronic use of some hypnotics may result in serious adverse events and rebound symptoms (see Discontinuation Syndrome, p. 285)
- Stop medications/substances contributing to insomnia (e.g., nicotine, stimulants, alcohol)
- Melatonin CR, ramelteon, or zolpidem CR tablets should not be split, crushed, or chewed

Patient Instructions

- For detailed patient instructions on hypnotics/sedatives, see the Patient and Caregiver Information Sheet (details p. 429)

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Drug Interactions

- Only clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Antibiotic/Anti-infective	Ciprofloxacin	Ramelteon: Increased plasma level, possibly due to inhibited metabolism via CYP1A2
	Clarithromycin	Eszopiclone, ramelteon, tasimelteon, zopiclone, zaleplon, and zolpidem: Increased plasma level of hypnotic due to inhibited metabolism via CYP3A4
	Erythromycin	Daridorexant, lemborexant, suvorexant: Increased plasma level due to inhibited metabolism via CYP3A4. Avoid combination
Anticoagulant	Warfarin	Chloral hydrate can displace warfarin from plasma proteins and subsequently increase INR
Anticonvulsant	Carbamazepine, phenytoin Valproate	Daridorexant, eszopiclone, lemborexant, suvorexant, zolpidem, zopiclone: Decreased plasma level due to induced metabolism via CYP3A4 Zolpidem: Case report of somnambulism
Antidepressant		
NDRI	Bupropion	Lemborexant: Decreased bupropion concentration 45% via CYP 2B6 induction. Concentration of active metabolite 6-hydroxybupropion also decreased
SSRI	Fluoxetine, fluvoxamine	Chloral hydrate: Increased sedation and side effects of chloral hydrate due to inhibited metabolism
	Fluvoxamine	Melatonin: Increased C_{max} (12-fold) and AUC (23-fold) due to inhibited metabolism via CYP 1A2 Ramelteon: DO NOT COMBINE; increased C_{max} (70-fold) and AUC (190-fold) due to inhibited metabolism via CYP1A2 Tasimelteon: Increased C_{max} (2-fold) and AUC (7-fold) due to inhibited metabolism via CYP1A2
SSRI, NDRI	Bupropion, fluoxetine, paroxetine, sertraline	Trazodone: Possible reduced antidepressant effect when combining with CYP2D6-inhibiting antidepressants Zolpidem: Case reports of hallucinations and delirium with bupropion, fluoxetine, paroxetine, and sertraline
SSRI, RIMA, MAOI	Fluoxetine, moclobemide, phenelzine, tranylcypromine	General: Possible additive antidepressant effect in treatment-resistant patients Trazodone: Possible reduced antidepressant effect when combining with CYP2D6-inhibiting antidepressants
SNRI	Venlafaxine	Diphenhydramine: May increase plasma level of antidepressants metabolized primarily by CYP2D6 due to inhibited metabolism Zolpidem: Case report of hallucinations and delirium
Tricyclics	Amitriptyline, clomipramine, desipramine, imipramine	Diphenhydramine: May increase plasma level of antidepressants metabolized primarily by CYP2D6 due to inhibited metabolism
	Desipramine	Zolpidem: Case report of visual hallucinations with combination
	Imipramine	Zolpidem: In one study, 5 of 8 patients on combination experienced anterograde amnesia
Antifungal	Fluconazole	Ramelteon: Increased AUC and C_{max} (150%) due to inhibited metabolism via CYP2C9
	Itraconazole, ketoconazole	Eszopiclone: Increased C_{max} (1.4-fold) and half-life (1.3-fold) due to inhibited metabolism via CYP3A4 Ramelteon: Increased C_{max} (36%) and AUC (84%) due to inhibited metabolism via CYP3A4 Suvorexant: Increased AUC (approximately 2-fold) due to inhibited metabolism via CYP3A4 Tasimelteon: Increased AUC by approximately 50% due to inhibited metabolism via CYP3A4 Zaleplon: Increased plasma levels due to inhibited metabolism via CYP 3A4 Zolpidem: Decreased clearance (41%) and increased elimination half-life (26%) due to inhibited metabolism via CYP3A4 Zopiclone: Increased AUC and elimination half-life due to inhibited metabolism via CYP3A4
Antipsychotic	Aripiprazole, chlorpromazine, fluphenazine, perphenazine, quetiapine, risperidone, etc.	Diphenhydramine: May increase plasma level of antipsychotic metabolized via CYP2D6 due to inhibited metabolism Additive CNS depression and psychomotor impairment

Hypnotics/Sedatives (cont.)

Class of Drug	Example	Interaction Effects
Antitubercular drug	Rifampin	Eszopiclone: Decreased AUC due to induced metabolism via CYP3A4 Ramelteon: Decreased C_{max} and AUC (40–90%) due to induced CYP metabolism Suvorexant: Decreased AUC (88%) due to induced metabolism via CYP3A4 Tasimelteon: Decreased AUC (by 90%) due to induced metabolism via CYP2C19 and CYP3A4 Zaleplon: Decreased AUC (80%) due to induced metabolism via CYP3A4 Zolpidem: Decreased peak plasma level (60%) and elimination half-life (36%) due to induced metabolism via CYP2C9, CYP2C19, CYP2D6, and CYP3A4 Zopiclone: Decreased AUC (80%) due to induced CYP metabolism via CYP3A4
Anxiolytic	General Lorazepam	Additive CNS effects Eszopiclone: C_{max} of both drugs increased by 22%
Barbiturates		Barbiturates are potent inducers of several CYP450 enzymes (see p. 289). Since these agents are rarely utilized as hypnotic agents, many important drug interactions have not been included in this handbook. Please refer to a drug interaction text/database for a list of drugs interacting with barbiturates
β-blocker	Metoprolol	Diphenhydramine: Decreased clearance of metoprolol (2-fold) due to inhibited metabolism via CYP2D6
Calcium channel blocker	Diltiazem Nifedipine	Diphenhydramine: Initial sharp increase seen in diltiazem concentration secondary to displacement from tissue binding sites, followed by an increase in steady-state plasma levels secondary to inhibited metabolism via CYP2D6 Melatonin: Impaired blood pressure control and increased heart rate
Caffeine	Tea, coffee, caffeine-containing soft drinks, "energy drinks"	May counteract sedation and increase insomnia
CNS depressant	Alcohol	Increased CNS depression and psychomotor impairment; in "high" doses coma and respiratory depression can occur Chloral hydrate: Disulfiram-like reaction may occur
CNS stimulant	Dextroamphetamine, lisdexamfetamine, methylphenidate, modafinil, etc.	May counteract sedation and increase insomnia
Flumazenil		Benzodiazepines, eszopiclone, zaleplon, zolpidem, and zopiclone: Antagonism of hypnotic effects
Grapefruit juice		Daridorexant, eszopiclone, lemborexant, suvorexant, tasimelteon, zaleplon, zolpidem, and zopiclone: Increased plasma level of hypnotic due to inhibited metabolism via CYP3A4 in gut wall; may result in increased bioavailability
H_2 antagonist	Cimetidine	Zaleplon: Increased peak plasma level and AUC (85%) due to inhibited metabolism via CYP3A4 and aldehyde oxidase Zopiclone: Increased plasma level of hypnotic due to inhibited metabolism via CYP3A4
Opioid	Codeine, tramadol Methadone	Diphenhydramine: Inhibited conversion of opioid to its active moiety via CYP2D6, resulting in decreased analgesic efficacy; additive effects on gastric hypomotility and CNS depression Diphenhydramine, zolpidem: Increased plasma levels of methadone, possibly due to inhibited metabolism via CYP2D6
Protease inhibitor	Ritonavir	Daridorexant, eszopiclone, lemborexant, suvorexant, tasimelteon, zaleplon, zolpidem, zopiclone: Increased plasma level of hypnotic due to inhibited metabolism via CYP3A4
St. John's wort		Daridorexant, eszopiclone, lemborexant, suvorexant, tasimelteon, zaleplon, zolpidem, zopiclone: May reduce plasma level of hypnotic due to induced metabolism via CYP3A4

For drugs interacting with benzodiazepines see pp. 270–271

Comparison of Hypnotics/Sedatives

	Dose in Children & Adolescents	Onset of Action	Time to Peak Plasma Level (T_{max})	Bio-availability	Protein Binding (PB) Volume of distribution (Vd)	Elimination Half-life ($T_{1/2}$)	Metabolizing Enzymes (CYP450)*	CYP450 Effect**	Comments
ANTIDEPRESSANTS									
Mirtazapine (Remeron)	(See p. 135)								
Trazodone (Desyrel)	(See p. 134)								
ANTIHISTAMINES									
Diphenhydramine (Benadryl, Nytol, Simply Sleep, Sominex, Unisom, ZzzQuil)	*Hypnotic*: 1 mg/kg/day PO/IM/IV: 0.5 mg/kg/day to a maximum of 50 mg/dose or 300 mg/day	60–80 min	2–4 h	40–60%	PB: 98–99% Vd: 3.3–6.8 L/kg	2–10 h	3A4, 2D6[D]	Inhibitor of 2D6 (weak)	Tolerance to hypnotic effect develops over time; paradoxical excitation may occur
Doxylamine[B] (NyQuil, Sleep Aid, Unisom Sleeptabs)	Over age 12: 12.5–50 mg/day	1–2 h	2–4 h	25%	PB: 93% Vd: 2.5 L/kg	10 h	–	–	
Hydroxyzine (Atarax[C], Vistaril[B])	*Anxiety*: Under age 6: 50 mg/day in divided doses 6–12 years: 50–100 mg/day in divided doses *Perioperative sedation*: 0.6 mg/kg PO or 1.1 mg/kg IM	15–30 min	2–4 h	80%	Vd: 16 L/kg	3–7 h (shorter in children)	–	Inhibitor of 2D6	
Promethazine (Histanil[C], Phenergan[B])	*Preoperative sedation*: Over age 2: 12.5–25 mg PO/IM/IV; maximum of 25 mg/dose	2–3 h		25%	PB: 93% Vd: 98 L/kg	16–19 h	2D6	Inhibitor of 2D6	
BARBITURATES									Not recommended for use as hypnotics/sedatives because they are habit forming, causing physical dependence and relatively more adverse effects than other options
Pentobarbital (Nembutal)	*Preoperative sedation*: 2–6 mg/kg to a maximum of 100 mg/dose po/IM or 50 mg IV (with additional doses if needed at 1 min intervals)	1 min	15 min	70–90%	PB: 35–55% Vd: 1 L/kg	35–50 h	?	Inducer of 2A6, 2B6, 2C9, 3A4	
Phenobarbital	*Preoperative sedation*: 1–3 mg/kg PO/IM	over 60 min	8–12 h	90%	PB: 20–45% Vd: 0.5–0.7 L/kg	80–120 h	3A4, 2C9, 2C19, 2E1	Inducer of 1A2, 2A6, 2B6, 2D6, 2C9, 2C19, 3A4	

Comparison of Hypnotics/Sedatives (cont.)

	Dose in Children & Adolescents	Onset of Action	Time to Peak Plasma Level (T_{max})	Bio-availability	Protein Binding (PB) Volume of distribution (Vd)	Elimination Half-life ($T_{1/2}$)	Metabolizing Enzymes (CYP450)*	CYP450 Effect**	Comments
Benzodiazepines (See pp. 272–276)									Used for night terrors, sleepwalking; paradoxical excitation may occur
Chloral hydrate (Aquachloral[B])	*Sedative* (oral or rectal): 25 mg/kg/dose *Hypnotic* (oral or rectal): 50–100 mg/kg/dose	15–30 min	?	> 95% (active metabolite trichloroethanol)	PB: 70–80% (trichloroethanol) 94% (trichloroacetic acid metabolite) Vd: 0.61 L/kg	4–12 h (trichloroethanol) 100 h (trichloroacetic acid metabolite)	2E1	?	Tolerance develops after 2 weeks; paradoxical excitation may occur C_{max} decreases and $T_{½}$ increases with chronic dosing No impact on EEG reading when used as pre-EEG sedation
Clonidine (Catapres, Dixarit[C])	*Sedative* (immediate-release formulation): 50–200 micrograms	30–60 min	1–3 h	100%	PB: 20–40% Vd: 2.9 L/kg	8–12 h	50–80% excreted unchanged in urine		Tolerance develops with time; short duration of hypnotic effect (may wear off in middle of night)
Daridorexant (Quviviq[B])	Not established; 25–50 mg	30–40 min	1–2 h (high-fat, high-calorie meal delays T_{max} by 1.3 h)	62%	PB: 99.7% Vd: 31 L/kg (adults)	8 h	3A4[D]	–	Not studied in youth; no tolerance reported
Eszopiclone (Lunesta)	Not established Children: 1–2 mg Adolescents: 2–3 mg	30–60 min	1 h (2 h after high-fat meal)	80%	PB: 52–59% Vd: 1.4 L/kg	6 h	3A4, 2E1	–	Negative RCT in ADHD-related insomnia No tolerance reported
Lemborexant (Dayvigo)	Not established; 5–10 mg	15–20 min	1–3 h (high-fat, high-calorie meal delays T_{max} by 2 h)		PB: 94% Vd: 1970 L (adults)	17–19 h	3A4[D]	Inducer of 2B6 (weak)	Not studied in youth; no tolerance reported
Melatonin	0.5–10 mg Infants: 1 mg Children: 3–6 mg Adolescents: 3–9 mg		30–60 min Sustained-release: 4 h		PB: 61–85%	30–50 min	1A2[D], 2C9, 2C19	–	For acute or chronic circadian rhythm disturbance; used in children with developmental disabilities; no tolerance reported

	Dose in Children & Adolescents	Onset of Action	Time to Peak Plasma Level (T_{max})	Bio-availability	Protein Binding (PB) Volume of distribution (Vd)	Elimination Half-life ($T_{1/2}$)	Metabolizing Enzymes (CYP450)*	CYP450 Effect**	Comments
Ramelteon[B] (Rozerem)	Not established; 8 mg	30 min	0.5–1.5 h (fasting) food delays T_{max} by 45 min	2% (extensive first-pass metabolism)	PB: 82% Vd: 1.05 L/kg	1–2.6 h (M-II metabolite: 2–5 h)	1A2[D], 2C9, 3A4	–	Not studied in youth; no tolerance reported
Suvorexant[B] (Belsomra)	Not established; 5–20 mg	30 min	2 h (food delays T_{max} by 90 min)	82%	PB: > 99% Vd: 49 L (adults)	12 h	2C19, 3A4[D]	–	Not studied in youth; evidence for sleep maintenance insomnia in adults
Tasimelteon[B] (Hetlioz)	Not established; 20 mg	Weeks to months	0.5–3 h	38%	PB: 90% Vd: 56–126 L/kg	1.3 h	1A2, 3A4	–	Not studied in youth; no tolerance reported
Zaleplon[B] (Sonata)	Not established; 5–20 mg	15–30 min	0.9–1.5 h (delayed up to 3 h after high-fat meal)	30%	PB: 60% Vd: 1.4 L/kg	0.9–1.1 h	3A4, aldehyde oxidase[D]	?	Not studied in youth; no tolerance reported
Zolpidem (Ambien[B], Ambien CR[B], Edluar[B], Sublinox[C], Zolpimist[B])[E]	Not established IR: 5–10 mg CR: 6.25–12.5 mg	30 min	IR: 1.6 h; 2.2 h with food CR: 1.5 h; 4 h with food SL: 0.5–3 h (delayed 28% with food) Spray: 0.9 h (mean; delayed with food)	70%	PB: 93% Vd: 0.54 L/kg	1.5–4.5 h CR: 2.8 h SL: 1.57–6.73 h (5 mg), 1.75–3.77 h (10 mg) Spray: 1.7–5 h (5 mg), 1.7–8.4 h (10 mg) (Increased significantly in hepatic impairment)	1A2, 2C9, 2C19, 2D6, 3A4[D]	–	Negative RCT in ADHD-related insomnia; no tolerance reported
Zopiclone[C] (Imovane)	Not established 3.75–7.5 mg	30 min	< 2 h	> 75%	PB: 45% Vd: 0.54 L/kg	3.8–6.5 h	2C8, 3A4[D]	?	Not studied in youth; no tolerance up to 4 weeks reported

* Cytochrome P-450 enzymes involved in drug metabolism, ** Effect of drug on cytochrome enzymes, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Primary route of metabolism, [E] Sublingual and oral disintegrating tablets have been formulated in two strengths and may have a faster onset of action

Comparison of Hypnotics/Sedatives (cont.)

	Effect on Sleep Architecture	Main Adverse Effects	Precautions	Pregnancy/Lactation◊
ANTI-DEPRESSANTS				
Mirtazapine	Decreased sleep onset latency, increased duration and reduced waking; little effect on REM	See p. 98	See p. 100	See p. 100
Trazodone	Decreased sleep onset latency and REM; improves sleep efficiency; increased slow-wave sleep	See p. 83	See p. 84	See p. 85
Antihistamines	Decreased sleep onset latency	Daytime sedation, incoordination, anticholinergic effects (dry mouth, blurred vision, confusion, delirium, urinary retention), GI disturbances, paradoxical CNS excitation can occur, acute generalized exanthematous pustulosis Tolerance to effects occurs within days or weeks	CNS depression; patients with respiratory disease, cardiovascular disease, increased intraocular pressure; urinary obstruction; thyroid dysfunction; focal lesions Low abuse potential	Diphenhydramine: Fetal risk: Considered safe for use in pregnancy Breastfeeding: Excreted into milk; drowsiness or irritability may occur; manufacturer states use contraindicated in nursing Doxylamine: Fetal risk: Approved for use in pregnancy-associated nausea and vomiting Breastfeeding: Likely excreted into breast milk; drowsiness or irritability may occur Hydroxyzine: Fetal risk: Considered safe for use in pregnancy Breastfeeding: Unknown passage into milk; unknown effects on nursing infants
Barbiturates	Suppress REM sleep and delta sleep; REM rebound on withdrawal	Confusion, hangover, drowsiness, lethargy, nightmares, excitement if given to patients in severe pain, bradycardia, hypotension, syncope Can cause severe depression (risk of suicide) Skin rash (1–3%), nausea, vomiting Weight gain	Avoid in severe hepatic impairment, porphyria, uncontrolled pain (delirium may result) pulmonary insufficiency Watch for CNS depression, hypotension, paradoxical stimulatory response (agitation and hyperactivity), and respiratory depression Risk of tolerance; high potential for abuse and dependence	Fetal risk: Limited human data but barbiturates cross the placenta; an increase in congenital defects and hemorrhagic disease of newborns reported; withdrawal symptoms seen in neonate Breastfeeding: Excreted into breast milk; not recommended
Benzo-diazepines	Suppressed slow wave sleep	See p. 267	High abuse potential Rebound insomnia on withdrawal. Watch for paradoxical stimulatory response (agitation and hyperactivity)	See p. 269
Chloral hydrate	Decreased sleep onset latency and nighttime awakenings with minimal effects on REM sleep	Nausea, vomiting, unpleasant taste, flatulence, hangover, ataxia, nightmares, skin rash Does not accumulate with chronic use; will displace other highly protein-bound drugs from plasma proteins	Caution in hepatic and renal impairment, gastritis, peptic ulcer, and cardiac distress Doses above 2 g can impair respiration and decrease blood pressure Tolerance can occur with chronic use; withdrawal reactions reported. Watch for paradoxical stimulatory response (agitation and hyperactivity)	Fetal risk: Crosses placenta; no human or animal studies on teratogenicity; prolonged use during pregnancy may cause withdrawal symptoms in the neonate Breastfeeding: Excreted into human breast milk; use by nursing mothers causes neonatal sedation

	Effect on Sleep Architecture	Main Adverse Effects	Precautions	Pregnancy/Lactation◊
Clonidine	Decreased sleep onset latency; reduced REM, slow-wave sleep; middle of night awakenings may occur as blood levels drop	See p. 47	Has a narrow therapeutic index; reports of overdose Rebound hypertension on discontinuation Avoid in patients with Raynaud syndrome	Fetal risk: Crosses placenta; animal studies suggest teratogenic effects; no adequate well-controlled studies in pregnant women; may lower fetal heart rate; transient rise in blood pressure in the newborn cannot be excluded postpartum Breastfeeding: Excreted into human milk; effects on infant unknown
Daridorexant	Decreased sleep onset and REM latency; sleep architecture appears to be preserved	Headache, somnolence, fatigue, dizziness, nausea, complex sleep-related behaviors	Higher doses may increase risk of impaired coordination, sleep paralysis, hallucinations, cataplexy, and daytime somnolence Moderate abuse potential Caution with sleep apnea	Fetal risk: No evidence of teratogenicity in animals; no controlled data in human pregnancy Breastfeeding: Excretion into breast milk likely; no human data
Eszopiclone	Decreased sleep onset latency, decreased nighttime awakenings, increased total sleep time	> 10%: Unpleasant taste, headache > 5–10%: Dry mouth, dyspepsia, dizziness, somnolence, respiratory infection Memory impairment reported in the morning, often only in the first week of treatment	High doses (> 6 mg) can produce amnesia, euphoria, and hallucinations Caution in respiratory impairment, hepatic dysfunction, depression, and in combination with CYP3A4 inhibitors Dependence, withdrawal, and rebound insomnia are possible Moderate abuse potential	Fetal risk: No evidence of teratogenicity in animals or congenital anomalies in humans Breastfeeding: Excretion into breast milk likely given pharmacokinetic parameters; effects on nursing infant unknown but potential for sedation
Lemborexant	Decreased sleep onset latency and REM latency; increased REM and total sleep time[10]	Somnolence, fatigue, headache, nightmares, abnormal dreams, complex sleep-related behaviors	Higher doses may increase risk of impaired coordination, sleep paralysis, hallucinations, cataplexy, and daytime somnolence Moderate abuse potential	Fetal risk: Animal data suggests possible risk; no controlled data in human pregnancy Breastfeeding: Excretion into breast milk likely; no human data
Melatonin	Decreased sleep onset latency; main effect on circadian rhythms	Nausea, headache, hypotension, bradycardia; possible exacerbation of comorbid arthritis, asthma Suppression of hypothalamic-gonadal axis. No rebound or withdrawal effects	May elevate blood glucose levels, increase risk of bleeding, and produce changes in mood Caution in seizure disorders and cardiovascular disease	Avoid in pregnancy and breastfeeding due to hormonal effects including decreases or increases in levels of luteinizing hormone, progesterone, estradiol, thyroid hormone (T4 and T3), growth hormone, prolactin, cortisol, oxytocin, and vasopressin
Ramelteon	Decreased sleep onset latency; no effect on night waking; small decreases in stages 3 and 4	Drowsiness, dizziness, fatigue, headache, nausea No behavioral impairment reported	Reported to decrease testosterone and increase prolactin levels; not known what effect chronic or even chronic intermittent use may have on the reproductive axis AUC and T_{max} increased 4-fold in mild hepatic impairment	Fetal risk: Animal data suggests possible risk; no controlled data in human pregnancy Breastfeeding: Excretion into breast milk likely; no human data
Suvorexant	Decreased sleep onset latency; small reduction in REM latency; sleep architecture appears to be preserved	Somnolence, fatigue, headache, abnormal dreams, muscle weakness, dry mouth	Higher doses may increase risk of impaired coordination, sleep paralysis, hallucinations, and daytime somnolence Moderate abuse potential	Fetal risk: Animal data suggests possible risk; no controlled data in human pregnancy Breastfeeding: Excretion into breast milk likely; no human data
Tasimelteon	Entrains circadian rhythm in totally blind patients; increases nighttime sleep duration; reduces daytime sleep	Headache, nightmares or abnormal dreams, increased ALT	Potential to impair performance of activities requiring mental alertness	Fetal risk: Animal studies revealed evidence of teratogenicity in doses 240 times higher than used in humans; no controlled data in human pregnancy Breastfeeding: Excretion into breast milk unknown; no human data

Comparison of Hypnotics/Sedatives (cont.)

	Effect on Sleep Architecture	Main Adverse Effects	Precautions	Pregnancy/Lactation◊
Zaleplon	Decreased sleep onset latency and short-wave sleep	> 10%: Headache 1–10%: Dizziness, somnolence, amnesia, malaise, pruritus, dysmenorrhea, nausea, paresthesia, tremor < 1%: Alopecia, ALT & AST increased, anemia, angina, ataxia, bundle branch block, palpitation Case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)	Due to rapid onset of action, should be taken immediately before bedtime Dependence, withdrawal, and rebound insomnia are possible Moderate abuse potential Caution in hepatic dysfunction	Fetal risk: No controlled data in pregnancy; limited data suggests no teratogenic effects Breastfeeding: Excreted into breast milk; not believed to be clinically important
Zolpidem	Decreased sleep onset latency and increased total sleep time Time spent in REM sleep decreased with higher doses No effect on stages 3 and 4	> 10%: Drowsiness, dizziness, headache, somnolence 1–10%: Abnormal dreams, anxiety, apathy, retrograde amnesia, ataxia, attention disturbance, disinhibition, euphoria, constipation, diarrhea < 1%: Agitation, anorexia, bronchitis, diaphoresis, hepatic function abnormalities, postural hypotension Case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls); residual sedation upon awakening	Caution in hepatic dysfunction, respiratory impairment Dependence, withdrawal, and rebound insomnia are possible Moderate abuse potential	Fetal risk: Increased risk of low-birth-weight, preterm deliveries, congenital anomalies, and caesarian deliveries in humans. No risk of major congenital malformations found using Swedish Medical Birth Registry Breastfeeding: Excreted into breast milk; can cause sedation, lethargy, and changes in feeding habits in exposed infants
Zopiclone	Little effect on slow-wave sleep REM delayed but duration the same; stage 1 shortened; stage 2 increased	Somnolence, dizziness, confusion, anterograde amnesia or memory impairment, agitation, nightmares, bitter taste, dry mouth, bad breath, dyspepsia, palpitations, tremor, rash, chills, sweating Severe drowsiness, confusion, and incoordination are signs of drug intolerance or excessive dosage Rarely hallucinations and behavioral disturbances	Caution in hepatic dysfunction Dependence, withdrawal, and rebound insomnia are possible Moderate abuse potential	Fetal risk: No evidence of major congenital anomalies in humans Breastfeeding: Excretion into breast milk likely; no human data for nursing infants

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Further Reading

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Additional Suggested Reading

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MOOD STABILIZERS

Classification

- Mood stabilizers can be classified as follows:

Chemical Class	Agent	Page
Lithium	Example: Lithium carbonate	See p. 296
Anticonvulsant	Examples: Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproate	See p. 305
Antipsychotics		
Second-generation	Examples: Asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone	See p. 175
Third-generation	Aripiprazole, brexpiprazole, cariprazine	See p. 206
Antidepressant/antipsychotic combination	Fluoxetine/olanzapine[B] (Symbyax)	See p. 53 and p. 176

[B] Not marketed in Canada

Lithium

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Lithium carbonate	Lithium salt	Lithium/Enzyme modulator	Lithane[C], Carbolith[C] Lithobid[B], Lithmax[C]	Capsules: 150 mg, 300 mg, 600 mg Tablets: 300 mg[B] Extended-release (ER) tablets: 300 mg, 450 mg[B]	Safety and efficacy not established in children under age 12
Lithium citrate	Lithium salt	Lithium/Enzyme modulator	(Only available as generic)[B]	Oral solution: 8 mEq/5 mL (each 5 mL equivalent to 300 mg lithium carbonate)	

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

In children and adolescents:

- 👍 Bipolar disorder (BD): Long-term maintenance (USA – children 12 years and up)
- Mania, hypomania, and depression: Prevention or diminution of the intensity. Decreases relapse (vs. placebo) [OR 0.66, 95% CI 0.52–0.85][2]
- Mania: Single RCT in children and adolescents, which enrolled a large proportion of pediatric bipolar disorder NOS patients (high prevalence of patients with young age of onset, comorbid ADHD, disruptive behavior disorders, and mixed symptoms)[3]
- Bipolar disorder and comorbid substance use disorder: One double-blind study suggests benefits in adolescents
- Refractory depression and OCD: Augmentation of the action of antidepressants
- Suicidal behavior/risk: See General Comments (p. 297)
- Behavioral symptoms of autism spectrum disorders, treatment of chronic aggression/antisocial behavior/impulsivity; may be useful in patients with an affective component to symptoms; reduces aggression in conduct disorders (moderate effect)
- Acute psychotic episodes with affective features
- Migraine, cluster headaches

In adults:

- 👍 Long-term maintenance for bipolar disorder
- 👍 Treatment of acute mania or mixed episodes
- Suicidal behavior/risk: See General Comments (p. 297)

General Comments

- Considered first-line therapy for the treatment of acute mania, a second-line option for acute bipolar depression, and a first-line maintenance treatment[4]
- A guideline for pediatric bipolar disorder in patients with mixed presentations on maintenance treatment recommends no first-line options due to lack of evidence; Lithium monotherapy is a second-line option[5]
- "Classic" or narrowly defined mania responds best to lithium treatment (up to 80%). Other possible predictors of response include: Family history of lithium response in first-degree relatives, few prior episodes of mania or depression, complete recovery between episodes, and no neurological impairment
- In certain geographies and medical cultures, there has been significant growth in rates of diagnosis of "pediatric bipolar disorder" when the diagnosis "disruptive mood dysregulation disorder" (DMDD) would be more accurately applied. The clinician treating a child with suspected BD should refer to the psychiatric disorders chapter (pp. 10–12) regarding the difference between the two conditions
- Several clinical trials in pediatric BD have been conducted using patient populations, which, in retrospect, may be viewed as having DMDD, and results from these trials may not be generalizable to treatment of patients with a classic bipolar illness (and vice versa)
- Less response noted in patients with dysphoric/psychotic mania or mania with mixed features (30–40%), rapid-cycling BD (20–30%), in patients with multiple prior episodes, comorbid medical conditions, in adolescents, in patients with substance use disorder and those with high anxiety ratings
- Suggested to be more effective in augmenting antidepressants in bipolar than in unipolar depression
- May be more effective in preventing manic/hypomanic episodes or mania with mixed features than depressive episodes, especially if mania precedes depression
- As long-term lithium treatment is potentially thyrotoxic, it is important to regularly assess thyroid function[6]
- Efficacious in reducing clinical symptoms in those with rapid-cycling BD[7]
- Risk of death from suicide may be equally reduced among patients treated with lithium or valproate in adults
- Lithium in suicide prevention:
  - Large population-based studies provide contradictory evidence regarding natural lithium in groundwater correlating to reduced suicide rates[8]
  - An analysis in Japan demonstrated an inverse correlation between lithium levels in local drinking water and adolescent psychotic experiences[9]
  - Multiple studies and meta-analyses show an absolute reduction of suicide risk for adults taking lithium therapeutically with and without a BD diagnosis[10]
  - Due to uncertainty (publication bias, heterogeneity of studies), lithium may be used in the prevention of suicide but should be reserved for cases in which treatment of underlying disorders has failed or risk is severe

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Lithium (cont.)

Pharmacology

- Exact mechanism of action remains unknown; postulated that lithium may stabilize catecholamine receptors, alter calcium-mediated intracellular functions, and increase GABA activity. Lithium modulates intracellular signaling through actions on second messenger systems that include:
  (1) inhibition of inositol monophosphatase that alters neurotransmission via the phosphatidyl inositol system,
  (2) reduction of protein kinase C activity that affects genomic expression associated with neurotransmission,
  (3) activation of the signaling cascade utilized by endogenous growth factors, and
  (4) inhibition of glycogen synthase kinase 3 (GSK3), which is associated with inflammation and the circadian rhythm[11].
  Collectively, these mechanisms are thought to reduce the responsiveness of neurons to stimuli from muscarinic, cholinergic, and α-adrenergic neurotransmitters
- Research data suggest that chronic lithium administration exerts a beneficial effect on neurotrophins
- Administration of lithium requires 10–14 days before the complete effect is typically observed, therefore acute mania symptoms are often treated with an antipsychotic or benzodiazepine in conjunction with lithium (or initially as monotherapy, and lithium may subsequently be added)

Dosing

- See baseline monitoring recommendations (p. 301)
- Lithium has a low therapeutic index and a narrow therapeutic range; effective serum levels are close to toxic concentrations
- An initial test dose of 300 mg is recommended to assess how well lithium is tolerated
- Increase dose slowly (150–300 mg every 2–3 days) to minimize adverse effects; the following *target* doses have been suggested in patients with normal renal function: weight less than 25 kg, give 600 mg/day; 25–39 kg, give 900 mg/day; 40–50 kg, give 1200 mg/day; if over 50 kg, give 1500 mg/day; final dose should be guided by plasma level and clinical response. Maximum dose: 60 mg/kg/day
- A pharmacokinetic evaluation of children 8–18 years of age, using total body weight, suggests a maintenance dose of 25 mg/kg/day of lithium in two divided doses achieved $\geq$ 50% reduction in YMRS in 74% of patients, while causing a lithium level greater than 1.4 mmol/L in 8% of patients
- Acute treatment goal level: 0.8–1.2 mmol/L
- Maintenance treatment goal level: 0.6–1 mmol/L
- Chronic aggressive disorders: levels of 0.8–1.2 mmol/L were studied[12]
- Lithium level below 0.6 mmol/L have been shown in controlled trials to be less effective in preventing relapse[13]
- Renal dysfunction: If creatinine clearance is 10–50 mL/min, use 50–75% of the standard dose; if creatinine clearance is below 10 mL/min, use 25–50% of the standard dose. Patients undergoing dialysis should take their dose AFTER each dialysis treatment
- Once patient is stabilized, once-daily dosing is preferable (if patient can tolerate this), usually given at night. Note: conversion from bid to once daily bedtime dosing (at same total daily dose) may increase 12-hour post-dose lithium level by 10–30%
- It is important to be aware of the symptoms of mild–severe lithium toxicity, as many children and adolescents resist bloodwork for serum level monitoring
- Patients sensitive to side effects that are related to high peak plasma levels, e.g., tremor, urinary frequency, and GI effects (i.e., nausea), may better tolerate ER formulations. Alternatively, continued administration of lithium in divided doses may be required to decrease adverse effects related to peak serum levels
- Missed doses or drug interactions may reduce lithium level and precipitate relapse; most drug interactions, however, precipitate toxicity

Pharmacokinetics

- Lithium is completely absorbed from the GI tract
- Peak plasma level: 1–2 h (ER formulation = 4–5 h); ER forms produce lower C_{max} but similar AUC
- Half-life: 8–35 h; half-life increases with duration of therapy (e.g., up to 58 h after 1 year's therapy). In children, half-life shorter and clearance faster than in adults
- Excreted primarily (95%) by the kidney; therefore, adequate renal function is essential in order to avoid lithium accumulation and intoxication (see Dosing, above); clearance is significantly correlated with total body weight. 80% of filtered lithium is reabsorbed in the proximal convoluted tubules; therefore, clearance approximates 20% of GFR or 20–40 mL/min
- Lithium is secreted in saliva, reaching concentrations 3 times those observed in plasma – saliva composition is altered (see GI Effects below)

Adverse Effects

- Younger children may experience more adverse effects than older children
- See table p. 330

CNS Effects

- General weakness (up to 33%), fatigue, dysphoria, and restlessness are usually transient and may coincide with peaks in lithium concentration
- Drowsiness, tiredness
- Dizziness and vertigo [Management: Administer with food, use ER formulation to avoid peak lithium levels, or reduce or split dosage]
- Cognitive blunting, memory difficulties (up to 28%), decreased speed of information processing, confusion, lack of drive, productivity or creativity [Management: Assess lithium plasma level and thyroid function; ER formulation, lower dose, or liothyronine may improve cognitive function]
- Slight negative effect on vigilance, alertness[14], learning, and short-term memory after long-term use
- Slurred speech, ataxia – evaluate for lithium toxicity
- Neuromuscular: Incoordination, muscle weakness, fine tremor/shakiness
- Tremor – incidence reported to be about 27% (range of 4–65% in individual studies). Generally symmetric, related to dose and blood level, and non-progressive. Usually limited to hands or upper limbs, worsening with fine motor activities (e.g., writing). The tremor is at a higher frequency than with antipsychotics[15] (8–13 Hz vs. 4–7 Hz, respectively). Coarse or severe tremor may be a sign of lithium toxicity. Tremor is more frequent in combination with an antidepressant or antipsychotic, valproic acid, or carbamazepine, with excessive caffeine use, or alcoholism. Frequency of tremor decreases with time [Management: Reduce dose, eliminate dietary caffeine (caution: this can elevate lithium level); β-blocker (e.g., propranolol or atenolol) may be of benefit]. Chronic treatment can affect the peripheral nervous system involving motor and sensory function
- Seizures may occur rarely
- Headaches; rarely, papilledema/elevated intracranial pressure (pseudotumor cerebri) reported

Cardiovascular Effects

- Bradycardia
- ECG changes: 20–30% benign T-wave changes (flattening or inversion) and QRS widening at therapeutic doses[16]; use lithium cautiously in patients with pre-existing cardiac disease; arrhythmias and sinus node dysfunction including AV block occurs less frequently (sinus node dysfunction reported with lithium-carbamazepine combination, with high plasma levels of lithium, and in patients taking other drugs that may affect conduction; first degree AV block has been reported in some cases[17]); sporadic case reports have suggested lithium is associated with Brugada syndrome (a cardiac conduction disorder that has led to sudden cardiac death). [Assess patient who has a syncopal episode]

Endocrine & Metabolic Effects

- Long-term effects: Clinical hypothyroidism occurs in up to 34% of patients, often within the first year – risk greater in women over age 40 and in patients with rapid-cycling BD – may be more common in regions of high dietary iodine (monitor TSH level – may require levothyroxine therapy). Subclinical hypothyroidism (high TSH and normal free T_4) found in 25% of patients taking lithium. Rare cases of hyperthyroidism and induction of anti-thyroperoxidase antibodies[18] reported
- Goiter (not necessarily associated with hypothyroidism) – may be more common in regions of dietary iodine deficiency
- Hyperparathyroidism with hypercalcemia reported in 10–40% of patients on maintenance therapy; may predispose to decreased bone density or to cardiac conduction disturbances; occasional reports of parathyroid adenoma and hyperplasia
- Reports of irregular or prolonged menstrual cycles in up to 15% of females
- Weight gain – up to 60% incidence (25% of patients gain more than 4 kg); may be related to increased appetite, fluid retention, altered metabolism or to hypothyroidism. Mean gain is 7.5 kg (range 3–28 kg) on lithium alone (may be higher with drug combinations) and may be related to dose [Management: Reduce caloric intake]
- Abnormal sugar and insulin metabolism appear to relate less closely to lithium concentrations than to being overweight, which may be induced by lithium. In controlled studies, lithium did not influence glucose tolerance[15]

GI Effects

- Usually coincide with peaks in lithium concentration and are likely due to rapid absorption of lithium; most stop after a few weeks; in chronic use, evaluate for lithium toxicity
- Nausea – up to 50% incidence, abdominal pain [Management: Administer with food or use ER formulation or lithium citrate liquid]
- Vomiting – 20% incidence; higher with increased plasma level [Management: Use multiple daily dosing, ER formulation or lower dose]
- Diarrhea, loose stools – up to 20% incidence. ER formulation may worsen this side effect in some patients [Management: If on an ER formulation, change to a regular lithium formulation; fewer problems noted with lithium citrate formulation; if all else fails and cannot decrease the lithium dose, consider loperamide prn]
- Metallic taste: Composition of saliva altered (ions and proteins)
- Excessive thirst (up to 36% incidence), dry mouth, mucosal ulceration (rare), hypersalivation occasionally reported

Lithium (cont.)

Renal Effects

- Polyuria and polydipsia – up to 60% risk (dose related); monitor for fluid and electrolyte imbalance – usually reversible if lithium stopped (after medium-term treatment, i.e., up to 6 years, but often irreversible after 15 years); however, several cases of persistent diabetes insipidus reported up to 57 months after lithium stopped [potassium-sparing diuretic (amiloride 10–20 mg/day) or DDAVP tablets may be useful]; ER formulations dosed once daily may cause less impairment of urine concentrating function
- One study found polyuria strongly associated with concomitant serotonergic antidepressants
- Reduced GFR reported with chronic treatment, especially in patients who have had one or more episodes of lithium intoxication
- Histological changes include: (a) interstitial fibrosis, tubular atrophy, and glomerulosclerosis, seen in 26% of patients after treatment beyond 2 years – primarily those with impaired urine concentrating ability; (b) distal tubular dilatation and macrocyst formation
- Rare cases of nephrotic syndrome with proteinuria, glycosuria and oliguria, edema, and hypoalbuminemia
- Renal failure may still progress after discontinuation of lithium and may depend on severity of renal disease

Dermatological Effects

- New onset or exacerbation of acne (common) [topical benzoyl peroxide, tretinoin, differin or antibiotic preparations; avoid oral isotretinoin due to risk of worsening mood symptoms/relapse][19]
- Dry skin common
- Skin rash, pruritus, exacerbation or new onset of psoriasis. Incidence of exacerbation has ranged widely (3.4–45%). A 2012 meta-analysis suggested there was no significant difference in prevalence of skin disorders in patients on lithium[20]
- Dryness and alopecia (possibly related to hypothyroidism); alopecia reported in 12–19% of chronic lithium users
- Folliculitis
- Case reports of nail pigmentation

Other Adverse Effects

- Blurred vision may be related to peak plasma levels; reduction in retinal light sensitivity, nystagmus
- Changes in sexual function – up to 10%; includes decreased libido, erectile dysfunction, priapism, and decreased sperm motility; rare soreness or ulceration of genitals
- Edema, swelling of extremities – evaluate for sodium retention [use diuretics with caution – see Drug Interactions p. 304 – spironolactone may be preferred]
- Anemia, leukocytosis (common), leukopenia, albuminuria; rarely aplastic anemia, agranulocytosis, thrombocytopenia, occasional eosinophilia and thrombocytosis

D/C Discontinuation Syndrome

- Rarely anxiety, instability, and emotional lability reported following abrupt withdrawal
- Rapid discontinuation (over 1–14 days) led to a more rapid (5-fold) recurrence risk of mania or bipolar depression than a gradual discontinuation over 2–4 weeks[21]
- Isolated case of hyperthyroidism developing after cessation or reduction of lithium therapy

Precautions

- **Narrow therapeutic window** – toxic dose is only 50% greater than therapeutic dose, can be lethal in overdose; assess factors affecting adherence and fluid status, e.g., chaotic family situation, uncooperative patient, purging behaviors, disordered eating (especially fluid and salt intake) before prescribing
- Good kidney function; consistent salt and fluid intake are essential
- Excessive loss of sodium (due to vomiting, diarrhea, use of diuretics, heavy sweating, etc.) causes increased lithium retention, possibly leading to toxicity; lower doses of lithium are necessary if patient is on a salt-restricted diet (which includes most low-calorie diets)
- Do not rapidly increase lithium and antipsychotic dosage at the same time, due to risk of neurotoxicity
- Patients with developmental delays and/or intellectual disability may be more susceptible to neurotoxicity
- **ECT** – there are some case reports of lithium toxicity (excessive cognitive disturbance, prolonged nausea, prolonged seizures) when ECT is added to lithium therapy for bipolar disorder, however, removal of lithium may result in rebound mania or return of severe symptoms. The evidence currently favors continuing lithium therapy if ECT is needed, but clinical judgment is required.[22, 23] Also see ECT chapter p. 148

Contraindications

- Brain damage
- Renal disease – especially if low sodium diet required; absolute contraindication in severe insufficiency
- Cardiovascular disease
- Severe debilitation
- Disorders associated with purging

Toxicity

- Three types of toxicity:
  - Acute overdose (someone not taking lithium on a chronic basis):
    - 10–20% of cases
    - Mainly CNS (confusion, tremor, dysarthria, ataxia, nystagmus) with fasciculations, fibrillations, myoclonus, and polyneuropathy seen occasionally; GI symptoms – frequent nausea, vomiting, and diarrhea; renal symptoms of polyuria, polydipsia or nephrogenic diabetes insipidus and cardiovascular signs of arrhythmia, Brugada syndrome, low blood pressure, and rarely shock may occur
    - Usually carries less risk and patients usually show only mild symptoms despite lithium concentration
  - Acute on chronic overdose (someone taking lithium on a chronic basis): Largest group, more likely to develop clinical toxicity as brain concentration has already reached equilibrium with their plasma concentration. Even moderately high serum concentrations may be associated with severe symptoms. Elimination half-life of lithium may be prolonged
  - Chronic poisoning: Can occur at any time during lithium therapy. Contributing factors include change in daily dose, chronic excessive dosing, changes in sodium or hydration status, renal disease, drug interactions, infection, and surgery. This type of poisoning demonstrates the closest correlation between clinical signs, lithium concentration, and prognosis
- ER formulations: Delayed onset of toxicity, may result in severe or prolonged symptoms. Repeated determinations of serum lithium levels should be performed due to sustained absorption

☞ **Clinicians should specifically evaluate the following side effects for evidence of elevated dose or toxicity, in the predictable sequence of toxicity based upon serum concentration:**

	Mild Toxicity (1.5–2 mmol/L)	Moderate/Severe Toxicity (> 2 mmol/L)
Gastrointestinal symptoms	Nausea, pain, vomiting, diarrhea	Severe pain, recurrent or intractable diarrhea or vomiting
Movement/neurological symptoms	Fatigue, weakness, slurred speech, drowsiness, mild tremor, fasciculations, ataxia, confusion, dysarthria	Hyperreflexia, stupor, coma, seizure, ataxia, cerebellar signs
Cardiovascular symptoms	T-wave changes (flattening/inversion)	Bradycardia, tachycardia, hypotension, cardiovascular collapse
Notes	• May progress slowly, follow symptoms carefully	• Usually requires ICU-level intervention • Beware of rebound in 6–12 h
Treatment	• Hold lithium dose or switch to other agent until confirmation lithium levels safe	• Discontinue lithium • Symptomatic treatments • May need forced alkaline diuresis or peritoneal dialysis/hemodialysis • Benzodiazepines for seizure

- Deaths have been reported; when serum lithium level exceeds 4 mmol/L, the prognosis is poor

Lab Tests/Monitoring

- At beginning of treatment: Personal and family medical history, including thyroid function, previous heart disease, renal disease, co-medications
- Labs at initiation and every admission:
  1. Fasting blood glucose
  2. CBC and differential
  3. TSH
  4. BUN, creatinine, electrolytes
  5. Calcium
  6. ECG, parathyroid hormone[24]
  7. Lithium level (at every admission and as per below, see p. 302)
  8. Pregnancy test, if appropriate; ensure adequate contraception in place for females of child-bearing potential

Lithium (cont.)

- Monitoring of renal function: Baseline testing (as outlined above) at 3 months, then minimally every 6–12 months thereafter (depending on stability and concurrent medications, e.g., NSAIDs, ACE inhibitors, diuretics). Patients require further investigation if creatinine levels consistently trend upwards. Urinalysis to evaluate for hematuria and proteinuria if indicated by an unexplained rise in serum creatinine
- On an outpatient basis, repeat tests (1) and (2) if clinically indicated; (3) and (4) at 3 months, then every 6–12 months in stable patients; (5) at 6 months and annually; (6) and (8) as clinically indicated to identify or rule out QT prolongation, hyperparathyroidism, and pregnancy
- Plasma level monitoring: Measure first plasma level 5 days after starting therapy (sooner if toxicity is suspected). Measure once weekly for the first 2 weeks, thereafter at clinical discretion – at least q3–6 months, whenever a new drug is prescribed or if the dose is increased
- Blood levels should be measured at TROUGH, i.e., 9–13 h after last dose. Note that a.m. trough levels will be 10–30% higher if moving from twice or three times daily dosing to once daily dosing at bedtime if serum levels are taken the following morning
- In one study, serum levels were 17% higher when moving from twice daily dosing to bedtime only dosing when serum levels were taken 12 h later
- Symptoms of moderate toxicity are not always evident, so regular lithium levels are needed. In one study, 6.8% of patients had levels greater than 1.5 mmol/L, with only 28% showing toxic symptoms

Use in Pregnancy◊

- Treatment with lithium is effective in the prevention of mood episodes in bipolar disorder during pregnancy, but there is a lack of consensus on its use. Some data suggest women with bipolar 1 disorder and good response to lithium may have lower risk of mood destabilization while pregnant, even without pharmacotherapy
- If possible, avoid lithium in pregnancy (esp. first trimester), overall risk of fetal malformations is 4–12%; cardiovascular malformations risk ratio is 1.2–7.7 (level A evidence; e.g., tricuspid valve malformations; 0.05–0.1% risk of Ebstein's anomaly) – fetal echocardiography may be considered if exposure in first trimester (level C evidence) and high-resolution ultrasound at 16–18 weeks gestation
- If possible, withhold lithium during first trimester and restart in second trimester. In patients with bipolar disorder, the peripartum period is associated with high risk of relapse. Relapse during this period may affect fetal and child development
- Discontinuation of lithium is associated with an increase in bipolar recurrences. Gradual cessation over 2–4 weeks instead of abrupt discontinuation is advised whenever the risk is considered acceptable
- Serum lithium levels should be monitored more frequently (e.g., every 4 weeks, then weekly from 36th week)
- A statistically significant association noted between higher doses of lithium in the first trimester and premature deliveries; a higher rate of macrosomia reported in these premature infants; consider dose lowering if appropriate, and use divided daily doses to minimize peak concentrations
- Lithium clearance increased by 30–50% in the third trimester because of increases in plasma volume and greater GFR; rate returns to pre-pregnancy levels after delivery; dose should be decreased, or drug discontinued, 2–3 days prior to delivery
- Use of lithium near term may produce severe toxicity in the newborn, which is usually reversible, including nontoxic goiter, atrial flutter, T-wave inversion, nephrogenic diabetes insipidus, floppy baby syndrome, cyanosis, and seizures; can be minimized by withholding maternal lithium 2–3 days before delivery
- Lithium should be discontinued during labor to avoid lithium toxicity in the infant
- Observe infant for lithium toxicity for first 10 days of life
- If lithium was discontinued during the pregnancy, strongly consider restarting immediately after delivery due to high frequency of postpartum mood episodes

Breast Milk

- Breastfeeding may be appropriate in women with stable mood on lithium monotherapy or simplified drug regimens, however, lithium may pose toxicity risks to the baby
- Present in breast milk at a concentration of 30–80% of mother's serum concentration (infant's serum concentration is approximately 10–50% of the mother's). Reported symptoms in infant include lethargy, hypothermia, hypotonia, dyskinesias, dehydration, hypothyroidism, cyanosis, heart murmur, and T-wave changes
- Infants have decreased renal clearance (in general, so may retain lithium in their bodies); the American Academy of Pediatrics recommends that lithium should be given to nursing mothers only if benefits outweigh risks, and with caution
- If breastfeeding is undertaken, the mother should be educated about signs and symptoms of lithium toxicity and risk of infant dehydration; monitor infant lithium levels and consider periodic thyroid evaluation

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Nursing Implications

- Accurate observation and assessment of patient's behavior before and after lithium therapy is initiated is important
- Be alert for any signs of side effects or symptoms of toxicity; if signs or suspicions occur (see p. 301), withhold the next dose and call doctor immediately
- Advise patient to maintain consistent salt intake and check fluid intake and output; adjust fluid and salt ingestion to compensate if excessive loss occurs
- Expect nausea, thirst, frequent urination, and generalized discomfort during the first few days; therapeutic effects occur gradually and may take up to 3 weeks
- Lithium may be given with meals to avoid GI disturbances
- Caffeine intake should not be dramatically altered while taking lithium
- When lithium is prescribed in divided doses, withhold morning dose until after the blood draw on mornings when blood is drawn for a lithium level
- The patient and family should be educated regarding lithium effects and toxicities and prevention of same
- ER preparations should not be broken or crushed. The therapeutic benefit of the intact ER formulation is reduction of side effects such as tremor and gastrointestinal symptoms that occur as a result of high peak plasma levels (i.e., 1–2 h post dose) that occur with the immediate-release formulation
- Because lithium may cause drowsiness, caution patient to avoid activities requiring alertness until response to drug has been determined

Patient Instructions

- For detailed patient instructions on lithium, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Alcohol		Increased tremor/shakiness with chronic alcohol use
Angiotensin-converting enzyme inhibitor (ACE-I)	Captopril, enalapril, lisinopril	Increased lithium toxicity – although mechanism not clearly established, it may involve angiotensin II and decreased aldosterone levels, resulting in sodium depletion; average increase in lithium level of 36% reported; delayed onset of interaction may occur several weeks after introduction of ACE-I
	Candesartan, losartan, valsartan	Reports of lithium toxicity, possibly due to reduced renal elimination of lithium; delayed interaction
Antibiotic	Doxycycline, metronidazole, sulfamethoxazole-trimethoprim, tetracycline	Case reports of increased lithium effect and toxicity due to decreased renal clearance of lithium. Monitor lithium level, electrolytes, and creatinine if combination used
Anticonvulsant	Carbamazepine, phenytoin, valproate	Increased neurotoxicity of both drugs at therapeutic doses Valproate may aggravate action tremor
Antidepressant		
SSRI, SNRI	Duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine	Elevated lithium serum level with possible neurotoxicity; serotonin syndrome (see p. 59) reported
Cyclic, RIMA	Tricyclic antidepressants, moclobemide	May increase lithium tremor, neurotoxicity
Irreversible MAOI	Phenelzine, tranylcypromine	Avoid due to risk of malignant hyperthermia
Antihypertensive	Acetazolamide, mannitol	Increased renal excretion of lithium, decreasing its effect
	Methyldopa	Increased lithium effects and toxicity due to decreased renal clearance of lithium
Antipsychotic	Clozapine	Possible increased risk of agranulocytosis with clozapine; lithium has also been used to support neutrophil count in clozapine-treated patients[25] due to lithium-induced leukocytosis; case report of rapid onset agranulocytosis following lithium discontinuation in patients rechallenged on clozapine/lithium combination; case reports of seizures and diabetic ketoacidosis reported with combination

Lithium (cont.)

Class of Drug	Example	Interaction Effects
	Haloperidol, perphenazine, phenothiazines	Increased neurotoxicity possible at therapeutic doses; may increase EPSE; cases of NMS reported
	Risperidone	Case report of severe neurotoxicity
Antiviral agent	Zidovudine	Reversal of zidovudine-induced neutropenia
β-blocker	Oxprenolol, propranolol	Beneficial effect in treatment of lithium tremor; propranolol lowers GFR and has been associated with a 19% reduction in lithium clearance
Benzodiazepine	Clonazepam	Increased incidence of sexual dysfunction (up to 49%) reported with the combination
Caffeine		Increased renal excretion of lithium, resulting in decreased plasma level May increase lithium tremor
Calcium channel blocker	Verapamil, diltiazem	Increased neurotoxicity of both drugs; increased bradycardia and cardiotoxicity with verapamil due to combined calcium blockade. Does not appear to involve dihydropyridine class (e.g., felodipine, nifedipine)
Diuretic	Amiloride	May be used to treat polyuria/nephrogenic diabetes insipidus
	Furosemide	Isolated reports of lithium toxicity
	Spironolactone, triamterene	Monitor for increased effect of lithium
	Thiazides	Increased lithium effects and toxicity due to decreased renal clearance of lithium; 50% decrease in lithium dose recommended
Herbal diuretic	Agrimony, dandelion, juniper, licorice, horsetail, uva ursi	Elevated lithium level possible due to decreased renal clearance
	Cola nut, guarana, maté	Increased excretion and decreased lithium level possible due to high content of caffeine in herbal medications, may increase lithium tremor
Iodide salt	Calcium iodide, potassium iodide	May act synergistically to produce hypothyroidism. AVOID
Laxative	Lactulose	Case series of 3 acutely manic patients developing lithium toxicity when lactulose added for hyperammonemia or constipation, possibly due to volume depletion
	Psyllium	Decreased lithium level if drugs taken at the same time. Increased water drawn into the colon by the bulk laxatives would increase the amount of ionized lithium, which would remain unabsorbed
Local anesthetic	Lidocaine with epinephrine	Cases of extremely prolonged anesthesia
L-tryptophan		Increased plasma level and efficacy and/or toxicity of lithium
Methylene blue		Increased serotonergic effects possible – monitor for signs of serotonin syndrome
NSAID	Celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, mefenamic acid, naproxen, sulindac (no interaction with ASA or acetaminophen)	Increased lithium level and possible toxicity due to decreased renal clearance of lithium (up to 133% increase reported with celecoxib, up to 300% with mefenamic acid); serum creatinine increased in several reports. Use caution and monitor lithium level every 4–5 days until stable
Neuromuscular blocker	Succinylcholine, pancuronium	Potentiation of muscle relaxation
Sodium chloride (table salt)		Increased intake results in decreased lithium plasma level; decreased intake causes increased lithium plasma level
Theophylline and derivatives	Aminophylline, oxtriphylline, theophylline	Enhanced renal lithium clearance and reduced plasma level (by approx. 20%) May increase lithium tremor
Triptan	Sumatriptan, zolmitriptan	Increased serotonergic effects possible – monitor for signs of serotonin syndrome
Urinary alkalinizer	Potassium citrate, sodium bicarbonate	Enhanced renal lithium clearance and reduced plasma level

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Carbamazepine	Second-generation anticonvulsant	Glutamate/Channel blocker	Tegretol, Epitol[B]	Tablets: 100 mg[B], 200 mg, 300 mg[B], 400 mg[B] Chewable tablets: 100 mg, 200 mg	Dosage recommendations available for children
			Tegretol (liquid)[B], Teril (liquid)[B]	Oral suspension: 100 mg/5 mL	
			Tegretol CR[C]	Controlled-release tablets: 200 mg, 400 mg	
			Carbatrol[B], Equetro[B]	Extended-release capsules: 100 mg, 200 mg, 300 mg	
			Tegretol XR[B]	Extended-release tablets: 100 mg, 200 mg, 400 mg	
Divalproex sodium	Second-generation anticonvulsant	Glutamate/Unclear	Depakote sprinkle[B]	Capsules: 125 mg	Dosage recommendations available for children
			Depakote[B]	Delayed-release tablets: 125 mg, 250 mg, 500 mg Delayed-release pellets: 125 mg[B]	
			Depakote ER[B]	Extended-release tablets: 250 mg, 500 mg	
			Epival ECT[C]	Enteric-coated tablets: 125 mg, 250 mg, 500 mg	
Gabapentin[D]	Third-generation anticonvulsant	Glutamate/Channel blocker	Gralise[B]	Tablets: 300 mg, 600 mg	Safety and efficacy not established in children and adolescents under age 18
			Neurontin	Capsules: 100 mg, 300 mg, 400 mg, 800 mg[B] Tablets: 100 mg[B], 300 mg[B], 400 mg[B], 600 mg, 800 mg Oral solution[B]: 250 mg/5 mL	Dosage recommendations available for children
Gabapentin enacarbil[D]	Third-generation anticonvulsant	Glutamate/Channel blocker	Horizant[B]	Extended-release tablets: 300 mg, 600 mg	Safety and efficacy not established in children and adolescents under age 18
Lamotrigine	Third-generation anticonvulsant	Glutamate/Channel blocker	Lamictal Lamictal CD[B]	Tablets: 25 mg, 100 mg, 150 mg, 200 mg[B] Chewable/dispersible tablets: 2 mg, 5 mg, 25 mg[B]	Dosage recommendations available for children
			Lamictal ODT[B]	Oral disintegrating tablets: 25 mg, 50 mg, 100 mg, 200 mg	
			Lamictal XR[B]	Extended-release tablets: 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg	Safety and efficacy not established in children and adolescents under age 13

Anticonvulsants (cont.)

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Levetiracetam[D]	Third-generation anticonvulsant	Not llisted	Elepsia XR[B]	Extended-release tablets: 1000 mg, 1500 mg	Dosage recommendations available for children age 12 and above
			Keppra	Tablets: 250 mg, 500 mg, 750 mg, 1000 mg Oral solution: 100 mg/mL Injection: 500 mg/5 mL, 500 mg/100 mL[B], 250 mg/50 mL[B], 1000 mg/100 mL[B], 1500 mg/100 mL[B]	Dosage recommendations available for children
			Keppra XR[B]	Extended-release tablets: 500 mg, 750 mg	Dosage recommendations available for children age 12 and above
			Spritam[B]	Tablet for suspension: 250 mg, 500 mg, 750 mg, 1000 mg	Dosage recommendations available for children
Oxcarbazepine	Third-generation anticonvulsant	Glutamate/Channel blocker	Trileptal	Tablets: 150 mg, 300 mg, 600 mg Oral suspension: 300 mg/5 mL	Dosage recommendations available for children
			Oxtellar XR[B]	Extended-release tablets: 150 mg, 300 mg, 600 mg	Dosage recommendations available for children age 6 and above
Phenytoin[D]	First-generation anticonvulsant	Not llisted	Dilantin	Extended-release capsules: 30 mg[B], 100 mg, 200 mg[B], 300 mg[B] Chewable tablets: 50 mg[B] Injection: 50 mg/1 mL Oral syrup: 30 mg/5 mL[B], 125 mg/5 mL	Dosage recommendations available for children
Topiramate[D]	Third-generation anticonvulsant	GABA, glutamate/Unclear	Topamax	Tablets: 25 mg, 50 mg[B], 100 mg, 200 mg Sprinkle capsules: 15 mg, 25 mg	Dosage recommendations available for children
			Eprontia[B]	Oral solution: 25 mg/mL	Dosage recommendations available for children
			Trokendi XR[B], Qudexy XR[B]	Extended-release capsules: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg	Dosage recommendations available for children
Valproic acid	Second-generation anticonvulsant	Glutamate/Unclear	Depakene	Capsules: 250 mg Enteric-coated capsules: 500 mg[C] Oral syrup: 250 mg/5 mL	Dosage recommendations available for children
Valproate sodium	Second-generation anticonvulsant	Glutamate/Unclear	Depacon[B]	Injection: 100 mg/mL	Dosage recommendations available for children age 10 and above

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Phenytoin, gabapentin, levetiracetam, and topiramate are not very effective mood stabilizers relative to other anticonvulsants but have been included here as they are anticonvulsants with some psychotherapeutic effects

Indications‡ (👍 approved)

Indication	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin[a]	Lamotrigine[a]	Oxcarbazepine[a]	Topiramate[a]
Acute bipolar disorder (BD) mania	? No recommendation for use Case reports and open trials in C&A	+ Third-line agent	– Not recommended for adults Limited C&A data	– Not recommended for adults Limited C&A data	– Not recommended Negative study in C&A	– Not recommended for adults Limited C&A data
Acute BD depression	? No recommendation for use in C&A	? No recommendation for use in C&A	? No recommendation for use in C&A	+ Second-line agent	– Not recommended Negative study in C&A	? No recommendation for use in C&A
Acute BD mixed feature	+ Last-line agent	+ Third-line agent	? No recommendation for use in C&A	–/? No recommendation for use in C&A Not recommended in adults	? No recommendation for use in C&A	–/? No recommendation for use in C&A Not recommended in adults
Maintenance treatment following BD mixed features	? No recommendation for use in C&A	? No recommendation for use in C&A	? No recommendation for use in C&A	+ Second-line agent when used as adjunct	? No recommendation for use in C&A	? No recommendation for use in C&A
Maintenance treatment of BD	? No recommendation for use in C&A	+ First-line agent	? No recommendation for use in C&A	+ First-line agent when used as adjunct in age 13 years and older	? No recommendation for use in C&A	? No recommendation for use in C&A
Epilepsy/seizures	👍 Partial onset and primary generalized tonic-clonic seizures. Not effective for absence, myoclonic or atonic seizures	👍 Complex partial, simple, complex absence seizures (monotherapy or adjunctive) 👍 Multiple seizure types (adjunctive)	👍 Partial onset seizures	👍 Partial onset seizures, primary generalized tonic-clonic, generalized seizures associated with Lennox-Gastaut (adjunctive) 👍 Partial onset seizures (monotherapy in age 16 and over)	👍 Partial seizures (monotherapy or adjunctive)	👍 Partial onset or primary generalized tonic-clonic seizures (monotherapy) 👍 Partial onset seizures, primary generalized tonic-clonic seizures, seizures associated with Lennox-Gastaut (adjunctive)
Migraine headaches	?	👍[a] – in C&A (RCT)	?	?	?	👍 +/–[a] in C&A (RCTs)

‡ Indications listed here do not necessarily apply to all anticonvulsants or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications

Anticonvulsants (cont.)

Indication	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin[a]	Lamotrigine[a]	Oxcarbazepine[a]	Topiramate[a]
Movement disorders	+ Dystonic disorder in children	–[a]	+/?[a] Essential tremor +[a] Restless legs syndrome	–[a]	+/?[a] Essential tremor and restless legs syndrome (case reports)	+[a] Essential tremor
Obsessive-compulsive disorder (OCD)	+/–[a] Adjunctive drug Preliminary data	+/–[a] Adjunctive drug	–[a]	+/–[a] Case report Adjunctive drug	+/?[a] Case report Adjunctive drug	+/–[a] Open trial Adjunctive drug
Panic disorder	+/?[a] Open trial in adults reducing frequency	+/?[a] Open trial in adults reducing frequency	+/–[a] Contradictory RCT in adults	+/?[a] Open trial in adults reducing frequency	?[a] One positive case report in adults	–[a] No data Topiramate can cause panic attacks
Paroxysmal pain syndromes	+[a] Trigeminal neuralgia Glossopharyngeal neuralgia	+[a] Diabetic neuropathy Postherpetic neuralgia	[a] Postherpetic neuralgia Neuropathic pain	–[a] Central pain – Cochrane review: ineffective in neuropathic pain and fibromyalgia	+/–[a] Neuropathic pain Trigeminal neuralgia	–[a] Neuropathic pain Cochrane review: ineffective
Posttraumatic stress disorder (PTSD)	+[a] Third-line agent in adults	+/–[a] Not recommended in adults	+[a] Third-line agent in adults (adjunctive)	+[a] Third-line agent in adults	+/?[a] Case reports in adults	+[a] Third-line agent in adults
Social anxiety disorder (SAD), generalized anxiety disorder (GAD)	?[a]	+[a] Third-line agent in adults for SAD and GAD	+[a] Second-line agent in adults for SAD	?[a]	?[a]	+[a] Third-line agent in adults for SAD
Severe behavior disturbances (Conduct disorder, disruptive mood dysregulation disorder, intellectual disability, traumatic brain injury)	+ Alone or in combination with lithium, antipsychotics, or β-blockers	+ Mild evidence in reducing irritability of autism	+ Preliminary	+/– Mild evidence in reducing irritability of autism	+ Preliminary	+ Mild evidence in reducing irritability of autism
Substance use disorder (see Treatment of Substance Use Disorders pp. 370–396)	+[a] Aid in alcohol/hypnotic withdrawal –[a] Cocaine use disorder	+/–[a] Aid in alcohol withdrawal	+[a] Alcohol use disorder (monotherapy) Adjunctive for opioid or cannabis withdrawal Gabapentin can be abused	+/?[a] Aid in alcohol withdrawal	–[a]	+[a] Alcohol use disorder –[a] Cocaine or methadone use disorder

[a] Data relate to use in adults; no data available in children or adolescents (C&A) unless specified

+ = positive data; – = negative data; +/– =data contradictory; ? = no data available or data of poor quality to guide therapy

General Comments

- Few controlled trials have been done with anticonvulsants in children and adolescents and guideline recommendations are provided to simplify treatment decisions
- A guideline for pediatric bipolar disorder in patients with acute mania recommends first-line options of lithium, risperidone, aripiprazole, asenapine, and quetiapine; second-line options of olanzapine, ziprasidone, or adjunctive quetiapine; third-line option of divalproex; and oxcarbazepine is NOT recommended due to negative results[4]
- A guideline for pediatric bipolar disorder in patients with acute depression recommends first-line option of lurasidone; second-line options of lithium and lamotrigine; third-line options of fluoxetine/olanzapine combination or quetiapine; and oxcarbazepine is NOT recommended due to negative results[4]
- A guideline for pediatric bipolar disorder for patients on maintenance treatment recommends first-line options of aripiprazole, lithium, divalproex, and adjunctive lamotrigine in patients $\geq$ 13 years old; due to limited evidence, there are no second-line recommendations; third-line options include asenapine, quetiapine, risperidone, or ziprasidone for patients who responded to these medications in the acute treatment phase[4]
- A guideline for pediatric bipolar disorder in patients with acute mixed presentations, recommends first-line options of asenapine or risperidone; second-line options of olanzapine, ziprasidone, and lurasidone; third-line options of quetiapine, divalproex, lithium, and lastly carbamazepine due to drug-interaction and adverse event potential[5]
- A guideline for pediatric bipolar disorder in patients with mixed presentations on maintenance treatment recommends no first-line options due to lack of evidence; second-line options of lithium monotherapy or the adjunctive use of lamotrigine with another mood stabilizing drug[5]
- The younger the patient, the less chance of robust response to a mood stabilizer; only about 30% of young adults do well on monotherapy; for optimal response, combination therapy may be required, e.g., with another mood stabilizer, antipsychotic, antidepressant, or ECT
- Anticonvulsants have been found useful to treat aggression in children and adolescents with conduct disorder, autism spectrum disorder, and organic brain syndromes

Dosing

- See table p. 323 for specific agents
- Carbamazepine and valproate: Plasma level monitoring (measured at trough) can help guide dosing
- Lamotrigine: Dosage titration as per product monograph is strongly recommended to decrease risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- Gabapentin: Dosing in renal dysfunction: If CrCl 30–59 mL/min, give drug bid to a maximum dose of 1400 mg/day. If CrCl 15–29 mL/min, give drug once daily to a maximum dose of 700 mg/day. If CrCl is less than 15 mL/min, give drug to a maximum of 300 mg once daily; reduce dose proportionally with decreasing CrCl

Pharmacokinetics

- See table p. 324 for specific agents

Carbamazepine

- Induces its own metabolism. Single-dose studies show half-life ranges of 30–40 h that decrease to 20 h after 3 weeks. During chronic monotherapy, half-life is 12 h, and during polytherapy with enzyme inducers is 8 h
- The 10,11-epoxide metabolite of carbamazepine can reach up to 50% of the plasma concentration of the parent drug; it is pharmacologically active and associated with neurological adverse effects
- Clearance is higher in children than in adults; children may be at risk for major toxicities at lower serum concentrations due to increased production of toxic metabolite; case reports of behavior disturbances, mania, and worsening of tics. Males may have higher/faster clearance than females of similar age and weight
- Extended release carbamazepine capsules contain variable-release beads; should not be chewed or crushed, but can be opened and sprinkled on food

Valproate

- Pharmacokinetics show significant variation with changes in body weight. Valproate exhibits concentration-dependent protein binding, therefore at high doses and plasma concentrations a larger proportion may exist in unbound (free) form; the free fraction of drug increases from 10% at a concentration of 40 micrograms/mL (280 micromol/L) to 18.5% at a concentration of 130 micrograms/mL (900 micromol/L). Patients with low albumin levels, or those on other highly protein-bound drugs will exhibit a higher free fraction of valproate and therefore may exhibit signs of toxicity within the normal serum level range
- As binding sites become saturated and the free fraction increases, valproate clearance also increases, reducing total serum concentrations such that at higher dosing non-linear changes in serum concentrations occur

Anticonvulsants (cont.)

- Absorption of divalproex extended-release tablets may be delayed such that levels taken in the morning after evening doses may more closely approximate a peak concentration
- Switching from divalproex tablets to a liquid for adherence purposes may result in a decline in serum levels

Gabapentin

- Gabapentin shows dose-dependent bioavailability as a result of a saturable transport mechanism (better bioavailability with more frequent dosing; plasma level is proportional to the dose). Children under the age of 5 may require approximately 30% larger dose to achieve desired serum concentration due to enhanced clearance. Elimination is almost entirely by the kidneys, and is reduced in patients with renal dysfunction (see Dosing p. 323)

Lamotrigine

- Large individual variation seen in plasma lamotrigine concentration in patients with renal impairment; half-life is also prolonged in hepatic dysfunction. Age, gender, and smoking do not affect pharmacokinetics. Altered metabolism in children results in greater formation of reactive arene oxide metabolite and a higher incidence of rash – use lower starting dose and titrate slowly

Oxcarbazepine

- Rapidly metabolized to its active 10-monohydroxy metabolite, MHD
- Half-life of MHD is reduced and renal clearance is higher in children than in adults; a higher dose may be required to achieve a therapeutic range
- Dose-normalized AUC values of MHD were 30% lower in children age 2–5 than in children age 6–12 after single administration of oxcarbazepine

Topiramate

- Children have lower topiramate concentrations than adults receiving the same dose per kg of body weight

Adverse Effects

- See table pp. 325–327 for specific agents
- Many adverse effects can be minimized with slower dosage titration
- Common (for all anticonvulsants):
  - GI complaints, e.g., nausea [Management: Take with food, change to an enteric-coated formulation, use famotidine 20 mg/day]
  - Dose-related lethargy, sedation, behavior changes/deterioration, reversible dementia/encephalopathy; cognitive effects are more prominent on drug initiation and are minimized with slow dosage increases
  - Dose-related tremor; tends to be rhythmic, rapid, symmetrical, and most prominent in upper extremities [reduce dose if possible; responds to propranolol]
  - Ataxia
  - Changes in appetite, weight gain (except topiramate and lamotrigine) – more common in females; may be associated with features of insulin resistance, hyperlipidemia, impaired glucose tolerance, and hyperinsulinemia. Weight increases with duration of treatment. Obesity may increase risk of hyperandrogenism in females [Management: metformin 500 mg tid]
  - Menstrual disturbances (except gabapentin and topiramate), including: Prolonged cycles, oligomenorrhea, amenorrhea, polycystic ovaries; elevated testosterone – rates may be higher in females who begin taking valproate before age 20. Clinical features of polycystic ovary syndrome include hirsutism, alopecia, acne, menstrual irregularities, and obesity; lab indices show increased total and free testosterone, decreased FSH, increased serum prolactin and LH, and LH/FSH ratio greater than 2, incidence most common with valproic acid. Potentially reversible upon discontinuation of valproate treatment
- Occasional (for all anticonvulsants):
  - Dysarthria, incoordination
  - Diplopia, nystagmus
- Rare: Anticonvulsant hypersensitivity syndrome with fever, rash, and internal organ involvement; cross-sensitivity reported between carbamazepine, oxcarbazepine, and lamotrigine
- Osteoporosis reported with carbamazepine and valproate; bone loss is related to treatment duration and decreased 25-hydroxy vitamin D levels. Some clinicians recommend baseline bone mineral density in adolescents requiring chronic treatment. Possible that effects on bone could be additive when antipsychotics that elevate prolactin levels are used concurrently [optimize vitamin D and calcium intake]

D/C Discontinuation Syndrome

- No evidence of psychological or physical dependence to anticonvulsants (except gabapentin)
- Abrupt discontinuation (especially in patients with a seizure disorder) may provoke rebound seizures – dose tapering recommended even in absence of seizure history, unless severe adverse effects (e.g., Stevens-Johnson syndrome) preclude tapering
- Myoclonic jerks have been reported following the tapering of carbamazepine or valproate
- Case of anhedonia, tremor, tachycardia, and hyperhidrosis reported following rapid discontinuation of lamotrigine
- Rare reports of psychiatric symptoms on withdrawal, including psychosis (exacerbation of schizophrenia)

Precautions

- Prior to treatment, laboratory investigations should be performed (see p. 314)
- Ensure adequate contraception in place for females of child-bearing potential (see Drug Interactions pp. 316–320)
- Suicide risk: According to the FDA[26], patients receiving antiepileptic drugs have a slightly increased risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). A reanalysis of this data showed elevated risk for gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate. However, overall risk of suicide deaths was 17.4 per 100,000 per year, which closely approximates the baseline North American age 15+ rate of 16.5 per 100,000 per year.[27] Monitor all patients starting drug treatment for behavioral changes that could indicate emergence or worsening of depression, or suicidal thoughts or behaviors

Carbamazepine

- **Serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis)** – patients with a positive test for HLA-B*15:02 (particularly in East Asians) and/or HLA-A*31:01 (particularly in East Asians, Indigenous North and South Americans, and Latinos) are at increased risk. Screen for eligibility prior to use and avoid if the patient tests positive. Frequency of HLA-B*15:02 occurs in 4.6% of East Asians and 2.6% of South and Central Asians. Frequency of HLA-A*31:01 occurs in 6.2% of Indigenous North and South Americans, 4.5% of Latinos, about 3.5% of Asians, and 2.6% of Caucasians in Europe and North America[28]
- **Potentially fatal blood cell abnormalities** (e.g., aplastic anemia and agranulocytosis) have been reported. Mild degree of blood cell suppression can occur; stop therapy if WBC levels drop below 3,000 white cells/mm^3; erythrocytes less than $4 \times 10^6/mm^3$; platelets less than 100,000/mm^3
- Carbamazepine induces the metabolism of many drugs metabolized by the CYP450 system (see pp. 316–318). Monitoring of clinical status and dosage adjustment of contraceptives (both oral and patch formulations), in particular, may be required
- Because of its anticholinergic action, give cautiously to patients with increased intraocular pressure or urinary retention
- Hepatocellular/cholestatic jaundice and hepatitis reported
- Hypersensitivity syndrome with fever, skin eruptions, and internal organ involvement occurs rarely – cross-sensitivity with other anticonvulsants can occur; discontinue carbamazepine at first sign of drug-induced rash
- Hyponatremia (SIADH) occurs in 10–15% of patients; risk appears to be dose-related and may be higher in older adults
- Children at risk for toxicity at lower serum concentrations due to increased production of toxic metabolite; case reports of behavior disturbances, mania, and tics
- Do not administer carbamazepine suspension together with any other liquid medication as formation of an insoluble precipitate can occur
- Tolerance to therapeutic effects has been reported; efficacy not improved with dose increase
- While therapeutic serum levels of carbamazepine have not been established for patients with BD, serum concentrations established for treatment of seizure disorders (4–12 mg/L) (SI units: 15–50 micromol/L) are generally applied. Level monitoring is suggested during the initiation phase to establish nontoxic and reference levels for the individual patient. Carbamazepine induces its own hepatic metabolism; therefore, levels 4 weeks apart are suggested, after which further dose adjustment may be required (see suggestions p. 315)

Valproate

- **Hepatic toxicity** – may show no relation to hepatic enzyme levels. Monitor liver function prior to therapy. In high-risk patients, monitor serum fibrinogen and albumin for decreases in concentration, and ammonia for increases secondary to decrease in carnitine levels. Stop drug if hepatic transaminases (ALT, AST) 2–3 times the upper limit of normal. Children ages 3–10 taking other anticonvulsants are at higher risk for developing fatal hepatotoxicity than adults
- **Pancreatitis** – cases of life-threatening pancreatitis at any point in treatment. In patients with severe abdominal pain, lethargy, and weight loss, rule out pancreatitis
- **Fetal risk** – major congenital malformations, particularly neural tube defects (e.g., spina bifida), decreased IQ scores, and neurodevelopmental disorders following *in utero* exposure
- **Mitochondrial disease** – increased risk of acute liver failure and death in patients with hereditary neurometabolic syndromes (e.g., Alpers Huttenlocher Syndrome)

Anticonvulsants (cont.)

- Thrombocytopenia – platelet counts and bleeding time determinations are recommended prior to therapy and at periodic intervals; withdraw if bleeding, bruising, or coagulopathy is detected
- Hyperammonemia and/or encephalopathy, sometimes fatal, have been reported following initiation of valproic acid therapy and may be present with normal transaminase levels. Ammonia levels should be measured in patients who develop unexplained lethargy and vomiting, altered mentation, or hypothermia
- Drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity reported in a few cases. Monitor for fever and lymphadenopathy. Discontinue if confirmed. Increased risk when combined with lamotrigine
- Diabetic patients taking valproic acid may show false-positive ketone results
- Use in children and adolescents may result in increased risk of hyperandrogenism and polycystic ovary syndrome, delayed or prolonged puberty, excessive weight gain, hyperinsulinemia, and dyslipidemia. Due to risk of polycystic ovary syndrome, consider alternate therapy or monitoring for bioavailable androgens (free testosterone) as well as prolactin, LH, and TSH in females with menstrual irregularities, obesity, hirsutism, alopecia, and evidence of anovulation
- In patients with altered protein binding it may be more useful to monitor unbound (free) valproate concentrations rather than total concentrations
- Valproate may inhibit the metabolism of drugs that are substrates for cytochrome p450 or UDP-glucuronosyltransferase (UGT) enzymes (see interactions listed pp. 320–321)

Gabapentin

- Drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity reported, including fatal cases; discontinue drug
- Neuropsychiatric adverse effects in pediatric patients age 3–12 years old with epilepsy (e.g., hyperactivity, aggression, and irritability)
- Respiratory depression, somnolence, sedation, and dizziness

Lamotrigine

- **Serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis)** – higher incidence in children, rapid dosage titration, and in combination with valproate. Most occur within first 8 weeks of starting lamotrigine. Patient should be educated to immediately report any rash or systemic symptoms (fever, malaise, pharyngitis, flu-like symptoms), sores or blisters on soles, palms or mucus membranes. Rechallenge may be considered if rash is benign[29]
- If lamotrigine has been withheld/not taken for longer than 5 half-lives, consider restarting according to initial dosing titration recommendations
- Use cautiously in patients with renal dysfunction as elimination half-life of lamotrigine is increased
- Avoid exposure to new foods, detergents, and pets, and minimize exposure to other potential allergens during dose titration period to reduce incidence of drug discontinuation due to benign rash from other (non-drug) cause
- Drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity reported. Monitor for rash, fever, and lymphadenopathy; discontinue if confirmed
- Due to potential for PR interval prolongation, lamotrigine should be used cautiously in patients with cardiac conduction abnormalities
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia) – may occur with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding
- Aseptic meningitis: 40 cases reported[30]; advise patients to immediately report symptoms of headache, fever, stiff neck, nausea, vomiting, rash, and light sensitivity

Oxcarbazepine

- Monitor sodium levels with chronic use due to risk of hyponatremia – particularly in first 3 months
- **Serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis)** – patients with a positive test for HLA-B*15:02 (particularly in East Asians) and/or HLA-A*31:01 (particularly in East Asians, Indigenous North and South Americans, and Latinos) are at increased risk. Screen for eligibility prior to use and avoid if the patient tests positive. Frequency of HLA-B*15:02 occurs in 4.6% of East Asians and 2.6% of South and Central Asians. Frequency of HLA-A*31:01 occurs in 6.2% of Indigenous North and South Americans, 4.5% of Latinos, about 3.5% of Asians, and 2.6% of Caucasians in Europe and North America[28]
- 25–30% of patients who exhibited hypersensitivity reactions to carbamazepine may also have these reactions with oxcarbazepine
- Rare reports of blood dyscrasias (e.g., neutropenia, leukopenia, pancytopenia)

Topiramate

- Acute myopia secondary to angle closure glaucoma reported or visual field defects; ophthalmological consult recommended for complaints of acute visual problems and/or painful/red eyes

- Oligohidrosis and hyperthermia – monitor for decreased sweating and increased body temperature
- Hypothermia reported with concurrent valproate use
- Ten-fold increased risk of renal stones (calcium phosphate) – ensure adequate fluid intake and avoid excessive antacid use and use of other carbonic anhydrase inhibitors
- Chronic metabolic acidosis may increase risk for nephrolithiasis or nephrocalcinosis and may result in osteomalacia and/or osteoporosis with increased risk of fractures [reduce dose or taper and discontinue drug]
- Decrease in sodium bicarbonate (up to 30% incidence); symptoms include fatigue, anorexia, hyperventilation, cardiac arrhythmia, and stupor
- Cognitive adverse effects (word-finding difficulties, memory problems) are related to dose and rate of dose titration

Contraindications

- Patients with a history of hepatic or cardiovascular disease or with a blood dyscrasia (gabapentin excluded)
- Known urea cycle disorders or mitochondrial disorders caused by mutations in mitochondrial DNA polymerase gamma (valproate)
- Hypersensitivity to any tricyclic compound (carbamazepine), and demonstrated hypersensitivity to any of the other agents
- Patients taking clozapine due to increased risk of agranulocytosis (carbamazepine, oxcarbazepine)
- Patients with history of bone-marrow suppression (carbamazepine)
- In conjunction with itraconazole and voriconazole or combined use with monoamine oxidase inhibitors (carbamazepine)
- Patients with known porphyria (valproate and carbamazepine)
- Atrioventricular (AV) heart block (carbamazepine)
- Concurrent use with nefazodone, delavirdine, or other non-nucleoside reverse transcriptase inhibitors that are substrates of CYP3A4 (carbamazepine)
- Pregnancy and females of childbearing potential not using effective contraception (valproate and topiramate – contraindicated for migraine prophylaxis)

Toxicity

Carbamazepine

- Usually occurs with plasma levels above 12 mg/L (50 micromol/L); children may be at risk for toxicity at lower serum concentrations due to increased production of toxic epoxide metabolite. Measurement of epoxide level may be beneficial in patients with signs of carbamazepine toxicity at therapeutic concentrations of the parent drug
- Maximum plasma concentration may be delayed for up to 70 h after an overdose; onset of symptoms begins 1–3 h after ingestion of extended-release formulation
- Signs/symptoms:
  - Dizziness, blood pressure changes, sinus tachycardia, ECG changes
  - Drowsiness, stupor, agitation, disorientation, EEG changes, seizures, and coma
  - Nausea, vomiting, decreased intestinal motility, urinary retention
  - Tremor, involuntary movements, opisthotonos, abnormal reflexes, myoclonus, ataxia
  - Mydriasis, nystagmus
  - Flushing, respiratory depression, cyanosis
- No known antidote, treat symptomatically. Hemodialysis if refractory seizures, hemodynamic instability, life-threatening dysrhythmias

Valproate

- Maximum plasma concentration may not occur for up to 18 h following an overdose, and serum half-life may be prolonged
- Onset of CNS depression may be rapid (within 3 h); enteric-coated formulations may delay onset of symptoms
- Signs/symptoms: severe dizziness, hypotension, supraventricular tachycardia, bradycardia; severe drowsiness; trembling; irregular, slow or shallow breathing, apnea, and coma; loss of tendon reflexes, generalized myoclonus, seizures; cerebral edema – evident 2–3 days after overdose and may last up to 15 days; hematological changes, electrolyte, and metabolic abnormalities; optic nerve damage reported
- Overdose can result in heart block, coma, and death; naloxone may reverse the CNS depressant effects, and may also reverse anti-epileptic effects
- Supportive treatment [L-carnitine supplementation 100 mg/kg/day (maximum 6 g) followed by 15 mg/kg every 4 h until clinical improvement recommended for patients with CNS depression, evidence of hepatic dysfunction, and hyperammonemia]

Anticonvulsants (cont.)

Gabapentin

- Signs/symptoms generally appear within 2–5 h following ingestion: double vision, slurred speech, drowsiness, ataxia, lethargy, and diarrhea
- Active charcoal recommended for recent ingestion; treat symptomatically; gabapentin can be removed by hemodialysis in case of life-threatening toxicity

Lamotrigine

- Signs/symptoms generally appear within 2–5 h following ingestion: ataxia, nystagmus, delirium, seizures, intraventricular conduction delay, and coma ingestions
- Active charcoal recommended for recent ingestion; treat symptomatically; lamotrigine can be removed by hemodialysis in case of life-threatening toxicity

Oxcarbazepine

- No deaths reported following overdose of up to 24,000 mg; no known antidote – treat symptomatically
- Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered

Topiramate

- Signs/symptoms generally appear within 2–5 h following ingestion: drowsiness and ataxia are common
- Administration of active charcoal emesis and gastric lavage recommended for recent ingestions; treat symptomatically
- Overdose can result in severe metabolic acidosis; topiramate can be removed by hemodialysis in case of life-threatening toxicity

Lab Tests/Monitoring

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Work-up	1) CBC including platelets and differential 2) Serum electrolytes, BUN, creatinine 3) Liver function 4) ECG (> age 45 or with a cardiac history) 5) HLA-B*15:02/HLA-A*31:03 genotyping in patients with high-risk ancestry 6) Pregnancy test (if appropriate)	1) CBC including platelets and differential 2) Liver function 3) Total and HDL cholesterol and triglycerides 4) Body weight/BMI 5) Menstrual history 6) Bone density 7) Pregnancy test (if appropriate)	BUN and serum creatinine	Liver function, BUN, and serum creatinine	Serum electrolytes Serum creatinine (dose needs to be adjusted with CrCl below 30 mL/min)	Baseline serum bicarbonate, BUN, and serum creatinine
Follow-up	Repeat CBC, LFT, electrolytes, urea, creatinine monthly for 3 months, then annually Bone density if risk factors for osteopenia are present	1) and 2): Repeat monthly for 2 months, then 2–3 times a year 4) and 5): q3 months for first year, then annually 6) If risk factors for osteopenia are present Ammonia level in event of lethargy, mental status changes	Renal function if suspect toxicity	None required; monitor for rash during titration	Sodium levels periodically and when patient has symptoms of hyponatremia	Periodic serum bicarbonate (to rule out metabolic acidosis) Renal function if suspect toxicity; ammonia level in event of lethargy, mental status changes

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Plasma level monitoring[31]	AGNP* level of recommendation: 2 (recommended for dosage titration and special indications or problem solving) Recommended level for seizure disorders is 4–12 mg/L (15–50 micromol/L) and not clearly established in bipolar disorder. Levels are suggested during initiation phase to establish nontoxic and reference levels for the individual patient. Carbamazepine induces its own hepatic metabolism; therefore, levels of 4 weeks apart are suggested, after which dose adjustment may be required. Levels also suggested 5 days after change in dose or addition or deletion of possibly interacting medications (see Drug Interactions pp. 316–318) or as clinically indicated. It may be necessary to check serum levels of other drugs if carbamazepine is added/subtracted to the regimen due to CYP induction/de-induction respectively	AGNP level of recommendation: 2 (recommended for dosage titration and special indications or problem solving) Recommended level for seizure disorders is 50–100 mg/L (350–700 micromol/L) and not clearly established in bipolar disorder. Two levels to establish therapeutic dose (at least 3–5 days after start of therapy) and after change in dose or addition/deletion of interacting drug (see Drug Interactions pp. 320–321 and Precautions p. 311) or as clinically indicated	AGNP level of recommendation: 3 (useful for special indications or problem solving) Recommended level for seizure disorders is 2–20 mg/L (12–117 micromol/L) and not established in bipolar disorder	AGNP level of recommendation: 2 (recommended for dosage titration and special indications or problem solving) Recommended level for seizure disorders is 3–15 mg/L (12–59 micromol/L) and not established in bipolar disorder. Consider obtaining level if interacting drug is co-prescribed	AGNP level of recommendation: 2 (recommended for dosage titration and special indications or problem solving) Recommended level for seizure disorders is 3–15 mg/L (40–139 micromol/L) and not established in bipolar disorder. It may be necessary to check serum levels of other drugs if oxcarbazepine is added/subtracted to the regimen due to CYP3A4 induction/de-induction respectively	AGNP level of recommendation: 3 (useful for special indications or problem solving) Recommended level for seizure disorders is 2–10 mg/L (6–30 micromol/L) and not established in bipolar disorder

* Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (https://agnp.de/)[31]

Nursing Implications

- Monitor patients starting drug treatment for behavioral changes that could indicate emergence or worsening of depression, or suicidal thoughts or behaviors
- Watch for signs of fever, sore throat, and bruising or bleeding
- Close clinical/laboratory supervision recommended (see Adverse Effects pp. 325–327 and Monitoring p. 314) during treatment for signs of blood dyscrasias or liver involvement
- A rash, especially with carbamazepine or lamotrigine, may signal onset of blood dyscrasia or severe dermatological and systemic reaction; advise the physician immediately
- Anorexia, nausea, vomiting, edema, malaise, and lethargy may signify hepatotoxicity
- Since drowsiness can occur, patients should exercise caution when performing tasks that require alertness; anticonvulsants may enhance the effects of alcohol and other CNS drugs
- Monitor patient's height, weight, and body mass index
- Advise patient to store medication away from heat and humidity as the drug may lose potency
- Enteric-coated or controlled-release tablets should not be broken or crushed but should be swallowed whole; chewing capsules can cause local irritation to mouth and throat; extended-release capsules can be opened and sprinkled on food

Carbamazepine

- Check for urinary retention and constipation with carbamazepine; increase fluids to lessen constipation
- Liquid carbamazepine should not be mixed or taken at the same time as any other liquid medication
- Grapefruit juice should be avoided as it can elevate the blood level of carbamazepine

Valproate

- Liquid valproate should not be administered with carbonated beverages as mouth irritation can occur
- To treat occasional pain, avoid use of acetylsalicylic acid (ASA or aspirin) as it can affect the blood level of valproate; acetaminophen or ibuprofen (and related drugs) are safer alternatives
- In females, obtain baseline body weight/BMI and measure periodically, monitor for menstrual disturbances, hirsutism, obesity, alopecia, and infertility – two or more of these symptoms may be associated with polycystic ovary syndrome

Anticonvulsants (cont.)

Lamotrigine

- Minimize exposure of patient to new foods, detergents, and other environmental triggers of allergic reactions during period of lamotrigine dose titration to avoid confusion about the cause of any new skin rash and to avoid unnecessarily interrupting therapy
- Immediately evaluate all reports of skin rash or unexplained fever in patients receiving lamotrigine and inform physician
- Following development of benign skin rash, re-challenging with very low dose titration of lamotrigine may be appropriate (i.e., suggested regimen of 5 mg every other day or daily for 14 days, then raised every 14 days by daily-dose increments of 5 mg; after reaching 25 mg/day, proceed according to the manufacturer's guidelines[29]

Oxcarbazepine

- Monitor for symptoms of hyponatremia – i.e., nausea, malaise, headache, lethargy, confusion
- Fever or rash may be a sign of serious skin reaction or organ involvement

Topiramate

- Patients should drink plenty of fluids and avoid the regular use of antacids (e.g., Tums, Maalox, Rolaids, etc.) to reduce risk of renal stone formation
- Patients should report memory or word-finding problems, eye pain or continued visual disturbances to their physician

Patient Instructions

- For detailed patient instructions on Anticonvulsant Mood Stabilizers, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

DRUGS INTERACTING WITH CARBAMAZEPINE

Class of Drug	Example	Interaction Effects
Androgen	Danazol	Plasma levels of carbamazepine increased by 50–100%; half-life is doubled and clearance halved
Anesthetic	Halothane	Enzyme induction may result in hepatocellular damage
	Isoflurane, sevoflurane	Enzyme induction may result in renal damage
	Ketamine	Decreased serum concentration of ketamine due to CYP2B6 induction
Antiarrhythmic	Disopyramide	Increased metabolism and decreased plasma level of disopyramide
Antibiotic	Clarithromycin, erythromycin	Increased plasma levels of carbamazepine due to reduced clearance (by 5–41%)
	Doxycycline (no interaction with other tetracyclines)	Decreased serum level and half-life of doxycycline due to enhanced metabolism (alternatively, tetracycline can be used or doxycycline can be dosed q12 h)
	Metronidazole	Increased plasma level of carbamazepine due to inhibited metabolism
	Quinupristin/dalfopristin	Increased plasma level of carbamazepine due to inhibited metabolism via CYP3A4
Anticoagulant	Apixaban, dabigatran, edoxaban	Increased metabolism of anticoagulant; combined use is not recommended
	Rivaroxaban	Case report of pulmonary embolism suspected due to increased clearance of rivaroxaban
	Warfarin	Enhanced metabolism of warfarin and decreased INR. Average warfarin dose increase of 49% observed in one study
Anticonvulsant	Brivaracetam, levetiracetam	May increase serum concentrations of active carbamazepine metabolite. Carbamazepine may decrease serum concentrations of brivaracetam
	Cenobamate	May decrease serum concentration of carbamazepine
	Clobazam, clonazepam, ethosuximide, oxcarbazepine, tiagabine, topiramate, zonisamide	Clearance of the anticonvulsant is increased by carbamazepine, with possible decrease in efficacy (40% decrease in concentration of topiramate and of oxcarbazepine metabolite)
	Ezogabine, tiagabine	Decreased serum concentration of ezogabine and tiagabine
	Felbamate	Decreased carbamazepine level by 50%, but increased level of epoxide metabolite Decreased felbamate level

Class of Drug	Example	Interaction Effects
	Lacosamide	May enhance adverse/toxic effects (e.g., bradycardia, ventricular arrhythmia, prolonged PR interval)
	Lamotrigine	Increased plasma level of epoxide metabolite of carbamazepine (by 10–45%) Increased metabolism of lamotrigine; half-life and plasma level decreased by 30–50%
	Phenytoin, primidone, phenobarbital	Decreased carbamazepine level due to increased metabolism via CYP3A4, but ratio of epoxide metabolite increased Altered plasma level of co-prescribed anticonvulsant
	Topiramate	Increased plasma level of carbamazepine by 20%
	Valproate, valproic acid	Increased plasma level of epoxide metabolite of carbamazepine; may result in toxicity even at therapeutic carbamazepine concentrations Effects on carbamazepine levels are variable and inconsistent Decreased valproate level due to increased clearance and displacement from protein binding
Antidepressant		
SSRI	Fluoxetine, fluvoxamine	Increased plasma level of carbamazepine with fluoxetine; increased nausea with fluvoxamine
	Citalopram, sertraline	Decreased plasma level of sertraline or citalopram due to enzyme induction via CYP3A4 (case report)
NDRI	Bupropion	Decreased serum concentration of bupropion due to CYP2B6 induction
SARI	Trazodone	Decreased plasma level of trazodone
	Nefazodone	Increased plasma level of carbamazepine with nefazodone due to decreased metabolism via CYP3A4
SPARI	Vilazodone	Up to 50% decreased plasma level of vilazodone
SMS	Vortioxetine	Decreased serum concentration of vortioxetine due to CYP3A4 induction
NaSSA	Mirtazapine	Decreased serum concentration of mirtazapine due to CYP3A4 induction
Nonselective cyclic	Amitriptyline, imipramine, nortriptyline	Decreased plasma level of antidepressant (by up to 46%) due to enzyme induction
MAOI	Phenelzine, tranylcypromine	Possible decrease in metabolism and increased plasma level of carbamazepine
Antifungal	Fluconazole, ketoconazole	Increased plasma level of carbamazepine with ketoconazole (by 29%) due to inhibited metabolism via CYP3A4; clearance decreased by 50% with fluconazole
	Caspofungin, fluconazole, itraconazole, ketoconazole, voriconazole	Decreased plasma levels of antifungals
Antipsychotic	Clozapine	Avoid combination due to possible potentiation of bone marrow suppression; decreased plasma level of clozapine by up to 63%
	Aripiprazole, brexpiprazole, cariprazine, flupenthixol, haloperidol, lumateperone, lurasidone, olanzapine, paliperidone, phenothiazines, quetiapine, risperidone, thiothixene, ziprasidone, zuclopenthixol	Decreased plasma level of antipsychotic (64% with aripiprazole, up to 100% with haloperidol, 44% with olanzapine, 45–65% with paliperidone, depending on carbamazepine dose, 70% with risperidone, 35% with ziprasidone). Quetiapine may also increase levels of the epoxide metabolite; olanzapine may increase carbamazepine levels Increased akathisia Increased neurotoxicity of both antipsychotic and carbamazepine at therapeutic doses
	Haloperidol, loxapine	Increased plasma level of carbamazepine and metabolite
Antiretroviral CCR5 antagonist Integrase inhibitor Non-nucleoside reverse transcriptase inhibitor (NNRTI) Protease inhibitor	General	Decreased concentrations of antiretroviral regimens containing cobicistat; avoid combination or use with extreme caution

Anticonvulsants (cont.)

Class of Drug	Example	Interaction Effects
Antitubercular drug	Isoniazid	Increased plasma level of carbamazepine; clearance reduced by up to 45%
	Rifampin	Decreased plasma level of carbamazepine
Anxiolytic	Alprazolam, clonazepam	Decreased plasma level of alprazolam (> 50%) and clonazepam (19–37%) due to enzyme induction
	Buspirone	Decreased serum concentration of buspirone due to enzyme induction
β-blocker	Propranolol	Decreased plasma level of β-blocker due to enzyme induction
Calcium channel blocker	Diltiazem, verapamil	Increased plasma levels of carbamazepine due to decreased metabolism (total carbamazepine increased 46%, free carbamazepine increased 33%)
	Flunarizine, nifedipine, nimodipine	Decreased serum concentration due to CYP3A4 induction
Corticosteroids	Dexamethasone, prednisolone	Decreased plasma level of corticosteroid due to enzyme induction
DDAVP (desmopressin)		Concurrent use may increase antidiuretic effect, resulting in decreased plasma sodium and seizures
Folic acid		Decreased plasma level of folic acid
Grapefruit juice		Decreased metabolism of carbamazepine due to CYP3A4 inhibition resulting in increased plasma level (by up to 40%)
H_2 antagonist	Cimetidine	Transient increase in carbamazepine levels and possible toxicity due to inhibited metabolism No interaction with famotidine, or nizatidine
Hormone	Medroxyprogesterone acetate injection	Concomitant administration is expected to decrease medroxyprogesterone concentrations
	Oral contraceptive	Increased metabolism of oral contraceptive and increased binding of progestin and ethinyl estradiol to sex hormone binding globulin, may result in decreased contraceptive efficacy
Immunosuppressant	Cyclosporine, sirolimus, tacrolimus	Decreased plasma level and efficacy due to enzyme induction
	Everolimus	Decreased plasma level and efficacy due to enzyme induction and p-glycoprotein induction
	Sarilumab	May decrease the concentration of carbamazepine
Influenza vaccine		Decreased elimination and increased half-life of carbamazepine
Isotretinoin		Decreased plasma level of carbamazepine and its metabolite
Lithium		Increased neurotoxicity of both drugs; sinus node dysfunction reported with combination
Muscle relaxant (non-depolarizing)	Pancuronium	Decreased duration of action and efficacy of muscle relaxant
NSAID	Diclofenac	Increased plasma level of carbamazepine due to decreased metabolism
Opioid	Buprenorphine, codeine, hydrocodone, methadone, tramadol	Decreased plasma level of methadone (up to 60%) due to enhanced metabolism; lower efficacy expected with other opioids
Proton pump inhibitor	Omeprazole	Increased carbamazepine levels
Quinine		Increased plasma level of carbamazepine (by 37%) and AUC (by 51%) due to inhibited metabolism
Stimulant	Armodafinil	Carbamazepine may decrease the serum concentration of armodafinil and armodafinil may decrease serum concentration of carbamazepine
	Methylphenidate	Decreased plasma level of methylphenidate and its metabolite
	Modafinil	Decreased plasma level of modafinil due to enhanced metabolism
Theophylline		Decreased theophylline level due to induction by carbamazepine Decreased carbamazepine level by up to 50%
Thyroid hormone		Decreased plasma level of thyroid hormone due to enzyme induction

DRUGS INTERACTING WITH GABAPENTIN

Class of Drug	Example	Interaction Effects
Antacid	Aluminum/magnesium-containing antacids	Co-administration reduces gabapentin bioavailability by up to 24%; administer gabapentin at least 2 h after antacid
CNS depressant	Alcohol, hypnotics	Increased sedation, disorientation
Opioid	Hydrocodone	Decreased concentration of hydrocodone reported
	Morphine	Increased gabapentin concentrations

DRUGS INTERACTING WITH LAMOTRIGINE

Class of Drug	Example	Interaction Effects
Analgesic	Acetaminophen	AUC of lamotrigine decreased by 20% when co-administered with 4 g of acetaminophen daily due to induction of glucuronidation pathways
Antiarrhythmic	Procainamide	Increased procainamide concentrations
Anticonvulsant	Carbamazepine, phenobarbital, phenytoin, primidone	Plasma level and half-life of lamotrigine decreased due to increased metabolism (clearance increased 30–50% with carbamazepine; by 125% with phenytoin) Increased plasma level of epoxide metabolite of carbamazepine by 10–45% with resultant increased side effects
	Topiramate	Decreased plasma level of lamotrigine
	Valproate	Increased plasma level of lamotrigine (by up to 200%) and half-life (by up to 50%), and decreased clearance (by up to 60%), leading to an increased risk of lamotrigine toxicity and life-threatening rashes; both decreases and increases in valproate levels reported Increased risk of life-threatening rash with combination (Stevens-Johnson syndrome and toxic epidermal necrolysis)
Antidepressant		
SSRI	Escitalopram	Case reports of myoclonus
	Sertraline	Case reports of increased plasma level of lamotrigine resulting in toxicity
Antipsychotic	Olanzapine	AUC of lamotrigine decreased by 24%
Antitubercular	Rifampin	Decreased lamotrigine levels and half-life
Biguanide	Metformin	Increased plasma levels of metformin via inhbition of tubular secretion via organic cationic transporter 2 (OCT2). Co-administration not recommended with narrow therapeutic index OCT2 substrates
CNS depressant	Alcohol, hypnotics, opioids	Increased sedation, disorientation
Herbal preparation	Ginseng	Case report of drug reaction with eosinophilia and systemic symptoms (DRESS)
Hormone	Oral contraceptive	Decreased plasma level of lamotrigine (by 27–64%) Reports of breakthrough bleeding and unexpected pregnancies
Protease inhibitor	Lopinavir/ritonavir	Decreased plasma level of lamotrigine (by 50%) due to increased metabolism; use ritonavir-boosted regimens with caution

DRUGS INTERACTING WITH OXCARBAZEPINE

Class of Drug	Example	Interaction Effects
Anticonvulsant	Carbamazepine, phenobarbital, phenytoin, valproate	Decreased plasma levels of oxcarbazepine MHD metabolite by 40% (carbamazepine); 30% (phenytoin); 25% (phenobarbital); 18% (valproate) Increased level of phenytoin (by 40%) and phenobarbital (by 14%) due to inhibited metabolism via CYP2C19
Antidepressant	Citalopram	May increase risk of QTc prolongation
	Sertraline	Case report of fatal serotonin syndrome in elderly patient when oxcarbazepine added, thought to be mediated through CYP2C19 inhibition

Anticonvulsants (cont.)

Class of Drug	Example	Interaction Effects
Antipsychotic	Aripiprazole, brexpiprazole, cariprazine, haloperidol, lurasidone, quetiapine	May reduce concentrations of antipsychotics that are CYP3A4 substrates
Antiretroviral		Decreased concentrations of antiretrovirals; avoid combination or use with extreme caution
Calcium channel blocker	Felodipine	AUC of felodipine lowered by 28% – similar effect anticipated with other dihydropyridine calcium channel blockers
	Verapamil	Reduced oxcarbazepine MHD metabolite plasma level (by about 20%) – mechanism unknown
CNS depressant	Alcohol, hypnotics, opioids	Increased sedation, disorientation
Diuretic	Furosemide	Increased risk of hyponatremia with oxcarbazepine
Hormone	Oral contraceptives	Increased metabolism of ethinyl estradiol and levonorgestrel through induction of CYP3A4

DRUGS INTERACTING WITH TOPIRAMATE

Class of Drug	Example	Interaction Effects
Antacid	Calcium-containing antacids	Excessive use may increase renal stone (calcium phosphate) formation
Anticonvulsant	Carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone	Decreased plasma levels of topiramate reported; by 40% with carbamazepine and 48% with phenytoin Increased plasma level of carbamazepine (by 20%) and of phenytoin
	Lamotrigine	Decreased plasma level of lamotrigine
	Valproate	Case reports of delirium and elevated ammonia levels; decreased clearance of topiramate by 25%
Biguanide	Metformin	May increase risk of lactic acidosis as topiramate may decrease sodium bicarbonate levels
Carbonic anhydrase inhibitor	Acetazolamide, zonisamide	Excessive use may increase renal stone (calcium phosphate) formation and/or hyperthermia
CNS depressant	Alcohol, hypnotics, opioids	Increased sedation, disorientation
Diuretic	Furosemide, hydrochlorothiazide	Increased risk of hypokalemia
Hormone	Oral contraceptive	Possibly decreased levels of estrogen, resulting in decreased efficacy of oral contraceptive

DRUGS INTERACTING WITH VALPROATE

Class of Drug	Example	Interaction Effects
α_2 agonist	Guanfacine	Increased valproate concentration (and decreased valproate concentration after guanfacine discontinuation)
Anesthetic	Propofol	Valproate reduces dose required to induce anesthesia for ECT
Antibiotic	Carbapenems	Significantly decreased valproate plasma levels
	Erythromycin	Increased valproate plasma level due to decreased metabolism; may also occur with clarithromycin
Anticoagulant	Warfarin	Inhibits secondary phase of platelet aggregation by valproate, thus affecting coagulation; increased INR response Displacement of protein binding of warfarin (free fraction increased by 33%)
Anticonvulsant	Carbamazepine	Decreased valproate levels due to increased clearance and displacement from protein binding Effects on carbamazepine levels are variable and inconsistent
	Ethosuximide	Increased half-life of ethosuximide (by 25%)
	Felbamate	Increased plasma level of valproate (by 31–51%) due to decreased metabolism
	Lamotrigine	Increased lamotrigine plasma level (by up to 200%), half-life (by up to 50%), and decreased clearance (by up to 60%) Both decreases and increases in plasma level of valproate reported. This combination may be dangerous due to high incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis

Class of Drug	Example	Interaction Effects
	Phenobarbital, primidone	Increased level of anticonvulsant (by 30–50%) due to decreased metabolism caused by valproate. Increased clearance of valproate and additive CNS depression (possibly severe)
	Phenytoin	Enhanced anticonvulsant effect due to displacement from protein binding (free fraction increased by 60%) and inhibited clearance (by 25%); toxicity can occur at therapeutic levels Possible decrease in valproate level
	Topiramate	Case reports of delirium and elevated ammonia levels; topiramate increases risk of valproate encephalopathy
Antidepressant		
SSRI	Fluoxetine	Increased plasma level of valproate (up to 50%)
SNRI	Venlafaxine	Significantly increased levels of active metabolite O-desmethlyvenlafaxine
Cyclic (nonselective)	Amitriptyline, doxepin, nortriptyline	Increased plasma level and adverse effects of antidepressant – consider therapeutic drug monitoring and monitor for adverse effects of increased antidepressant levels
Antipsychotic	Clozapine	Increased risk of myocarditis during clozapine titration period – increase dose very slowly and monitor weekly C-reactive protein along with required CBC and differential to identify inflammation. Both increased and decreased clozapine levels reported; changes in clozapine/norclozapine ratio Case report of hepatic encephalopathy
	Haloperidol	Increased plasma level of haloperidol (by an average of 32%)
	Olanzapine	Combination associated with high incidence of weight gain Significantly lower levels of olanzapine in combination with valproic acid
	Phenothiazines	Increased EPSE and neurological adverse effects due to decreased valproate clearance (by 14%)
	Risperidone	Case report of encephalopathy with initiation of risperidone
Antitubercular	Isoniazid	Increased plasma level of valproate due to inhibited metabolism
	Rifampin	Increased clearance of valproate (by 40%)
Antiviral	Acyclovir	Decreased level of valproate
	Zidovudine	Increased level of zidovudine (by 38%) due to decreased clearance Severe anemia reported with combination; use combination with caution and monitor for zidovudine toxicity
	Ritonavir/nevirapine	Decreased level of valproate with ritonavir due to increased metabolism; use with caution Cases of hepatoxicity with antiretroviral regimens containing ritonavir, saquinavir, stavudine, and nevirapine
Anxiolytic	Chlordiazepoxide, clonazepam, lorazepam	Decreased metabolism and increased pharmacological effects of benzodiazepines resulting in increased sedation, disorientation (lorazepam clearance reduced by 41%)
	Clonazepam	Concomitant use may induce absence status in patients with a history of absence type seizures
	Diazepam	Increased plasma level of diazepam due to displacement from protein binding (free fraction increased by 90%)
Barbiturate	Thiopental	Displacement of thiopental from protein binding, resulting in an increased hypnotic/anesthetic effect
CNS depressant	Alcohol, hypnotics	Increased sedation, disorientation
H_2 antagonist	Cimetidine	Decreased metabolism and increased half-life of valproate
Hypnotic	Zolpidem	Case of somnambulism with combination
Lithium		Valproate may aggravate action tremor
Salicylate	ASA, bismuth subsalicylate	Displacement of valproate from protein binding and decreased clearance, leading to increased level of free drug (4-fold), with possible toxicity
Sulfonylurea	Tolbutamide	Increase in free fraction of tolbutamide from 20 to 50% due to displacement from protein binding

Comparison of Anticonvulsants

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
General Comments (C&A population unless otherwise specified)	No recommendation for use in acute mania, depression, or maintenance treatment in bipolar disorder (BD). Considered a last line agent in acute BD mixed episode	Considered a third-line agent in acute bipolar disorder (BD) manic/mixed episode and first-line agent for BD maintenance. No recommendation for use in acute BD depression	No recommendation for use in acute manic/mixed episode, depression, or maintenance treatment in bipolar disorder (BD). Not recommended in adults for BD	Considered a second-line agent in acute bipolar disorder (BD) depression and first-line agent for BD as an adjunct in age 13 years and older for maintenance. No recommendation for use in acute BD manic/mixed episodes	Not recommended for use in acute manic/mixed episode or depression in bipolar disorder (BD). No recommendation for maintenance treatment in BD. Not recommended in adults for BD	No recommendation for use in acute manic/mixed episode, depression, or maintenance treatment in bipolar disorder (BD). Not recommended in adults for BD
Pharmacology	Anticonvulsant, anti-kindling, and GABA-ergic activity Blocks voltage-dependent sodium channels May also act on other ion channels for calcium and potassium	Anticonvulsant, anti-kindling, and GABA-ergic activity Indirectly blunts excitatory activity of glutamatergic system Blocks calcium channels Indirectly blocks voltage-dependent sodium channels Increases serotonergic function	Anticonvulsant, anti-kindling, and GABA-ergic activity Blocks voltage-dependent sodium channels and calcium channels Inhibits excitatory amino acids (glutamate)	Anticonvulsant and GABA-ergic activity Blocks voltage-dependent sodium channels and calcium channels Inhibits excitatory amino acids (glutamate)	MHD metabolite has anticonvulsant, anti-kindling, and GABA-ergic activity Blocks voltage-dependent sodium channels and calcium channels	Anticonvulsant, anti-kindling, and GABA-ergic activity Inhibits excitatory amino acids (glutamate) Inhibits carbonic anhydrase Blocks voltage-dependent sodium channels and calcium channels

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Dosing	Age < 5: Begin at 10–20 mg/kg/day in divided doses and increase weekly as needed to a maximum of 35 mg/kg/day Ages 6–12: Begin at 100–200 mg/day in divided doses and increase by 100 mg twice weekly until either side effects limit dose or therapeutic plasma level reached	Children: Begin at 125 mg bid-tid and increase gradually until either side effects limit dose or therapeutic plasma level reached Adolescents: begin at 250 mg bid-tid and increase dose gradually until either side effects limit dose or therapeutic plasma level reached	Begin at 10–15 mg/kg/day given tid and increase gradually q3–5 days Ages 3–4: usual dose 40 mg/kg/day Age ≥ 5: usual dose 30 mg/kg/day Maximum dose: 50 mg/kg/day	Rapid titration associated with serious rash. Initial dose based on concomitant drugs prescribed; follow titration schedule as set out in product monograph Antidepressant dose: 200 mg/day (monotherapy)	Age 4–16: Begin at 8–10 mg/kg/day or 600 mg/day (whichever is lower) in 2 divided doses and increase weekly up to the maintenance dose: < 20 kg = 600–900 mg daily, 20–29 kg = 900 mg daily, 29.1–39 kg = 1200 mg once daily, > 39 kg = 1800 mg once daily	Age < 12: give 1–3 mg/kg/day (max 25 mg) hs and increase dose weekly by 1–3 mg/kg/day (given bid) Usual dose: 5–9 mg/kg/day Higher doses may be needed if given with enzyme inducers (up to 22 mg/kg/day) Age > 12: give 25–50 mg hs and increase dose weekly by 25–50 mg (given bid) to a usual dose of 400 mg/day
	Dose range: Children: 200–600 mg/day, Adolescents: 300–1200 mg/day in single or divided doses (capsules can be opened and sprinkled on food)	Dose range: Age ≤ 12: 1000–1250 mg/day Age ≥ 12: 1000–2500 mg/day in divided doses *ER:* Only available in the USA, usually given once daily. Conversion from regular formulations may require 8–20% increase in total daily dose to maintain similar serum concentrations	Usual dose range: 900–1800 mg/day Anxiety and neuropathic pain: up to 2400 mg/day	When starting lamotrigine monotherapy in adolescents, recommended to follow adult monotherapy titration (25 mg daily for 2 weeks, then 50 mg daily for 2 weeks, then 100 mg daily for 1 week, then 200 mg daily). See product monograph for dosing guidelines for combined use with valproate or enzyme-inducing anti-epileptic drugs	Children age < 8 have increased clearance When switching from carbamazepine, the equivalent dose is 50% higher	Increased clearance observed in young children (low initial dose and gradual increases minimize cognitive and behavioral side effects)
Renal impairment	No change	Free valproate level doubles in renal impairment	Decrease dose if CrCl below 60 mL/min (see Precautions, p. 312)	Reduced clearance; half-life prolonged 63% in renal failure	Decrease dose by 50% if CrCl below 30 mL/min	Clearance reduced by 42%–54% in moderate–severe impairment If CrCl below 70 mL/min/1.73 m^2: Administer 50% dose and titrate more slowly
Hepatic impairment	Reduced clearance – plasma concentrations increased by approximately 30% Do not use in active hepatic disease	See hepatic adverse effects (p. 326) and Precautions (p. 311) Hepatic disease is also associated with decreased albumin concentrations and 2- to 2.6-fold increase in unbound fraction. Free concentrations of valproate may be elevated while total concentrations appear normal. Use is contra-indicated in severe impairment	Does not undergo hepatic metabolism	Reduce initial and maintenance doses by 50% in mild–moderate impairment and 75% in severe impairment	No dose adjustments required in mild–moderate impairment	Reduced clearance – plasma concentrations increased by approximately 30%; initiate same dose and titrate according to clinical outcome

Comparison of Anticonvulsants (cont.)

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
AGNP* recommended plasma level[31]	4–12 mg/L = 15–50 micromol/L	50–100 mg/L = 350–700 micromol/L Higher end of dosing range recommended for acute mania[32]	2–20 mg/L = 12–117 micromol/L reported for epilepsy	3–15 mg/L = 12–59 micromol/L reported for epilepsy	10–35 mg/L = 40–139 micromol/L (MHD metabolite) reported for epilepsy	2–10 mg/L = 6–30 micromol/L reported for epilepsy
Pharmacokinetics						
Bioavailability	75–85%	78–90%	Approx. 60% (dose dependent; higher with qid dosing)	100%	> 95%	80%
Peak plasma level	1–6 h	Oral valproic acid: 1–4 h (may be delayed by food) Divalproex and extended-release: 3–8 h	2–3 h	1–5 h (rate may be reduced by food)	1–3 h (parent) 4–12 h (MHD metabolite) 2–4 h at steady state	2–3 h (delayed by food)
Protein binding	75–90%	60–95% (concentration dependent); increased by low-fat diets	minimal	55%	40% (MHD)	15–41%
Half-life	15–35 h (acute use); 10–20 h (chronic use) – induces own metabolism	5–20 h; mean of 9 h in children ages 2–14	5–7 h	33 h mean (acute use) 26 h mean (chronic use)	Parent: 1–5 h MHD metabolite: 7–20 h	19–23 h; increased clearance in children
Metabolizing enzymes	CYP3A4$^{(m)}$, 2B6, 2C8, 2C9; UGT2B7; P-gp	CYP2C9; UGT1A6, 1A9, 2B7	Not metabolized – eliminated by renal excretion	Metabolized primarily by glucuronic acid conjugation; also by UGT1A4, 2B7	Rapidly metabolized by cytosolic enzymes to active metabolite MHD	P-gp; 70% eliminated unchanged in urine
Metabolism effects	Inducer of CYP1A2$^{(p)}$, 2B6$^{(p)}$, 2C8$^{(p)}$, 2C9$^{(p)}$, 2C19$^{(p)}$, 3A4$^{(p)}$; UGT1A4; P-gp; Induces own metabolism	Inhibitor of CYP2D6$^{(w)}$, 2C9, 2C19; UGT2B7$^{(p)}$, 2B15, 3A4$^{(w)}$	–	–	Moderate inducer of CYP3A4 Inhibitor of CYP2C19$^{(w)}$ and UGT1A4 (does not induce own metabolism)	Weak inhibitor of CYP2C19; weak inducer of 3A4

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Adverse Effects						
CNS	Sedation (11%), cognitive blunting, confusion (higher doses)	Sedation (> 10%), lethargy, behavior changes/deterioration, cognitive blunting, encephalopathy	Sedation (19%), fatigue (11%), abnormal thinking, amnesia	Sedation (> 10%), asthenia, cognitive blunting, "spaced-out" feeling	Sedation (19%), lethargy	Sedation (6–15%), lethargy, fatigue (8–15%), deficits in word finding, concentration, and memory (dose dependent, 1–11%)
	Agitation, restlessness, irritability, insomnia May exacerbate schizophrenia on withdrawal Case reports of behavioral disturbances and mania in patients with intellectual disability	Hyperactivity, aggression Case of delirium (following loading-dose strategy) Rare cases of psychosis Case reports of disinhibition	Nervousness, anxiety, hostility Rare switches to hypomania/mania Cases of depression Case reports of disinhibition	Agitation, activation, irritability, insomnia Switches to hypomania/mania		Anxiety, agitation, insomnia Increased panic attacks, worsening of depression or psychosis
	Headache	Headache (3%)	Headache (3%)	Headache (> 25%)	Headache (31%)	Headache
	Tremors, ataxia (up to 50%), paresthesias (3%), acute dystonic reactions, chronic dyskinesias Case reports of worsening of tic disorders	Tremors (10% in adults; 15% in children – tend to be rhythmic, rapid, symmetrical, and most prominent in the upper extremities), ataxia, dysarthria, incoordination	Tremors (7%), ataxia, incoordination, dysarthria, myalgia Case report of acute dystonia; asterixis	Tremors, ataxia (22%), incoordination (14%), myalgia, arthralgia, fever Case report of dystonia	Ataxia (> 25%), gait disturbances, tremor	Tremors, ataxia; paresthesias (19–51%)
Anticholinergic	Blurred vision (6%), mydriasis, cycloplegia, ophthalmoplegia, dry mouth, slurred speech Constipation, urinary retention		Dry mouth or throat (2%) Constipation	Blurred vision Constipation Dry mouth (> 5%)	Blurred vision	Blurred vision, sweating Acute angle closure glaucoma reported
Gastro-intestinal	Nausea (4%) and vomiting	Nausea common, vomiting	Nausea (4%), diarrhea, dyspepsia (2%)	Nausea (19%), vomiting (9%), diarrhea (6%) Rarely esophagitis	Nausea (22%), vomiting (15%)	Nausea (4–13%), anorexia (4–15%) Change in taste of carbonated beverages
Cardiovascular	Dizziness, vasculitis Cardiac conduction disorders – rare	Rarely dizziness, vasculitis Case report of hyperkalemia	Dizziness (17%), hypotension Occasionally hypertension, peripheral edema	Breathlessness, dizziness (38%), conduction changes (prolongation of PR interval)	Dizziness (28%), peripheral edema, hypotension	Dizziness common

Comparison of Anticonvulsants (cont.)

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Dermatological	Rash (10–15%) – severe dermatological reactions may signify impending blood dyscrasias Hair loss (6%), photosensitivity reactions Rarely: Fixed drug eruptions, lichenoid-like reactions, bullous reactions, exfoliative dermatitis Hypersensitivity syndrome – rare; with fever, skin eruptions, and internal organ involvement, Stevens-Johnson syndrome, toxic epidermal necrolysis	Rash Hair loss (up to 12% – higher incidence with higher doses); changes in texture or color of hair Case reports of nail pigmentation Rare cases of Stevens-Johnson syndrome (increased risk in combination with lamotrigine), toxic epidermal necrolysis, lupus, erythema multiforme, or skin pigmentation	Pruritus (1%), rash (1%)	Rash (up to 10%); in 2–3% require drug discontinuation – risk of severe rash increased with rapid dose titration, in children, and in combination with valproate Stevens-Johnson syndrome in 1–2% of children and 0.1% of adults (usually within first 8 weeks of therapy) Rarely, erythema multiforme, hypersensitivity syndrome Photosensitivity reactions	Rash less common than with carbamazepine; 25–30% of patients are cross-sensitive Stevens-Johnson syndrome and toxic epidermal necrolysis reported in adults and children	Rash
Hematologic	Transitory leukopenia (10%), persistent leukopenia (2%) Rarely, eosinophilia, aplastic anemia, thrombocytopenia, purpura, and agranulocytosis	Reversible thrombocytopenia – may be related to high plasma levels; rare episodes of bleeding Macrocytic anemia, coagulopathies Case of pancytopenia (following rapid loading-dose strategy)	Leukopenia (1%), purpura	Neutropenia Rarely, hematemesis, hemolytic anemia, thrombocytopenia, pancytopenia, aplastic anemia	Rare	Purpura
Hepatic	Transient enzyme elevation (5–15%) – evaluate for hepatotoxicity if transaminase elevation more than 3 times upper limit of normal Rarely, hepatocellular and cholestatic jaundice, granulomatous hepatitis, and severe hepatic necrosis	Asymptomatic hepatic transaminase elevation (44%) Cases of severe liver toxicity Steatosis or nonalcoholic fatty liver disease (a symptom of insulin resistance)	Case reports of abnormal liver function	Rare	Rare Case report of increased LFT in patient with elevated levels at baseline	Cases of severe liver damage

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Endocrine	Menstrual disturbances in females (up to 45%) Decreased libido in males Elevation of total cholesterol (primarily HDL) Can lower thyroxine levels and TSH response to TRH Polycystic ovaries reported in up to 22% of females; Hyperandrogenism in up to 17% Weight gain – may be independent of or secondary to peripheral edema/SIADH Occasional weight loss	Menstrual disturbances (up to 60%) including prolonged cycles, oligomenorrhea, amenorrhea, polycystic ovaries (up to 67%) – higher incidence in obese women In females: Hyperandrogenism (increased testosterone in 33%), android obesity (in up to 53%), hirsutism, hyperinsulinemia Can cause subclinical hypothyroidism in about 15% of children after 1 year of treatment Decreased levels of HDL, low HDL/cholesterol ratio, increased triglyceride levels Weight gain (59%) – more common in females and with high plasma levels; may be associated with features of insulin resistance Weight loss (5%)	Weight gain common with higher doses	Menstrual disturbances, dysmenorrhea, vaginitis No weight gain	Decreased T4 levels reported with normal T3 and TSH	Decreased sweating, hyperthermia resulting in hospitalization and some deaths; more common in children – caution with anticholinergic agents and carbonic anhydrase inhibitors Anorexia; weight loss (4–13%)
Ocular	Diplopia (16%), nystagmus (up to 50%), visual hallucinations, lens abnormalities 2 cases of pigmentary retinopathy	Diplopia, nystagmus, asterixis (spots before the eyes)	Diplopia (6%), nystagmus (8%), amblyopia (4%)	Diplopia (28%) nystagmus, amblyopia	Diplopia (12%), nystagmus	Diplopia, nystagmus Cases of acute myopia and secondary angle closure glaucoma Slight increase in glaucoma risk among current users of topiramate
Other	Hyponatremia and water intoxication (4–12%) – more common with higher plasma levels Rarely: Acute renal failure, pancreatitis, splenomegaly, lymphadenopathy, systemic lupus erythematosus, and serum sickness Can decrease vitamin D levels by increasing its metabolism, resulting in increased bone resorption, osteomalacia, osteoporosis, and fractures [bone density evaluation, supplement with calcium and vitamin D]	Gingival hyperplasia Carnitine deficiency Increased bone resorption with osteoporosis, osteopenia [bone density evaluation, supplement with calcium and vitamin D] Rarely: Osteomalacia, cholecystitis, pancreatitis and serum sickness Elevated ammonia levels common in valproate-treated patients. Consider in patients showing signs of lethargy, mental status changes	Rhinitis (4%), pharyngitis (3%)	Rhinitis, pharyngitis, flu-like syndrome (7%) Rarely: Apnea, pancreatitis	Hyponatremia (29%), upper respiratory tract infection (10%)	Hyponatremia (up to 25%) Nephrolithiasis (renal stone formation) in up to 1.5% with chronic use Decrease in serum bicarbonate (in up to 30% of patients) usually mild but can be significant – see Precautions p. 312 Metabolic acidosis (may increase risk for nephrolithiasis or nephrocalcinosis and may result in osteomalacia and/or osteoporosis Epistaxis Hyperammonemia and encephalopathy – rare reports Upper respiratory tract infection (13–26%)

Comparison of Anticonvulsants (cont.)

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Use in Pregnancy◇	AVOID, especially in first trimester (level A evidence)[33]. If necessary, use lowest amount possible in divided doses Monitor drug levels throughout pregnancy, maternal α fetoprotein around week 16, and do fetal ultrasound around week 20 Concentration of drug in cord blood equals that in maternal serum Caution: Overall incidence of major malformations is 5.7%, with lower birth rates reported	AVOID, especially in first trimester (level A evidence)[33] Incidence of malformations is 11.1% – related to dose and drug plasma level. Fetal serum concentrations are 1.4 times that of the mother; half-life prolonged in infant Evidence that fetal exposure to valproate compared with other commonly used antiepileptic drugs is associated with an increased risk of impaired cognitive function at age 3[34] If absolutely necessary, limit use to less than 1000 mg/day in 3 or more divided doses and monitor plasma levels throughout pregnancy, maternal α fetoprotein around week 16, and do fetal ultrasound around week 20	Crosses placenta, fetotoxicity reported in animal studies; risk to humans is currently unknown	Crosses placenta; levels comparable to those in maternal plasma; considered a potential maintenance therapy option for pregnant women with mood disorders (level B evidence)[33] Half-life increased in infant 3.2% risk of malformations with use in first trimester; risk noted to increase to 5.4% when total daily dose above 200 mg	Crosses placenta; teratogenic effects reported in animals; likely to cause teratogenic effects in humans (folic acid supplementation recommended) Data on a limited number of pregnancies report cleft palate and other malformations Case report of renal and cardiac malformations with hyponatremia and withdrawal symptoms at birth	Fetotoxicity reported in animal studies and evidence of increased risk of oral clefts

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Specific Birth Defects	Risk of spina bifida up to 1%, congenital heart defects 2.9% One prospective study reported craniofacial defects in 11%, fingernail hyperplasia in 26%, and developmental delays in 20% of children exposed prenatally May cause vitamin K deficiency during latter half of pregnancy, resulting in bleeding [vitamin K and folic acid supplementation recommended] Clearance increased 2-fold during pregnancy; dose may need to be increased by 100%	Risk of spina bifida 1–2%, neural tube defects up to 5%, neurological dysfunction and developmental deficits seen in up to 71% (FDA warning of lower cognitive test scores in children); musculoskeletal, cardiovascular, pulmonary, craniofacial, genital, and skin defects also reported May cause vitamin K deficiency during latter half of pregnancy, resulting in bleeding [vitamin K and folic acid supplementation recommended] Infants may be at higher risk for hypoglycemia Total plasma valproate concentration decreased during pregnancy as a result of increased volume of distribution and clearance; plasma protein binding decreased		Increased risk of cleft lip and/or cleft palate when used in first trimester (2–5%) Decreases fetal folate levels [folic acid supplementation recommended] Lamotrigine metabolism appears to be induced during pregnancy (decreased levels) and plasma levels increase rapidly after delivery	May cause vitamin K deficiency during latter half of gestation, resulting in bleeding [vitamin K supplementation recommended]	North America Antiepileptic Drug Pregnancy Registry data suggests topiramate monotherapy in first trimester is associated with a 1.4% prevalence of oral clefts compared to 0.38–0.55% for infants exposed to other antiepileptic drugs; hypospadias in male infants [folic acid supplementation recommended] and anomalies involving various body systems
Breast Milk	American Academy of Pediatrics considers carbamazepine compatible with breastfeeding Breast milk contains 7–95% of maternal drug concentration; infant serum level is 6–65% of mother's Educate mother about signs and symptoms of hepatic dysfunction and CNS effects of drug in the infant Monitor liver enzymes and CBC of infant and mother No long-term cognitive or behavioral effects reported in infant	American Academy of Pediatrics considers valproate compatible with breastfeeding Infant plasma level of valproate is up to 40% of that of mother; half-life in infants is significantly longer than in adults Educate mother about the signs and symptoms of hepatic dysfunction and those of hematological abnormalities in the infant Monitor liver enzymes and CBC of infant and mother No long-term cognitive or behavioral effects reported in infant	Gabapentin is excreted in breast milk No long-term cognitive or behavioral effects reported in infant but data is limited Monitor infant for drowsiness, adequate weight gain, and developmental milestones	Excreted in breast milk; the milk/plasma ratio is about 0.6 Infant serum levels are 25–30% of those of mother Effect on infant unknown but may be of concern – monitor serum levels in infant and for sedation and rash; consider risk of life-threatening rash in infant. If lamotrigine required, not a reason to stop breastfeeding	Excreted into breast milk at levels up to 50% of those in maternal plasma Effects on infant unknown Monitor for poor suckling, vomiting, and sedation. Breast feeding not recommended	Breastfeeding is not recommended due to possible psychomotor slowing and somnolence in infant Monitor infant for signs of toxicity including changes in alertness, behavior, and feeding habits

(m) moderate, (p) potent, (w) weak, * Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (https://agnp.de/)[31], ◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

P-gp = p-glycoprotein [*a transporter of hydrophobic substances across extra- and intra-cellular membranes that include the intestinal lumen and the blood-brain barrier*]; MHD = monohydroxy derivative metabolite of oxcarbazepine (10,11-dihydro-10-hydroxy-carbazepine); UGT = uridine diphosphate glucuronosyl transferase [*involved in Phase II reactions (conjugation)*]

Frequency of Adverse Reactions to Mood Stabilizers at Therapeutic Doses

Reaction	Lithium	Second-Generation Agents		Third-Generation Agents			
		Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
CNS							
Drowsiness, sedation	< 2%[a]	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%[b]
Headache	> 2%	> 2%	> 2%	> 2%	> 30%	> 10%	> 2%
Cognitive blunting, memory impairment	> 10%	> 2%	> 2%	> 2%	> 2%	> 2%	> 2%[b]
Weakness, fatigue	> 30%[a]	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%
Insomnia, agitation	< 2%	< 2%	> 2%	> 2%	> 2%	> 2%	> 10%
Neurological							
Incoordination	< 2%[a]	> 10%	> 2%	> 2%	> 2%	> 2%	> 2%
Dizziness	–	> 10%	> 10%	> 30%	> 2%	> 10%	> 10%[b]
Ataxia	< 2%[a]	> 10%	> 2%	> 10%	> 2%	> 2%	> 2%[b]
Tremor	> 30%[a]	> 30%	> 10%	> 10%	> 10%	> 2%	> 2%
Paresthesias	–	> 2%	> 2%	< 2%	> 2%	> 2%	> 10%
Diplopia	–	> 10%	> 2%	> 10%	> 10%	> 10%	> 2%
Anticholinergic							
Blurred vision	> 2%[a]	> 2%	> 2%	> 10%	> 2%	> 2%	> 2%
Cardiovascular							
ECG changes[c]	> 10%	> 2%	–	< 2%	< 2%	< 2%	–
Gastrointestinal							
Nausea, vomiting	> 30%	> 10%	> 10%	> 10%	> 10%	> 10%	> 2%
Diarrhea	> 10%[a]	> 2%	> 2%	> 2%	> 2%	> 2%	> 2%
Weight gain	> 30%	> 2%	> 10%	< 2%	> 2%	> 2%	–
Weight loss	< 2%	< 2%	> 2%	> 2%	< 2%	< 2%	> 10%[b]
Endocrine							
Hair loss, thinning	> 10%	> 2%	> 10%	–	< 2%	< 2%	< 2%
Menstrual disturbances	> 10%	> 30%	> 30%	> 2%	< 2%	< 2%	–
Polycystic ovary syndrome	–	> 10%	> 2%	–	< 2%	–	–
Hypothyroidism	> 30%	< 2%	< 2%	< 2%	< 2%	–	–
Polyuria, polydipsia	> 30%	> 2%	–	–	< 2%	< 2%	–
Skin reactions							
Rash	> 10%[d]	> 10%[e]	> 2%	> 10%[e]	> 2%	> 2%	< 2%
Sexual dysfunction	> 2%	< 2%	> 2%	–	–	–	–
Blood dyscrasias							
Transient leukopenia	< 2%	> 10%	< 2%	< 2%	< 2%	< 2%	< 2%
Leukocytosis	> 30%	< 2%	< 2%	–	< 2%	< 2%	–
Thrombocytopenia	–	> 2%	> 30%[b]	< 2%	–	< 2%	–
Hepatic							
Transient enzyme elevation[f]	–	> 10%	> 30%[b]	< 2%	< 2%	< 2%	–

[a] Higher incidence and more pronounced symptoms with higher serum lithium concentration; may indicate early toxicity – monitor level [b] Greater with higher doses; [c] ECG abnormalities usually without cardiac injury, including ST segment depression, flattened T waves, and increased U wave amplitude; [d] Worsening of psoriasis reported; [e] May be first sign of impending blood dyscrasia; [f] Evaluate for hepatotoxicity if transaminases elevated > 3 times upper limit of normal

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SUBSTANCES OF ABUSE

Classification

- This chapter gives a general overview of common drugs of abuse and is not intended to deal in detail with all drugs of abuse or to be a complete guide to treatment
- Slang names of street drugs change frequently and vary with country, region, and drug subculture. A list of common drug names is available from the NIH-sponsored website https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts
- Drugs of abuse can be classified as follows:

Chemical Class	Agent*	Page
Alcohol	(Ethyl) Alcohol	See p. 336
Stimulants	Examples: Amphetamine, caffeine, cocaine, crystal meth, ephedrine, MDMA (ecstasy)	See p. 341
Hallucinogens	Examples: Cannabis, lysergic acid diethylamide (LSD), mescaline, psilocybin	See p. 347
Opioids	Examples: Dextromethorphan, fentanyl, heroin, hydromorphone, morphine, oxycodone	See p. 356
Inhalants/Aerosols	Examples: Glue, nitrous oxide, paint thinner	See p. 361
Sodium oxybate (gamma-hydroxybutyrate – GHB)		See p. 363
Hypnotics/Sedatives	Examples: Antihistamines **(dimenhydrinate, diphenhydramine)**, barbiturates**, hypnotics** Benzodiazepines** Flunitrazepam	See p. 282 See p. 263 See p. 365
Nicotine	Examples: Cigarettes, cigars, chewing tobacco, vaping devices	See p. 366

* Only includes examples of most commonly used substances, ** Not dealt with specifically in this chapter

Definitions

- While DSM-5 combines substance abuse and substance dependence into a single disorder called substance use disorder, the following terms are still commonly used, and their definitions have been retained here for readers' convenience

Tolerance
- Phenomenon in which increasing doses of a drug are needed to produce a desired effect or effect intensity decreases with repeated use

Withdrawal
- Phenomenon in which ceasing the use or decreasing the use of the drug creates a physiological reaction (often in "rebound" to the physiological reaction of the drug)

Drug Abuse
- Acute or chronic intake of any substance that: (a) has no recognized medical use, (b) is used inappropriately in terms of its medical indications or its dose. Drug abuse is commonly associated with harm to the individual or others

Drug Dependence

Behavioral aspects
- Craving or desire for repeated administration of a drug to provide a desired effect or to avoid discomfort

Physical aspects
- A physiological state of adaptation to a drug which usually results in development of tolerance to drug effects and withdrawal symptoms when the drug is stopped

Addiction
- Intense persistent drug use associated with craving and compulsion to continue use, despite consequences or personal harm
- Chronically relapsing, loss of control in limiting intake, and emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented

Substances of Abuse (cont.)

General Comments

- Early substance use has consistently been linked to negative consequences, including regular heavy use, dependence, and physical and social problems during young adulthood. It may alter brain maturation (brain develops until around age 25) and contribute to lasting cognitive impairment
- The effect which any drug of abuse has on an individual depends on a number of variables:
  1. Dose (amount consumed)
  2. Potency and purity of drug
  3. Route of administration
  4. Past experience of the user (this will affect both physiological and psychological response to drug)
  5. Environmental factors, including other people present and concurrent drug use
  6. Personality and genetic profile of user
  7. Age of user
  8. Clinical status of user, i.e., psychiatric illness, recent stress, user's expectations, and present feelings
- Some users may have different experiences with the same drug on different occasions. They may encounter both pleasant and unpleasant effects during the same drug experience
- Many street drugs are adulterated with other chemicals and may not be what the individual thinks they are; potency and purity of street drugs vary greatly
- Accidental drug overdose deaths on the rise due to many street drugs being contaminated with illicitly manufactured substance (most commonly fentanyl and derivatives)
- It remains unclear whether drugs of abuse cause persistent psychiatric disorders in otherwise healthy individuals, or whether they precipitate latent psychiatric illness in predisposed individuals. Overall, in non-treatment community samples, it is estimated that over 50% of drug users have at least one other psychiatric disorder and those with certain psychiatric disorders (e.g., bipolar disorder, schizophrenia) are more likely to abuse substances than the general population
- Most evidence currently points to a causative (rather than associative) relationship between early/high THC cannabis use and the development of psychotic symptoms[1]
- Dual diagnosis or concurrent disorders refer to the co-occurrence of substance use disorder in a patient with a psychiatric illness. Substance use disorder can occur during any phase of the psychiatric illness; it is associated with a variety of physical/psychosocial problems, can destabilize treatment, and lead to relapse
- Substance use disorder has been associated with earlier onset of schizophrenia, decreased treatment responsiveness of positive symptoms, and poor clinical functioning; similarly decreased treatment responsiveness in bipolar disorder can occur

Detection of Drugs/ Substances of Abuse

- Factors affecting detection of a drug in urine depend on dose and route of administration, drug metabolism, and characteristics of screening and confirmation assays (i.e., immunoassays targeted for specific drugs/metabolites for screening compared to gas chromatography/mass spectrometry (GCMS) for confirmatory testing); for instance:
  - Amphetamines in urine can be positive for up to 5 days
  - Cannabis (THC) in urine can be positive 2–4 days after acute use and for up to 1–3 months after chronic use
  - Cocaine can be positive, as its metabolite, in urine for up to 1.5 days after IV use, for up to 1 week with street doses used by different routes, and for up to 3 weeks after use of very high doses
  - Immunoassay screening tests for benzodiazepines typically detect the presence of oxazepam; therefore, parent compounds of oxazepam (e.g., chlordiazepoxide, clorazepate, diazepam, halazepam, and temazepam) will be detected.[2] Benzodiazepines that are not metabolized to oxazepam (e.g., alprazolam, clonazepam, lorazepam) may not be detected by immunoassay testing
  - Heroin can be positive, as its metabolite, in urine for up to 1.5 days after use when administered parenterally or intranasally
  - Prescription drugs can sometimes cause false-positive results due to interference with lab assays (e.g., quetiapine for TCAs or methadone)[2, 4]

Pharmacology

- Research data have demonstrated that most drugs of abuse increase dopamine activity in the nucleus accumbens of the brain; the increased dopamine is suggested to be associated with the pleasurable effects produced by the drug

Adverse Effects

- See pharmacological/psychiatric effects under specific drugs
- Reactions are unpredictable and depend on the potency and purity of drug taken
- Psychiatric reactions secondary to drug abuse may occur more readily in individuals already at risk
- Renal, hepatic, cardiorespiratory, neurological, and gastrointestinal complications can occur with chronic abuse of specific agents
- Intravenous drug users are at risk for infection, including cellulitis, endocarditis, hepatitis, and HIV
- Impurities in street drugs (especially if inhaled or injected) can cause tissue and organ damage (blood vessels, heart valves, kidney, lungs, and liver)
- Psychological dependence can occur; the drug becomes central to a person's thoughts, emotions, and activities, resulting in craving
- Physical dependence can occur; the body adapts to the presence of the drug and withdrawal symptoms occur when the drug is stopped abruptly

D/C Discontinuation Syndrome

- See specific agents
- Identification of drug(s) abused is important; some drug withdrawals have the potential to be life-threatening withdrawal syndromes (e.g., alcohol, barbiturates), whereas others are less so (e.g., opioids, stimulants); toxicology may help in identification whenever multiple drug use is suspected
- If 2 or more drugs have been chronically abused, consider withdrawing one drug at a time, starting with the one that potentially represents the greatest problem

Treatment

Acute

- Treatment of substance use disorder presents special challenges in patients with a diagnosed psychiatric disorder and is best done with an integrated treatment program that combines pharmacotherapy with psychosocial interventions
- See specific agents (alcohol p. 338, stimulants p. 342, hallucinogens p. 348, opioids p. 357, inhalants p. 362, nicotine/tobacco p. 368) and Treatment of Substance Use Disorders (pp. 370–396)
- Evaluation must include mental status, physical and neurological examination, as well as a drug history. Whenever possible, collateral history should be sought
- In severe cases, monitor vitals and fluid intake
- Agitation can be treated conservatively by talking with the patient and providing reassurance until the drug wears off (i.e., "talking down"). When conservative approaches are inadequate or if symptoms persist, pharmacological intervention should be considered
- Avoid low-potency antipsychotics (e.g., chlorpromazine) due to anticholinergic effects, hypotension, and tachycardia
- Use of zuclopenthixol acetate formulation (Clopixol Acuphase) is contraindicated in acute alcohol, barbiturate, or opioid intoxication

Long-Term

- The presence of comorbid psychiatric disorders in substance users can adversely influence outcome in treatment of the substance use disorder as well as the psychiatric disorder

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Alcohol

General Comments

- Slang: Booze, hooch, juice, brew, sauce
- Alcohol is the most common substance used by youth, often in the form of binge-drinking
- Binge drinking defined as 4 or more drinks per occasion for women and 5 or more drinks per occasion for men
- High-intensity binge drinking more common in adolescents (10–15 drinks per occasion)
- Up to 50% of individuals with alcohol dependence meet the criteria for lifetime diagnosis of major depression
- Short-term risks (often from binge drinking): Injury or death (from motor vehicle accidents, falls, drownings, and burns), violence (including suicide, homicide, sexual assault), alcohol poisoning, risky sexual behaviors (can result in unintended pregnancy or sexually transmitted infections)
- Long-term risks: Alcohol use disorders, learning and memory issues, deteriorating school performance, school dropout, mental health problems (e.g., depression, anxiety), social problems (e.g., family, unemployment), development of chronic diseases (e.g., hypertension, hypertriglyceridemia, stroke, liver disease, digestive problems), and cancers (e.g., breast (females), mouth, throat, esophagus, voice box, liver, colon, rectum)
- Alcohol acts on numerous central neurotransmission pathways and has been labeled a CNS disorganizer; produces both CNS stimulant and depressant effects

Pharmacological/ Psychiatric Effects

- Effects of alcohol have a close relationship with blood alcohol levels:
  - 2.2–8.8 mmol/L (10–40 mg/100 mL): Mild euphoria, relaxation, and increased social interactions
  - 11–17.6 mmol/L (50–80 mg/100 mL): Euphoria, some impairment of motor skills
  - 17.6–33 mmol/L (80–150 mg/100 mL): Severe impairment of motor skills, speech, and judgment; impulsivity (increased chance of assault/aggression)
  - 33–44 mmol/L (150–200 mg/100 mL): Appears "drunk," severe visual impairment
  - 44–66 mmol/L (200–300 mg/100 mL): Vomiting, incontinence, symptoms of alcohol intoxication
  - 66–88 mmol/L (300–400 mg/100 mL): Stupor, anterograde amnesia (blackouts), loss of consciousness
  - 88–110 mmol/L (400–500 mg/100 mL): Coma and potential death
- Effects of a single drink occur within 15 min and peak at approximately 30–60 min, depending on amount taken; elimination is about 10 g alcohol per hour (about 30 mL (1 oz) whiskey or 1 bottle of regular beer). Blood alcohol level declines by 3–7 mmol/L per hour (~ 15 mg/100 mL)

Acute

- Disinhibition, relaxation, euphoria, agitation, drowsiness, impaired cognition, judgment, and memory, perceptual and motor dysfunction
- Alcohol intoxication is associated with aggression and violence, especially among young males. Surveys show that about 5% of junior high and high school students report having been in trouble with the police because of their alcohol or drug use

☞ **Acute alcohol intake decreases hepatic metabolism of co-administered drugs by competition for microsomal enzymes**

Chronic

- Chronic use results in an increased capacity to metabolize alcohol and a concurrent CNS tolerance; psychological as well as physical dependence may occur; hepatic metabolism decreases with liver cirrhosis

☞ **Chronic alcohol use increases hepatic metabolism of co-administered drugs**

Physical
- Hand tremor, dyspepsia, diarrhea, morning nausea and vomiting, polyuria, impotence, pancreatitis, headache, hepatomegaly, peripheral neuropathy

Mental
- Memory blackouts, nightmares, insomnia, hallucinations, paranoia, intellectual impairment, dementia, Wernicke-Korsakoff syndrome, and other organic mental disorders

Pharmacokinetics
- Absorption occurs slowly from the stomach, and rapidly from the upper small intestine
- Approximately 10% of ingested alcohol is eliminated by first-pass metabolism (less in females); percentage decreases as amount consumed increases
- Alcohol is distributed in body fluids (is not fat soluble) and the blood alcohol level depends on gender, age, and body fluid volume/fat ratio
- Metabolized in the liver primarily by alcohol dehydrogenase, CYP2E1, and CYP450 reductase (also by CYP3A4 and CYP1A2); activity of CYP2E1 is increased 10-fold in chronic heavy drinkers

Toxicity
- Risk of injury or harm increases with more than 3 standard drinks for females and 4 for males on any single occasion (standard drink = approximately 5 oz/142 mL wine, 12 oz/355 mL beer, 1.5 oz/45 mL spirits); the legal blood alcohol concentration (BAC) threshold for impaired driving in the Criminal Code of Canada is 80 mg in 100 mL blood (0.08%). Some provinces impose administrative sanctions for drivers with BAC between 0.05% and 0.079%. In the USA, the threshold is 50 mg or 80 mg in 100 mL (0.05% or 0.08%), depending on the state
- Risk increases when combined with drugs with CNS depressant activity
- Symptoms include: CNS depression, decreased or absent deep tendon reflexes, cardiac dysfunction, flushed skin progressing to cyanosis, hypoglycemia, hypothermia, peripheral vasodilation, shock, respiratory depression, and coma

D/C Discontinuation Syndrome
- Occurs after chronic use
- Severe discontinuation syndrome (Phase II and higher below) is significantly less common in children and adolescents with maladaptive drinking than in adults with maladaptive drinking, due to a variety of factors (e.g., pattern of consumption, general physical health)
- Most effects seen within 5–7 days after stopping
- Two most commonly used tools for assessment of withdrawal symptoms: 1) Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) completed by a health care professional and 2) Short Alcohol Withdrawal Scale (SAWS) self-assessment completed by the patient

Mild Withdrawal
- Insomnia, irritability, headache
- Usually transient and self-limiting

Severe Reactions
- Phase I: Begins within hours of cessation and lasts 3–5 days. Symptoms: Tremor, tachycardia, diaphoresis, labile BP, nausea, vomiting, anxiety
- Phase II: Perceptual disturbances (usually visual or auditory)
- Phase III: 10–15% of untreated alcohol withdrawal patients reach this phase; seizures (usually tonic-clonic) last 0.5–4 min and can progress to status epilepticus (3%)
- Phase IV: Delirium tremens (DTs) is usually a late complication of untreated alcohol withdrawal; includes autonomic hyperactivity, confusion, agitation, and severe hyperthermia; mortality associated with alcohol withdrawal reduced due to early treatment preventing delirium tremens
- Wernicke's encephalopathy can occur in patients with thiamine deficiency; if untreated, up to 20% of cases can be fatal and approximately 85% of survivors will develop Korsakoff syndrome

Protracted Abstinence Syndrome
- Patients may experience subtle withdrawal symptoms that can last from weeks to months – include sleep dysregulation, anxiety, irritability, and mood instability
- Cognitive impairment from chronic alcohol use will persist for several weeks after abstinence is achieved
- Individuals are at high risk for relapse during this period
- Hepatic metabolism of co-administered drugs may decrease following abstinence from chronic alcohol use

Precautions
- Increased risk of drug toxicity possible in patients with alcohol-induced liver impairment or cirrhosis
- Risk and type of drug–drug interaction varies with acute and chronic alcohol consumption
- Caution with caffeine (e.g., energy drinks are commonly mixed with alcohol); caffeine can mask the CNS-depressant effects of alcohol, making drinkers feel more alert than they would otherwise. As a result, increased likelihood of binge drinking and increased risk of injury

Alcohol (cont.)

Use in Pregnancy◊

- Drinking alcohol while pregnant increases the risk of problems in fetal development; fetal alcohol spectrum disorder (FASD) indicates full range of possible effects on the fetus; fetal alcohol syndrome (FAS) is characterized by severe effects of alcohol, including brain damage, facial deformities, and growth deficits. Infants should be reassessed and followed up regularly as early intervention improves long-term educational outcomes
- There is no safe level of alcohol consumption during pregnancy
- Neonatal withdrawal reactions reported; seen 24–48 h after birth if mother is intoxicated at birth

Breast Milk

- Milk levels attain 90–95% of blood levels; prolonged intake can be detrimental

Treatment

- In acute intoxication, minimize environmental stimulation (e.g., dim light) to reduce agitation; effects will diminish as blood alcohol level declines (rate of 3–7 mmol/L per hour). Pharmacologic intervention is rarely required; fluid replacement with glucose-containing fluids is generally the only treatment needed for recovery
- Withdrawal reactions following chronic alcohol use may require (evidence in adults):
  a) Vitamin supplementation (thiamine 50–250 mg orally or IM (or IV in high-risk patients) daily for at least 3 days; dosage and duration not well established) to prevent Wernicke-Korsakoff syndrome. While there is no consensus on treatment of confirmed Wernicke encephalopathy, thiamine 500 mg IV three times/day for 3–5 days, followed by 250 mg IV/day for at least 3–5 additional days is recommended[1]
  b) Benzodiazepine (chlordiazepoxide, lorazepam, diazepam, or oxazepam) for symptomatic relief (to control agitation) and to prevent seizures; these drugs reduce mortality, reduce the duration of symptoms, and are associated with fewer complications compared to antipsychotic drugs; a loading dose strategy can be used with diazepam (i.e., patient dosed until light somnolence is achieved as its long duration of action prevents breakthrough symptoms and possible withdrawal seizures)
  c) If benzodiazepine is contraindicated, gabapentin, carbamazepine, or phenobarbital may be used as monotherapy for symptomatic relief
  d) If symptoms persist despite benzodiazepine use, gabapentin, carbamazepine, or valproate may be used as adjunct
  e) α-adrenergic agonists (e.g., clonidine) or β-blockers (e.g., atenolol, metoprolol) may be considered for use in conjunction with benzodiazepines in select patients for control of persistent hypertension or tachycardia
  f) Hydration and electrolyte correction
- Evidence does not support: Oral or IV alcohol, baclofen, or magnesium in prophylaxis and treatment of alcohol withdrawal
- No effective medication for Korsakoff syndrome; memantine, donepezil, or methylphenidate may be options for those with persistent memory impairment
- SSRIs may be useful as treatment for late-onset alcoholism, or alcoholism complicated by comorbid major depression. Buspirone may have some utility for treating alcoholism with comorbid anxiety disorder
- Naltrexone and acamprosate reported to be effective adjuncts to treatment for relapse prevention following alcohol detoxification, see p. 371 and p. 376; the efficacy of each is increased significantly when combined with psychosocial treatments
- See p. 373 for use of disulfiram in treatment

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Analgesic	Acetaminophen	Chronic excessive alcohol use increases susceptibility to acetaminophen-induced hepatotoxicity due to enhanced formation of toxic metabolites through CYP2E1 induction
	ASA	Increased gastric hemorrhage with ASA; reduced peak plasma concentration of ASA reported ASA may increase blood alcohol concentration by reducing ethanol oxidation by gastric alcohol dehydrogenase
	NSAIDs (ibuprofen, naproxen)	Increased risk of gastric hemorrhage
Anesthetic	Enflurane, halothane	Chronic consumption increases risk of liver damage
	Propofol	Chronic consumption increases the dose of propofol required to induce anesthesia
Antibiotic	Cephalosporins, metronidazole	Disulfiram-like reaction with nausea, hypotension, flushing, headache, tachycardia
	Doxycycline	Chronic alcohol use induces metabolism and decreases plasma level of doxycycline
Anticoagulant	Warfarin	Acute alcohol intake may increase INR by decreasing warfarin metabolism Chronic, heavy alcohol use may decrease INR by increasing warfarin metabolism; a recent decrease in alcohol intake may increase INR – close monitoring required
Anticonvulsant	Barbiturates, phenytoin, valproate	Additive CNS effects Acute intoxication inhibits phenobarbital and phenytoin metabolism, increasing their bioavailability; chronic intoxication enhances metabolism
Antidepressant		
NaSSA	Mirtazapine	Additive CNS effects
Nonselective cyclic	Tricyclics	Additive CNS and orthostatic hypotensive effects; impairment of psychomotor performance Metabolism of tricyclic modified by acute and chronic alcohol use
Irreversible MAOIs		Possible risk of hypertensive crisis with consumption of beer or wine, due to tyramine content (see p. 117)
Antifungal	Ketoconazole	Disulfiram-like reaction
Antipsychotic	Chlorpromazine, haloperidol, olanzapine, risperidone	Additive CNS effects Extrapyramidal side effects may be worsened by alcohol
Antitubercular drug	Isoniazid	Increased risk of hepatotoxicity Possible risk of hypertensive crisis with consumption of beer or wine, due to tyramine content (see p. 117) Disulfiram-like reaction
Antiviral	Abacavir	Increased AUC of abacavir (by 41%)
Ascorbic acid		Increased ethanol clearance
Benzodiazepine	Alprazolam, diazepam, lorazepam	Potentiation of CNS effects. Respiratory depression reported following use of lorazepam in intoxicated individuals
Biguanide	Metformin	Possible increased levels of lactic acid in the blood after alcohol consumption
Calcium channel blocker	Verapamil	Increased concentration of ethanol due to inhibited metabolism
Cannabis		Cannabis may suppress alcohol-induced emetic reflex which could lead to high alcohol levels Increased heart rate, blood pressure; further slowing of mental processing and reaction time
Cardiovascular drugs	Hydralazine, methyldopa	Increased dizziness or fainting upon standing up
CNS depressant	Benzodiazepines, sedating antihistamines, hypnotics, muscle relaxants, valerian	Potentiation of CNS effects. Caution with high doses due to risk of respiratory depression. Respiratory depression reported following use of lorazepam in intoxicated individuals

Alcohol (cont.)

Class of Drug	Example	Interaction Effects
Disulfiram		Flushing, sweating, palpitations, headache due to formation of acetaldehyde (see p. 373)
H_2 blocker	Cimetidine, ranitidine	Inhibit alcohol dehydrogenase in the stomach, reduce first-pass metabolism of alcohol, and increase gastric emptying – increase bioavailability of alcohol
Hypnotic	Chloral hydrate, zolpidem	Potentiation of CNS effects. Caution with high doses due to risk of respiratory depression Increased plasma level of metabolite of chloral hydrate (trichloroethanol), which inhibits the metabolism of alcohol and increases blood alcohol levels
Hypoglycemic	Gliclazide, glyburide, insulin	Increased risk of hypoglycemia; delayed hypoglycemia may occur up to 24 h after alcohol consumption Disulfiram-like reaction (rare) with gliclazide and glyburide: Flushing, sweating, palpitations, headache due to formation of acetaldehyde
Immunosuppressive	Methotrexate, leflunomide Pimecrolimus, tacrolimus	Increased risk of liver damage Facial flushing
Nitrate	Nitroglycerin	Increased risk of hypotension, dizziness and fainting upon standing up
Opioid	All opioids Slow-release opioids (morphine sustained-release: Kadian) Methadone	Additive CNS effects; caution with excessive doses due to risk of respiratory depression Alcohol can speed the release of opioids from certain slow-release opioid formulations into the bloodstream by dissolving the slow-release system (not all products affected; no problems noted with Codeine Contin, Hydromorph Contin, MS Contin). Use caution with other slow-release products Additive CNS depression
Prokinetic agent	Metoclopramide	Increases absorption rate of alcohol by speeding gastric emptying
Stimulant	Cocaine	Additive effects; increased heart rate; variable effect on blood pressure Reports of enhanced hepatotoxicity

Further Reading

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Stimulants

Pharmacological/ Psychiatric Effects

- Differ somewhat, depending on type of drug taken, dose, and route of administration
- Effects occur rapidly, especially when drug used parenterally
- Acute toxicity reported with doses ranging from 5 to 630 mg of amphetamine; chronic users can ingest up to 1000 mg/day
- Following acute toxicity, psychiatric state usually clears within one week of amphetamine discontinuation

Physical

- Elevated BP, tachycardia, increased respiration and temperature, sweating, pallor, tremors, decreased appetite, dilated pupils, reduced fatigue, insomnia, increased sensory awareness, increased or decreased sexual arousal/libido

Mental

- Euphoria, exhilaration, alertness, improved task performance, exacerbation of obsessive-compulsive symptoms
- Methamphetamine reported to produce paranoia and hallucinations; flashbacks reported

High Doses

- Anxiety, excitation, panic attacks, grandiosity, delusions, visual, auditory and tactile hallucinations, paranoia, mania, delirium, increased sense of power, violence
- Fever, sweating, headache, flushing, pallor, hyperactivity, stereotypic behavior, chest pain, cardiac arrhythmias, respiratory failure, loss of coordination, collapse, cerebral hemorrhage, convulsions, myocardial infarction, and death
- Unexpected cardiac events (e.g., chest pain, arrhythmia) in young patients should raise concerns about stimulant drug abuse

Chronic Use

- Decreased appetite and weight, abdominal pain, vomiting, difficulty urinating, skin rash, increased risk of stroke, high blood pressure, irregular heart rate, erectile dysfunction, headache, anxiety, delusions of persecution, violence, dental caries
- Tolerance to physical effects occurs but vulnerability to psychosis remains
- Chronic high-dose use causes physical dependence; psychological dependence can occur even with regular low-dose use
- Recovery occurs rapidly after amphetamine withdrawal, but psychosis can become chronic

Complications

- Exacerbation of hypertension or arrhythmias
- Strokes and retinal damage due to intense vasospasm, especially with “crack” and “ice”
- With methamphetamine, cerebral side effects reported include: vasculopathy with or without parenchymal infarction, hypertensive encephalopathy, and hemorrhage
- Can exacerbate harmful effects of co-occurring infections, such as neurological damage in HIV infection
- Cellulitis at injection site (MRSA infection common)

D/C Discontinuation Syndrome

- Symptoms are very similar to those of major depressive disorder, including, depression, anxiety, hypersomnia, fatigue, irritability, difficulty concentrating, craving, suicidal or homicidal ideation, paranoid psychosis
- Patients in acute abstinence from stimulants should be routinely assessed for suicidality
- Stimulants typically have very short half-lives and discontinuation can happen very quickly, leading to behaviors to “maintain the high”

Stimulants (cont.)

Treatment

- Use calming techniques, reassurance, and supportive measures
- Supportive care of excess sympathomimetic stimulation may be required (e.g., BP, temperature); monitor hydration, electrolytes, and for possible serotonin syndrome
- For severe agitation and to prevent seizures, sedate with benzodiazepine (e.g., diazepam, lorazepam)
- For psychosis (usually transient), use a moderate- or high-potency antipsychotic; avoid low-potency antipsychotics (e.g., chlorpromazine can lower seizure threshold). Consider delaying antipsychotic therapy until acute effects of stimulants have resolved in order to reduce adverse cardiovascular effects
- Non-pharmacological treatment approaches are the current mainstay for the treatment of stimulant use disorder
- Agents under investigation with mixed results include GABAergic medications (e.g., baclofen, topiramate, vigabatrin), modafinil, the cocaine vaccine, and disulfiram

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

GENERAL

Class of Drug	Example	Interaction Effects
Antidepressant		
Irreversible MAOI	Phenelzine	Severe palpitations, tachycardia, hypertension, headache, cerebral hemorrhage, agitation, seizures; AVOID Serotonin syndrome reported with MDA, MDMA
Antipsychotic	Chlorpromazine, clozapine	Decreased seizure threshold
	Loxapine, risperidone	Diminished pharmacological effects of stimulants

AMPHETAMINES

Class of Drug	Example	Interaction Effects
Antidepressant	General	Enhanced antidepressant effect
SNRI	Venlafaxine	Increased blood pressure
Nonselective cyclics	Tricyclics	Enhanced stimulant effects. Increased plasma level of amphetamine Cardiovascular effects increased
Urinary acidifier	Ammonium chloride	Increased elimination of amphetamine due to decreased renal tubular reabsorption and increased elimination
Urinary alkalinizer	Sodium bicarbonate	Prolonged pharmacological effects of amphetamine due to decreased urinary elimination of unchanged drug

COCAINE

Class of Drug	Example	Interaction Effects
Alcohol		Additive effects; increased heart rate; variable effect on blood pressure Ethanol promotes the formation of a highly addictive metabolite, cocaethylene Reports of enhanced hepatotoxicity
Aldehyde dehydrogenase inhibitor	Disulfiram	Increased plasma level (3-fold) and half-life (60%) of cocaine with possible increased risk of cardiovascular effects

Class of Drug	Example	Interaction Effects
Antibiotic	Clarithromycin, erythromycin	Combination could result in cocaine overdose, due to inhibition of metabolism via CYP3A4, with rhabdomyolysis, arrhythmia, and cardiovascular collapse
Antidepressant		
SSRI	Fluoxetine	Decreased craving
SARI	Nefazodone	Combination could result in cocaine overdose, due to inhibition of metabolism via CYP3A4, with rhabdomyolysis, arrhythmia, and cardiovascular collapse
Tricyclic	Desipramine	Decreased seizure threshold Elevated heart rate and diastolic pressure (by 20–30%); increased risk of arrhythmia
Antifungal	Itraconazole, ketoconazole	Combination could result in cocaine overdose, due to inhibition of metabolism via CYP3A4, with rhabdomyolysis, arrhythmia, and cardiovascular collapse
Antipsychotic	Clozapine	Increased EPS (in patients also using alcohol or cannabis)
	Quetiapine	Increased EPS (in patients also using alcohol or cannabis) Report of desirable hallucinogenic effects with intravenous use of cocaine mixed with quetiapine
Antiretroviral	Nevirapine	Potentially increased metabolism of cocaine to the hepatotoxic metabolite norcocaine, via CYP3A4
Barbiturate	Phenobarbital	Reports of enhanced hepatotoxicity
β-blocker	Propranolol	May increase the magnitude of cocaine-induced myocardial ischemia. Labetalol and carvedilol have less "unopposed α-adrenergic" effects and possibly less risk of vasospasm
Cannabis	Marijuana	Increased heart rate; blood pressure increased only with high doses of both drugs Increased plasma level of cocaine and increased subjective reports of euphoria
Catecholamine	Norepinephrine	Potentiation of vasoconstriction and cardiac stimulation
Opioid	Heroin, morphine	May potentiate cocaine euphoria
Protease inhibitor	Ritonavir, indinavir, efavirenz	Combination could result in cocaine overdose, due to inhibition of metabolism via CYP3A4, with rhabdomyolysis, arrhythmia, and cardiovascular collapse
Sympatholytic	Yohimbine	Enhanced effect of cocaine on blood pressure

Stimulant Agents

Drug	Comments
AMPHETAMINE, DEXTROAMPHETAMINE (Dexedrine, Adderall) Taken orally as tablet, capsule, sniffed, smoked, injected Slang: Bennies, hearts, pep-pills, dex, beans, benn, truck-drivers, ice, jolly beans, black beauties, crank, pink football, dexies, crosses, hearts, LA turnaround	• Cause the release of monoamines (NE, DA, 5-HT) from central and peripheral neurons • Onset of action: 30 min after oral ingestion • Physical effects: Increased heart rate, BP, metabolism, decreased appetite, weight loss, rapid breathing, tremor, loss of coordination • CNS effects: Euphoria, increased energy and mental alertness, nervousness, anxiety, insomnia, irritability, restlessness, panic, impulsive or aggressive behavior • Active drug use may be terminated by exhaustion with excessive sleeping • Tolerance and psychic dependence occurs with chronic use • Excessive doses can lead to heart failure, delirium, psychosis (can last up to 10 days), coma, convulsions, and death • Pregnancy: Increase in premature births; withdrawal symptoms and behavioral effects (hyperexcitability) noted in offspring • Breastfeeding: Irritability and poor sleeping pattern reported in infants

Stimulants (cont.)

Drug	Comments
METHAMPHETAMINE (Desoxyephedrine) – Crystal Meth (Desoxyn) Powder taken as tablets, capsules, liquid, injected, snorted, inhaled, smoked Slang: Speed, meth, uppers, crystal, shit, moth, crank, crosses, methlies, quick, jib, fire, chalk, glass, go fast, tweak, yaba Crystal ("ice") is methamphetamine washed in a solvent to remove impurities – smoked in a glass pipe, "chased" on aluminum foil or injected	• Synthetic drug related chemically to amphetamine and ephedrine; can be manufactured in "home laboratories" from common household products • Enhances release of dopamine, norepinephrine, and serotonin • Very rapid onset of action; can last 10–12 h • Powerful effects produced are referred to as a "rush"; used as a club drug at "raves" to increase alertness, energy, sociability, euphoria; has aphrodisiac effects and causes loss of inhibitions • A "run" refers to the use of the drug several times a day over a period of several days • "Ice" can be mixed with cannabis and smoked or injected • Physical effects: Tachycardia, tachypnea, diaphoresis, hyperthermia, mydriasis, hypertension; stroke reported • CNS effects: Anxiety, agitation, confusion, insomnia, delirium, hallucinations, paranoia, violence; powerful psychological dependence and addiction occurs, particularly with "ice" • Chronic use can result in weight loss, bruxism, cardiovascular problems, decreases in lung function, pulmonary hypertension, rapid tooth decay ("meth mouth"), punding (stereotyped behavior), hyperprolactinemia, choreoathetoid movements, dyskinesias, mood disturbances, decreased cognitive functioning, anxiety, psychosis with suicidal or homicidal thoughts; may persist for months after drug use is stopped; has been associated with neuronal damage • Abuse of methamphetamine can produce impaired memory and learning, hyperawareness, hypervigilance, psychomotor agitation, irritability, aggression; chronic intoxication (use) may result in a psychotic state with delusions, hallucinations, and delirium • Users are at high risk of sexually transmitted and blood-borne diseases due to disinhibitory high-risk behaviors that can occur (e.g., shared needles, multiple partners, unprotected sex) • Toxic effects: Arrhythmias, hypertension, heart failure, hyperthermia, seizures, encephalopathy, rhabdomyolysis (see Complications p. 341) • After abrupt discontinuation, withdrawal effects peak in 2–3 days and include GI distress, headache, depression, irritability, and poor concentration • Methamphetamine exposure during pregnancy is associated with decreased growth in infants; withdrawal effects reported in newborns and potential developmental delays
COCAINE Extract from leaves of coca plant Leaves chewed, applied to mucous membranes Powder taken orally, snorted, smoked, injected Slang: Coke, coca, snow, flake, lady, toot, blow, big C, candy, crack, joy dust, stardust, rock, nose, boulders, bump, bianca, perico, nieve, soda "Crack": Free base cocaine	• Inhibits DA, NE, 5-HT reuptake • Onset of action and plasma half-life varies depending on route of use (e.g., IV: Peaks in 30 sec, half-life 54 min; snorting: Peaks in 15–30 min, half-life 75 min). Metabolized by hydrolysis to its major urinary metabolite, benzoylecgonine • Crack is a free-based and more potent form of cocaine (volatilized and inhaled) • Often adulterated with amphetamine, ephedrine, procaine, xylocaine or lidocaine • Used with heroin ("dynamite", "speedballs"), morphine ("whizbang") or cannabis ("cocoa puffs") for increased intensity • Used with flunitrazepam to moderate stimulatory effect • CNS effects: Rapid euphoria, increased energy and mental alertness, insomnia, anxiety, agitation, delusion, hallucinations • Physical effects: Nausea, vomiting, headaches, tachycardia, hypertension, chest pain, pyrexia, diaphoresis, mydriasis, ataxia, anorexia; tactile hallucinations ("coke bugs") • Tolerance develops to some effects (appetite), but increased sensitivity (reverse tolerance) develops to others (convulsions, psychosis) • Powerful psychological dependence occurs; dysphoria can last for weeks or months • Depression commonly occurs after drug use; dysphoria promotes repetitive use • Chronic users can develop panic disorder, paranoia, dysphoria, irritability, assaultive behavior, paranoia, and delirium • Snorting can cause stuffy or runny nose, eczema around nostrils, atrophy of nasal mucosa, bleeding, and perforated septum • Smokers are susceptible to respiratory symptoms and pulmonary complications

Drug	Comments
	• Sexual dysfunction is common • Chronic users of "crack" can develop microvascular changes in the eyes, lungs, and brain; respiratory symptoms include asthma and pulmonary hemorrhage and edema • Dehydration can occur due to effect on temperature regulation, with possible hyperpyrexia • Toxic effects: Hypertension, paroxysmal atrial tachycardia, hyperreflexia, irregular respiration, hyperthermia, seizures, unconsciousness, death; fatalities more common with IV use or when cocaine-filled condoms are swallowed (by smugglers), then burst • Pregnancy: Associated with spontaneous labor and abortion; increase in premature births; infants have lower weight, length, and head circumference, jitteriness, irritability, poor feeding, EEG abnormalities • Breastfeeding during cocaine intoxication reported to cause irritability, vomiting, diarrhea, tremulousness, and seizures in infants
KHAT (*Catha edulis*) Leaves typically chewed, sometimes brewed as tea, rarely smoked Slang: Kat, qat, ghat, chat	• Grown in East Africa and southern Arabia; used by certain communities to attain socio-cultural and religious euphoria • Cathinone (amphetamine analogue) is principal psychoactive agent; has CNS-stimulant and sympathomimetic effects • Single session: 100–500 g of leaves chewed over several hours • 60% absorbed through oral mucosa; further absorbed in stomach and small intestine • Onset of effect: 30 min; duration of effect: 3 h • Inhibitor of CYP2D6 • Acute effects include: Mostly desirable effects in first hour – euphoria, increased alertness and excitation, enhanced self-esteem, increased libido, increased blood pressure and heart rate; then, undesirable effects for the next 3–4 h – depression, lack of energy, headache, loss of appetite, insomnia, nightmares, low blood pressure, fine tremors, short-term memory loss • Chronic use can cause: Constipation, esophagitis, gastritis, oral mucosal keratosis (can develop into oral cancer), myocardial infarction and arrhythmia, liver disease, decreased sperm count and motility • Rare effects (associated with high doses): Paranoia, hallucinations, grandiosity, anxiety • Pregnancy: Teratogenic (retardation of growth rate) • Breastfeeding: Excreted in breast milk; trace amounts in breastfed infant's urine; unknown effects on infant; DO NOT USE
METHYLPHENIDATE (e.g., Ritalin) Tablets crushed and snorted, swallowed, injected Slang: Vitamin R, R-ball, skippy, the smart drug, JIF, MPH	• See p. 25 • Large doses can cause psychosis, seizures, stroke, and heart failure
SYMPATHOMIMETICS (Ephedrine, pseudoephedrine, phenylpropanolamine, caffeine) Taken as capsules, tablets Slang: Look alikes, herbal bliss, cloud 9, herbal X	• Known as Herbal Ecstasy and sold as "natural" alternative to Ecstasy • Misrepresented as amphetamines and sold in capsules or tablets that resemble amphetamines • Doses of ingredients vary widely • Reports of hypertension and seizures; death due to stroke can occur after massive doses

Stimulants (cont.)

Drug	Comments
SYNTHETIC CATHINONES[2, 3] **Mephedrone** (4-methylmethcathinone), **Methylone** (3,4-methylenedioxy-methcathinone), **MDPV** (3,4-methylenedioxypyrovalerone), flephedrone, ethylcathinone Sold as capsules, tablets, or white crystalline powder that can be swallowed, snorted or injected Slang: "Bath salts", bath powder, plant food, plant fertilizer, meph, drone, meow, rush, ivory, ivory wave, cloud 9, (9), blizzard, ocean snow, scarface, hurricane charlie, fine china, silverback, blue magic, vanilla sky, energy-1, bliss, bolivian bath, MDPK, MTV, magic, maddie, black rob, super coke, PV, peeve, zoom, bloom, insect repellant, potpourri, vacuum freshener, heavenly soak	• Mephedrone and methylone: Nonspecific substrates of DA, NE, and 5-HT transporters preventing reuptake • MDPV: Specific inhibitor of DA and NE transporters • Effects similar to other stimulants such as cocaine, methamphetamine, MDMA • CNS effects last 3–4 h, while some physical effects (e.g., tachycardia, hypertension) can last 6–8 h • CNS effects: Euphoria, increased alertness and awareness, increased wakefulness and arousal, increased energy and motivation, mental stimulation/increased concentration, increased sociability, sexual stimulation/aphrodisiac effects, agitation/hypertonia, anxiety, psychosis, seizures, suicidal and homicidal thoughts and actions • Physical effects: Tachycardia, hypertension, vasoconstriction, insomnia, hyper-reflexia, nausea, stomach cramps and digestive problems, anorexia, bruxism, increased body temperature, chills, sweating, pupil dilation, headache, and tinnitus • Strong cravings and addiction reported • Withdrawal symptoms include: Depression, lethargy, headache, anxiety, postural hypotension, and severely bloodshot eyes – usually subside within 4–8 h

Further Reading

References

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Additional Suggested Reading

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- Gregg RA, Rawls SM. Behavioral pharmacology of designer cathinones: a review of the preclinical literature. Life Sci. 2014;97(1):27–30. doi:10.1016/j.lfs.2013.10.033
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Hallucinogens

General Comments

- Marijuana is the second most frequently abused drug (after alcohol) by youth
- Marijuana is the most widely used illicit drug of abuse in the world; despite legalization and medicalization of cannabis, rates in adolescents have remained consistent or generally decreased (e.g., the CDC surveys school-aged youth every two years, and rates of lifetime cannabis use have decreased from 47.2% in 1999 to 36.9% in 2019)
- The term medical marijuana refers to using the whole unprocessed marijuana plant or its basic extracts to treat a disease or symptom
- In children (age 2 years and older), the only FDA approved cannabidiol product is Epidiolex; used for refractory seizures, Dravet syndrome (DS), or Lennox-Gastaut syndrome (LGS)
- Dried marijuana is not an approved drug or medicine in Canada. However, reasonable access to a legal source of marijuana is provided when authorized by a healthcare practitioner. Recreational use of marijuana legalized federally in Canada as of October 2018
- Medical marijuana has been used to treat chronic pain, muscle spasms, and nausea during chemotherapy, improve appetite in HIV/AIDS, improve sleep, and improve tics in Tourette's disorder
- Medical marijuana is legal in some jurisdictions of the USA for use in PTSD (literature suggests benefit for PTSD symptoms as well as worsening of symptoms). Recreational use of marijuana legalized at the state level in several US states (interactive map at https://disa.com/maps/marijuana-legality-by-state)

Pharmacological/Psychiatric Effects

- Differ, depending on type of drug taken and route of administration (see specific agents below)
- Effects occur rapidly and last from 30 min (e.g., DMT) to several days (e.g., PCP)

Physical

- Increased BP, tachycardia, dilated pupils, nausea, sweating, flushing, chills, hyperventilation, incoordination, muscle weakness, trembling, numbness
- Cannabinoids may be effective for anorexia associated with weight loss in AIDS, nausea and vomiting associated with chemotherapy, and treating neuropathic pain (marketed in Canada under the name of Sativex or Cesamet [indicated for chemotherapy-induced nausea and vomiting, as adjunctive treatment for spasticity in multiple sclerosis, and as adjunctive treatment for neuropathic pain] and in the USA under the name Marinol [indicated for chemotherapy-associated nausea and vomiting and anorexia associated with weight loss in patients with AIDS]); mixed effects found on multiple sclerosis symptoms, may have some benefit in Tourette's disorder

Mental

- Alteration of perception and body awareness, impaired attention and short-term memory, disturbed sense of time, depersonalization, euphoria, mystical or religious experiences, grandiosity, anxiety, panic, visual distortions, hallucinations (primarily visual), erratic behavior, aggression

High Doses

- Confusion, restlessness, excitement, anxiety, emotional lability, panic, mania, paranoia, "bad trip"
- Cardiac depression and respiratory depression (mescaline), hypotension, convulsions and coma (PCP)

Chronic Use

- Anxiety, depression, personality changes
- Tolerance (tachyphylaxis) can occur with regular use (except with DMT); reverse tolerance (supersensitivity) has been described
- "Woolly" thinking, delusions, and hallucinations reported; may persist for months after drug discontinuation
- Flashbacks – recurrent psychotic symptoms, may occur years after discontinuation
- Cohort studies suggest that chronic use of cannabis by teenagers is associated with a more than 5-fold increase in risk of later-life depression and anxiety as well as an increased risk of early-onset psychosis. Prolonged exposure to cannabis may cause an initial increase in synaptic dopamine and then lead to prolonged changes in the endogenous cannabinoid systems – may be more profound in adolescents
- Randomized, open-label, controlled trial showed that continued cannabis use after the onset of a first-episode psychosis is correlated with worse social outcomes
- Regular (weekly) cannabis use has been associated with increased risk of tardive dyskinesia in patients with schizophrenia taking antipsychotics
- Hallucinogen persisting perception disorder (HPPD) – total or partial recurrence of perceptual disturbances that appeared during previous hallucinogenic "trips" or intoxications, and reemerged without recent use; rare; mostly associated with LSD or PCP use but also linked with psilocybin, mescaline, ketamine, dextromethorphan, MDMA, MDA, cannabis, synthetic cannabinoids, and ayahuasca

Hallucinogens (cont.)

D/C Discontinuation Syndrome

- Withdrawal symptoms identified in frequent cannabis users consist of irritability, nervousness, anxiety, sleep disturbance, decreased appetite or weight loss, stomach pain, nausea, vomiting, shakiness/tremors, sweating, fever, chills

Treatment

- Provide reassurance and reduction of threatening external stimuli
- Supportive care for excess CNS stimulation may be required; monitor hydration, electrolytes, and for possible serotonin syndrome
- In severe cases, the "trip" should be aborted chemically as rapidly as possible. This reduces the likelihood of flashbacks or recurrences in the future; in mild cases, "talking down" may be more appropriate
- Use a moderate- or high-potency antipsychotic (e.g., loxapine or haloperidol) for psychotic symptoms
- Avoid low-potency antipsychotics with anticholinergic and α_1-adrenergic properties (e.g., chlorpromazine) to minimize hypotension, tachycardia, disorientation, and seizures
- Use benzodiazepines (diazepam, lorazepam) to control agitation and to sedate, if needed
- Propranolol and ascorbic acid may minimize effects of PCP and aid in its excretion
- Hallucinogen persisting perception disorder (HPPD)[1]: Up to 50% of cases have spontaneous remission within a few months; if symptoms persist, no mainstay treatment; recommendations based on observational studies or case reports: clonidine, benzodiazepines, anticonvulsants, first-generation antipsychotics, or naltrexone; mixed effects with second-generation antipsychotics or SSRIs; calcium channel blockers or β-blockers for comorbid anxiety

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

CANNABIS/MARIJUANA

Class of Drug	Example	Interaction Effects
Alcohol		Cannabis may suppress alcohol-induced emetic reflex which could lead to high alcohol levels Increased heart rate and blood pressure; further slowing of mental processing and reaction time
Aldehyde dehydrogenase inhibitor	Disulfiram	Synergistic CNS stimulation reported, hypomania
Anticonvulsant	Clobazam	Elevated clobazam and norclobazam levels with cannabidiol (CBD) use in children with refractory epilepsy via CYP2C19 inhibition by CBD
Antidepressant		
Tricyclic	Desipramine	Case reports of tachycardia, lightheadedness, mood lability, and delirium with combination Cardiac complications reported in children and adolescents
MAOI	Tranylcypromine	Caution: Cannabis increases serotonin levels and may result in a serotonin syndrome
Antipsychotic	Chlorpromazine, clozapine, quetiapine, thioridazine	Drugs with anticholinergic and α_1-adrenergic properties can cause marked hypotension and increased disorientation
Barbiturate	Phenobarbital	Additive effect causing anxiety and hallucinations
Lithium		Clearance of lithium may be decreased
Opioid	Morphine	THC blocks excitation produced by morphine
Protease inhibitor	Indinavir, nelfinavir	Inhaled cannabis reported to reduce indinavir AUC by 17% and C_{max} of nelfinavir by 21%; no effect on viral load
Smoking (tobacco)		Smoking of dried cannabis has additive effects on the induction of CYP1A2
Stimulant	Cocaine	Increased heart rate; blood pressure increased with high doses of both drugs; increased plasma level of cocaine and euphoria

KETAMINE[2]

Class of Drug	Example	Interaction Effects
Antibiotic	Clarithromycin	Increased S-ketamine exposure (2.6-fold) via CYP3A4 inhibition
	Itraconazole	No effect (unexpected) on ketamine metabolism via CYP3A4 inhibition
	Rifampin	Reduced S-ketamine and S-norketamine exposure (by 10% and 50% respectively) via CYP 3A4 and 2B6 induction
Antiplatelet	Ticlopidine	Increased ketamine exposure (> 2-fold) via CYP2B6 inhibition
Glutamate modifier	Clozapine, lamotrigine, memantine	Theoretically may decrease effects of ketamine
Grapefruit juice		Increased ketamine exposure (3-fold) via CYP3A4 inhibition
Protease inhibitor	Ritonavir, nelfinavir	Elevated ketamine exposure possible due to inhibited metabolism
St. John's wort		Reduced ketamine exposure (by 58%) via CYP3A4 induction

LSD

Class of Drug	Example	Interaction Effects
Antidepressant	Fluoxetine, sertraline, paroxetine	Generalized tonic-clonic seizures reported Recurrence or worsening of flashbacks reported with fluoxetine, sertraline, and paroxetine
Protease inhibitor	Ritonavir	Elevated levels of LSD possible due to inhibited metabolism

MDA/MDMA

Class of Drug	Example	Interaction Effects
Antidepressant	Fluoxetine	Diminished pharmacological effects of MDA
Protease inhibitor	Ritonavir	Case reports of increased plasma levels of MDMA due to inhibited metabolism via CYP2D6; death reported

PCP (Phencyclidine)

Class of Drug	Example	Interaction Effects
Acidifying agent	Cranberry juice, ammonium chloride	Increased excretion of PCP
Protease inhibitor	Ritonavir	Elevated levels of PCP possible due to inhibited metabolism

Hallucinogenic Agents

Drug	Comments
AYAHUASCA (*Psychotria viridis* and *Banisteriopsis caapi*) Brewed as tea	• Combination of two psychoactive Amazonian plants *Psychotria viridis* (contains hallucinogen DMT; see Tryptamines below) and *Banisteriopsis caapi* (contains MAO inhibitor which prevents breakdown of DMT by stomach enzyme MAO) • Used historically in Amazonian religious and healing rituals • Effects last 4–6 h • Small observational study: Symptoms of depression, anxiety, and stress were reduced in both ayahuasca and placebo groups after the ceremony • Short-term effects: Strong hallucinations including visual and auditory; increased heart rate and blood pressure; nausea; burning sensation in the stomach; tingling sensations and increased skin sensitivity • Long-term effects: Limited data; possible changes to the serotoninergic and immune systems

Hallucinogens (cont.)

Drug	Comments
CANNABIS **Marijuana** – crushed leaves, stems, and flowers of female hemp plant (*Cannabis sativa*) Smoked (cigarettes or water pipe), inhaled (e-cigarettes), swallowed Slang: Grass, pot, joint, hemp, weed, reefer, smoke, Mary Jane, Indian hay, ace, ganja, gold, J, locoweed, shit, herb, Mexican, ragweed, bhang, sticks, blunt, dope, sinsemilla, skunk, Hydro (hydroponic marijuana) **Hashish** – resin from flowers and leaves; more potent than marijuana Smoked, cooked, swallowed Slang: Hash, hash oil, weed oil, weed juice, honey oil, hash brownies, tea, black, solids, grease, smoke, boom, chronic, gangster, hemp **Concentrated cannabis extracts** (typically 50–90% THC) Vaporized/inhaled Slang: Shatter, budder, crumble, wax, dabs, butane hash oil (BHO), rosin, sap, sugar, snap-n-pull	• Tetrahydrocannabinol (THC) is the active ingredient; 18–30% in marijuana and up to 60% in hashish • Cannabidiol (CBD) is the second most common psychoactive cannabinoid ingredient in marijuana, typically in the range of 0–13% • THC undergoes first-pass metabolism to form psychoactive metabolite 11-OH-THC. Half-life is 24–36 h for infrequent users, and up to 10 days for frequent users. THC and CBD are metabolized primarily by CYP3A4, also by 2C9, 2C19, and 2D6. Weak inhibitor of CYP3A4, 2C9, 2C19, and 2D6 • Smoking dried cannabis induces CYP1A2 through activation of the aromatic hydrocarbon receptor • Effects occur rapidly and last up to several hours; accumulates in fat tissue for up to 4 weeks before being released back into bloodstream; effects may persist • Cannabidiol (Epidiolex) is FDA approved for refractory seizures Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) in children aged 2 years and older • Results of short-term controlled trials indicate that smoked cannabis reduces neuropathic pain, improves appetite and caloric intake, especially in patients with reduced muscle mass, and may relieve spasticity and pain in patients with multiple sclerosis • THC may have beneficial effects in chemotherapy-induced nausea/vomiting • Review of 2 trials suggests THC may have some benefit on the frequency and severity[3] of tics in Tourette's disorder • Small cohort study suggests CBD may subjectively (parents' reports) improve self-injury and rage attacks, hyperactivity, sleep problems, and anxiety in children and adolescents with autism spectrum disorder[4] • Tolerance and psychic dependence may occur; reverse tolerance (supersensitivity) described • Combined with other drugs including PCP ("killer weed"), opium ("o.j."), heroin ("A-bomb"), crack cocaine ("cocoa puffs"), or flunitrazepam to enhance effect • Short-term effects: Most users experience euphoria with feelings of self-confidence and enhanced sensory perception followed by drowsiness/relaxation; some become dysphoric, anxious, agitated, and suspicious. Slowed reaction time, problems with balance and coordination; increased heart rate and appetite (craving for carbohydrates; the "munchies"); problems with learning and memory. Can cause psychotic symptoms with confusion, hallucinations, emotional lability (very prolonged or heavy use can cause serious and potentially irreversible psychosis) • Chronic use: Bronchitis, chronic cough, weight gain, bloodshot eyes, loss of energy, apathy, "fuzzy" thinking, slow reaction time, impaired judgment, decreased testosterone in males; increased risk of depression, anxiety, and schizophrenia • Withdrawal symptoms: Irritability, insomnia, decreased appetite, anxiety • Cannabis hyperemesis syndrome described (syndrome of cyclic nausea and vomiting following weekly or more frequent cannabis use; compulsive use of hot baths for symptom relief, and resolution of symptoms following cessation of cannabis use) • Link between cannabis use and early age at onset of psychosis suggested; results point to cannabis as a dangerous drug in young people at risk of developing psychosis[5] • Initiation of cannabis use in adolescence is associated, in a dose-dependent fashion, with emergence and severity of psychotic symptoms and functional impairment – individuals who initiate use earlier and use at higher frequencies demonstrate poorer illness and treatment outcomes[6] • Exogenous THC modulates release of neurotransmitters (including dopamine and glutamate) by interacting with specific cannabinoid receptors that are distributed in brain regions implicated in schizophrenia • Cannabis cigarettes have a higher tar content than ordinary cigarettes and are potentially carcinogenic • Vitamin E acetate, a thickening agent in THC vaping products, is strongly linked to serious lung injuries and deaths • Pregnancy: Can retard fetal growth and cause mild withdrawal reactions in the infant; developmental problems (attention, memory, and problem solving) in children born to cannabis-dependent parents have been reported in some studies • Breastfeeding: Can reach high levels in breast milk

Drug	Comments
CANNABINOIDS, SYNTHETIC Psychoactive chemicals dissolved in solvent, applied to plant material; usually smoked or prepared as a herbal infusion Slang: K2, spice, black mamba (*Turnera diffusa*), bombay blue, fake weed, genie, zohai, bliss, blaze, JWH-018, -073, -250, Yucatan fire, skunk, moon rocks	• Synthetic designer drugs that mimic the effects of cannabis • Contain a mixture of herbs and synthetic cannabinoids, which may include: Cannabicyclohexanol, JWH-018, JWH-073, JWH-200, CP-47,497 or HU-210; chemicals are frequently changed and concentrations are unpredictable • Marketed as "synthetic marijuana," "herbal incense," "herbal smoking blends" or "potpourri" and sold online, in head shops, and some stores • Physical effects: 2–3 times more likely to be associated with sympathomimetic effects (i.e., tachycardia and hypertension) than THC; vomiting; high doses reported to cause convulsions, myocardial infarction • Contaminant, (1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone, has been associated with acute kidney injury • CNS effects: Elevated mood, relaxation, altered perception, anxiety, agitation, confusion, paranoia, and hallucinations reported; psychosis can be prolonged • Regular users may experience symptoms of addiction and withdrawal
KETAMINE (Ketalar) General anesthetic in day surgery and veterinary medicine Taken orally as capsules, tablets, powder, crystals, and solution; injected, snorted (using a nasal inhaler called a "bullet" or "bumper"; an inhalation is called a "bump"), smoked Slang: K, special K, vitamin K, ket, green, jet, kit-kat, cat valiums, Ketalar SV	• NMDA receptor antagonist, prevents glutamate activation, inhibits reuptake of catecholamines (5-HT, NE, DA) • Dissociative drug; user feels detached from reality • Used as a club drug at "raves" and involved in "date rapes"; most ketamine users are sporadic and polydrug users • Difficult to manufacture; most of the illicit supply is diverted from human and veterinary anesthesia products • Doses of 60–100 mg injected; consciousness maintained at this dose, but disorientation develops • Effects start within 60 sec (IV) and 10–20 min (PO); metabolized primarily by CYP2B6 and also by CYP3A4 and 2C9. Weak inhibitor of CYP3A4 • Physical effects: Increased heart rate and blood pressure, nausea, vomiting, increased muscle tone, nystagmus, stereotypic movements, impaired motor function, numbness; synthetic ketamine linked to serious urinary tract infections and bladder-control problems (related to dose and frequency of use)[7] • CNS effects: Dream-like state, depersonalization, confusion, hostility, mild delirium, hallucinations, amnesia, problems with attention and learning, sedation • Long-term effects: Ulcers and pain in bladder, kidney problems, stomach pain, depression, poor memory • A small, randomized, double-blind, crossover clinical trial of 17 adolescents found a significant reduction in depressive symptoms 24 h after infusion that remained for 14 days[8] • Toxic effects: Severe delirium, respiratory depression, loss of consciousness, catatonia • Recently, researchers have determined IV infusions of ketamine are effective in adults with treatment-resistant depression
LYSERGIC ACID DIETHYLAMIDE (LSD) Semi-synthetic drug derived from ergot (grain fungus) White powder used as tablet, capsule, liquid, liquid-impregnated paper; swallowed, snorted, smoked, inhaled, injected Slang: Acid, cubes, purple haze, Raggedy Ann, sunshine, yellow sunshines, LBJ, big D, blotters, domes, hits, tabs, doses, window-pane, microdot, boomers	• 5-HT_{2A} receptor agonist • Used as a club drug at "raves" • Effects occur in less than 1 h and last 2–18 h • Physical effects: Mydriasis, nausea, loss of appetite, muscle tension, hyperthermia, hypertension, tachycardia, weakness, numbness, tremors • CNS effects: Agitation, visual hallucinations, suicidal, homicidal, and irrational behavior, rapid mood swings, and dysphoria; panic, psychotic reactions can last several days • Long-term effects: Frightening flashbacks (called Hallucinogen persisting perception disorder; may occur without drug having been taken recently), visual hallucinations, disorganized thoughts, paranoia, mood swings • Tolerance develops rapidly; psychological dependence occurs • Combined with cocaine, mescaline, or amphetamine to prolong effects • Pregnancy: Increased risk of spontaneous abortions; congenital abnormalities have been reported • Breastfeeding: No reported risk; LSD has a relatively low molecular weight which facilitates transfer into milk, and psychotomimetic effects are produced at extremely low concentrations; the use of LSD during lactation is contraindicated

Hallucinogens (cont.)

Drug	Comments
MESCALINE (3,4,5-trimethoxyphenethylamine) From cactus *Lophophora williamsii*, San Pedro cactus (*Echinopsis pachanoi*) and/or the Peruvian torch cactus (*Echinopsis peruviana*); pure product not readily available Cactus buttons are dried, then sliced, chopped, or ground; used as powder, capsule (masks bitter taste), tablet, solution, inhaled or injected Slang: Mesc, peyote, buttons, cactus	• Binds to 5-HT_{2A} receptor as a partial agonist and acts on 5-HT_{2C} receptor • Less potent than LSD, but cross-tolerance reported • Effects occur 1–2 h after ingestion and last 10–18 h • Physical effects: Headache, dry skin, increased temperature and heart rate, hypotension or hypertension, numbness, tremors, dizziness, nausea, cardiac and respiratory depression • CNS effects: Euphoria, time distortion, brilliant colors, weightlessness, anxiety, disorientation, impaired reality testing, and flashbacks • Dependence not reported but tolerance to effects occurs quickly
MORNING GLORY SEEDS Active ingredient is lysergic acid amide; 1/10th as potent as LSD Seeds eaten whole or ground, mushed, soaked, and solution injected Slang: Flying saucers, licorice drops, heavenly blue, pearly gates	• Effects occur after 30–90 min when seeds ingested and immediately when solution injected • Commercial seeds are treated with insecticides, fungicides, and other chemicals and can be poisonous
PHENCYCLIDINE (PCP) General anesthetic used in veterinary medicine; often misrepresented as other drugs Powder, chunks, crystals used as tablets, capsules, liquid, inhaled, smoked, snorted, injected (IM or IV) Slang: PCP, angel dust, hog, horse tranquilizer, animal tranquilizer, illy, wet, PeaCe Pill, embalming fluid, dust, rocket fuel, boat, love boat In combination with marijuana: killer weed, supergrass, Krystal Joint (KJ), Crystal Joint (CJ), mintweed, killer, wet stick, fry stick, happy stick, sherm, leak, amp, lovely, toe tag, dipper In combination with cocaine: space base, space cadet, tragic magic	• Glutamate antagonist at NMDA receptor • Dissociative drug; user feels detached from reality • Effects occur in a few minutes and can last several days to weeks (half-life 18 h); metabolized primarily by CYP3A4 and also by CYP2C19. Weak inhibitor of CYP2B6 • Frequently sold on street as other drugs (easily synthesized); mis-synthesis yields a product that can cause abdominal cramps, vomiting, coma, and death • Physical effects: Intermittent vomiting, drooling, loss of appetite, diaphoresis, miosis, nystagmus, hypertension, and ataxia can occur • CNS effects: Can cause apathy, estrangement, feelings of isolation, indifference to pain, delirium, disorientation with amnesia, schizophrenia-like psychosis, and violence (often self-directed); can feel intermittently anxious, fearful to euphoric • Toxic effects: Hypoglycemia, rhabdomyolysis, depression, delirium, CNS depression, coma; deaths have occurred secondary to uncontrollable seizures or to hypertension resulting in intracranial hemorrhage • Flashbacks occur; Hallucinogen persisting perception disorder (may occur without drug having been taken recently) • Psychological dependence occurs • Withdrawal symptoms: Headache, increased appetite, drowsiness, depression • Pregnancy: Signs of toxicity have been reported in newborns • Breastfeeding: Drug concentrates in milk and detectable for weeks after heavy use
PSILOCYBIN From *Psilocybe mexicana* mushroom Used as dried mushroom, white crystal, powder, capsule; eaten raw, cooked or steeped as tea, swallowed, snorted Slang: Magic mushrooms, sacred mushrooms, mushroom, shrooms, purple passion	• Chemically related to LSD and DMT (see Tryptamines below); psilocybin is a prodrug for psilocin (4-HO-DMT (4-hydroxy-N,N-dimethyltryptamine)) • Effects occur within 15–45 min, peak within 60–90 min, and last 4–6 h • Partial agonist at 5-HT_{1A} and 5-HT_{2A} receptors • Increasing interest and research in psilocybin therapeutic use in psychiatric disorders • Results of small open-label studies suggest psilocybin increases smoking cessation, and decreases heavy drinking days and alcohol craving • In a DBPC-RCT[9], there was no difference between psilocybin and escitalopram in patients with moderate to severe major depressive disorder; a RCT showed psilocybin immediate treatment group reduced depression more compared to delayed treatment group • Two small trials suggest psilocybin improves depression and anxiety in patients with advanced-stage cancer

Drug	Comments
	• Physical effects: Dry mouth, nausea, vomiting, headache, mydriasis, muscle relaxation or weakness, numbness in face, hypertension, tachycardia, sweating, pyrexia followed by chills and shivering, urinary incontinence • CNS effects: Hallucinations (visual, auditory), sensory distortions (synesthesia) (e.g., seeing music or hearing colors), distorted time perceptions (users sometimes think they had a longer trip than the actual effect), nervousness, panic, confusion, paranoia, and flashbacks • "Bad trip" with high doses: Paranoia, loss of boundaries, distorted sense of self • Tolerance develops rapidly; cross-tolerance occurs with LSD • Should not be injected intravenously; case reports of intravenous injection of psilocybin – one developed vomiting, severe myalgias, hyperpyrexia, hypoxemia, and mild methemoglobinemia; another grew mushroom in the blood and had multi-organ failure requiring antifungal and prolonged hospital stay • Mistaken identity with "death-cap" (Amanita) mushroom can result in accidental poisoning
SALVIA DIVINORUM Member of the mint family Leaves chewed or crushed and the juice ingested as tea, smoked Slang: Diviner's sage, magic mint, Maria Pastora	• Main active ingredient is Salvinorin A; a potent κ-opioid agonist • Used in traditional spiritual practices by native people of Mexico • Effects, when taken orally, depend on the absorption of Salvinorin A through the oral mucosa as it is inactivated by the GI tract; when absorbed through oral mucosa, effects detected in 5–10 min, peak at 1 h, and subside after 2 h. If inhaled, effects seen after 30 sec, peak in 5–10 min, and subside in 20–30 min; potency increased dramatically when smoked • Taken in combination with cannabis to prolong effect • Physical effects: Ataxia, incoherent speech, hysterical laughter, unconsciousness • CNS effects: Altered perception; can cause dramatic, and sometimes frightening, hallucinogenic experiences with doses higher than 1 mg
TRYPTAMINES **Dimethyltryptamine (DMT), Alpha-methyltryptamine (AMT), 5-methyl-di-isopropyl-tryptamine (5-MeO-DIPT)** Oil or crystal smoked in a water pipe; oil soaked in parsley; dried and snorted or smoked, used as liquid (tea), injected Slang: Lunch-hour drug, businessman's trip, FOXY	• Found in several plants in South America • Effects vary widely, depending on amount taken; occur almost immediately with DMT and last 10–30 min when smoked or injected intravenously (called "businessman's trip" due to its short duration of action) • DMT is psychoactive when smoked or injected intravenously • When taken orally, broken down by stomach enzyme MAO, making its psychoactive properties void; often taken with MAO inhibitor to prevent breakdown; e.g., ayahuasca (see above) • Often mixed with marijuana • CNS effects: Anxiety and panic frequent due to quick onset of effects; produce intense visual hallucinations, loss of awareness of surroundings; depersonalization, auditory distortions, altered perception of time and body image • Physical effects: Tachycardia, hypertension, agitation, seizures, mydriasis • High doses reported to cause cardiac and respiratory arrest

DRUGS WITH HALLUCINOGENIC AND STIMULANT PROPERTIES

Drug	Comments
2,5-dimethoxy-4-methylamphetamine (STP/DOM) Chemically related to both mescaline and amphetamine Used orally Slang: Serenity, tranquility, peace	• Effects last 16–24 h • More potent than mescaline but less potent than LSD • "Bad trips" occur frequently; prolonged psychotic reactions reported in people with psychiatric history • Tolerance reported; no evidence of dependence • Anticholinergic effects, exhaustion, convulsions, excitement, and delirium reported
3,4-methylene-dioxyamphetamine (MDA) Chemically related to both mescaline and amphetamine (synthetic drug) Used orally as liquid, powder, tablet; injection Slang: Love drug	• Typical doses: 60–120 mg • Effects occur after 30–60 min (orally), or sooner if injected, and last about 8 h • CNS effects: Hallucinations and perceptual distortions rare; feeling of peace and tranquility occurs • High doses: Hyperreactivity to stimuli, agitation, hallucinations, violent and irrational behavior, delirium, convulsions, and coma

Hallucinogens (cont.)

Drug	Comments
3,4-methylene-dioxymethamphetamine (MDMA) Powder, usually in tablets or capsules; may also be snorted or smoked, "bimped" or cooked on lollypops or pacifiers Slang: Ecstasy, MDMA, Adam, Molly, XTC, X, E, EVE, love drug, clarity, lover's speed, hugs, beans Herbal Ecstasy: MDMA mixed with ephedrine	• Increases levels of serotonin, norepinephrine and, to a lesser extent, dopamine • Many MDMA products are contaminated with other compounds including dextromethorphan, caffeine, phenylpropanolamine, ephedra, MDA, PMA, ketamine, methylone, MDPV, 4-MEC, 4-MMC, pentedrone, MePP, methylsalicylate • Typical dose varies from 50–150 mg, but amount of drug per tablet can be from 0 to 100 mg • Onset of effects 30–60 min; duration of action 3–6 h; half-life is about 8 h; metabolized primarily by CYP2D6 and also by CYP1A2, 2B6, and 3A4. May inhibit its own metabolism via CYP2D6; slow metabolizers of CYP2D6 may develop toxicity at moderate doses due to drug accumulation • Commonly used at "raves" • CNS effects: Wakefulness, increases energy and decreases fatigue and sleepiness; creates feelings of euphoria and well-being together with derealization, depersonalization, impaired memory and learning, and heightened tactile sensations (action believed to be mediated through release of serotonin) • Physical effects: Increased blood pressure and heart rate, increased endurance and sexual arousal, salivation, mydriasis, bruxism, trismus, increased tension, headache, restless legs, blurred vision, dry mouth, urinary retention, nausea, and suppressed appetite, thirst, and sleep • Severe physical reactions include: Hypertension, tachycardia, dysrhythmia, hyperthermia, seizures; followed by hypotension, ischemic stroke, fatal brain hemorrhage, and coma; death can occur from excessive physical activity ("raves") that may result in disseminated intravascular coagulation, rhabdomyolysis, hyponatremia, acute renal and hepatic failure, and multiple organ failure • High doses can precipitate panic attacks, hallucinations, paranoid psychosis, aggression, and flashbacks • After-effects include: Anorexia, drowsiness, muscle aches, generalized fatigue, irritability, anxiety, and depression (last 1–2 days due to half-life of drug of about 8 h) • Tolerance to euphoric effects with chronic use • Chronic regular use may result in mood swings, depression, impulsivity, and lack of self-control, memory loss, and parkinsonism; can lead to psychological dependence • May also stress the immune system and increase susceptibility to infectious diseases
Benzylpiperazine (BZP) and 3-trifluoromethyphenylpiperazine (3-TFMPP) Slang: Peaq, Freq, PureRush, PureSpun	• Promoted as a special tonic and a "natural" alternative to more dangerous street drugs • Mechanism of action is believed to be similar to MDMA and the effects produced by BZP are comparable to those of amphetamine • Doses of 50–200 mg BZP ingested • Effects last 4–8 h • Metabolized via CYP2D6 and COMT • Physical effects: Nausea, hyperthermia, increased blood pressure, dilated pupils, tingling skin, and decreased appetite • CNS effects: Alertness, increased euphoria, and paranoia • With high doses: Hallucinations, respiratory depression, renal toxicity, and convulsions • Withdrawal effects include: Nausea, headache, fatigue, hangover, confusion, and insomnia
N-ethyl-3,4-methylene-dioxyamphetamine (MDE) Chemically related to MDMA (synthetic drug) Slang: Eve	• Effects as for MDMA (above) • Onset of effects within 30 min; duration of action 3–4 h
NBOMes (N-2-methoxy-benzyl substituted 2C class of hallucinogens) marketed online as "research chemicals" under various names: N-bomb, Smiles, Solaris, Cimbi-5, 251, Bom-25, 2C-I-NBOMe, 25-I-NBOMe, 25I, Pandora, Divination, wizard, Smiley Paper	• 25I-NBOMe was originally synthesized as a radiotracer for positron emission tomography • Potent agonists of 5-HT_{2A} receptor with stimulant and hallucinogenic properties – potency varies depending on product (easily synthesized) • 25I-NBOMe effects usually last 6–10 h if taken sublingually or buccally. When inhaled, effects usually last 4–6 h, but can be significantly longer depending on dosage; durations longer than 12 h reported

Drug	Comments
Used sublingually, buccally, and snorted. 25I-NBOMe is often applied to sheets of blotter paper of which small portions (tabs) are held in the mouth to allow absorption through the oral mucosa. There are reports of intravenous injection of 25I-NBOMe solution and smoking the drug in powdered form	• Effects similar to LSD, but more potent; tolerance reported • Physical effects: tachycardia, hyperpyrexia, mydriasis, increased sex drive • CNS effects: heightened senses, visual and auditory hallucinations, euphoria • Higher doses can cause: nausea, hypertension, confusion, paranoia, agitation, aggression, seizures, elevated white blood cell count, elevated creatine kinase, metabolic acidosis, acute kidney injury, death
NUTMEG Active ingredient related to trimethoxyamphetamine and to mescaline Seeds eaten whole, ground, powdered; sniffed	• Effects occur slowly and last several hours (duration of hallucinogenic effects is dose related) • Hallucinations are usually preceded by nausea, vomiting, diarrhea, and headache • Physical effects: Lightheadedness, drowsiness, thirst, and hangover can occur
Paramethoxyamphetamine (PMA) Synthetic drug Used as powder, capsules	• Often sold as MDMA but has more pronounced hallucinogenic and stimulant effects • Metabolized by CYP2D6 • Physical effects: Causes major increase in BP and pulse, hyperthermia, increased and labored breathing • Highly toxic; convulsions, coma, and death reported
Trimethoxyamphetamine (TMA) Synthetic drug related to mescaline Used orally, as powder, injection	• Effects occur after 2 h • Often misrepresented as MDA • More potent than mescaline • More toxic if injected or higher doses used • Can cause unprovoked anger and aggression

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Opioids

General Comments

- High rate of comorbidity, specifically depression, alcohol use disorder, and antisocial personality disorder (often not clear if these are cause or effect)
- The term "opioid" is an umbrella term for substances that bind opioid receptors, while the term "opiate" refers only to drugs derived from the opium poppy plant (i.e., heroin, morphine, and codeine)
- Prescription opioid abuse (e.g., codeine, oxycodone) in the general population is relatively high in North America
- Polysubstance use and co-dependence on benzodiazepines appears particularly common among individuals using opioids. This drug combination carries an FDA boxed-warning for increased risk of extreme sleepiness, respiratory depression, coma, and death
- High incidence of overdose and deaths reported through illicit use/abuse of prescription opioids (e.g., oxycodone, oxymorphone, fentanyl) and increasingly due to many street drugs being contaminated with illicitly manufactured opioids (commonly fentanyl)
- Pediatric cases of opioid intoxications are increasing. A prospective cohort study of children who presented to medical centers with an opioid intoxication showed 45% were exposed to opioids prescribed to family members; children who had been exposed to fentanyl and those aged 10 years or more had 3.6 and 2.5 higher odds of ICU admission or death, respectively
- During the COVID-19 pandemic, opioid supply chains were severely disrupted, creating significant deficits in opioid supply that resulted in dealers and producers using synthetic, fentanyl-containing, or toxin-containing opioids. There was a sharp and profound increase in opioid-related deaths during the pandemic

Pharmacological/Psychiatric Effects

- Differ, depending on type of drug taken, the dose, the route of administration, and whether combined with other drugs

Physical
- Analgesia, slow pulse and respiration, increased body temperature, dry mouth, constricted pupils, decreased GI motility

Mental
- Euphoria, "rush" sensation followed by relaxation, decreased tension, state of gratification, sedation

High Doses
- Respiratory depression, cardiovascular complications, coma, and death

Chronic Use
- General loss of energy, ambition, and drive, motor retardation, attention impairment, sedation, slurred speech
- Tolerance and physical dependence; withdrawal
- Cross-tolerance occurs with other opioids

D/C Toxicity

- Signs of opioid overdose:
  - Drowsiness or loss of consciousness
  - Hypopnea, bradypnea; can progress to apnea
  - Bronchoconstriction; dyspnea, wheezing, frothy sputum
  - Choking or gurgling sounds
  - Hypoxia; purple or blue fingernails or lips
  - Cold and/or clammy skin
  - Miosis (may not be present)

Management

- Arouse patient to wake them up; if no response, rub your knuckles into their chest bone
- If still no response, call emergency line immediately
- First-line is rescue breathing: 2 breaths into the mouth then give 1 breath every 5 sec while preparing and after administering naloxone until the patient breathes on their own or until medical help arrives
- Administer naloxone (e.g., IM/IV/SC injection, intranasal spray)
- Onset of action of naloxone is 2–5 min for IM/SC injection, 2 min for IV injection, 8–13 min for intranasal spray; if patient does not respond, administer another dose of naloxone
- Duration of naloxone is 30–90 min for IM/IV/SC injection, 2 h for intranasal spray; stay with patient until emergency assistance arrives or until naloxone wears off
- If you need to leave, lay patient on their side (recovery position) to prevent choking

D/C Discontinuation Syndrome

- Symptoms include: Yawning, runny nose, sneezing, lacrimation, mydriasis, vasodilation, tachypnea, tachycardia, elevated BP, vomiting and diarrhea, restlessness, tremor, chills, diaphoresis, piloerection, bone pain, abdominal pain and cramps, anorexia, anxiety, irritability, and insomnia
- Onset and duration of withdrawal symptoms depend on the specific opioid and its half-life
- Acute symptoms can last 10–14 days (longer with methadone)
- Methadone withdrawal: May develop more slowly; lethargy, malaise, anxiety, and insomnia may persist up to several months; craving may persist for years

Treatment

- Opioid withdrawal states are generally not life-threatening; stopping "cold turkey" is acceptable to some opioid-dependent individuals
- Non-opioid alternatives (e.g., benzodiazepines, antipsychotics) usually do not work
- Drugs are prescribed for the following reasons:
  a) to reverse effects of toxicity using opioid antagonists (e.g., naloxone – can precipitate withdrawal)
  b) to treat the immediate withdrawal reaction (e.g., clonidine, buprenorphine, methadone)
  c) to aid in detoxification, or for maintenance therapy in a supervised treatment program (e.g., methadone, buprenorphine)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

OPIOIDS (GENERAL)

Class of Drug	Example	Interaction Effects
Antibiotic	Erythromycin, clarithromycin	Increased plasma concentration of fentanyl, alfentanil due to inhibited metabolism via CYP3A4, resulting in prolonged analgesia and adverse effects
Anticonvulsant	Gabapentin, pregabalin	Respiratory depression Increased risk of opioid-related overdose death with concomitant gabapentin (OR 1.5) or pregabalin (OR 1.7) vs. opioids alone
Antidepressant		
SSRI, SNRI	Fluoxetine, paroxetine	Serotonin syndrome reported when combined with serotonergic opioids such as tramadol Decreased efficacy of codeine and tramadol due to CYP2D6 inhibition; must be metabolized to active metabolites morphine and O-desmethyltramadol respectively (by CYP2D6) for therapeutic effects
MAOI, RIMA	Moclobemide, phenelzine	Increased excitation, sweating, and hypotension reported (especially with meperidine, pentazocine, and tramadol); may lead to development of encephalopathy, convulsions, coma, respiratory depression, and serotonin syndrome
Antihistamine	Cyclizine, tripelennamine	"Opiate high" reported in combination with opium; euphoria
Antipsychotic	Quetiapine	Methadone: Increased plasma concentration of (R)-methadone (active form) but resulted in no toxicity effects
CNS depressant	Alcohol	Additive CNS effects; can lead to respiratory depression
	Benzodiazepines	Increased risk of extreme sleepiness, respiratory depression, coma, and death (10-fold higher with concurrent benzodiazepines vs. opioids alone)

Opioids (cont.)

Class of Drug	Example	Interaction Effects
H_2 antagonist	Cimetidine	Enhanced effect of opioid and increased adverse effects due to decreased metabolism; 22% decrease in clearance of meperidine
Opioid antagonist	Naloxone, naltrexone	Will precipitate withdrawal reaction
Protease inhibitor	Ritonavir	Decreased clearance of opioid due to inhibited metabolism, resulting in increased plasma level (caution with fentanyl, alfentanil, and meperidine)
Stimulant	Cocaine	May potentiate cocaine euphoria

Opioids

Drug	Comments
HEROIN Diacetylmorphine – synthetic derivative of morphine Injected (IV – "mainlining", or SC – "skin popping"), smoked, inhaled, taken orally Slang: "H", horse, junk, snow, stuff, lady, dope, shill, poppy, smack, scag, black tar, Lady Jane, white stuff, brown sugar, white horse	• Effects almost immediate following IV injection and last several hours; effects occur in 15–60 min after oral dosing • Risk of accidental overdose as street preparations may contain various concentrations of heroin or other more potent opioids (e.g., fentanyl) • Physical dependence and tolerance occur within 2 weeks; withdrawal occurs within 8–12 h after last dose, peaks in 36–72 h, and can last up to 10 days • Physical effects: Pain relief, nausea, constipation, staggering gait, and respiratory depression • CNS effects: Euphoria, drowsiness, and confusion • Toxicity: Sinus bradycardia or tachycardia, hypertension or hypotension, palpitations, syncope, respiratory depression, coma, and death • Pregnancy: High rate of spontaneous abortions, premature labor and stillbirths – babies are often small and have an increased mortality risk; withdrawal symptoms in newborn reported • Breastfeeding: Tremors, restlessness, vomiting and poor feeding reported in infants
MORPHINE Principal active component of opium poppy Taken as powder, capsule, tablet, liquid, injected, rectally Slang: "M", dreamer, sweet Jesus, junk, morph, Miss Emma, monkey, white stuff	• Effects as for heroin, but slower onset and longer-acting • Effects occur in 15–60 min after oral dosing and last 1–8 h; metabolized primarily by UGT1A3 and 2B7; inhibits metabolism of UGT2B7 • Physical effects: Pain relief, nausea, constipation; with high doses, can get respiratory depression, unconsciousness, and coma • CNS effects: Drowsiness, confusion, and euphoria • High dependence liability (second to heroin) due to powerful euphoric and analgesic effects
METHADONE (see p. 384) (Dolophine, Metadol, Methadose) Used as tablets, liquid, injected Slang: The kick pill, dolly, meth	• Drug used in withdrawal and detoxification from opioids, but subject to abuse • Effects occur 30–60 min after oral dosing and last 7–48 h • Chronic use causes constipation, blurred vision, sweating, decreased libido, menstrual irregularities, joint and bone pain, cardiac arrhythmia, and sleep disturbances • Physical dependence and tolerance occur; withdrawal effects peak in 72–96 h, and can last up to 14 days • Pregnancy: Dosing needs should be reassessed (decreased between weeks 14 and 32 and increased prior to term); withdrawal effects reported in neonates • Breastfeeding: Small amounts of methadone enter milk; nurse prior to taking dose or 2–6 h after
OPIUM Resinous preparation from unripe seed pods of opium poppy; available as dark brown chunks or as powder Soaked, taken as solution, smoked Slang: Big O, black stuff, block, gum, hop	• Contains a number of alkaloids including morphine (6–12%) and codeine (0.5–1.5%) • Physical effects: Nausea and constipation; with high doses, can get respiratory depression, unconsciousness, and coma • CNS effects: Drowsiness, confusion, and euphoria

OTHER FREQUENTLY ABUSED PRESCRIPTION OPIOIDS AND RELATED DRUGS

Drug	Comments
CODEINE Methylmorphine Used orally, liquid, injected Slang: 3s, 4s, Captain Cody, Cody, Lean, Purple Drank, Schoolboy, Sizzurp	• Naturally occurring alkaloid from opium poppy • Metabolized primarily by UGT2B7 and also by CYP2D6 and 3A4. Inhibits metabolism of UGT2B7 • Codeine must be metabolized to its active metabolite, morphine (by CYP2D6) for its therapeutic effect. A significant proportion of the population are poor or rapid metabolizers of CYP2D6, resulting in unpredictable opioid effects or adverse effects, including toxicity in ultra-rapid metabolizers • Common ingredient of both prescription and over-the-counter analgesics and antitussives (e.g., Fiorinal-C, Tylenol #1, etc.; not recommended in children) • Physical effects: Pain relief, constipation • CNS effects: Euphoria, drowsiness, and confusion • Toxic effects: Respiratory depression and arrest, decreased consciousness, coma, and death • Tolerance develops gradually; physical dependence is infrequent; withdrawal will occur with chronic high-dose use
DEXTROMETHORPHAN (Robitussin DM) Used orally Slang: Robo, robo-trip, poor man's PCP, candy, CCC, DM, DXM, skittles, triple C, velvet	• Higher doses can cause agitation, euphoria, altered perceptions, ataxia, nystagmus, hypertension, tachycardia, visual disturbances, and disorientation; may progress to panic attacks, delusions, psychotic/manic behavior, hallucinations, paranoia, and seizures • If combination product abused (e.g. cough/cold preparation) must consider toxic effects of other ingredients • Risk of serotonin syndrome when used with various serotonergic agents (SSRIs, SNRIs, linezolid, MAOIs, etc.)
FENTANYL (Duragesic, Sublimaze) Smoked, ingested, applied topically (patch) Slang: Tango, cash, Apache, China girl, China white, dance fever, friend, goodfella, jackpot, murders, murder 8, TNT	• Effects almost immediate following IV injection and last 30–60 min; with IM use, onset slower and duration of action up to 120 min; exposing application site of fentanyl patch to an external heat source (e.g., heating pad, hot tub) can increase drug absorption and result in increased drug effect • Skin exposure to fentanyl powder is extremely unlikely to cause harm immediately • Metabolized primarily by CYP3A4 • Physical effects: Dizziness, dry mouth, constipation, and GI distress • CNS effects: Primarily sedation, confusion, and euphoria occurs quickly • Overdoses reported in children accidentally exposed to fentanyl patch due to improper storage or disposal. Toddlers may think discarded fentanyl patch is a sticker, tattoo, or bandage and apply to their skin, resulting in toxicity • High doses can produce muscle rigidity (including respiratory muscles) respiratory depression, unconsciousness, and coma • Various street drugs commonly found to be adulterated with fentanyl and/or fentanyl derivatives • Risk of serotonin syndrome when used with various serotonergic agents (SSRIs, SNRIs, linezolid, MAOIs, etc.) • Fentanyl analogues (e.g., carfentanil) may be hundreds of times more potent than morphine, street heroin or fentanyl, producing significantly more respiratory depression
HYDROCODONE (e.g., Novahistex DH, Vicodin) Slang: vike, Watson-387	• Related to codeine but more potent • An ingredient in prescription antitussive preparations; sought by abusers due to easy availability and purity of product • Metabolized primarily by CYP2D6, 3A4, and by UGTs • Physical, CNS, and toxic effects as for codeine • Tolerance develops rapidly • Lethal dose: 0.5–1 g
HYDROMORPHONE (Dilaudid, Hydromorph Contin) Used orally, rectally Slang: Juice, dillies	• Semisynthetic opioid • Metabolized by UGT1A3 • At low doses, side effects less common than with other opioids; high doses more toxic due to strong respiratory depressant effect

Opioids (cont.)

Drug	Comments
KRATOM (*Mitragynia speciosa*) Leaves Taken as capsules, tablets, extract or gum; fresh leaves chewed, smoked or eaten in food; dried/powdered leaves smoked or brewed as tea Slang: 4x100, herbal heroin, kapow	• Tropical tree native to Southeast Asia; "natural" opioid agonist • Leaves contain two psychoactive components, mitragynine and 7-hydroxymitragynine: Agonists at μ- (primarily), κ-, and δ-opioid receptors; antagonists at 5-HT_{2A} receptors and agonists at α_2 receptors • Doses 1–5 g produce stimulant effect: Increased energy, sociability and alertness • Doses 5–15 g produce opioid effect: Sedation, euphoria, decreased pain • Doses higher than 15 g may produce opioid-like toxicity • Short-term adverse effects: Nausea, dizziness, itching, sweating, dry mouth, constipation, increased urination, loss of appetite • Long-term adverse effects: Anorexia, weight loss, insomnia, skin hyperpigmentation, dry mouth, frequent urination, constipation, kidney and thyroid injuries • Rare hepatotoxicity with high doses or chronic use • Reports of serious adverse effects: Agitation, tachycardia, torsades de pointes, seizures, psychosis, coma, death • Dependence potential • Withdrawal symptoms: Muscle aches, insomnia, hostility, aggression, emotional changes, runny nose, jerky movements; onset 4–24 h following the last use; physical effects last 4–5 days
LEVORPHANOL (Levo-Dromoran)	• Synthetic opioid analgesic with effects similar to morphine • High doses can produce cardiac arrhythmias, hypotension, respiratory depression, and coma
MEPERIDINE/PETHIDINE (Demerol) Synthetic opioid derivative Used orally, injected Slang: Demmies, pain killer, peth	• Metabolite (normeperidine) is highly toxic; may accumulate in renal failure or with chronic use and cause convulsions • High doses produce disorientation, hallucinations, respiratory depression, stupor, and coma • Risk of serotonin syndrome when used with various serotonergic agents (SSRIs, SNRIs, linezolid, MAOIs, etc.)
OXYCODONE (OxyContin (US), OxyNeo, Percocet, Percodan, Supeudol) Semisynthetic derivative Used orally; tablets chewed, crushed and snorted, powder boiled for injection Slang: Percs, OC, OXY, oxycotton, killers	• An ingredient in combination analgesic products and on its own (OxyNeo, Supeudol) • Metabolized by CYP2D6, 3A4, and UGTs • Very high abuse potential • Physical effects: Nausea, constipation; with high doses can get respiratory depression and coma • Mental effects: Drowsiness, disorientation, and euphoria
PENTAZOCINE (Talwin) Used orally, injected Slang: T's, big T, Tee, Tea	• Has both agonist and antagonist properties at opioid receptors • Repeated injections can result in tissue damage at injection site
TRAMADOL (Tramacet, Ultracet, Ultram) Used orally, snorted (crushed tablets) Slang: Ultras	• Agonist at μ- and κ-opioid receptors; serotonin and norepinephrine reuptake inhibitor • Tramadol must be metabolized to its active metabolite, O-desmethyltramadol (by CYP2D6) for its therapeutic effect. A significant proportion of the population are poor or rapid metabolizers of CYP2D6, resulting in unpredictable opioid effects or adverse effects • Physical, CNS, and toxic effects as for codeine • Risk of serotonin syndrome when used with various serotonergic agents (SSRIs, SNRIs, linezolid, MAOIs, etc.)

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Inhalants/Aerosols

General Comments

- High rate of psychopathology, specifically alcoholism, depression, and antisocial personality disorder, has been demonstrated in individuals with a history of inhalant use
- Considered "poor man's" drug of abuse, inexpensive and readily available; primarily used by children and in third world countries to lessen hunger pain
- Fourth most commonly abused substance among teens in Canada; high use in Aboriginal populations
- Use is often episodic, and "fads" determine current inhalant of choice; users often abuse/misuse other drugs
- Nitrite abuse often associated with "club" scene; amyl nitrite used to promote sexual excitement and orgasm; may cause a temporary loss of social inhibitions, thereby leading to higher-risk sexual practices

Slang

- Glue, gassing, sniffing, chemo, snappers
- Amyl and butyl nitrites: Pearls, poppers, rush, locker room, Bolt, Kix
- Nitrous oxides: Laughing gas, balloons, whippets

Substances Abused

- Volatile gases: Butane, propane, aerosol propellants
- Solvents: Airplane glue, gasoline, toluene, printing fluid, cleaning solvents, benzene, acetone, spray paint ("chroming"), amyl nitrite ("poppers"), etc.
- Aerosols: Deodorants, hair spray, freon
- Anesthetic gases: Nitrous oxide (laughing gas), chloroform, ether

Methods of Use

- "Bagging" – pouring liquid or discharging gas into plastic bag or balloon
- "Sniffing" – holding mouth over container as gas is discharged
- "Huffing" – holding a soaked rag over mouth or nose
- "Torching" – inhaling fumes discharged from a cigarette lighter, then igniting the exhaled air

Pharmacological/ Psychiatric Effects

- Differ, depending on type of drug taken
- Fumes sniffed, inhaled; use of plastic bag can lead to suffocation
- Inhaled product enters the bloodstream quickly via the lungs and CNS penetration is rapid – intoxication occurs within minutes and can last from a few minutes to an hour

Physical

- Dizziness, slurred speech, impaired motor function, muscle weakness, cramps, light sensitivity, headache, nausea or vomiting, salivation, sneezing, coughing, wheezing, decreased breathing and heart rate, hypotension, and cramps
- Fatalities can arise from cardiac arrest or inhalation of vomit while unconscious

Mental

- Drowsiness, changing levels of awareness, impaired judgment and memory, loss of inhibitions, hallucinations, euphoria, excitation, vivid fantasies, feeling of invincibility, and delirium

High Doses

- Loss of consciousness, convulsions, cardiac arrhythmia, seizures, and death

Inhalants/Aerosols (cont.)

Chronic Use

- Fatigue, chronic headaches, encephalopathy, hearing loss, visual impairment, sinusitis, rhinitis, laryngitis, weight loss, kidney and liver damage, bone marrow damage, cardiac arrhythmias, and chronic lung disease
- Inability to think clearly, memory disturbances, depression, irritability, hostility, and paranoia
- Tolerance develops to desired effect; psychological dependence is frequent

Toxicity

- CNS: Acute and chronic effects reported (e.g., ataxia, peripheral neuropathy)
- Cardiac: Myocardial infarction can occur, primarily with use of halogenated solvents
- Renal: Acidosis and hypokalemia
- Hepatic: Hepatitis and hepatic necrosis
- Hematologic: Bone marrow suppression, primarily with benzene and nitrous oxide use
- Accidental suffocation from plastic bag used over the head

Use in Pregnancy◊

- Associated with increased risk of miscarriage, birth defects, low birth weight, and sudden infant death syndrome (SIDS); in a meta-analysis of 10 studies of maternal solvent exposure, 5 showed major malformations
- There is some evidence that prenatal exposure may cause long-term neurodevelopmental impairments, such as deficits in cognitive, speech, and motor skills
- Residual withdrawal symptoms reported in babies of mothers who used volatile substances during pregnancy. Symptoms in babies include excessive and high-pitched crying, sleeplessness, hyperreflexia, tremor, hypotonia, and poor feeding

Breast milk

- Risk of inhalants entering breast milk and exposing infant to adverse effects

Treatment

- Effects are usually short lasting; use calming techniques, reassurance

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
CNS depressant	Alcohol, benzodiazepines, hypnotics, opioids	Increased impairment of judgment, distortion of reality
PDE-5 inhibitor	Sildenafil, tadalafil, vardenafil	Deaths reported when used with amyl nitrate due to additive vasodilation

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◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Sodium Oxybate (Gamma-Hydroxybutyrate – GHB)

Indications (approved)

- Narcolepsy: Oral treatment of cataplexy and excessive daytime sleepiness (Xyrem)
- Alcohol dependency (has been used in Europe)
- Used for sedation and to treat opioid withdrawal

General Comments

- Xyrem is available in the USA via the Xyrem REMS Program, using a centralized pharmacy 1-866-XYREM88 (1-866-997-3688)
- Xyrem is available in Canada via the Xyrem Success program using a single wholesaler 1-866-5XYREM5 (1-866-599-7365)
- Prescribing and dispensing restrictions apply for use of Xyrem in patients 7 years and older with narcolepsy
- Xyrem is available as an oral solution containing 500 mg/mL
- Abused as a powder mixed in a liquid; usually sold in vials and taken orally; has a salty or soapy taste (may be masked in flavored or alcoholic beverages)
- Used for its hallucinogenic and euphoric effects at "raves"
- Meta-analysis for alcohol dependence reported it was better than naltrexone and disulfiram in maintaining abstinence and had a better effect on alcohol cravings than disulfiram or placebo. Single studies suggest comparable efficacy to benzodiazepines in reducing alcohol withdrawal syndrome[1]
- Distributed as a "controlled drug" with generic name of sodium oxybate; improves nighttime sleep and reduces daytime sleep attacks and cataplexy at doses of 6–9 g/night; initial starting doses are recommended to be 4.5 g/night (divided into two doses of 2.25 g each). The second dose is taken 2.5–4 h after the first
- Sodium oxybate is a CNS depressant and should not be used with alcohol or other CNS depressants; patients should not drive or operate machinery for at least 6 h after taking Xyrem
- Originally researched as an anesthetic; shown to have limited analgesic effects and increased seizure risk
- Promoted illegally as a health food product, an aphrodisiac, and for muscle building
- Commonly used as a "date-rape" drug by assailants in sexual assault because it acts rapidly, produces disinhibition and relaxation of voluntary muscles, and provides a euphoric mood effect
- Alcohol potentiates the drug's effects, and sexual assailants often use alcohol as a delivery mechanism for sodium oxybate
- Promotion of safe drinking practices (not leaving drinks uncovered, not accepting drinks from strangers, opening your own drinks yourself, looking out for friends) should be encouraged to reduce the impact of predatory use
- Products converted to GHB in the body include: Gammabutyrolactone (GBL – also called Blue Nitro Vitality, GH Revitalizer, GHR, Remforce, Renewtrient, and Gamma G – is sold in health food stores) and the industrial solvent butanediol (BD – also called tetramethylene glycol or Sucol B, and sold as Zen, NRG-3, Soma Solutions, Enliven, and Serenity)

Slang

- Liquid ecstasy, liquid X, liquid F, goop, GBH = Grievous Bodily Harm, easy lay, ghost breath, G, somatomax, Gamma-G, Growth Hormone Booster, Georgia home boy, nature's quaalude, organic quaalude, G-riffick, soapy, salty water, fantasy, scoop, soap

Pharmacology

- Produced naturally in the body and is a metabolite of gamma aminobutyric acid (GABA); acts on $GABA_B$ receptor to potentiate gaba-ergic effects
- Reduces cataplexy
- Some effects of GHB are blocked by opioid receptor antagonists

Pharmacological/ Psychiatric Effects

- Deep sleep reported with doses of 2 g
- At 10 mg/kg produces anxiolytic effect, muscle relaxation, and amnesia
- At 20–30 mg/kg increases REM and slow-wave sleep
- Stimulates slow-wave sleep (stages 3 and 4) and decreases stage 1 sleep; with continued use, decreases REM sleep
- Caution: Doses above 60 mg/kg can result in anesthesia, respiratory depression, and coma
- Chronic use may result in tolerance and/or psychological dependence

Sodium Oxybate (Gamma-Hydroxybutyrate – GHB) (cont.)

Pharmacokinetics

- Quickly absorbed orally; onset of action occurs within 15–30 min; peak plasma concentration reached in 20–60 min
- Food significantly decreases the bioavailability of sodium oxybate. Therefore, the first dose should be taken at least 2 h after eating. To minimize variability, the drug should be taken consistently in relation to meals
- Elimination half-life approx. 20–30 min; no longer detected in blood after 2–8 h and in urine after 8–12 h

Adverse Reactions

Physical

- With high doses: High frequency of drop attacks – "victim" suddenly loses all muscular control and drops to the floor, unable to resist the "attacker"
- Drowsiness, dizziness, nausea, vomiting, headache, hypotension, bradycardia, hypothermia, ataxia, nystagmus, hypotonia, tremors, muscle spasms, seizures, decreased respiration; symptoms usually resolve within 7 h, but dizziness can persist up to 2 weeks
- Use of sodium oxybate in narcolepsy has been associated with headache, nausea, dizziness, sleepwalking, confusion and urinary incontinence; worsening of sleep apnea
- Use of high doses may lead to unconsciousness and coma (particularly dangerous in combination with alcohol)

Mental

- Lowered inhibitions, sedation, poor concentration, confusion, amnesia, euphoria, and hallucinations; can cause agitation and aggression

D/C Discontinuation Syndrome

- Symptoms occur 1–6 h after abrupt cessation and can last for 5–15 days after chronic use
- Initial symptoms include nausea, vomiting, insomnia, anxiety, confusion, and/or tremor; after chronic use, symptoms can include mild tachycardia and hypertension, and can progress to delirium with auditory and visual hallucinations; in severe cases, treatment-resistant psychosis

Toxicity

- Low therapeutic index; dangerous in combination with alcohol
- Overdoses can occur due to unknown purity and concentration of ingested product
- Symptoms: Bradycardia, seizures, apnea, sudden (reversible) coma with abrupt awakening and violence
- Coma reported in doses above 60 mg/kg (4 g)
- Several deaths reported secondary to respiratory failure

Management

- No known antidote

Use in Pregnancy◊

- No adequate or well-controlled studies in human pregnancy. Increased stillbirths, decreased offspring viability, and weight in animal models

Breast milk

- Unknown excretion in human breast milk

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Benzodiazepine	Diazepam	Has been used to treat GHB withdrawal; theoretically may worsen respiratory depression
CNS depressant	Alcohol, opioids	Synergistic CNS depressant effects can occur, especially with high doses of GHB, leading to respiratory depression
Cannabis		Increased pharmacological effects
Protease inhibitor	Ritonavir-saquinavir combination	Increased pharmacological effects/toxicity – may cause bradycardia, respiratory depression, and seizures
Stimulant	Amphetamines	Increased pharmacological effects

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Further Reading

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Flunitrazepam (Rohypnol)

General Comments

- Used as a sedative/tranquilizer in some European countries; flunitrazepam not marketed in Canada or USA
- Commonly used as a "date-rape" drug by assailants in sexual assault because it acts rapidly, produces disinhibition and relaxation of voluntary muscles, and causes anterograde amnesia for events that occur under the influence of the drug
- Alcohol potentiates the drug's effects, and sexual assailants often use alcohol as a delivery mechanism for flunitrazepam
- Promotion of safe drinking practices (not leaving drinks uncovered, not accepting drinks from strangers, opening your own drinks yourself, looking out for friends) should be encouraged to reduce the impact of predatory use

Slang

- Roofies, R-2s, Roches Dos, forget-me pill, Mexican Valium, roofinol, rope, rophies

Method of Use

- Purchased in doses of 1 and 2 mg (legal manufacturers have added blue or green dye to formulation to color beverages and make them murky); illegal manufacturing is common
- Ingested, snorted, or injected
- Added to alcoholic beverages of unsuspecting victim; tasteless, odorless

Pharmacology

- Fast-acting benzodiazepine, structurally related to clonazepam and diazepam (but 10 times more potent)
- See p. 266

Pharmacokinetics

- Effects begin in 30 min, peak within 2 h, and last up to 8–10 h

Adverse Reactions

- These reactions are reported following restoration of consciousness

Physical

- Dizziness, impaired motor skills, "rubbery legs," weakness, unsteadiness, visual disturbances, blood-shot eyes, slurred speech, and urinary retention
- Decreased blood pressure and pulse, slowed breathing; may lead to respiratory depression and arrest

Mental

- Rapid loss of consciousness and anterograde amnesia; residual symptoms include drowsiness, fatigue, confusion, impaired memory and judgment, aggression, agitation, anxiety, excitability, and reduced inhibition
- If some memory of the event remains, the "victim" may describe a disassociation of body and mind – a sensation of being paralyzed, powerless, and unable to resist

Discontinuation Syndrome

- Like other benzodiazepines, chronic use can produce dependence
- Withdrawal symptoms: Headache, tension, anxiety, restlessness, muscle pain, photosensitivity, numbness and tingling of the extremities, and increased risk of seizures

Flunitrazepam (Rohypnol) (cont.)

Toxicity

- See Benzodiazepines p. 269
- Effects much greater with concurrent ingestion of alcohol or other sedating drugs

Drug Interactions

- See Benzodiazepines pp. 270–271

Further Reading

Additional Suggested Reading

- Gahlinger PM. Club drugs: MDMA, gamma-hydroxybutyrate (GHB), rohypnol, and ketamine. Am Fam Physician. 2004; 69(11):2619–2627. Retrieved from: http://www.aafp.org/afp/2004/0601/p2619.html

Nicotine/Tobacco

General Comments

- Slang:
  E-cigarettes: Vape pipes, vapes, hookah pens, e-hookahs
  Waterpipe smoking: Shisha, hookah, narghile, goza, hubble bubble
  Cigarettes: Smokes, butt, square, cigs, ciggies, snuff, stogs, stogies, stokes, snouts, tabs, loosey (a single cigarette), backwards, bogeys, boges, bidis, gorts, ciggy wiggy dilly's, darts, refries, straights, dugans, hairy rags, jacks, joes, grits, grants, tailies, fags, coffin nails, cancer sticks, lung darts, sweet cancer, gaspers, or even black lungs
  Chewing tobacco: Snuff, spit tobacco, smokeless oral tobacco, chaw, dip, lipper, snarl
- Waterpipe smoking has been used for ages in the Middle East, and has recently grown in popularity in the western world. A recent meta-analysis suggests that a single session of waterpipe use produces a urinary cotinine level that is equivalent to smoking 2 cigarettes/day; daily waterpipe smoking produces a nicotine absorption rate equivalent to smoking 10 cigarettes/day
- Electronic cigarettes, also known as e-cigarettes or vapor cigarettes, are battery-operated devices that resemble traditional cigarettes. Instead of burning tobacco, they contain cartridges filled with nicotine and other chemicals. When the e-cigarette is used, the liquid chemicals in the cartridge are turned into a vapor or steam that is inhaled by the smoker. The liquid comes in a wide range of flavors, from tobacco and coffee to fruit flavors. Nicotine content varies widely among products and nicotine exposure depends on the user's inhalation and experience. E-cigarettes contain varying amounts of toxicants, carcinogens, and metal particles and are associated with increased risk of cardiovascular diseases and lung disorders (e.g., current or ever use of e-cigarettes associated with asthma in adolescents). In adolescents and young adults, e-cigarette use increases the risk of using tobacco cigarettes later in life. Electronic cigarettes are NOT believed to cause CYP1A2 induction, which is a risk of general tobacco smoking
- Increased rates and higher levels of smoking have been associated with a number of psychiatric disorders, including schizophrenia, depression, and anxiety disorders, resulting in high rates of morbidity and mortality
- Tobacco smoking is the leading cause of premature death in developed countries; tobacco smoke contains over 4,000 chemicals, approximately 50% are carcinogenic
- Smoking-related diseases include: Cancers (lung, oral, cervix, pancreas, kidneys, stomach), cardiovascular disease, chronic bronchitis, emphysema, pneumonia, COPD, aortic aneurysms, acute myeloid leukemia, cataracts, and gum disease
- Nicotine can affect adolescent brain development and cognition; linked to poor impulse control, impaired attention and learning

Pharmacological/ Psychiatric Effects

- Nicotine is an alkaloid found in the nightshade family of plants (*Solanaceae*), which constitutes approximately 0.6–3% of dry weight of tobacco. In low concentrations (an average cigarette yields about 1 mg of absorbed nicotine), the substance acts as a stimulant in mammals and is the main factor responsible for the dependence-forming properties of tobacco smoking

- By binding to nicotinic acetylcholine receptors, nicotine stimulates the release of many chemical messengers including acetylcholine, norepinephrine, epinephrine, vasopressin, arginine, dopamine, autocrine agents, and β-endorphin. This release of neurotransmitters and hormones is responsible for most of nicotine's effects. Nicotine appears to enhance concentration and memory, due to the increase of acetylcholine. It also appears to enhance alertness, due to the increases of acetylcholine and norepinephrine. Arousal is increased by the increase of norepinephrine. Pain is reduced by the increases of acetylcholine and β-endorphin. Anxiety is reduced by the increase of β-endorphin. Nicotine also extends the duration of positive effects of dopamine and increases sensitivity in brain reward systems
- It is thought that increased levels of dopamine in the reward circuits of the brain are responsible for the euphoria and relaxation and eventual addiction caused by nicotine consumption. Other neurochemical systems also participate in the addictive effects of nicotine, including glutamate, cannabinoids, GABA, and opioids

Pharmacokinetics

- As nicotine enters the body, it is distributed quickly through the bloodstream and can cross the blood-brain barrier. On average, it takes about 7 sec for nicotine to reach the brain when inhaled
- The amount of nicotine absorbed by the body from smoking depends on many factors, including the type of tobacco, whether the smoke is inhaled, and whether a filter is used. For chewing tobacco, dipping tobacco, snus (moist tobacco powder), and snuff (ground tobacco leaves used for inhalation), which are held in the mouth between the lip and gum, or taken in the nose, the amount released into the body tends to be much greater than from smoked tobacco
- Nicotine is metabolized in the liver by CYP450 enzymes (mostly CYP2A6 and also CYP2B6). A major metabolite is cotinine; other primary metabolites include nicotine *N'*-oxide, nornicotine, nicotine isomethonium ion, 2-hydroxynicotine, and nicotine glucuronide. Glucuronidation and oxidative metabolism of nicotine to cotinine are both inhibited by menthol, an additive to mentholated cigarettes, thus increasing the half-life of nicotine *in vivo*.
- Half-life of nicotine in the body is around 2 h

Toxicity

- It is impossible to overdose on nicotine through smoking alone (though a person can overdose on nicotine through a combination of nicotine patches, nicotine gum, and/or tobacco smoking at the same time)
- Severe nicotine poisoning may cause nausea, vomiting, pallor, sweating, abdominal pain, salivation, lacrimation, muscle weakness, confusion, and lethargy
- Nicotine overdose can cause seizures; observed in adults who were poisoned with nicotine and in young children who have consumed liquid nicotine
- E-cigarette products mixed with a thickening agent Vitamin E acetate have led to serious lung illnesses and deaths
- Increasing reports of burn injuries secondary to e-cigarette battery explosions from thermal runaway (overheating of the device battery)

D/C Discontinuation Syndrome

- Approximately 40% of smokers attempt to quit each year, but only 4–7% are likely to be successful on their first attempt; most relapse in the first week[1]. Motivational interviewing techniques (practical counseling, support, encouragement) appear to be effective in increasing a patient's likelihood to try to quit and maintain abstinence
- Nicotine withdrawal symptoms peak within a few days and usually subside after a few weeks; however, some symptoms can last for months:
  - Withdrawal symptoms, lasting a few days to a few weeks: Dizziness, restlessness, anxiety, insomnia, irritability, frustration, anger, difficulty concentrating, drowsiness, cough, dry throat or mouth, constipation, bloating, and bad breath
  - Withdrawal symptoms lasting weeks to months: Increased appetite, fatigue, "boredom", depression, craving for tobacco, and exacerbation of an underlying psychiatric disorder
- Many behavioral factors can also affect the severity of withdrawal symptoms. For some people, the feel, smell, and sight of a cigarette and the ritual of obtaining, handling, lighting, and smoking the cigarette are all associated with the pleasurable effects of smoking and can make withdrawal or craving worse. Behavioral therapies can help smokers identify environmental triggers of craving so they can employ strategies to prevent or circumvent these symptoms and urges

Use in Pregnancy◊

- Smoking (or exposure to second-hand smoke) during pregnancy results in babies with a lower-than-average birth weight and more health problems, as smoking exposes the baby to chemicals and carcinogens in tobacco and provides less oxygen and nutrients

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Nicotine/Tobacco (cont.)

- Smokers have a greater chance of having a miscarriage, stillbirth, and ectopic pregnancy than nonsmokers. During birth, they are more likely to have complications
- Babies born to mothers who smoked may have more ear infections as well as more colds and respiratory problems; long-term effects on the offspring include impaired fertility, type 2 diabetes, obesity, hypertension, learning problems, sleep problems, and neurobehavioral defects
- Children regularly exposed to second-hand smoke are more likely to suffer damage to their lungs and to develop breathing problems such as asthma

Treatment

- Tobacco use disorder is a chronic problem that often requires repeated interventions and multiple attempts to quit. Behavior therapies, counseling, and support have shown to improve outcomes
- Medications which have been found to be effective as first-line smoking cessation treatments in adults include:
  - Bupropion SR (see p. 67)
  - Nicotine replacement therapy (gum, lozenge, patch, inhaler; see p. 390)
  - Partial nicotine receptor agonist varenicline (see p. 390)
  - Second-line treatments include: nortriptyline (see p. 102), clonidine (see p. 46)

Drug Interactions

- Polycyclic aromatic hydrocarbons are some of the major lung carcinogens found in tobacco smoke. They are potent inducers of CYP 1A1, 1A2, and possibly 2E1. CAUTION: Upon smoking cessation, smokers may require a reduced dose of interacting medications metabolized by these enzymes
- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Alcohol		Positive correlation reported between cigarette smoking and alcohol use; alcohol potentiates rewarding effects of nicotine
Anticoagulant	Heparin	Increased clearance of heparin and decreased half-life; unknown mechanism
	Warfarin	Increased metabolism of warfarin R-enantiomer due to induction of CYP1A2; however, S-enantiomer is more potent and effect on INR is inconclusive
Antidepressant	Duloxetine	Reduced serum levels of duloxetine by 50% due to increased metabolism via CYP1A2 induction. Higher doses of duloxetine (~15%) seem to be necessary to reach adequate serum levels[2]
	Fluvoxamine	Decreased plasma level of fluvoxamine by 25% due to increased metabolism via CYP1A2
	Tricyclic	Increased clearance of antidepressant due to induction of CYP1A2
Antiplatelet	Clopidogrel	Increased metabolism of clopidogrel to its active metabolite via induction of CYP1A2
Antipsychotic	Asenapine, clozapine, olanzapine	Decreased plasma level of antipsychotics due to increased metabolism via CYP1A2. Dosage modifications not routinely recommended but smokers may require higher doses for efficacy. Caution when patient stops smoking, as level of antipsychotic will increase (case report of serious clozapine toxicity following smoking cessation; serum increases of 72–261% reported); monitor clozapine levels and reduce antipsychotic dose as necessary
	Chlorpromazine, thioridazine	Decreased plasma level of chlorpromazine (by 24%) and thioridazine (by 46%) due to induction of metabolism via CYP1A2. Similar interaction with other phenothiazines possible. Caution when patient stops smoking as level of antipsychotic will increase; monitor antipsychotic levels and reduce dose as necessary
	Haloperidol	Decreased plasma level of haloperidol (by 70%) due to induction of CYP1A2
Benzodiazepine	Alprazolam	Alprazolam concentration reduced by 50%
	Chlordiazepoxide, diazepam	Increased clearance of benzodiazepines due to enzyme induction
β-blocker	Propranolol	Increased clearance of propranolol (by 77%) via side-chain oxidation and glucuronidation

Class of Drug	Example	Interaction Effects
Caffeine		Increased metabolism of caffeine due to increased metabolism via CYP1A2
Corticosteroid	Inhaled corticosteroids	Efficacy of corticosteroids for asthma reduced in smokers
Hormone	Oral contraceptives	Increased risk of serious cardiovascular effects in females over age 35 who smoke 15 or more cigarettes daily
Insulin		Faster onset of action and higher insulin levels in smokers
Theophylline		Decreased plasma level of theophylline due to increased metabolism via CYP1A2

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TREATMENT OF SUBSTANCE USE DISORDERS

Classification

- Drugs available for treatment of substance use disorders may be classified as follows:

Substance Use Disorder	Agent	Page
Alcohol use disorder	👍 Acamprosate	See p. 371
	👍 Disulfiram[B]	See p. 373
	👍 Naltrexone	See p. 376
Opioid use disorder	👍 Buprenorphine	See p. 380
	👍 Buprenorphine/Naloxone	See p. 380
	👍 Methadone	See p. 384
	👍 Naltrexone	See p. 376
Tobacco use disorder	👍 Bupropion	See p. 67
	👍 Nicotine replacement therapies (nicotine patches, gum, lozenges, inhalers)	See p. 390
	👍 Varenicline	See p. 390
Opioid and nicotine withdrawal	Clonidine	See p. 46

👍 Approved for this indication in adults; not approved for children or adolescents, [B] Not marketed in Canada

General Comments

- No medication has been approved for withdrawal management, but benzodiazepine taper is considered standard in the treatment of alcohol withdrawal, and clonidine is well established as medication to treat opioid and tobacco withdrawal. Methadone and buprenorphine are also used to reduce withdrawal symptoms during opioid taper
- In patients with concurrent disorders (also known as dual diagnoses; co-occurrence of a psychiatric disorder and a substance use disorder), integrated treatment is considered the gold standard, regardless of the status of the concurrent condition
- Given the lack of empirical evidence based on randomized clinical trials, treatment of concurrent conditions is often guided by clinical consensus and evidence established for individuals without concurrent disorders
- For psychological intervention, meta-analyses show most evidence for ecologically based family therapy, and individual or group cognitive behavioral therapy (CBT) in adolescents with substance use disorder

Acamprosate

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Acamprosate calcium	Calcium acetyl-homotaurine	Glutamate/Unclear	Campral	Delayed-release enteric-coated tablets: 333 mg (equiv. to 300 mg acamprosate)	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications

In adults:

👍 Alcohol use disorder: Maintenance of abstinence; reduces alcohol cravings and prevents relapse

General Comments

- Acamprosate treatment should be part of a comprehensive alcohol management program that includes psychosocial support
- Initiate treatment as soon as possible after alcohol withdrawal; treatment should be continued during relapses
- May not be effective in patients who are actively drinking at the start of treatment; it is not effective for acute withdrawal and does not treat delirium tremens
- Mostly beneficial in reducing the frequency of relapse during early remission by decreasing the pleasant sensation associated with alcohol consumption
- In a double-blind, placebo-controlled study of 26 adolescents (retracted in 2012 for copyright violation), alcohol abstinence occurred in 54% and 15% of acamprosate- (1332 mg/day) and placebo-treated patients, respectively, after three months; mean abstinence duration was 80 days (acamprosate) and 33 days (placebo)[1]
- Meta-analyses have shown that adult patients treated with acamprosate had significantly higher continuous abstinence rates than with placebo
- Mixed results seen in adults when combined with naltrexone as to increased efficacy and success of abstinence (see Drug Interactions p. 372); acamprosate appears more useful in maintaining abstinence as it reduces dysphoric effects that trigger some patients to resume drinking, while naltrexone controls alcohol consumption by reducing the pleasurable effects of alcohol
- Efficacy for promoting abstinence from alcohol has not been demonstrated in patients who abuse multiple substances

Pharmacology

- Chronic alcohol use is hypothesized to produce overexpression of N-Methyl-D-aspartate (NMDA) receptors and to stimulate the release of glutamate
- Acamprosate is an N-Methyl-D-aspartate (NMDA) receptor modulator, decreases activity at NMDA receptors
- Decreases dopamine hyperexcitability
- Restores glutamatergic tone and modulates neuronal hyperexcitability following withdrawal from alcohol, decreases activity of glutamate
- Weak inhibitor of presynaptic $GABA_B$ receptors in the nucleus accumbens, increases GABA-ergic system

Dosing

- Adolescents: 666 mg every morning, 333 mg at noon and at bedtime was used in a small trial (publication retracted for copyright reasons)[1]
- Adults over 60 kg: 666 mg tid; under 60 kg: 666 mg bid; to minimize GI effects, can initiate more gradually (i.e., 333 mg tid and increase dose by 1 tablet per week until target dose is reached); give 333 mg tid if CrCl is 30–50 mL/min; avoid in patients with CrCl below 30 mL/min
- Hepatic disorders: No dosage adjustment needed
- Can be safely used for 6–12 months

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Acamprosate (cont.)

Pharmacokinetics

- Bioavailability = 11%; food reduces bioavailability by 20%; not clinically significant
- T_{max} = 3–8 h once steady state is reached (in 5–7 days)
- Elimination half-life = 20–33 h
- Has low protein binding
- Is not metabolized by the liver (no CYP450 interactions) and is primarily excreted as unchanged drug by the kidneys

Adverse Effects

- Most common: Diarrhea (dose-related, decreases after first 4 weeks but may persist)
- Common: Nausea, flatulence, headache, insomnia, asthenia, and pruritus
- Depression, anxiety, and suicidal ideation reported
- Less common: Vomiting, dizziness, fluctuations in libido, dermatologic reactions, syncope, palpitations, edema (peripheral), weight gain, myalgia, diaphoresis; acute renal failure reported

Precautions

- Use of acamprosate does not diminish withdrawal symptoms
- Renal impairment
- Depression or suicidality

Contraindications

- Avoid in severe renal insufficiency (CrCl below 30 mL/min)

Toxicity

- Diarrhea reported after overdose of 56 g in an adult
- Provide supportive treatment

Use in Pregnancy◊

- Safety in pregnancy not established; first-trimester exposure may increase risk of fetal malformation; may be used after a careful benefit/risk assessment, when the patient cannot abstain from drinking alcohol without being treated with acamprosate and when there is consequently a risk of fetotoxicity or teratogenicity due to alcohol

Breast Milk

- Not known if excreted in breast milk; use not recommended

Nursing Implications

- Acamprosate treatment should be part of a comprehensive alcohol management program that includes psychosocial support
- Tablets are enteric-coated; they should not be broken or chewed but swallowed whole
- Monitor patients for symptoms of depression or suicidal thinking
- Diarrhea occurs commonly during therapy, is dose related and generally transient
- Adherence plays an important role in acamprosate efficacy

Patient Instructions

- For detailed patient instruction on acamprosate, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Opioid antagonist	Naltrexone	Increased concentrations of acamprosate; C_{max} increased by 33% and AUC by 25%; no change in concentration of naltrexone or its metabolite, 6-β-naltrexone; no dosage adjustment needed

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Disulfiram

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Disulfiram[B]	Carbamate derivative	Alcohol/Enzyme inhibitor	Antabuse	Tablets: 250 mg, 500 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. * Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada; may be available through specialty compounding pharmacies

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications

In adults:

- 👍 Alcohol use disorder: Deterrent
- Comorbid alcohol dependence and posttraumatic stress disorder: Has shown benefit in treatment

General Comments

- Anti-alcohol drugs are not generally recommended in children or adolescents since the motivation to abstain and to participate in alcohol use disorder treatment is often lacking; behavioral treatment approaches should be used
- Acts as an aversive agent or psychological deterrent; clinical efficacy is limited due to poor adherence (efficacy is dependent on adherence to treatment)
- Recommended in the maintenance phase of abstinence; using disulfiram to reduce drinking is not advised due to difficult adherence and toxicity when taken with alcohol
- A meta-analysis of adult RCTs found no difference between disulfiram and placebo – placebo effect may simply be from being aware of potential adverse reaction
- Supervised disulfiram use may have short-term efficacy; long-term effects on abstinence require evaluation
- Disulfiram treatment should be part of a comprehensive alcohol management program that includes psychosocial support (level 1 evidence[2])
- In an open-label, medication-controlled study of 58 adolescents, mean time to alcohol use relapse was 84 days for disulfiram (250 mg/day) and 51 days for naltrexone (50 mg/day); abstinence after 3 months was 79% (disulfiram) and 51% (naltrexone)[3]
- In a double-blind, placebo-controlled study of 26 adolescents, abstinence from alcohol occurred in 54% of disulfiram-treated patients (200 mg/day) vs. 15% with placebo; mean abstinence after a 3-month trial was 68 days (disulfiram) and 30 days (placebo). Diarrhea was seen disproportionately in the disulfiram group[4] [This study and the retracted acamprosate study (above) were written by the same authors, published in the same year, and have multiple passages of identical or similar language]
- A report of two adolescents suggests judicious use of disulfiram for serious alcohol use disorder following a thorough medical and psychiatric evaluation and careful assessment for comorbid diagnoses, along with family involvement, education, and signed informed consent. Both disulfiram-treated (250 mg/day) patients relapsed to alcohol and self-discontinued therapy

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Disulfiram (cont.)

Pharmacology

- Inhibits alcohol metabolism by irreversibly inhibiting acetaldehyde dehydrogenase; the accumulating acetaldehyde (toxic metabolite of alcohol) produces an unpleasant reaction consisting of headache, sweating, flushing, choking, nausea, vomiting, tachycardia, and hypotension; response is proportional to the dose and amount of alcohol ingested; can occur 5–10 min after alcohol ingestion and may last for several hours
- Increases brain dopamine concentrations by inhibiting dopamine catabolizing enzymes, dopamine-β-hydroxylase

Dosing

- 125–500 mg daily; 200–250 mg/day used in adolescent studies

Pharmacokinetics

- Highly lipid soluble; bioavailability 80%
- Onset of action: 3–12 h
- Duration of action: Up to 14 days, due to slow restoration rate of acetaldehyde dehydrogenase activity
- Metabolized through multiple steps to active metabolites via CYP1A2, 2B6, 2E1, 3A4/5, and FMO3 (flavin monooxygenase)
- Selectively inhibits CYP2E1 with both acute and chronic administration; with chronic use, other enzymes (e.g., CYP1A2, 3A4, and P-glycoprotein) may also be inhibited

Adverse Effects

- Not well described in adolescent studies, but well tolerated; may include neuritis, depression, insomnia, and diarrhea
- Common: Headache, drowsiness, fatigue, metallic or garlic-like taste
- Rare: Hepatitis, hepatic failure (after many months), hepatotoxicity, psychosis, seizures, neuropathy, optic neuritis, dermatitis, rash, erectile dysfunction
- Neurological toxicity can occur proportional to dose and duration of therapy (e.g., central and peripheral neuropathy, movement disorders)
- Transient elevated liver function tests reported in up to 30% of individuals; baseline liver function testing recommended and repeat periodically and at first symptoms or sign of liver dysfunction (e.g., anorexia, dark urine, fatigue, jaundice, malaise, nausea, vomiting, and weakness)

Precautions

- Do not give to intoxicated individuals, or without their full knowledge; educate family members (boxed warning)
- Do not give within 12 h of alcohol consumption
- If alcohol reaction occurs, general supportive measures should be used; in severe hypotension, vasopressor agents may be required
- Use cautiously in pulmonary disorders, liver disease, renal disorders, epilepsy, diabetes mellitus
- Patients should be advised not to drink alcohol for two weeks after stopping disulfiram, since reactions may still occur

Contraindications

- Coronary occlusion, myocardial disease, psychosis, hypersensitivity
- Use of alcohol-containing products
- Use of metronidazole or related anti-infective agents (e.g., secnidazole and tinidazole – USA)

Toxicity

- Alcohol reaction is proportional to dose of drug and alcohol ingested; severe reactions may result in respiratory depression, cardiovascular collapse, arrhythmias, convulsions, and death

Use in Pregnancy◊

- Safety in pregnancy not established; first-trimester exposure may increase risk of fetal malformations; considered contraindicated

Breast Milk

- Unknown if excreted in breast milk; use not recommended

Nursing Implications

- Patient should be made aware of purpose of medication and educated about the consequences of drinking; informed consent to treatment is recommended
- Patient should avoid all products (food and drugs) containing alcohol, including tonics, cough syrups, mouth washes, and alcohol-based sauces and vinegars; exposure to alcohol-containing rubs, colognes or organic solvents may also trigger a reaction
- Before using alcohol-containing products on the skin, test the product by applying some to a small area of the skin. If no redness, itching, headache, or nausea occur after 1–2 h, the product should be able to be safely used
- Daily uninterrupted therapy must be continued until patient has established a basis for self-control
- Encourage patient to carry an identification card stating that they are taking disulfiram
- Tablets may be crushed and mixed with liquids

Patient Instructions

- For detailed patient instructions on disulfiram, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Anticoagulant	Warfarin	Increased INR response due to reduced metabolism
Anticonvulsant	Phenytoin	Increased anticonvulsant blood levels and toxicity due to reduced metabolism
Antidepressant		
SSRI	Sertraline oral solution	Alcohol-like reaction reported (as formulation contains alcohol)
Cyclic	Amitriptyline, desipramine	Increased plasma level of antidepressant due to reduced metabolism; neurotoxicity reported with combination
Irreversible MAOI	Tranylcypromine	Report of delirium and psychosis with combination
Antimicrobial	Clarithromycin	Case of toxic epidermal necrolysis
	Metronidazole	Acute psychosis, ataxia, and confusion
Antitubercular drug	Isoniazid	Unsteady gait, incoordination, behavioral changes reported due to reduced metabolism of isoniazid by CYP2E1
Benzodiazepine	Alprazolam, chlordiazepoxide, diazepam, triazolam	Increased activity of benzodiazepine due to decreased clearance (oxazepam, temazepam, and lorazepam not affected)
Caffeine		Reduced clearance of caffeine (by 24–30%)
Cocaine		Increased plasma level (3- to 6-fold) and half-life (by 60%) of cocaine; increased risk of cardiovascular effects
Paraldehyde		Alcohol-like reaction can occur as paraldehyde is metabolized to acetaldehyde
Protease inhibitor	Amprenavir solution	Toxicity reported – formulation contains propylene glycol; metabolism inhibited via aldehyde dehydrogenase
	Ritonavir solution	Alcohol-like reaction reported (as formulation contains alcohol)
	Tipranavir	May enhance the adverse/toxic effect of tipranavir
Proton pump inhibitor	Omeprazole	Confusion and catatonia reported with combination

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Naltrexone

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[(A)]	Dosage Forms and Strengths	Monograph Statement
Naltrexone	Opioid antagonist	Opioid/Antagonist	ReVia Vivitrol[(B)]	Tablets: 25 mg[(B)], 50 mg, 100 mg[(B)] Extended-release injection: 380 mg	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [(A)] Generic preparations may be available, [(B)] Not marketed in Canada

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications
- Alcohol use disorder: Limited evidence of benefit
- Opioid use disorder: Conflicting and limited evidence
- Has been studied in children for aggression, hyperactivity, stereotypic and ritualistic behavior, and self-injurious behavior in patients with autism and/or intellectual disability (dose: 0.5–2 mg/kg/day); effects noted within first hour of administration (however, worsening of hyperactivity and stereotypies in children with autism also reported)
- Early data suggest a role in impulse-control disorders and obsessive-compulsive disorders, e.g., binge-eating and purging in patients with eating disorders, trichotillomania, pathological gambling, alcohol dependence
- Adolescent sexual offenders – open trial suggests benefit in treatment with doses of 100–200 mg/day

In adults:

- 👍 Alcohol use disorder: In patients who are able to abstain from alcohol in an outpatient setting prior to initial treatment
- 👍 Opioid use disorder: Treatment adjunct following withdrawal
- Methamphetamine use disorder: Extended-release injection alone or combined with bupropion has conflicting results from RCTs
- Bulimia nervosa: Inconsistent results
- Impulse-control disorders (e.g., trichotillomania, kleptomania, gambling, and compulsive sexual behaviors)
- Few controlled studies for impulsive symptoms in patients with borderline personality disorder (e.g., self-harming behaviors; heroin, amphetamine, and alcohol use)
- Used alone and combined with varenicline to decrease both alcohol use and smoking in heavy drinkers
- Depression: Inconsistent results when combined with antidepressants; benefit in fibromyalgia patient (case report)
- Chronic pain (e.g., fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome): Low-dose naltrexone may reduce symptom severity
- Obesity: Used alone and combined with bupropion
- Pruritus, inflammatory skin disease (e.g., Hailey-Hailey disease, Sjögren's syndrome)

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

General Comments

- Recommended to be used together with psychosocial interventions
- Patient adherence plays a significant role in the efficacy of naltrexone
- Meta-analyses have shown variable effects on abstinence: Have shown a moderate decrease in the number of heavy drinking days; may be more effective in patients with high levels of alcohol craving[2] and in males with a family history of alcoholism; double-blind study suggests that it may not have long-term benefits in men with chronic severe alcohol dependence
- In a randomized, double-blind, placebo-controlled study of 140 young adults 18–25, the use of naltrexone vs. placebo did not alter the primary outcome measure of percentage of heavy-drinking days (22% vs. 23%, respectively) or percentage of days abstinent (57% vs. 63%, respectively), but was associated with secondary drinking measure changes such as reducing the number of drinks per day (4.9 vs. 5.9, respectively), and percentage of drinking days (35% vs. 46%, respectively)[5]
- In 58 adolescents, mean relapse to alcohol use occurred at 84 days for disulfiram (250 mg/day) and at 51 days for naltrexone (50 mg/day); abstinence after three months was 79% (disulfiram) and 51% (naltrexone)[3]
- Naltrexone reduced drinking and craving compared to placebo in adolescents (age 15–19) in a small RCT group of 20 patients. Post-hoc analysis: Greater alcohol consumption was associated with greater negative affect during naltrexone treatment which in turn, greater negative affect was associated with reduced subsequent alcohol consumption[6]
- Mixed results in adults in combination with acamprosate when used for alcohol use disorder (see Drug Interactions p. 379)
- Injectable (but not oral) naltrexone associated with retention in opioid use disorder; thus, injectable may be a more effective formulation
- Does not attenuate craving for opioids or suppress withdrawal symptoms; patients must undergo detoxification before starting naltrexone to avoid withdrawal
- Extended-release injection had no significant benefit compared to buprenorphine or no medication in youth (age 15–21) with moderate or severe opioid use disorder in a RCT; high non-adherence to assigned treatment[7]
- Does not produce euphoria

Pharmacology

- A competitive antagonist which has highest affinity for the μ-opioid receptor, some affinity for the κ-opioid receptor, and weak affinity for the δ-opioid receptor
- Blocks the "craving" mechanism in the brain, producing less of a high from alcohol; stops the reinforcing effect of alcohol by blocking the opioid system – promotes abstinence and reduces risk for relapse
- Also has partial agonist activities at all of these receptors
- Blocks the effects of opioid agonists

Dosing

Oral

- Alcohol use disorder: 25 mg once daily for 2 days, then 50 mg once daily (adolescents); 50 mg once daily (adults)
- Antisocial behavior/aggression/self-harming behaviors in children and adolescents: 0.5–2 mg/kg/day; begin at 25 mg/day and increase to 50 mg/day over several days to minimize side effects; dosage requirements in impulse-control disorders may be higher (up to 200 mg/day)
- Opioid use disorder: Patient must undergo detoxification prior to starting naltrexone and be opioid-free for 7–10 days to avoid precipitated withdrawal. Initiate dose at 12.5–25 mg/day and monitor for withdrawal signs; increase dose gradually based on response. For supervised administration, maintenance doses of 100 mg every other day or 150 mg every third day have been used in adults

Injection

- Anaphylaxis reported with naltrexone; it may be prudent to administer an oral naltrexone test dose prior to long-acting injectable, though manufacturer's prescribing information does not reflect this approach
- The extended-release injection is formulated as microspheres and 380 mg is administered by IM injection into the gluteal muscle every 4 weeks; was well tolerated in 16 adolescents and young adults (aged 16–20) with opioid dependence[8]
- Opioid use disorder: Patient must undergo detoxification prior to starting naltrexone and be opioid free for 7–10 days to avoid precipitated withdrawal

Naltrexone (cont.)

Pharmacokinetics

Oral

- Rapidly and completely absorbed from the GI tract
- Undergoes extensive first-pass metabolism; ~ 20% of drug reaches the systemic circulation
- Widely distributed; 21–28% is protein bound
- Onset of effect occurs in 15–30 min in chronic morphine users
- Duration of effect is dose dependent; blockade of opioid receptors lasts 24–72 h
- Metabolized in liver (not via CYP450); major metabolite (6-β-naltrexone) is active as an opioid antagonist
- Elimination half-life is 4 h for parent drug and 13 h for metabolite following oral administration; excreted primarily by the kidneys
- Naltrexone AUC increased 5–10-fold in patients with liver cirrhosis; contraindicated in patients with acute hepatitis or hepatic failure

Injection

- First peak occurs 2 h post injection; second peak occurs 2–3 days later; onset of effect seen within 48 h
- Elimination half-life is 5–10 days and dependent on the erosion of the polymer; plasma concentrations are sustained for at least 30 days
- Beginning 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month; however, some adolescents were able to overcome the blockade of opioid receptors in the last few days of the 30-day period in a case series[6]

Adverse Effects

- Common with oral naltrexone: Nausea and vomiting (~ 10% – more common in females), dysphoria
- Common with extended-release injection: Nausea, headache, fatigue, pain; injection site tenderness, swelling, bruising, pruritus or indurations; cellulitis, hematoma, abscess, and necrosis have been reported
- CNS effects: Insomnia, anxiety, depression, confusion, nervousness, fatigue; case reports of naltrexone-induced panic attacks
- Physical effects: Headache (6.6%), joint and muscle pain or stiffness; abdominal pain, cramps, anorexia, and weight loss; females are more sensitive to GI side effects (may be reduced with slower dose titration)
- Dose-related elevated enzymes and hepatocellular injury reported; increased ALT and AST associated with higher doses of naltrexone, obesity, and concurrent use of NSAIDs; liver function tests recommended at start of treatment and as clinically indicated
- Eosinophilic pneumonia, depression, and suicidality (rare)

Discontinuation Syndrome

- No data available

Precautions

- Do not give to patients who have used opioids in the previous 7–10 days or 14 days for patients who are transitioning from long-acting opioids (e.g., methadone, buprenorphine) – may result in symptoms of opioid withdrawal; consider naloxone challenge if opioid dependence suspected, despite negative history or urine drug screen negative for opioids
- Do not use in patients with liver disorders; baseline liver function tests recommended; repeat monthly for 6 months
- Attempts to overcome opioid receptor blockade of naltrexone with high doses of opioid agonists (e.g., morphine) may lead to respiratory depression and death
- Patients need to report injection site swelling, tenderness, induration, bruising, pruritus, or redness that worsens or doesn't improve over 2 weeks
- FDA has received many reports of injection site reactions such as cellulitis, induration, hematoma, abscess, and necrosis
- Patients previously treated with naltrexone may respond to lower opioid doses (than previously used) at end of dosing interval or after naltrexone is discontinued. This could potentially lead to accidental overdose
- Patients undergoing scheduled surgery should stop oral naltrexone at least 72 h before the surgery and IM naltrexone for at least 30 days before surgery, if opioid pain management is anticipated

Contraindications

- Patients receiving opioids or those in acute opioid withdrawal
- Acute hepatitis or liver failure; dose-related hepatocellular injury has been reported

Toxicity

- No experience in humans; 800 mg dose for 1 week showed no evidence of toxicity
- Risk for serious injection site reaction increased if injected subcutaneously or into fatty tissue rather than muscle

Lab Tests/Monitoring

- Baseline liver function tests recommended
- Repeat liver function tests monthly for 6 months
- May cause false positives with opioid immunoassays
- Screen for depression and/or suicidal ideation

Use in Pregnancy◊

- No adequate and well-controlled studies in pregnant women; may be used after a careful benefit/risk assessment, when the patient cannot abstain from drinking alcohol without being treated with naltrexone and when there is consequently a risk of fetotoxicity or teratogenicity due to alcohol

Breast Milk

- Naltrexone and its primary metabolite 6-β-naltrexone are excreted into breast milk in very low concentrations; due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother

Nursing Implications

- Naltrexone should be used in conjunction with established psychotherapy or self-help programs
- As naltrexone does not attenuate craving for opioids or suppress withdrawal symptoms, adherence problems may occur; individuals must undergo detoxification prior to starting drug. Advise patients receiving extended-release injections of naltrexone that administration of large doses of opioids may lead to serious adverse effects, coma, or death
- Advise patients to report shortness of breath, coughing, wheezing or significant redness and discomfort at the injection site to their physician
- Extended-release injection must be diluted only with the supplied diluent and administered with needle provided in kit. Store kit in the refrigerator; can be kept at room temperature for no more than 7 days. Once diluted, the injection should be administered IM right away (alternating buttocks); pain on injection possible; monitor patients for rash or indurations at injection site. Injection should alternate between the two buttocks
- Should a patient miss a scheduled appointment for receiving injectable naltrexone, the next dose of injection can be given as soon as possible
- Encourage patient to carry an identification card stating that they are taking naltrexone

Patient Instructions

- For detailed patient instructions on naltrexone, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Acamprosate		Increased concentrations of acamprosate; C_{max} increased by 33% and AUC by 25%
Indole alkaloid	Yohimbine	Increased anxiety possibly due to enhanced noradrenergic sensitivity
Opioid	Codeine, morphine, etc.	Decreased efficacy of opioid, may result in withdrawal
Sulfonylurea	Glyburide	Co-administration resulted in 2-fold increase in AUC and C_{max} of naltrexone following oral administration

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Buprenorphine

Product Availability*

Generic Name	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Buprenorphine	Opioid/Partial agonist	Belbuca[B],[D]	Buccal film: 75 micrograms, 150 micrograms, 300 micrograms, 450 micrograms, 600 micrograms, 750 micrograms, 900 micrograms	Safety and efficacy not established in children and adolescents under age 18
		Buprenex[B],[D]	Injection: 0.3 mg/mL	Safety and efficacy not established in children under age 2
		Butrans[D]	Transdermal patch: 5 micrograms/h, 7.5 micrograms/h[B], 10 micrograms/h, 15 micrograms/h, 20 micrograms/h	Safety and efficacy not established in children and adolescents under age 18
		Probuphine[C]	Subdermal implant: 80 mg	Safety and efficacy not established in children and adolescents under age 18
		Sublocade	Long-acting injection: 100 mg/0.5 mL, 300 mg/1.5 mL	Safety and efficacy not established in children and adolescents under age 18
		Subutex[B]	Sublingual tablet: 2 mg, 8 mg	Safety and efficacy not established in children and adolescents under age 16
Buprenorphine/Naloxone	Opioid/Partial agonist Opioid/Antagonist	Suboxone	Sublingual tablets: 2 mg/0.5 mg, 8 mg/2 mg, 12 mg/3 mg[C], 16 mg/4 mg[C] Buccal, sublingual film: 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg	Safety and efficacy not established in children and adolescents under age 16
		Zubsolv[B]	Sublingual tablets: 0.7 mg/0.18 mg, 1.4 mg/0.36 mg, 2.9 mg/0.71 mg, 5.7 mg/1.4 mg, 8.6 mg/2.1 mg, 11.4 mg/2.9 mg	Safety and efficacy not established in children and adolescents under age 16

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in USA, [D] Pain indication

Indications‡ (👍 approved)

In children and adolescents:
- Opioid use disorder and opioid withdrawal

In adults:
- 👍 Opioid use disorder: Used alone or together with naloxone
- 👍 Moderate to severe pain (acute and chronic)
- Opioid withdrawal
- Methamphetamine use disorder: Small studies showed greater reduction in withdrawal cravings compared to bupropion and methadone groups

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

General Comments

- The American Academy of Pediatrics recommends pediatricians consider offering medication-assisted treatment to adolescents and young adults with severe opioid use disorders or discuss referrals to other providers for this service
- Buprenorphine has significantly more data available in treatment of adolescents and young adults with opioid use disorder than methadone
- A study determined that buprenorphine and behavioral interventions were more effective in treating opioid-dependent adolescents than clonidine and behavioral interventions[10]
- Suboxone contains buprenorphine and naloxone in a 4:1 formulation – inclusion of naloxone is intended to deter IV abuse by attenuating the effect of buprenorphine and producing withdrawal symptoms if crushed or injected IV by those physically dependent on opioids. However, there are nonevidence based online sites that provide specific instructions for dissolving different preparations of buprenorphine/naloxone and injecting them intravenously without precipitating withdrawal symptoms, thus the addition of naloxone may be futile
- Suboxone film may be administered sublingually (for both induction and maintenance therapy) or buccally (for maintenance therapy); Suboxone sublingual tablet can only be administered sublingually
- Reduces use and craving for opioids; should be combined with concurrent behavior therapies and psychosocial programs
- Considered as effective as moderate doses of methadone; methadone is considered the treatment of choice in patients with higher levels of physical dependence
- Improvement noted in psychosocial adjustment and social functioning
- Causes fewer withdrawal symptoms than methadone due to partial agonist activity and "ceiling effect"
- Certain formulations of buprenorphine (i.e., patch, buccal film) are not approved for the treatment of opioid use disorder
- Transdermal patch and buccal film have a warning regarding QTc prolongation in higher doses

Pharmacology

- Buprenorphine is a partial μ-opioid receptor agonist and κ-opioid receptor antagonist (naloxone is an opioid antagonist)
- Opioid agonist effects increase linearly with increasing doses of buprenorphine, to a plateau or "ceiling effect"; less risk of fatal overdose
- When buprenorphine is taken by those physically dependent on high doses of opioids, buprenorphine may precipitate opioid withdrawal symptoms, due to its partial opioid activity. However, if taken while in opioid withdrawal, buprenorphine's partial agonist effects will be experienced as relief from withdrawal
- If switching to buprenorphine from methadone maintenance, it is recommended that the methadone dose be tapered down to 30 mg or less prior to starting buprenorphine, to minimize withdrawal symptoms[2]

Dosing

- Induction, stabilization, and maintenance dosing of buprenorphine in adolescents and youth is similar to that in adults
- 4–24 mg (buprenorphine) sublingually given once daily; due to long elimination half-life, some patients can be dosed every 2 days or 3 times per week
- Ceiling effect is usually reached at doses of 16–20 mg
- Phases of treatment:
  - Induction phase: Individual needs to abstain from opioids for 12–24 h (depending on the duration of action of the opioid used), to be exhibiting at least mild to moderate withdrawal symptoms prior to first dose to prevent precipitated withdrawal: 2–4 mg buprenorphine can be administered sublingually initially, with another dose later in the day if needed on day 1, and then dose titrated based on effect
  - Stabilization phase: Buprenorphine can be adjusted in increments/decrements of 2–4 mg to a dose that suppresses both cravings and withdrawal effects (4–24 mg/day)
  - Maintenance phase: Patient is on a stable dose of buprenorphine (or combination) and is doing well; the patient may require indefinite maintenance therapy
- Long-acting injection: Not studied in children or adolescents; dosing, safety, and efficacy unknown
- Renal impairment: No dosing adjustments required
- Hepatic impairment: No dosing adjustments required for mild–moderate impairment; for severe impairment, use with caution – reduce initial dose and titration increments; monitor for adverse effects and toxicity

Pharmacokinetics

- Sublingual buprenorphine provides moderate bioavailability while sublingual naloxone bioavailability is poor; therefore, buprenorphine's opioid agonist effects predominate. When the sublingual tablets are crushed and injected, the naloxone effect dominates and can precipitate opioid withdrawal symptoms

Buprenorphine (cont.)

- Suboxone film and sublingual tablets are not bioequivalent at all doses and routes of administration
- Peak effects seen in 3–4 h after dosing; C_{max} and AUC increase in a linear fashion with dose increases
- Buprenorphine is highly bound to plasma proteins (96%) – primarily to α and β globulin
- Metabolized by CYP3A4 to active metabolite, norbuprenorphine, and other inactive glucuronidated metabolites
- Inhibitor (weak) of CYP3A4
- Elimination half-life: Buprenorphine (oral) 24–60 h (37 h mean), buprenorphine (long-acting injection) 4–6 months; naloxone 1–2 h (mean)

Adverse Effects

- Most common in first 2–3 days of therapy and are dose related
- After the first dose, patient may experience some withdrawal symptoms, see pharmacology section p. 381
- Common: Headache, dizziness, insomnia, somnolence, anxiety, nausea, vomiting, abdominal pain, constipation, sweating, CNS depression, orthostatic hypotension, and various pains
- Increase in liver enzymes; cases of hepatitis, acute hepatic injury reported in the context of misuse, particularly IV use; monitor liver function tests periodically
- Lower risk of respiratory depression and overdose than with methadone due to ceiling effect
- Dental problems with sublingual tablets and buccal/sublingual film: Tooth decay, cavities, oral infections, and loss of teeth; reported even in patients with no history of dental issues
- QTc prolongation: Buccal film – do not exceed 900 mg every 12 h; transdermal patch – do not exceed 20 micrograms/h
- Long-acting injection: Pain, pruritus, erythema, induration, bruising, swelling, cellulitis

D/C Discontinuation Syndrome

- Withdrawal syndrome reported in patients on chronic therapy and with naloxone combination
- Causes milder withdrawal than full opioid agonist (i.e., methadone); onset may be delayed
- Symptoms include: Nausea/vomiting, diarrhea, muscle aches/cramps, sweating, lacrimation, rhinorrhea, dilated pupils, yawning, craving, mild fever, dysphoric mood, insomnia, and irritability

Precautions

- Buprenorphine can precipitate withdrawal in opioid-dependent individuals (see pharmacology section p. 381)
- Chronic administration produces opioid-type dependence, characterized by withdrawal upon abrupt discontinuation or rapid taper
- Buprenorphine can be abused; if sublingual combination tablets are crushed and injected by opioid-dependent individual, naloxone may exert effects and precipitate a withdrawal syndrome
- Use with caution in patients with compromised respiratory function, liver disease, opioid naïve, severe hepatic impairment, acute alcoholism, and delirium tremens
- Buprenorphine detoxification can occur faster than methadone detoxification; decrease dose by 2–4 mg every 2 weeks

Toxicity

- High doses can cause respiratory depression, which may be delayed in onset and more prolonged than with other opioids; reversal with naloxone is more difficult due to buprenorphine's high binding affinity to opioid receptors
- Safer in overdose than pure agonists due to poor bioavailability and ceiling effect
- Symptoms include: Pinpoint pupils, sedation, and hypotension; respiratory depression and deaths have been reported, particularly when buprenorphine was misused IV or in combination with alcohol or other opioids
- Treatment: Symptomatic
  - Monitor for respiratory depression
  - Naloxone (0.4–0.8 mg) may not always be effective in reversing respiratory depression

Use in Pregnancy◊

- Teratogenic effects reported in animal studies; A recent systematic review of over 30 studies has documented that buprenorphine is as efficacious and as safe as methadone during pregnancy; buprenorphine has not been associated with any teratogenic effects

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

- Enhanced clearance of buprenorphine has been demonstrated in pregnancy and doses may need to be adjusted; consider using divided doses[11]; fetal monitoring is recommended
- Neonatal abstinence syndrome may occur with onset generally within a day or two after birth, lasts a mean of 4 days; symptoms include hypertonia, tremor, agitation, myoclonus, and rarely apnea, bradycardia, and convulsions
- Combination of buprenorphine/naloxone is not recommended

Breast Milk

- Buprenorphine passes into breast milk; buprenorphine and its main metabolite, norbuprenorphine, were measured at low concentrations in breast milk; use in breastfeeding is recommended in stable patients[11]

Nursing Implications

- Buprenorphine is an opioid and is a controlled substance
- Buprenorphine should be used in conjunction with behavior/psychosocial therapies
- Sublingual tablets should not be handled, but tipped directly into the mouth from a medicine cup; they should be placed (all together) under the tongue, and do not swallow saliva until fully dissolved (takes 2–10 min); drinking fluids prior to taking the tablets may speed up the dissolution process; chewing or swallowing them reduces the bioavailability of the drug
- Buccal, sublingual film: For induction, it should only be administered sublingually. Once induction is complete, patients can be switched to sublingual or buccal administration without significant risk of over- or underdosing. For sublingual administration, place one film under the tongue, close to the base on the left or right side, and allow to completely dissolve. For buccal administration, place one film on the inside of the left or right cheek and allow to completely dissolve
- For buccal administration, moisten the inside of cheek with tongue or water, apply film with a dry finger immediately after removing from packaging. Place the yellow side of the film against the inside of cheek; press and hold the film for 5 sec with finger (until it stays in place); keep film in place until it dissolves completely (takes 30 min). Avoid eating or drinking until film dissolves
- After the sublingual tablet or buccal/sublingual film is completely dissolved, the patient should take a large sip of water, swish it gently around their teeth and gums, and swallow. The patient should wait at least 1 h before brushing their teeth to avoid damage to teeth
- Switching between sublingual film and sublingual tablet, or switching the location of where the film is placed inside the mouth, may affect how much medicine is absorbed into the body; patients should not switch between the tablet and the film unless directed by their doctor. Due to the greater bioavailability of the film compared to the tablet at certain strengths, patients switching from tablet to film should be monitored for symptoms of overdose. Those switching from film to tablet should be monitored for symptoms of underdosing, including opioid withdrawal
- Educate patient about not increasing his/her dose without physician approval; misuse/abuse may result in toxicity
- Serious CNS consequences may occur if buprenorphine is combined with benzodiazepines, hypnotics, or alcohol
- Long-acting injection: Refrigerate product in original packaging; may be stored at room temperature for up to 7 days; product to be prepared and administered by healthcare providers only; see prescribing information for complete administration details

Patient Instructions

- For detailed patient instructions on buprenorphine, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Potentially clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Antibacterial	Rifampin	Decreased level of buprenorphine possible due to increased metabolism via CYP3A4
Antibiotic	Clarithromycin, erythromycin	Increased levels of buprenorphine possible due to inhibited metabolism via CYP3A4 May enhance QTc prolongation
Anticonvulsant	Carbamazepine, phenobarbital, phenytoin	Decreased levels of buprenorphine possible due to increased metabolism via CYP3A4
Antidepressant		
SSRI	Citalopram	May enhance QTc prolongation
Reversible MAOI	Moclobemide	May enhance adverse or toxic effects of MAOIs

Buprenorphine (cont.)

Class of Drug	Example	Interaction Effects
Antifungal	Ketoconazole, voriconazole	Increased C_{max} and AUC of buprenorphine reported due to inhibited metabolism via CYP3A4
Antipsychotic	Quetiapine, ziprasidone	May enhance QTc prolongation
Anxiolytic	Benzodiazepine	Respiratory depression, coma, and death reported when IV or high doses of buprenorphine used in combination
CNS depressant	Alcohol, hypnotics/sedatives	CNS depression; deaths have been reported in combination
Opioid	Fentanyl, meperidine, morphine	Low doses of buprenorphine antagonize analgesic effects High doses are synergistic; increase risk of CNS and respiratory depression
	Methadone	Can precipitate withdrawal, may enhance QTc prolongation
Protease inhibitor	Atazanavir	Increased level of buprenorphine and decreased level of atazanavir
	Indinavir, ritonavir, saquinavir	Increased level of buprenorphine possible due to inhibited metabolism via CYP3A4

Methadone

Product Availability*

Generic Name	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Methadone	Opioid/Agonist		Oral solution: 5 mg/5 mL, 10 mg/5 mL Injection[B],[D]: 10 mg/mL	Government regulations govern the use of methadone in children and adolescents Safety and efficacy not established in children and adolescents under age 18
		Diskets[B]	Dispersible tablets: 40 mg	Safety and efficacy not established in children and adolescents under age 18
		Intensol[B]	Oral concentrate: 10 mg/mL	Safety and efficacy not established in children and adolescents under age 18
		Methadose	Oral concentrate (red, cherry-flavored): 10 mg/mL Oral concentrate (dye-free, sugar-free, unflavored): 10 mg/mL Dispersible tablets[B]: 40 mg	Safety and efficacy not established in children and adolescents under age 18
		Metadol[C],[D]	Tablets: 1 mg, 5 mg, 10 mg, 25 mg Oral solution: 1 mg/mL Oral concentrate: 10 mg/mL	Safety and efficacy not established in children and adolescents under age 18
		Metadol-D[C]	Oral solution: 1 mg/mL Oral concentrate: 10 mg/mL	Safety and efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Indicated for pain only

Indications‡ (👍 approved)

In children and adolescents:

- No approved indications
- Has been used for postoperative pain in children at doses of 0.1–0.2 mg/kg (max. 10 mg/dose) every 6 h as needed; longer duration of action than with morphine. Drug must be tapered (by 5–10% every 1–2 days) if used for longer than 5–7 days; the patient must be continually assessed for withdrawal symptoms
- Refractory cancer pain: Limited evidence for nociceptive and neuropathic pain

In adults:

- 👍 Detoxification and maintenance treatment in opioid use disorder
- 👍 Treatment of severe pain (chronic); acute pain indicated for injection only
- Cancer pain

General Comments

- The American Academy of Pediatrics recommends pediatricians consider offering medication-assisted treatment to adolescents and young adults with severe opioid use disorder or discuss referrals to other providers for this service[9]
- Buprenorphine has significantly more data available in treatment of adolescents and young adults with opioid use disorder than methadone
- Methadone for the treatment of opioid use disorder in adolescents has not been evaluated in a controlled trial; descriptive and observational studies found methadone supports treatment retention; an observational study has shown higher retention rate with methadone compared to buprenorphine/naloxone in adolescents who use heroin
- Useful in opioid-dependent patients who desire maintenance opioid therapy:
  - Effective orally and can be administered once daily, due to long elimination half-life
  - Suppresses withdrawal symptoms of other opioids
  - Suppresses chronic craving for opioids
  - When taken orally at appropriate doses, reduces euphoria due to slow onset
- Patients receiving methadone remain in treatment longer, demonstrate a decreased use of illicit opioids, and maintain social stability
- Methadone is an opioid and its prescribing, dispensing, and usage is governed by Federal regulations (regulations vary in different countries); when used for opioid dependence, it is dispensed as a tablet or liquid, and some formulations can be mixed with orange drink/juice to deter injection; most patients are administered methadone on a daily basis, from the pharmacy or specialized opioid treatment program; some stable patients are permitted to carry premeasured individual doses of methadone, up to several days' supply
- Signed informed consent should be obtained from a parent or legal guardian prior to use for substance-related disorders in children or adolescents
- Effects of prolonged methadone use on physiologic and psychological development of children is not known

Pharmacology

- A synthetic, full opioid agonist acting on the μ-opioid receptor
- Analgesic and sedative properties are similar to other opioids

Dosing

- Initial dose: 20–30 mg/day (lower if risk factors for toxicity); observe for oversedation and withdrawal symptoms for 2–4 h; may give additional 5–10 mg if withdrawal symptoms are not suppressed or reappear, not to exceed a total dose of 40 mg on the first day
- Increase by 5–10 mg every 5 or more days until an effective stabilization dose is reached (no withdrawal symptoms for at least 24 h, craving is reduced or eliminated, and no oversedation); usual dose 60–120 mg/day
  - More rapid dose titrations should only be attempted under close supervision of an experienced provider and/or close monitoring
  - Slower dose titration recommended for individuals at higher risk of toxicity (e.g., recent loss of tolerance, severe respiratory illness, liver dysfunction, and use of alcohol, benzodiazepines, sedatives, or CYP-interacting medications)
- Patients vary in dosage requirements; there is an up to 17-fold interindividual variation of methadone blood concentration for a given dosage, largely due to interindividual variability of CYP enzymes; dosage is adjusted to control abstinence symptoms without causing marked sedation or respiratory depression
- In rare cases, patients who are rapid metabolizers of methadone may require a divided (split) dose rather than one single daily dose; this situation should be carefully evaluated and monitored for toxicity and respiratory depression
- When tapering off methadone, decrease the dose by less than 10% every 10–14 days

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

Methadone (cont.)

Pharmacokinetics

- Onset of action: 0.5–1 h
- Bioavailability: mean 75% (range 36–100%); similar between tablet, liquid, and disket formulation
- Peak plasma level: 2.5–4 h; similar between tablet, liquid, and disket formulation
- 86–90% protein bound
- Elimination half-life: mean 22 h (range: 5–130 h) and increases with repeated dosing; longer than duration of action for pain treatment (4–8 h)
- Metabolized by the liver, primarily via CYP2B6 and 3A4, with minor elimination via CYP2D6, 2C9, and 2C19; weakly inhibits CYP2D6 – see Drug Interactions pp. 388–389
- Inhibits P-glycoprotein
- Urine testing should be done to monitor for illicit drug use and/or adherence with methadone

Adverse Effects

CNS Effects

- Drowsiness, insomnia, headache, euphoria, dysphoria, confusion, cognitive impairment, depression, seizure, and weakness; tolerance develops to sedating and analgesic effects
- With chronic use: Sleep disturbances, impairment in psychomotor and cognitive performance tests

Cardiovascular Effects

- Dizziness, lightheadedness, hypotension, cardiac failure, cardiomyopathy, edema, flushing, and various arrhythmias
- Cases of QTc prolongation and torsades de pointes – increased risk with higher doses (> 150 mg/day), drug accumulation, in patients with pre-existing heart disease, in combination with drugs that increase the QTc interval or with drugs that decrease the metabolism of methadone (see Drug Interactions pp. 388–389) [baseline ECG recommended; repeat periodically and if dose increased > 150 mg/day]

GI Effects

- Nausea, vomiting, constipation, xerostomia, and decreased appetite

Urogenital & Sexual Effects

- Decreased libido, erectile dysfunction, and ejaculatory problems

Dermatological Effects

- Diaphoresis, hemorrhagic urticaria, localized erythema, pruritus, rash, and urticaria

Other Adverse Effects

- With chronic use: Menstrual irregularities, gynecomastia, pain in joints and bones, and electrolyte abnormality
- Rarely, pulmonary edema and respiratory depression

D/C Discontinuation Syndrome

- Tapering off methadone should be individualized and duration of taper ranges from weeks to months in chronic users[12]
- Rapid withdrawal can result in opioid withdrawal syndrome, which includes:
  - CNS effects: restlessness, agitation, insomnia, headache
  - Autonomic effects: increased blood pressure, heart rate, body temperature and respiration, lacrimation, perspiration, congestion, itching, "goose-flesh"
  - Neurological effects: muscle twitching, cramps, tremors
  - GI effects: nausea, vomiting, diarrhea, anorexia
- Symptoms may begin 24–48 h after the last dose, peak in 72 h, and may last for 6–7 weeks
- If no dosing changes occurred, consider drug–drug interaction as a potential cause of withdrawal symptoms

Management

- Reinstitute previous dose (if stopped for more than 3 days, titrate back up slowly); restabilize patient and monitor while tapering dose at a slower rate
- Clonidine may ameliorate withdrawal symptoms

Precautions

- Methadone has a high physical and psychological dependence liability, therefore withdrawal symptoms will occur on abrupt discontinuation – decrease the dose slowly
- Prior to prescribing methadone, a baseline ECG should be done; repeat within 30 days of treatment and annually, or more frequently if dose > 150 mg/day, or unexplained syncope or seizures occur; consider discontinuing or reducing dose if QTc interval is > 500 msec; avoid methadone in patients with a history of structural heart disease, arrhythmia, or syncope
- Respiratory depression, arrest, and death can occur; respiratory effects generally occur later and persist longer than peak analgesic effects; due to long elimination half-life, methadone can accumulate to dangerous levels if increased too quickly, especially when combined with CYP (3A4, 2B6, 2C19, 2C9, 2D6) inhibitors, alcohol, benzodiazepines, or other sedatives
- Use with caution in patients with obesity, head injury, increased intracranial pressure, cardiovascular, pulmonary, renal or hepatic disease, or taking medications that reduce ventilator drive or increase risk of dysrhythmia
- Somnolence may preclude driving or operating equipment
- Tolerance to methadone is lost rapidly; if a regular dose is administered after a period of missed doses, there is a risk of overdose and possibly death; methadone should be re-started at a lower dose

Contraindications

- Severe respiratory compromise or obstructive disease, severe respiratory distress, acute alcohol intoxication, and delirium tremens
- Taking monoamine oxidase inhibitors (MAOIs) or use within past 14 days

Toxicity

- With excessive doses, can get shallow breathing, pinpoint pupils, flaccidity of skeletal muscles, low blood pressure, slowed heart rate, QTc prolongation, cold and clammy skin; can progress to cyanosis, coma, severe respiratory depression, circulatory collapse, and cardiac arrest
- Symptoms can begin up to 10 h after overdose and can last up to 24 h
- Methadone can accumulate slowly (due to long half-life) and cause delayed toxicity; high starting doses of methadone, rapid dose increases during titration, low tolerance, and drug interactions may contribute to toxicity during first two weeks of treatment; deaths have occurred in early treatment

Use in Pregnancy◊

- Methadone treatment throughout pregnancy reduces risk of perinatal and infant mortality in heroin-dependent women; use in pregnancy is recommended in stable patients[11]
- Pregnancy causes induction of CYP enzymes (3A4, 2B6, 2D6) and results in reduced methadone levels (~ 50% reduced elimination half-life in third trimester); twice-daily dosing of methadone is suggested in this context; higher (single) doses are associated with abnormal fetal physiology, fetal movement, and cardiac rhythms.[13] Dosing needs should be assessed during pregnancy – decreased between weeks 14 and 32, increased prior to term, reduced following birth, and reassessed regularly
- Short-term withdrawal effects reported in approximately 60% of infants (not dose related); no long-term effects demonstrated

Breast Milk

- A small amount of methadone enters breast milk; nurse prior to a dose of methadone or 2–6 h after dose; breastfeeding reduces neonatal abstinence syndrome

Nursing Implications

- Methadone must be prescribed in sufficient doses, on a maintenance basis, to prevent relapse; long-term treatment may be required; premature withdrawal may lead to relapse
- Methadone is an opioid and must be prescribed according to Federal regulations; it is usually dispensed as a tablet or liquid, and some formulations are mixed in water, orange drink/juice, or other acidic beverage prior to administration
- Each time the patient is to receive a dose of methadone, they should be assessed for impairment (i.e., drowsiness, slurred speech, forgetfulness, lack of concentration, disorientation, and ataxia); patients should not receive the dose if they appear impaired or smell of alcohol – the physician should be contacted as to management of the patient
- Encourage patients to carry a card in their wallet stating that they are taking methadone
- If a patient misses one or more appointments to receive their dose of methadone, this may indicate clinical instability and possible relapse (see precautions); use caution due to possible loss of tolerance to drug
- Contact the prescriber if more than two methadone doses have been missed or the patient has ingested other substances

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

Methadone (cont.)

Patient Instructions

- For detailed patient instructions on methadone, see the Patient and Caregiver Information Sheet (details p. 429)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

Class of Drug	Example	Interaction Effects
Alcohol		Acute alcohol use can decrease methadone metabolism and increase the plasma level – may result in intoxication and respiratory depression Chronic alcohol use can decrease methadone plasma level via CYP3A4 induction May enhance CNS depressant effect
Antacid	Al/Mg antacids	Decreased absorption of methadone
Antiarrhythmic	Amiodarone, quinidine	Possible risk of additive QTc prolongation
Antibiotic	Azithromycin, clarithromycin, erythromycin, moxifloxacin	Possible risk of additive QTc prolongation
Anticonvulsant	Barbiturates, carbamazepine, phenytoin	Decreased plasma level of methadone due to increased metabolism via CYP3A4 and CYP2B6 (phenytoin and barbiturates), or via CYP3A4 alone (carbamazepine)
Antidepressant		
SSRI	Citalopram, escitalopram, others	Possible risk of additive QTc prolongation and serotonin syndrome
	Fluvoxamine	Increased plasma level of methadone by (20–100%) with fluvoxamine, due to reduced metabolism via CYP2D6 and CYP3A4 inhibition
Cyclic	Amitriptyline, desipramine	Increased plasma level of desipramine (by about 108%) due to decreased metabolism via CYP2D6 Increased giddiness, euphoria; suspected potentiation of methadone's "euphoric" effects – abuse with amitriptyline reported Additive anticholinergic effects, additive QTc prolongation, and risk of serotonin syndrome
Antiemetic	Dolasetron, granisetron, ondansetron	Possible risk of additive QTc prolongation
Antifungal	Fluconazole	Increase in methadone peak and trough plasma levels by 27% and 48%, respectively; clearance decreased by 24% due to inhibition of CYP2D6, 3A4, 2C19; possible risk of additive QTc prolongation
	Itraconazole	Case report of prolonged QTc interval leading to torsades de pointes following two doses of itraconazole (200 mg), likely due to inhibition of methadone metabolism via CYP3A4
	Ketoconazole	May increase serum concentration of methadone
Antipsychotic	Risperidone	Case reports of precipitation of opioid withdrawal symptoms (mechanism unclear)
	Pimozide, quetiapine, thioridazine, ziprasidone	Possible risk of additive QTc prolongation
Antitubercular	Isoniazid	Increased plasma level of methadone due to decreased metabolism via CYP3A4
	Rifampin	Decreased plasma level of methadone (by up to 50%) due to enhanced metabolism via CYP3A4 – may cause withdrawal symptoms

Class of Drug	Example	Interaction Effects
Antiviral	Abacavir	Abacavir levels decreased by 34%, however, clearance remained the same Methadone plasma level decreased by 23% – may result in withdrawal
	Delavirdine	Likely to increase methadone levels via inhibition of CYP3A4
	Stavudine	Decreased bioavailability of antiretrovirals due to increased degradation in GI tract by methadone (C_{max} and AUC decreased by 44% and 25%)
	Efavirenz, nevirapine	Increased clearance of methadone and decreased total concentration (AUC) (by up to 60% with efavirenz and nevirapine) via enzyme induction – withdrawal symptoms reported within 7–10 days
	Zidovudine	Inhibited metabolism of zidovudine by methadone (AUC increased by 43%)
Benzodiazepine	Clonazepam, diazepam	Enhanced risk of respiratory depression Combined use suggested to negatively influence treatment outcomes
	Diazepam	"Opioid high" reported with combined use
Buprenorphine		Decreased metabolism of methadone through inhibition of CYP3A4; possibly reduced methadone effectiveness due to partial μ-opioid receptor agonism
Grapefruit juice		Decreased metabolism of methadone through inhibition of CYP3A4 and P-glycoprotein
H_2 antagonist	Cimetidine	Decreased clearance of methadone
Hypnotic	Zolpidem	Decreased metabolism of methadone through inhibition of CYP3A4
Methylene blue		Enhanced serotonergic effects through inhibition of MAO-A and B by methylene blue; risk for serotonin syndrome
Opioid	Butorphanol, nalbuphine, pentazocine	Occurrence of withdrawal symptoms due to partial antagonist effects of these opioids
	Morphine	Efficacy of opioid analgesic reduced; dosage may need to be increased
Opioid antagonist	Naltrexone	Diminished analgesic effect and may precipitate withdrawal
Prokinetic agent	Domperidone	Possible risk of additive QTc prolongation
Protease inhibitor	Amprenavir	AUC, C_{max} and C_{min} of amprenavir decreased by 30%, 27%, and 25%, respectively Methadone levels decreased an average of 35% with amprenavir/abacavir combination
	Indinavir	Variable effects reported on C_{max} of indinavir Reduced AUC of methadone (by 40%)
	Lopinavir/ritonavir	Methadone AUC decreased by 36% due to increased clearance (attributed to lopinavir) – may result in withdrawal
	Nelfinavir	AUC of nelfinavir metabolite decreased by 53% – significance unknown
	Ritonavir	Variable effects on clearance of methadone reported
	Ritonavir/saquinavir	Displacement from protein binding of methadone and decrease in AUC of both R-methadone and S-methadone
QTc prolonging agent		Higher risk of additive QTc prolongation; for high-risk combinations, may need to discontinue methadone and initiate buprenorphine treatment
St. John's wort		Decreased plasma level of methadone via CYP3A4 induction; symptoms of withdrawal reported
Stimulant	MDMA (Ecstasy)	Decreased metabolism of methadone through inhibition of CYP2D6
Urine acidifier	Ascorbic acid	Increased elimination of methadone
Urinary alkalinizer	Sodium bicarbonate	Decreased elimination of methadone

Pharmacotherapy for Nicotine/Tobacco Use Dependence

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
Bupropion	Antidepressant	Norepinephrine, dopamine/Reuptake inhibitor (NET, DAT), releaser (NE, DA)	Wellbutrin SR[D], Zyban[C]	Sustained-release tablets: 100 mg, 150 mg, 200 mg[B]	Safety and efficacy not established in children and adolescents under age 18
Nicotine			Nicorette, Nicorette DS[B], Thrive[C]	Gum: 2 mg, 4 mg	Safety and efficacy not evaluated in children and adolescents under age 18
			Nicorette, Thrive[C]	Lozenges: 2 mg, 4 mg	
			Nicorette[C], Nicotrol[B]	Inhalation cartridges: 10 mg (delivers 4 mg nicotine)	
			Nicorette QuickMist[C]	Oral spray: 1 mg/spray	
			Nicoderm[C], Nicoderm CQ[B], Habitrol[B]	Transdermal patch: 7 mg/24 h, 14 mg/24 h, 21 mg/24 h	
			Nicotrol NS[B]	Nasal spray: 0.5 mg/spray	
Varenicline	Nicotine receptor partial agonist	Acetylcholine/Partial agonist	Champix[C], Chantix[B]	Tablets: 0.5 mg, 1 mg	Efficacy not established in children and adolescents under age 18
			Tyrvaya[B],[E]	Nasal spray: 0.03 mg/spray	Efficacy not established in children and adolescents under age 18

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA, [D] Marketed for major depressive disorder (MDD), [E] Marketed for dry eye disease

Indications‡ (👍 approved)

In children and adolescents:

- No medication or nicotine replacement is approved for smoking cessation in children and adolescents

In adults:

- 👍 Aid in smoking cessation in conjunction with smoking cessation counseling or behavioral modification
- Varenicline: Alcohol use disorder (positive findings; used alone or with naltrexone), cannabis use disorder (preliminary results)

General Comments

- Counseling has been shown to be effective in treatment of adolescent smokers (Level of Evidence = B)[14]
- There is little empirical evidence that NRT is effective in young smokers. Studies using nicotine patch showed a decrease in the number of cigarettes smoked, but abstinence rates of only 5% after 6–12 months[15, 16]
- Several studies have shown that bupropion is safe and effective in adolescents, resulting in cessation rates of up to 13.9% at 6 months[17, 18, 19, 20]
- DBPC-RCTs showed varenicline for 12 weeks is safe in adolescents; however, abstinence rate did not differ significantly compared to placebo group at 12 weeks; all patients received smoking cessation counseling at each visit[21, 22]
- Patient preference, convenience, cost, and previous experiences/attempts to quit smoking should be considered when advising on treatment for nicotine dependence
- Regardless of smoking cessation option selected, 12-month abstinence rates are < 25%

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration's Drugs@FDA, Health Canada Drug Product Database) for the most current availability information and indications

- Several combinations of first-line drugs have been shown to be effective in maintaining abstinence (see Precautions p. 394), including:
  - Long-term (over 14 weeks) nicotine patch + nicotine gum or spray
  - Nicotine patch (6–14 weeks) + nicotine inhaler (up to 6 months)
  - Nicotine patch (6–14 weeks) + bupropion SR (up to 14 weeks)
- Long-term use (up to 6 months) of medications may be helpful for smokers who experience persistent withdrawal symptoms or who have relapsed in the past after stopping treatment
- Cytisine (not available in Canada or USA) and nortriptyline may be effective in treatment of adult smokers; clonidine may be effective but is limited by its adverse effects
- E-cigarettes with nicotine may increase quit rates compared to nicotine replacement therapy and e-cigarettes without nicotine; evidence limited by small number of RCTs

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

DRUG INTERACTIONS WITH NRT

Class of Drug	Example	Interaction Effects
Analgesic	Acetaminophen, pentazocine	Increased levels of analgesic due to inhibition of metabolism following smoking cessation
Adrenergic agonist	Isoproterenol, phenylephrine	May require an increase in dose due to a decrease in circulating catecholamine following smoking cessation
Adrenergic blocker	Labetalol, prazosin	May require a decrease in dose due to a decrease in circulating catecholamines following smoking cessation
Antidepressant	Clomipramine, duloxetine, imipramine	Increased level of antidepressant due to wearing off of CYP1A2 enzyme induction following smoking cessation
Antipsychotic	Asenapine, clozapine, olanzapine	May require a decrease in dose, due to wearing off of CYP1A2 enzyme induction following smoking cessation
β-blocker	Propranolol	Increased level of β-blocker due to wearing off of CYP1A2 enzyme induction following smoking cessation
Caffeine		Increased caffeine level and adverse effects/decreased tolerance due to wearing off of CYP1A2 enzyme induction following smoking cessation
Insulin		May require a decrease in insulin dosage following smoking cessation
Theophylline		Increased level due to wearing off of CYP1A2 enzyme induction following smoking cessation; may require dose reduction
Varenicline		Combination can increase adverse effects, including nausea, headache, vomiting, dizziness, dyspepsia, and fatigue

DRUG INTERACTIONS WITH VARENICLINE

Class of Drug	Example	Interaction Effects
Alcohol		Alcohol intake may increase the risk of patients experiencing psychiatric adverse effects Varenicline may increase alcohol intoxicating effects and unusual or aggressive behavior Varenicline may reduce daily amount of alcohol consumption, craving, and subjective intoxication when used in patients with alcohol use disorder
Antibiotic	Levofloxacin, trimethoprim	Increased varenicline level; avoid concomitant use in severe renal impairment (CrCrl < 30 mL/min)
H_2 blocker	Cimetidine, ranitidine	Increased serum concentration of varenicline by 29% due to decreased renal clearance
NRT	Transdermal nicotine	Combination can increase adverse effects including nausea, headache, vomiting, dizziness, dyspepsia, and fatigue

For DRUG INTERACTIONS WITH BUPROPION, see pp. 67–73

Comparison of Treatments for Nicotine/Tobacco Use Disorder

	Nicotine Replacement Therapy (NRT)	Varenicline	Bupropion SR
General Comments	Does not deliver nicotine to the circulation as fast as smoking Variable plasma levels occur if gum or lozenge chewed/sucked too quickly or too slowly Interindividual variability in nicotine pharmacokinetics; affected by sex (higher clearance in men), race (higher frequency of slow metabolizers in Asian and African American populations), and CYP2A6 genotype *Lozenge, gum, oral spray, and patch* are similar in effectiveness in reducing craving *Nicotine inhaler:* mimics hand-to-mouth smoking action (coping mechanism) *Nasal spray:* Fastest nicotine delivery system; reflects nicotine plasma levels observed after cigarette smoking the closest compared to other formulations; does not counter the habit/satisfaction of smoking Adherence rate highest with nicotine patch, moderate with nicotine gum, lozenge and inhaler, and low with nicotine nasal spray	Relieves craving and withdrawal symptoms Significant decrease in smoking satisfaction and psychological reward from smoking reported Meta-analysis suggests varenicline may increase the odds of quitting over NRT and bupropion	Relieves craving and withdrawal symptoms Effective in patients with a history of depression May be used in combination with NRT May minimize weight gain following smoking cessation Can be used in patients with cardiovascular disease
Pharmacology	Delivers nicotine that binds to the nicotinic acetylcholine receptor	Partial agonist at the $\alpha_4\beta_2$ nicotinic acetylcholine receptor	Blocks reuptake of dopamine and norepinephrine Noncompetitive inhibitor of brain nicotine receptors
Pharmacokinetics	*Gum and lozenge:* Rate of absorption depends on rate of chewing the gum or sucking the lozenge; peak plasma level = 30 min for gum and 45 min for lozenge; blood nicotine levels stabilize with repeated use every 30 min Metabolized by liver, and partly by kidney and lung; elimination half-life = 120 min; higher levels reported in renal insufficiency *Inhaler:* Peak plasma levels = 15 min after continuous inhalation for over 20 min; steady state maintained by 20 min inhalations for 12 h; half-life of primary metabolite, cotinine: 15–20 h *Oral spray:* Peak plasma levels = 10–12.5 min *Patch:* Eliminates variability of GI absorption; reduces nicotine first-pass metabolism; effects wear off in 20–24 h *Nasal spray:* Absorbed very quickly; peak plasma levels = 10–20 min	Peak plasma levels occur in 3–4 h; bioavailability not affected by food; C_{max} ~30% higher in patients $<$ 55 kg Steady state reached after 4 days Protein binding = 20% Elimination half-life = 17–24 h 92% excreted unchanged in urine	See p. 68
Dosing	*Gum:* Weeks 1–6: 1 gum (2–4 mg) q 1–2; at least 9 pieces/day (max. 80 mg/day); 2 mg if smoking fewer than 25 cigarettes/day Weeks 7–9: 1 gum q 2–4 h Weeks 10–12: 1 gum q 4–8 h *Lozenge:* Weeks 1–6: 1 lozenge (2–4 mg) q 1–2 h; at least 9 lozenges/day (max. 5 lozenges/6 h, 20 lozenges/day); 2 mg if smoking first cigarette more than 30 min after waking Weeks 7–9: 1 lozenge q 2–4 h Weeks 10–12: 1 lozenge q 4–8 h *Inhaler:* 6–16 cartridges/day for up to 12 weeks, then gradually reduce dose for 6–12 weeks; each cartridge delivers 4 mg nicotine over 80 inhalations *Oral spray:* 1–2 sprays q 0.5 h in mouth for 6 weeks (max. 2 sprays/episode, 4 sprays/h, 64 sprays/day); step-down dosage: reduce number of sprays/day by half for 2 weeks, then 2–4 sprays/day for 2 weeks	$\leq$ 55 kg: 0.5 mg daily x 12 weeks; or 0.5 mg daily x 2 weeks, then increase to 0.5 mg bid x 10 weeks $>$ 55 kg: 0.5 mg daily x 2 weeks, then 0.5 mg bid x 10 weeks; or 0.5 mg daily x 1 week, 0.5 mg bid x 1 week, then 1 mg bid x 10 weeks RCT showed abstinence rates for both low-dose (27%) and high-dose (20%) groups did not differ significantly compared to placebo group (18%)	150 mg q a.m. x 3 days, then 150 mg bid for 7–12 weeks; 150 mg XL daily x 7 days, then 300 mg XL daily for 7–11 weeks (off-label); consider for long-term therapy (up to 6 months after quitting)

	Nicotine Replacement Therapy (NRT)	Varenicline	Bupropion SR
	Patch: 28 mg/24 h for heavy smokers or 14 mg/24 h for light smokers for 6–8 weeks; step-down dosage: 21 mg/24 h x 4 weeks, then 14 mg/24 h x 2 weeks, then 7 mg/24 h x 2 weeks *Nasal spray:* 1 or 2 doses/h (one dose is 2 sprays, one in each nostril); max. 5 doses/h, 40 doses/day; use initial dose for 8 weeks, then taper over 4–6 weeks		
Dosing comments	*Gum:* Chew gum until "tingle" sensation, then park in cheek for 30–60 sec; repeat for 30 min *Lozenge:* Suck lozenge; when taste is "strong," park in cheek; repeat for 30 min; do not chew or swallow lozenge; use tongue to move the lozenge from one side of mouth to the other; it should take 20–30 min to dissolve *Oral spray:* Prime with first use or if not used in a few days (press top firmly until a fine mist appears); wait a few seconds before swallowing; if cravings do not disappear with one spray, use a second one; do not spray into throat or inhale spray With nicotine gum, lozenge, inhaler, or oral spray, do not eat or drink anything but water for 15 min before or during use; acidic beverages decrease absorption *Inhaler:* Puff similarly to a cigarette; best effect achieved by frequent continuous puffing (20 min) *Patch* should be removed overnight *Nasal spray:* Spray into nostrils with head tilted back slightly; the nicotine is quickly absorbed into the nasal membranes; do not sniff, swallow, or inhale through nose as spray is being administered	Start 1 week prior to quit date Take with food to reduce nausea Take second dose at supper to minimize insomnia Space at least 8 h between morning and evening doses	Start 1–2 weeks prior to quit date Target quit date should be after at least 1 week of treatment
Abstinence Rate After 6 Months	13–17% (adults)	20–27% (adolescents)	13.9% (adolescents)
Adverse Effects	*Gum or lozenge:* Jaw pain, throat irritation, taste perversion, stomatitis, gingivitis, hiccups (10%), dyspepsia, nausea, headache (11%), dizziness, and insomnia *Inhaler:* Mouth and throat irritation (small puffs less irritating than long puffs), sneezing, rhinitis, and pharyngitis *Oral spray:* Hiccups (most common; decreases with time), nausea, and headache *Patch:* Local skin irritation, insomnia, vivid dreams, and headache *Nasal spray:* Nose and throat irritation, cough, sneezing, and watery eyes Multiple trials confirm NRT is not associated with increased cancer risk	Nausea (30%), vomiting, headaches (15%), insomnia (18%), abnormal dreams (13%), somnolence, loss of consciousness, flatulence, constipation, dizziness, falls, abnormal spasms and movement; rare hypersensitivity reactions including angioedema, Stevens-Johnson syndrome, and erythema multiforme Loss of consciousness, changes in behavior, confusion, anxiety, hostility, agitation, restlessness, psychosis, depressed mood and suicidal ideation and acts reported Possible link to heart attacks, seizures, and diabetes	See p. 69 Insomnia (35–40%), vivid dreams (38%), agitation, headache, dry mouth (10%), disturbed concentration, dizziness, chest discomfort (14%), and nausea (14%) Changes in behavior, hostility, agitation, aggression, disinhibition, emotional lability, akathisia, depersonalization, depressed mood, and suicidal ideation and acts reported
Discontinuation	Taper use of NRT gradually to minimize withdrawal symptoms	Commonly discontinued after 12 weeks	Commonly discontinued after 7–12 weeks; some patients require up to 12 months of treatment

Comparison of Treatments for Nicotine/Tobacco Use Disorder (cont.)

	Nicotine Replacement Therapy (NRT)	Varenicline	Bupropion SR
Precautions	Caution in patients with recent MI, serious arrhythmias, and unstable angina Caution in endocrine disorders (e.g., diabetes, hyperthyroidism) due to release of catecholamines Avoid nicotine spray in patients with severe reactive airway disease; potential for dependence Smoking while using NRT can lead to nicotine toxicity with: Headache, nausea, vomiting, abdominal pain, diarrhea, salivation, sweating, flushing, and palpitations Discard patches by folding them with the sticky sides together to minimize risk to children and pets	Caution in patients with underlying psychiatric disorder, cardiac disease, or those operating machinery; angioedema and serious skin reactions Reduce dosage in patients with kidney impairment (CrCl < 30 mL/min), or those on dialysis	See p. 67
Contraindications	Unstable cardiac conditions *Lozenge:* Soy allergy *Patch:* Skin diseases that may complicate application	Unstable cardiac conditions	Anorexia, bulimia, seizures, bipolar disorder, heavy alcohol use, and use of MAOIs
Toxicity	In children, nicotine poisoning may develop after ingestion of 1 mg/kg; first signs include vomiting, diarrhea, tachycardia, hypertension, tremors; with higher doses, loss of consciousness, seizures, or respiratory failure may occur; most accidental poisonings involved young children using family member's new or improperly discarded patches		
Use in Pregnancy and Breastfeeding◊	Guidelines suggest that nicotine replacement may be used during pregnancy and breastfeeding; these agents are considered much safer than smoking in pregnancy (use suggested even over oral medications for smoking cessation)	Safety in pregnancy not established; animal studies did not result in major congenital malformations; no data on the presence or safety of varenicline in human breast milk; excreted in rat breast milk	Safety in pregnancy not established; does not appear to increase risk of congenital malformations in humans; present in human breast milk, use caution in nursing women

◊ See p. 428 for further information on drug use in pregnancy and effects on breast milk

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Pharmacotherapy for Nicotine/Tobacco Use Dependence (cont.)

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UNAPPROVED TREATMENTS OF PSYCHIATRIC DISORDERS

Product Availability*

Several drugs traditionally used to treat medical conditions have been helpful in ameliorating or preventing symptoms of certain psychiatric disorders in children and adolescents. This section presents a summary of some of these drugs and their uses. **As a general rule, unapproved treatments should be reserved for patients highly resistant to conventional therapies. Clinicians should be cognizant of medicolegal issues when prescribing drugs for non-approved indications as most of the listed medications have not been adequately studied in children and adolescents with mental health conditions.**

	ADHD	Anxiety Disorders	Autism Spectrum Disorder	Disruptive Behavior/ Aggression	Mood Disorders	Obsessive-Compulsive Disorder	PTSD	Substance Use Disorders	Tourette's Disorder
β-blockers, e.g., propranolol, pindolol (p. 398)		+	PR	+		PR/S/C			
Bumetanide (p. 405)			PR/C						
Cannabidiol (p. 405)			PR						
Celecoxib (p. 399)			PR/+		PR/+ (bipolar mania)				
Cholinesterase inhibitors (p. 400)	PR/C		PR						PR
D-cycloserine (p. 402)						PR/S/C			
Folinic acid (p. 405)			PR						
Ketamine (p. 405)					PR				
Memantine (p. 402)			PR/C			PR			
Minocycline (p. 399)			PR/+						
Modafinil (p. 401)	+								
N-acetylcysteine (p. 403)		PR/C	PR/C			PR/C		PR/C (cannabis use disorder)	
Pramipexole (p. 401)	PR								
Prazosin (p. 398)							PR		
Riluzole (p. 404)		PR/C	PR/C			PR/C			

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information

C = contradictory results, P = partial improvement, + = positive, PR = preliminary data supporting benefit, S = synergistic effect

Adrenergic Agents

β-blockers

Have membrane-stabilizing effect and GABA-mimetic activity; presynaptic 5-HT_{1A} antagonists (see p. 242 for treatment of EPSE/akathisia)

Antisocial Behavior/ Aggression

- Propranolol dose: 0.5–1 mg/kg/day given q 6–8 h; slowly increase to a maximum dose of 5 mg/kg/day or 120 mg/day
- Mean nadolol dose was 109 mg/day (range 30–220 mg/day) in 12 subjects with developmental and intellectual delay (mean age of 13.8 years)
- Response may take up to 8 weeks
- May be effective in controlling rage, irritability, and aggression due to a number of causes (e.g., autism, ADHD, PTSD)
- May be effective in controlling aggressive behavior in children and adolescents with organic brain dysfunction; meta-analysis suggests β-blockers show good evidence of efficacy for management of agitation and aggression in adult patients with acquired brain injury
- Potential side effects include hypotension, bradycardia, and worsening of asthmatic symptoms; monitor BP and EKG
- Rebound rage reactions on drug withdrawal reported; taper dose gradually

Fleminger S, Greenwood RJ, Oliver DL. Pharmacological management for agitation and aggression in people with acquired brain injury. Cochrane Database Syst Rev. 2006;(4):CD003299. doi:10.1002/14651858.CD003299.pub2
Grizenko N, Vida S. Propranolol treatment of episodic dyscontrol and aggressive behavior in children. Can J Psychiatry. 1988;33(8):776–778.
Silver JM, Yudofsky SC, Slater JA, et al. Propranolol treatment of chronically hospitalized aggressive patients. J Neuropsychiatry Clin Neurosci. 1999;11(3):328–335. doi:10.1176/jnp.11.3.328

Anxiety Disorders/ Obsessive-Compulsive Disorder

- Suggested to inhibit memory consolidation by interfering with protein synthesis
- Propranolol dose: Up to 160 mg/day (in divided doses)
- Efficacy reported in children with PTSD – early administration reported to treat intrusive memories and reduce severity of later symptoms
- Propranolol beneficial for somatic or autonomically mediated symptoms of anxiety (e.g., tremor, palpitations) as seen in social anxiety disorder and acute panic
- Pindolol dose: 2.5–7.5 mg/day reported to augment response to SSRIs in OCD and panic disorder (adult data)

Davidson JR. Pharmacotherapy of social anxiety disorder: What does the evidence tell us? J Clin Psychiatry. 2006;67(Suppl. 12):S20–S26.
Fontenelle LF, Nascimento AL, Mendlowicz MV, et al. An update on the pharmacological treatment of obsessive-compulsive disorder. Expert Opin Pharmacother. 2007;8(5):563–583. doi:10.1517/14656566.8.5.563
Glannon W. Psychopharmacology and memory. J Med Ethics. 2006;32(2):74–78. doi:10.1136/jme.2005.012575
Hurlemann R, Walter H, Rehme AK, et al. Human amygdala reactivity is diminished by the β-noradrenergic antagonist propranolol. Psychol Med. 2010;40(11):1839–1848. doi:10.1017/S0033291709992376
Le Melledo JM, Bradwejn J, Kosycki D, et al. The role of the beta-noradrenergic system in cholecystokinin-tetrapeptide-induced panic symptoms. Biol Psychiatry. 1998:44(5):364–366.
Nugent NR, Christopher NC, Crow JP, et al. The efficacy of early propranolol administration at reducing PTSD symptoms in pediatric injury patients: A pilot study. J Trauma Stress. 2010;23:282–287. doi:10.1002/jts.20517

Autism Spectrum Disorder

- Improvements in emotional, behavioral, and autonomic dysregulation, anxiety, and aggressive, self-injurious, and hypersexual behaviors

Sagar-Ouriaghli I, Lievesley K, Santosh PJ. Propranolol for treating emotional, behavioural, autonomic dysregulation in children and adolescents with autism spectrum disorders. J Psychopharmacol. 2018;32(6):641–653. doi:10.1177/0269881118756245

Prazosin

α_1-adrenergic antagonist

PTSD

- Dose: children and adolescents 1–4 mg/day; adults up to 16 mg/day
- Several positive RCTs in adults (mostly combat veterans) and case reports in children and adolescents suggest prazosin may reduce PTSD symptoms such as nightmares and sleep disturbance
- Daytime prazosin reported to decrease distress related to trauma cues
- Many patients experience no adverse effects; hypotension is the main adverse effect reported though, at higher doses, dizziness, headache, drowsiness, fatigue, weakness, palpitations, and nausea have been reported in 5% or more of patients

Akinsanya A, Marwaha R, Tampi RR. Prazosin in children and adolescents with posttraumatic stress disorder who have nightmares: A systematic review. J Clin Psychopharmacol. 2017;37(1):84–88. doi:10.1097/JCP.0000000000000638
Ferrafiat V, Soleimani M, Chaumette B, et al. Use of prazosin for pediatric post-traumatic stress disorder with nightmares and/or sleep disorder: Case series of 18 patients prospectively assessed. Front Psychiatry. 2020;11:724. doi:10.3389/fpsyt.2020.00724
Hudson N, Burghart S, Reynoldson J, et al. Evaluation of low dose prazosin for PTSD-associated nightmares in children and adolescents. Ment Health Clin. 2021;11(2):45–49. doi:10.9740/mhc.2021.03.045
Khachatryan D, Groll D, Booij L, et al. Prazosin for treating sleep disturbances in adults with posttraumatic stress disorder: A systematic review and meta-analysis of randomized controlled trials. Gen Hosp Psychiatry. 2016;39:46–52. doi:10.1016/j.genhosppsych.2015.10.007
Koola MM, Varghese SP, Fawcett JA. High-dose prazosin for the treatment of post-traumatic stress disorder. Ther Adv Psychopharmacol. 2014;4(1):43–47. doi:10.1177/2045125313500982
Racin PR, Bellonci C, Coffey DB. Expanded usage of prazosin in pre-pubertal children with nightmares resulting from posttraumatic stress disorder. J Child Adolesc Psychopharmacol. 2014;24(8):458–461. doi:10.1089/cap.2014.2482
Singh B, Hughes AJ, Mehta G, et al. Efficacy of prazosin in posttraumatic stress disorder: A systematic review and meta-analysis. Prim Care Companion CNS Disord. 2016;18(4). doi:10.4088/PCC.16r01943

Anti-inflammatory Agents

Celecoxib

Evidence suggests that inflammatory processes and immune responses are involved in the pathophysiology of mood disorders as well as autism

Autism Spectrum Disorder/ Bipolar Mania

- RCT of children with autism who received celecoxib 300 mg/day or placebo adjunctive to risperidone 3 mg/day resulted in significant improvement in irritability, lethargy/social withdrawal, and stereotypic behavior subscales of the Aberrant Behavior Checklist (ABC) compared to placebo
- RCT of adolescents who received celecoxib 100 mg twice daily or placebo adjunctive to lithium and risperidone for acute mania showed significant improvement in mania symptoms as measured by the Young Mania Rating Scale (YMRS) with celecoxib treatment compared to placebo

Asadabadi M, Mohammadi MR, Ghanizadeh A, et al. Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: A randomized, double-blind, placebo-controlled trial. Psychopharmacology (Berl). 2013;225(1):51–59. doi:10.1007/s00213-012-2796-8
Mousavi SY, Khezri R, Karkhaneh-Yousefi MA, et al. A randomized, double-blind placebo-controlled trial on effectiveness and safety of celecoxib adjunctive therapy in adolescents with acute bipolar mania. J Child Adolesc Psychopharmacol. 2017;27(6):494–500. doi:10.1089/cap.2016.0207

Minocycline

Anti-infective drug with anti-inflammatory and neuroprotective properties; blocks the neurotoxicity of N-methyl-D-aspartate (NMDA) antagonists and may exert a differential effect on NMDA signaling pathways

- RCT of children (age 4–12 years) with autism who received minocycline 50 mg twice daily or placebo adjunctive to risperidone 2 mg/day resulted in significant improvement in irritability and hyperactivity/non-compliance subscales of the Aberrant Behavior Checklist (ABC) compared to placebo
- Use of tetracyclines in children age 8 years or less is not recommended due to risk of hypoplasia of dental enamel and permanent tooth discoloration
- RCTs in adults with adjunctive minocycline for treatment of schizophrenia, OCD, depression, bipolar depression

Dean OM, Data-Franco J, Giorlando F, et al. Minocycline: Therapeutic potential in psychiatry. CNS Drugs. 2012;26(5):391–401. doi:10.2165/11632000-000000000-00000
Ghaleiha A, Alikhani R, Kazemi MR, et al. Minocycline as adjunctive treatment to risperidone in children with autistic disorder: A randomized, double-blind placebo-controlled trial. J Child Adolesc Psychopharmacol. 2016;26(9):784–791. doi:10.1089/cap.2015.0175

Cholinergic Agents

Cholinesterase Inhibitors

Increase the activity of acetylcholine in the brain

Autism Spectrum Disorder

- Dose: galantamine: 4–24 mg/day (in 2 divided doses)
- Open trial and case reports suggest donepezil, galantamine, and rivastigmine may benefit dysfunctional behaviors, irritability, hyperactivity, and expressive speech in patients with autism spectrum disorder
- Augmentation of galantamine with risperidone in children with autism spectrum disorder resulted in significant reduction of irritability (primary outcome) and lethargy/social withdrawal symptoms in an RCT

Chez MG, Aimonovitch M, Buchanan T, et al. Treating autistic spectrum disorders in children: Utility of the cholinesterase inhibitor rivastigmine tartrate. J Child Neurol. 2004;19(3):165–169.
Ghaleiha A, Ghyasvand M, Mohammadi MR, et al. Galantamine efficacy and tolerability as an augmentative therapy in autistic children: A randomized, double-blind, placebo-controlled trial. J Psychopharmacol. 2014;28(7):677–685. doi:10.1177/0269881113508830
Hardan AY, Handen BL. A retrospective open trial of adjunctive donepezil in children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol. 2002;12(3):237–241. doi:10.1089/104454602760386923
Nicolson R, Craven-Thuss B, Smith J. A prospective, open-label trial of galantamine in autistic disorder. J Child Adolesc Psychopharmacol. 2006;16(5):621–629. doi:10.1089/cap.2006.16.62

ADHD/ Tourette's Disorder

- Dose: donepezil: up to 10 mg/day
- Case series suggest that augmentation may improve organization, mental efficiency, and attention in treatment-resistant children and adolescents with ADHD
- Open trials of adjunctive donepezil did not result in clinically significant improvement in ADHD symptoms
- One open trial showed reduction in tic severity, but no reduction in ADHD symptoms, and high rate of adverse events
- Most adverse effects are due to cholinomimetic activity: nausea, vomiting, diarrhea, constipation, and anorexia

Cubo E, Fernández Jaén A, Moreno C, et al. Donepezil use in children and adolescents with tics and attention-deficit/hyperactivity disorder: An 18-week, single-center, dose-escalating, prospective, open-label study. Clin Ther. 2008;30(1):182–189. doi:10.1016/j.clinthera.2008.01.010
Hoopes SP. Donepezil for Tourette's syndrome and ADHD. J Clin Psychopharmacol. 1999;19(4):381–382.
Wilens TE, Waxmonsky J, Scott M, et al. An open trial of adjunctive donepezil in attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2005; 15(6):947–955. doi: 10.1089/cap.2005.15.947

Modafinil

The exact mechanism of action is unclear. Studies have shown it to increase the levels of dopamine in the striatum and nucleus accumbens, norepinephrine in the hypothalamus and ventrolateral preoptic nucleus, and serotonin in the amygdala and frontal cortex. Modafinil also activates glutamatergic circuits while inhibiting GABA neurotransmission

ADHD

- Dose: 100–425 mg/day in divided doses
- Beneficial results reported in open and double-blind trials of children aged 5–15; may be useful for inattention, hyperactivity/impulsivity and oppositional behavior, or when anorexia limits the use of stimulants
- Good response reported in double-blind placebo-controlled studies in children
- Common adverse effects include: insomnia, headache (20%), nausea, nervousness, hypertension, decreased appetite, and weight loss; serious dermatological reactions have been reported in children and adolescents
- Systematic review of studies in children and adolescents concluded that modafinil may improve symptoms of ADHD compared with placebo, but is associated with an increased risk of adverse effects compared with methylphenidate, dextroamphetamine, and atomoxetine
- **Development of modafinil for ADHD was discontinued following US FDA non-approvable decision and request for additional studies, citing serious dermatological reactions (erythema multiforme, Stevens-Johnson syndrome)**

Amiri S, Mohammadi MR, Mohammadi M, et al. Modafinil as a treatment for attention-deficit/hyperactivity disorder in children and adolescents: A double blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):145–149. doi:10.1016/j.pnpbp.2007.07.025

Biederman J, Pliszka SR. Modafinil improves symptoms of attention-deficit/hyperactivity disorder across subtypes in children and adolescents. J Pediatr. 2008;152(3):394–399. doi:10.1016/j.jpeds.2007.07.052

Vorspan F, Warot D, Consoli A, et al. Mania in a boy treated with modafinil for narcolepsy. Am J Psychiatry. 2005;162(4):813–814. doi:10.1176/appi.ajp.162.4.813-a

Wang SM, Han C, Lee SJ, et al. Modafinil for the treatment of attention-deficit/hyperactivity disorder: A meta-analysis. J Psychiatr Res. 2017;84:292–300. doi:10.1016/j.jpsychires.2016.09.034

Pramipexole

D_2/D_3 dopamine receptor agonist

ADHD/ Tourette's Disorder

- Dose: 0.0625–0.25 mg/day divided bid
- Single RCT: ineffective for symptoms of Tourette's disorder, but reduced ADHD symptoms (secondary outcome measure) in children and adolescents
- High incidence of nausea; sedation and dizziness reported in other trials; reports of compulsive behaviors and psychosis

Kurlan R, Crespi G, Coffey B, et al. A multicenter randomized placebo-controlled clinical trial of pramipexole for Tourette's syndrome. Mov Disord. 2012;27(6):775–778. doi:10.1002/mds.24919

NMDA Agents

D-Cycloserine

Partial receptor agonist at the glycine binding site on the N-methyl-D-aspartate (NMDA) receptor

Anxiety Disorders/ Obsessive-Compulsive Disorder

- Dose: 25–50 mg/day (approx. 0.7 mg/kg) pre-CBT (children and adolescents); 50–500 mg/day used in adults
- Believed to consolidate the learning that occurs during exposure to anxiety-provoking situations
- Data controversial as to efficacy in treatment of OCD
- RCTs in adults have demonstrated that exposure therapy augmented by D-cycloserine is superior to placebo augmentation in the treatment of specific phobias, social anxiety disorder, and panic disorder
- Recent negative RCTs in adolescents with anxiety (D-cycloserine and CBT not superior to CBT alone in one trial, D-cycloserine not superior to placebo in another)
- Recent negative RCT in children and adolescents with OCD (D-cycloserine and CBT not superior to CBT alone)
- One meta-analysis of studies suggests that D-cycloserine may increase the speed or efficiency of exposure treatment
- A more recent meta-analysis raises the question of the usefulness of D-cycloserine as an augmentation of exposure therapy for anxiety and OCD
- Adverse effects include sedation, headache, increased anxiety, and restlessness

Arman S, Soheilimehr A, Maracy MR. The efficacy of augment of D-cycloserine and cognitive-behavioral therapy on adolescent with one type of anxiety disorders: A double-blind randomized controlled trial. Adv Biomed Res. 2017;6:11. doi:10.4103/2277-9175.200786
Bontempo A, Panza KE, Bloch MH. D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders: A meta-analysis. J Clin Psychiatry. 2012;73(4):533–537. doi:10.4088/JCP.11r07356
Bürkner PC, Bittner N, Holling H, et al. D-cycloserine augmentation of behavior therapy for anxiety and obsessive-compulsive disorders: A meta-analysis. PLoS One. 2017;12(3):e0173660. doi:10.1371/journal.pone.0173660
Guastella AJ, Richardson R, Lovibond PF, et al. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. Biol Psychiatry. 2008;63:544–549. doi:10.1016/j.biopsych.2007.11.011
Otto MW, Tolin DF, Simon NM, et al. Efficacy of D-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. Biol Psychiatry. 2010;67:365–370. doi:10.1016/j.biopsych.2009.07.036
Rapee RM, Jones MP, Hudson JL. d-cycloserine does not enhance the effects of in vivo exposure among young people with broad-based anxiety disorders. Behav Res Ther. 2016;87:225–231. doi:10.1016/j.brat.2016.10.004
Rynn M, Puliafico A, Heleniak C, et al. Advances in pharmacotherapy for pediatric anxiety disorders. Depress Anxiety. 2011;28:76–87. doi:10.1002/da.20769
Storch EA, Murphy TK, Goodman WK, et al. A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry. 2010;68(11):1073–1076. doi:10.1016/j.biopsych.2010.07.015
Storch EA, Wilhelm S, Sprich S, et al. Efficacy of augmentation of cognitive behavior therapy with weight-adjusted d-cycloserine vs placebo in pediatric obsessive-compulsive disorder: A randomized clinical trial. JAMA Psychiatry. 2016;73(8):779–788. doi:10.1001/jamapsychiatry.2016.1128
Wilhelm S, Buhlmann U, Tolin DF, et al. Augmentation of behavior therapy with D-cycloserine for obsessive–compulsive disorder. Am J Psychiatry. 2008;165:335–341. doi:10.1176/appi.ajp.2007.07050776

Memantine

Via non-competitive antagonism of NMDA receptors, memantine blocks pathological activation, excitation, and overstimulation by the amino acid glutamate, preventing damage to those receptors while preserving their normal synaptic function and physiological activity and modulating excitability of these neuronal circuits

Autism Spectrum Disorder/ Obsessive-Compulsive Disorder

- Memantine 20 mg/day adjunctive to risperidone 3 mg/day was more effective than risperidone alone in reducing irritability (primary outcome), hyperactivity, and stereotypic behavior in children with autism in RCT
- A head-to-head randomized trial of memantine (up to 20 mg/day) vs risperidone (up to 3 mg/day) in children with autism showed no significant differences between the two drugs for multiple Aberrant Behavior Checklist (ABC) subscales, though a larger proportion of patients receiving risperidone were rated as “very much improved” on the Clinical Global Impressions-Improvement scale (CGI-I)
- A recent RCT using weight-based memantine (range: 3–15 mg/day) in children with autism was not superior to placebo at 12 weeks on the primary outcome measure of Social Responsiveness Scale (SRS) score

- Memantine appears to be generally well tolerated by children with autism in RCTs
- Case report of memantine efficacy as an augmenting agent in treatment-resistant OCD; RCT underway to evaluate tolerability and safety of memantine as treatment for children with autism or OCD
- Improvements in verbal recognition memory observed in children with ASD, but treatment was not associated with improvements in apraxia and expressive language

Aman MG, Findling RL, Hardan AY, et al. Safety and efficacy of memantine in children with autism: Randomized, placebo-controlled study and open-label extension. J Child Adolesc Psychopharmacol. 2017;27(5):403–412. doi:10.1089/cap.2015.0146

Ghaleiha A, Asadabadi M, Mohammadi MR, et al. Memantine as adjunctive treatment to risperidone in children with autistic disorder: A randomized, double-blind, placebo-controlled trial. Int J Neuropsychopharmacol. 2013;16(4):783–789. doi:10.1017/S1461145712000880

Häge A, Banaschewski T, Buitelaar JK, et al. Glutamatergic medication in the treatment of obsessive compulsive disorder (OCD) and autism spectrum disorder (ASD) – study protocol for a randomised controlled trial. Trials. 2016;17(1):141. doi:10.1186/s13063-016-1266-8

Hezel DM, Beattie K, Stewart SE. Memantine as an augmenting agent for severe pediatric OCD. Am J Psychiatry. 2009;166(2):237. doi:10.1176/appi.ajp.2008.08091427

Hosenbocus S, Chahal R. Memantine: A review of possible uses in child and adolescent psychiatry. J Can Acad Child Adolesc Psychiatry. 2013;22(2):166–171. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3647634/

Nikvarz N, Alaghband-Rad J, Tehrani-Doost M, et al. Comparing efficacy and side effects of memantine vs. risperidone in the treatment of autistic disorder. Pharmacopsychiatry. 2017;50(1):19–25. doi:10.1055/s-0042-108449

Soorya LV, Fogg L, Ocampo E, et al. Neurocognitive outcomes from memantine: A pilot, double-blind, placebo-controlled trial in children with autism spectrum disorder. J Child Adolesc Psychopharmacol. 2021;31(7):475–484. doi:10.1089/cap.2021.0010

N-Acetylcysteine

May activate metabotropic glutamate receptors and facilitate dopamine release; reduces inflammatory cytokines and promotes cell survival, growth factor synthesis, and neurite sprouting

Excoriation Disorder/ Trichotillomania

- Dose: 1200–3000 mg/day
- Large, statistically significant benefit for trichotillomania in RCT in adults; a pediatric RCT in trichotillomania showed no benefit
- Statistically significant benefit for excoriation disorder in RCT in adults; case report in a child

Bloch MH, Panza KE, Grant JE, et al. N-acetylcysteine in the treatment of pediatric trichotillomania: A randomized, double-blind, placebo-controlled add-on trial. J Am Acad Child Adolesc Psychiatry. 2013;52(3):231–240. doi:10.1016/j.jaac.2012.12.020

Grant JE, Chamberlain SR, Redden SA, et al. N-acetylcysteine in the treatment of excoriation disorder: A randomized clinical trial. JAMA Psychiatry. 2016;73(5):490–496. doi:10.1001/jamapsychiatry.2016.0060

Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: A double-blind, placebo-controlled study. Arch Gen Psychiatry. 2009;66(7):756–763. doi:10.1001/archgenpsychiatry.2009.60

Percinel I, Yazici KU. Glutamatergic dysfunction in skin-picking disorder: Treatment of a pediatric patient with N-acetylcysteine. J Clin Psychopharmacol. 2014;34(6):772–774. doi:10.1097/JCP.0000000000000210

Anxiety Disorder/ Obsessive-Compulsive Disorder

- Case report of benefit as adjunct in SSRI-resistant anxiety in an adolescent
- Case report of benefit as adjunct in SSRI-resistant OCD in an adult
- Negative RCT of n-acetylcysteine 3000 mg/day augmentation of SSRI treatment for 16 weeks in adults with OCD compared to placebo

Costa DLC, Diniz JB, Requena G, et al. Randomized, double-blind, placebo-controlled trial of N-acetylcysteine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2017;78(7):e766–e773. doi:10.4088/JCP.16m11101

Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: Current therapeutic evidence and potential mechanisms of action. J Psychiatry Neurosci. 2011;36(2):78–86. doi:10.1503/jpn.100057

Lafleur DL, Pittenger C, Kelmendi B, et al. N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Psychopharmacology (Berl). 2006;184(2):254–256. doi:10.1007/s00213-005-0246-6

Cannabis Use Disorder

- N-acetylcysteine 1200 mg daily for 8 weeks was associated with increased rates of abstinence in adolescents seeking treatment for cannabis use disorder
- Other factors associated with abstinence in this study included low impulsivity, baseline negative cannabinoid testing, and adherence to treatment
- In contrast to prior findings in adolescents, RCT of n-acetylcysteine 1200 mg twice daily plus contingency management compared to placebo plus contingency management was not more efficacious in terms of abstinence rates in cannabis use disorder in adults

NMDA Agents (cont.)

Bentzley JP, Tomko RL, Gray KM. Low pretreatment impulsivity and high medication adherence increase the odds of abstinence in a trial of N-acetylcysteine in adolescents with cannabis use disorder. J Subst Abuse Treat. 2016;63:72–77. doi:10.1016/j.jsat.2015.12.003
Gray KM, Sonne SC, McClure EA. A randomized placebo-controlled trial of N-acetylcysteine for cannabis use disorder in adults. Drug Alcohol Depend. 2017;177:249–257. doi:10.1016/j.drugalcdep.2017.04.020

Autism Spectrum Disorder

- Several RCTs of n-acetylcysteine (monotherapy or adjunctive to risperidone) for treatment of irritability of autism with conflicting results
- Several but not all trials used the Aberrant Behavior Checklist Irritability Subscale (ABC-I) as the primary outcome measure
- N-acetylcysteine doses ranged from 500 to 2700 mg/day and were generally well tolerated

Dean OM, Gray KM, Villagonzalo KA, et al. A randomised, double blind, placebo-controlled trial of a fixed dose of N-acetyl cysteine in children with autistic disorder. Aust N Z J Psychiatry. 2017;51(3):241–249. doi:10.1177/0004867416652735
Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. BMC Psychiatry. 2013;13:196. doi:10.1186/1471-244X-13-196
Hardan AY, Fung LK, Libove RA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biol Psychiatry. 2012;71(11):956–961. doi:10.1016/j.biopsych.2012.01.014
Nikoo M, Radnia H, Farokhnia M, et al. N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: A randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. Clin Neuropharmacol. 2015;38(1):11–17. doi:10.1097/WNF.0000000000000063
Wink LK, Adams R, Wang Z, et al. A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. Mol Autism. 2016;7:26. doi:10.1186/s13229-016-0088-6

Riluzole

Riluzole (1) inactivates voltage-dependent sodium channels on glutamatergic nerve terminals, thereby blocking glutamatergic neurotransmission, (2) blocks some of the postsynaptic effects of glutamic acid by noncompetitive blockade of the NMDA receptors, and (3) blocks GABA reuptake

Anxiety Disorders/ Obsessive-Compulsive Disorder

- Dose: 50–100 mg/day (children and adolescents), 50–100 mg bid (adults)
- Several studies have shown efficacy in the treatment of OCD, trichotillomania, eating disorders, and skin-picking
- Open-label study and case series suggest benefit of riluzole augmentation in children and adults with treatment-refractory OCD
- Open-label studies have shown efficacy as sole treatment or augmenting agent in GAD
- Riluzole is fairly well tolerated by adults and children; common side effects include headache, nausea, and fatigue. Elevations in transaminase levels reported but none resulted in drug discontinuation. Single report of pancreatitis in one pediatric patient (fully recovered). Increased appetite and weight gain observed in children when used adjunctively to risperidone (over and above these effects with risperidone monotherapy)
- A recent RCT of adjunctive riluzole 100 mg/day did not result in significant improvement in childhood-onset OCD; one patient in the trial experienced a serious adverse effect (pancreatitis)

Grant PJ, Joseph LA, Farmer CA, et al. 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. Neuropsychopharmacology. 2014;39(6):1453–1459. doi:10.1038/npp.2013.343
Grant P, Song JY, Swedo SE. Review of the use of the glutamate antagonist riluzole in psychiatric disorders and a description of recent use in childhood obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2010;20(4):309–315. doi:10.1089/cap.2010.0009
Pittenger C, Kelmendi B, Wasylink S, et al. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: A series of 13 cases, with long-term follow-up. J Clin Psychopharmacol. 2008;28(3):363–367. doi:10.1097/JCP.0b013e3181727548
Rynn M, Puliafico A, Heleniak C, et al. Advances in pharmacotherapy for pediatric anxiety disorders. Depress Anxiety. 2011;28:76–87. doi:10.1002/da.20769

Autism Spectrum Disorder

- RCT of adjunctive riluzole 50–100 mg/day in children and adolescents treated with risperidone resulted in significant improvement on measures of irritability (primary outcome) as well as lethargy/social withdrawal, stereotypic behavior, and hyperactivity/noncompliance
- No effect of riluzole 200 mg/day on treatment-refractory irritability in pilot study of 8 patients with ASD

Ghaleiha A, Mohammadi E, Mohammadi MR, et al. Riluzole as an adjunctive therapy to risperidone for the treatment of irritability in children with autistic disorder: A double-blind, placebo-controlled, randomized trial. Paediatr Drugs. 2013;15(6):505–514. doi:10.1007/s40272-013-0036-2
Wink LK, Adams R, Horn PS, et al. A randomized placebo-controlled cross-over pilot study of riluzole for drug-refractory irritability in autism spectrum disorder. J Autism Dev Disord. 2018;48(9):3051–3060. doi:10.1007/s10803-018-3562-5

Miscellaneous

Bumetanide

Diuretic that depletes intracellular chloride and may reduce GABA-mediated activation of neurons with altered excitatory function in autism spectrum disorder (ASD)

Autism Spectrum Disorder

- Dose: 0.5 mg bid was the most studied and best tolerated dose
- Modest reductions in ASD symptoms in children observed following 3 months of bumetanide use in one RCT
- 20% of patients receiving bumetanide required potassium supplementation during the trial
- Bumetanide combined with applied behavior analysis (ABA) was superior to ABA alone in reducing ASD symptoms in young children in a pilot study
- Recent RCT found no superior effect on Social Responsiveness Scale-2, but suggested efficacy on repetitive behavior symptoms for a subset of patients. Hypokalemia and orthostatic hypotension occurred commonly

Du L, Shan L, Wang B, et al. A pilot study on the combination of applied behavior analysis and bumetanide treatment for children with autism. J Child Adolesc Psychopharmacol. 2015;25(7):585–588. doi:10.1089/cap.2015.0045
James BJ, Gales MA, Gales BJ. Bumetanide for autism spectrum disorder in children: A review of randomized controlled trials. Ann Pharmacother. 2019;53(5):537–544. doi:10.1177/1060028018817304
Lemonnier E, Degrez C, Phelep M, et al. A randomised controlled trial of bumetanide in the treatment of autism in children. Transl Psychiatry. 2012;2:e202. doi:10.1038/tp.2012.124
Sprengers JJ, van Andel DM, Zuithoff NPA, et al. Bumetanide for core symptoms of autism spectrum disorder (BAMBI): A single center, double-blinded, participant-randomized, placebo-controlled, phase-2 superiority trial. J Am Acad Child Adolesc Psychiatry. 2021;60(7):865–876. doi:10.1016/j.jaac.2020.07.888

Cannabidiol

- 30% CBD oil with 1:20 CBD:THC ratio (median dose of CBD 90 mg/day)
- Open-label study reported improvement in parent-rated symptoms of self-injury, hyperactivity, insomnia, and anxiety
- Adverse effects included somnolence and increased appetite

Barchel D, Stolar O, De-Haan T, et al. Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. Front Pharmacol. 2019;9:1521. doi:10.3389/fphar.2018.01521
Fusar-Poli L, Cavone V, Tinacci S, et al. Cannabinoids for people with ASD: A systematic review of published and ongoing studies. Brain Sci. 2020;10(9):572. doi:10.3390/brainsci10090572

Folinic Acid

- Folinic acid 2 mg/kg/day (up to 50 mg/day) reduced ABC subscale scores for inappropriate speech, stereotypic behavior, and hyperactivity
- High-dose folinic acid treatment 2 mg/kg/day (up to 50 mg/day) for 12 weeks resulted in improvement in verbal communication compared with placebo, particularly in patients with folate receptor-α autoantibodies

Batebi N, Moghaddam HS, Hasanzadeh A, et al. Folinic acid as adjunctive therapy in treatment of inappropriate speech in children with autism: A double-blind and placebo-controlled randomized trial. Child Psychiatry Hum Dev. 2021;52(5):928–938. doi:10.1007/s10578-020-01072-8
Frye RE, Slattery J, Delhey L, et al. Folinic acid improves verbal communication in children with autism and language impairment: A randomized double-blind placebo-controlled trial. Mol Psychiatry. 2018;23(2):247–256. doi:10.1038/mp.2016.168

Ketamine

- General improvement in depressive symptoms, decreased acute suicidality, and reduced mood lability observed in open-label study and case reports with IV/intranasal ketamine
- A single IV infusion of ketamine (0.5 mg/kg) in treatment-resistant adolescents significantly reduced depressive symptoms 24 h post-infusion compared with active placebo (midazolam) treatment

Dwyer JB, Landeros-Weisenberger A, Johnson JA, et al. Efficacy of intravenous ketamine in adolescent treatment-resistant depression: A randomized midazolam-controlled trial. Am J Psychiatry. 2021;178(4):352–362. doi:10.1176/appi.ajp.2020.20010018
Kim S, Rush BS, Rice TR. A systematic review of therapeutic ketamine use in children and adolescents with treatment-resistant mood disorders. Eur Child Adolesc Psychiatry. 2021;30(10):1485–1501. doi:10.1007/s00787-020-01542-3

NATURAL HEALTH PRODUCTS

General Comments

- Natural health products have been utilized in patients of all ages to treat a variety of psychiatric conditions. Only a few of these products have been subjected to scientific scrutiny through standardized research methods. Clinicians should be cognizant of medicolegal issues when recommending herbal/natural products for non-approved indications in children and adolescents
  - Beware the "naturalistic fallacy" – "natural" does not mean "healthier," or "more effective." Cyanide, lithium, and St. John's wort are all natural products with known toxicities
  - Standards and regulations are lax – many DNA analysis studies show that due to lack of regulation, natural products may not even contain the substance(s) advertised on the product label
  - Natural health products can cause harm – by delaying access to evidence-based treatments, adding economic burden to families, and the natural health product industry's tendency to create distrust in conventional medical systems
  - Complex disorders have the highest rates of natural health product use – autism, for example, may have rates of use above 50%; complex disorders are prone to "treatment switching"/"treatment shopping" when, in fact, fewer treatment switches and establishing consistent and communicative treatment teams is indicated
  - Natural health products are extremely profitable – the global market for herbal medicines eclipsed USD 100 billion in 2020
- With this knowledge, however, it is important not to be judgmental about patients or families looking to use natural health products, and to evaluate all products – whether conventional, herbal, or alternative – for their evidence base, their potential risks and benefits, and advise patients and families accordingly

Product Availability

Despite the lack of evidence, many patients (up to 50%) elect to try some form of complementary and alternative medicine intervention (often these are natural health products) to help ease their mental health condition. This chapter looks at the evidence and safety of some commonly used natural health products that are used for a variety of conditions. Although in most cases the optimum dose of the natural health product (herb or supplement) is not known, the most frequently studied dose is provided, along with the proposed mechanism of action.

Drug	Anxiety/Obsessive-Compulsive Disorder/Excoriation Disorder/ Onychophagia/Trichotillomania	Depression	Bipolar Disorder	Sleep Disorders	Schizophrenia	ADHD	Irritability of Autism	Substance Use Disorders
Ginkgo biloba (p. 407)		PR/+[(A)]				PR/S/C	PR/–	
Inositol (p. 407)	PR/+[(A)]	PR/+[(A)]	PR/+			PR/–		
Melatonin (p. 408)			PR/C	+		C		
N-acetylcysteine (p. 409)	PR/C	PR/C[(A)]	+[(A)]		C[(A)]	PR/+[(A)]	C/S	PR/C
Omega-3 fatty acids (p. 411)		PR/S/C	PR/+/S		PR/S/C	C	C	
St. John's wort (p. 414)		PR/+[†]						
Valerian (p. 415)		PR/C[(A)]		C				
Vitamins and minerals (p. 415)								
Iron						PR/S		
Vitamin B_6[‡]					PR/S[(A)]			
Vitamin B_9							PR/–	
Vitamin B_{12}	PR/+	PR/+					PR/–	
Vitamin C					PR/S[(A)]			

Drug	Anxiety/Obsessive-Compulsive Disorder/Excoriation Disorder/ Onychophagia/Trichotillomania	Depression	Bipolar Disorder	Sleep Disorders	Schizophrenia	ADHD	Irritability of Autism	Substance Use Disorders
Vitamin D					C[(A)]		PR/–	
Vitamin E[‡]					PR/S[(A)]			
Zinc						PR/S		

† Mild to moderate depression only; ‡ May be helpful in drug-induced movement disorders (e.g., tardive dyskinesia) [(A)] Adult data only

C = contradictory results, + = positive findings, – = negative findings, PR = preliminary data, S = synergistic/adjunctive effect

Ginkgo Biloba

- Active ginkgolides obtained from the leaves of one of the oldest deciduous trees in the world (ginkgo – also called Maidenhair tree or kew tree). Standardized products contain flavone glycosides (24%) and terpenoids (6%)
- Appears to increase vascular circulation, has well documented antioxidant and free radical scavenging effects; inhibits adenosine diphosphate- and collagen-induced platelet aggregation; also inhibits binding of platelet activating factor, decreasing blood coagulation; may increase cholinergic transmission by inhibiting acetylcholinesterase; may have anticonvulsant activity through elevation of GABA levels
- Available by prescription in many parts of Europe

ADHD

- Dosing: 50–120 mg/day
- Open-label study suggests benefit of ginkgo biloba in combination with *panax quinquefolium* (American ginseng extract) 200 mg in children aged 3–17; improvement noted in hyperactivity, impulsiveness, and social problems
- Modest reduction in inattentive symptoms with standardized extract of gingko biloba compared to placebo as adjunct to methylphenidate treatment in small RCT
- Ginkgo biloba was less effective than methylphenidate for ADHD symptoms in an RCT in children

Salehi B, Imani R, Mohammadi MR, et al. Ginkgo biloba for attention-deficit/hyperactivity disorder in children and adolescents: A double blind, randomized controlled trial. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(1):76–80. doi:10.1016/j.pnpbp.2009.09.026
Shakibaei F, Radmanesh M, Salari E, et al. Ginkgo biloba in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. A randomized, placebo-controlled, trial. Complement Ther Clin Pract. 2015;21(2):61–67. doi:10.1016/j.ctcp.2015.04.001

Autism Spectrum Disorder

- Dosing: 80–120 mg/day
- Randomized, double-blind, placebo-controlled study of ginkgo biloba adjunctive to risperidone in 47 children showed no additional benefit in ABC-C scale

Hasanzadeh E, Mohammadi MR, Ghanizadeh A, et al. A double-blind placebo controlled trial of Ginkgo biloba added to risperidone in patients with autistic disorders. Child Psychiatry Hum Dev. 2012;43(5):674–682. doi:10.1007/s10578-012-0292-3

Depression

- Dosing: 40 mg 3 times/day
- In a randomized study, ginkgo biloba adjunctive to venlafaxine group showed greater improvement in depressive symptoms, neurological defect, and living function compared to venlafaxine-only group in treating post-stroke depression; ginkgo biloba group also needed lower dose of venlafaxine and experienced fewer adverse events (adult data)

Liang Z, Jia Y, Wang M, et al. Efficacy of ginkgo biloba extract as augmentation of venlafaxine in treating post-stroke depression. Neuropsychiatr Dis Treat. 2019;15:2551–2557. doi: 10.2147/NDT.S215191

Inositol

- A natural isomer of glucose (sometimes referred to as vitamin B_8) that is a constituent of the second messenger system, which is linked to serotonin, norepinephrine, and cholinergic receptors
- Myo-inositol is a common form in supplements
- Limited research suggests inositol *may* have benefits similar to SSRIs
- Occurs naturally in many foods (nuts, legumes, whole grains)
- Typical adult diet contains 1 g/day of inositol

Natural Health Products (cont.)

Anxiety Disorders

- Dosing: 6–18 g/day
- Preliminary data suggest efficacy in treating panic, phobic disorders, obsessive-compulsive disorder, and trichotillomania
- 4-week double-blind controlled randomized crossover study suggests inositol has similar effects as fluvoxamine in treatment of panic disorder (adult data)

Larzelere M, Campbell J, Robertson, M. Complementary and alternative medicine usage for behavioral health indications. Prim Care Clin Office Pract. 2010;37:213–236. doi:10.1016/j.pop.2010.02.002
Levine J. Controlled trials of inositol in psychiatry. Eur Neuropsychopharmacol. 1997;7(2):147–155.
Palatnik A, Frolov K, Fux M, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. J Clin Psychopharmacol. 2001;21(3):335–339.
Seedat S, Stein DJ, Harvey BH. Inositol in the treatment of trichotillomania and compulsive skin picking. J Clin Psychiatry. 2001;62(1):60–61.

ADHD

- Dosing: 200 mg/kg
- In a double-blind, cross-over, placebo-controlled study with 11 patients, inositol for 8 weeks aggravated symptoms of ADHD compared to dextrose (placebo) in children (mean age 8.9 ± 3.6 years)

Levine J, Ring A, Barak Y, et al. Inositol may worsin [sic] attention deficit disorder with hyperactivity. Hum Psychopharmacol. 1995;10(6):481–484. doi:10.1002/hup.470100608

Bipolar Disorder

- Dosing: 2 g/day if weight 25 kg or greater; 80 mg/kg/day rounded down to nearest 500 mg capsule if weight less than 25 kg
- A 12-week, randomized, double-blind, controlled pilot study with 17 patients showed inositol plus high EPA omega-3 fatty acids (6 capsules; 975 mg EPA and 675 mg DHA) group showed greater benefit than inositol plus placebo group and omega-3 fatty acids plus placebo group in reducing symptoms of mania and depression in children (age 5–12 years) with mild to moderate bipolar spectrum disorders; completion rate was 54%

Wozniak J, Faraone SV, Chan J, et al. A randomized clinical trial of high eicosapentaenoic acid omega-3 fatty acids and inositol as monotherapy and in combination in the treatment of pediatric bipolar spectrum disorders: A pilot study. J Clin Psychiatry. 2015;76(11):1548–1555. doi:10.4088/JCP.14m09267

Depression

- Dosing: 12 g/day
- 4-week double-blind randomized study showed significantly improved mood compared to placebo (adult data)
- Further studies required before use can be recommended

Levine J, Barak Y, Gonsalves M, et al. Double-blind controlled trial of inositol treatment of depression. Am J Psychiatry. 1995;152:792–794.
Mukai T, Kishi T, Matsuda Y, et al. A meta-analysis of inositol for depression and anxiety disorders. Hum Psychopharmacol. 2014;29(1):55–63. doi:10.1002/hup.2369

Melatonin

- Hormone produced by the pineal gland involved in regulation of circadian rhythms
- Dietary supplement in the USA, not regulated by FDA with regard to purity, efficacy, or safety, but standardized forms may be available; standardized formulations are licensed Natural Health Products in Canada
- Physiological synthesis and release of melatonin is stimulated by darkness (use room darkening shades) and inhibited by light exposure
- Acts on MT_1 and MT_2 receptors in the hypothalamic suprachiasmatic nuclei (master circadian clock site)
- Melatonin levels typically peak between 2 and 4 a.m.; physiologically, levels are highest between 1 and 3 years of age
- Many brands have been found to contain impurities as well as dissimilar amounts of actual hormone (https://www.consumerlab.com/ is a useful reference to look for brand quality)

Sleep Disorders

- Dosing: 1–12 mg/day (0.3 mg = physiological dose); children with neurological disorders may require higher doses; the administration of exogenous melatonin does not appear to affect endogenous production or secretion
- Peak plasma concentrations achieved within 60 min; metabolized by the liver; elimination half-life = 20–50 min
- A systematic review of 19 RCTs including 1021 patients showed short-term use (1–13 weeks) of melatonin (1–12 mg/day) improved sleep latency (mean 28 min), sleep duration (mean 33 min), and wake time after sleep onset, but not number of awakenings per night. Improvement in sleep was greatest in children with autism spectrum disorder, followed by neurodevelopmental disorders and ADHD, and smallest in adolescents and children with chronic delayed sleep onset. No improvement in behavior, quality of life, or global assessment in children with ADHD
- In a meta-analysis of 7 RCTs with 378 patients, fast-release melatonin (1–6 mg/day) for one to four weeks improved sleep onset time (mean 37 min), sleep onset latency (mean 22 min), and total sleep time (mean 23 min) in children and adolescents with high comorbidity of ADHD

- Multiple long-term follow-up studies (1–3.8 years) of melatonin (2–15 mg/night) showed long-term effectiveness and safety in children and adolescents with neurodevelopmental disabilities who had participated in RCTs. In one study (2-year follow-up) of children and adolescents with autism spectrum disorder, changes in weight, height, BMI, and pubertal status were within normal ranges for age
- Melatonin and CBT combination superior to either intervention alone for reducing persistent insomnia symptoms in children with autism spectrum disorder
- Useful in circadian-based sleep disorders – can shift circadian rhythms if taken when physiological plasma levels of melatonin are low (i.e., noon–evening)
- May be more effective given 2 h before bedtime, or may exert hypnotic effect only when endogenous concentrations of melatonin are low
- Data contradictory as to benefit for secondary sleep disorders (e.g., jet-lag, insomnia due to depression)
- May be helpful for medically ill patients with insomnia for whom conventional hypnotics may be problematic
- Reported to improve sleep quality in patients with diabetes with high HbA1C concentrations (adult data)
- May facilitate withdrawal from benzodiazepines (which can decrease nocturnal melatonin production)
- Shown to improve sleep efficiency in patients with schizophrenia, in double-blind study (adult data)
- Not recommended in patients with autoimmune disorders since melatonin may play a role in immune function
- Adverse effects:
  - Adverse effects are mild/rare (likely safe when used for short duration at doses of 5 mg/day or less)
  - Drowsiness is one of the most common side effects; patients should not drive or operate machinery after taking melatonin
  - High dose: Vivid dreams/nightmares, abdominal cramps , fatigue, headache, dizziness, daytime fatigue, and increased irritability
  - Very high doses (more than 75 mg): Exacerbate depression, cause coagulation abnormalities, and inhibit ovulation
  - Case reports of worsening of seizures in children with seizure disorders
- Drug interactions:
  - Caution in patients taking warfarin or other agents that affect coagulation
  - CNS depressants (including benzodiazepines and alcohol) should be avoided
  - Drugs that inhibit CYP1A2 can increase plasma levels of melatonin; also, drugs metabolized by CYP1A2 can increase plasma levels of melatonin via competitive metabolism

McDonagh MS, Holmes R, Hsu F. Pharmacologic treatments for sleep disorders in children: A systematic review. J Child Neurol. 2019;34(5):237–247. doi:10.1177/0883073818821030
Wei S, Smits MG, Tang X, et al. Efficacy and safety of melatonin treatment for sleep onset insomnia in children and adolescents: A meta-analysis of randomized controlled trials. Sleep Med. 2020;68:1–8. doi:10.1016/j.sleep.2019.02.017

Autism Spectrum Disorder

- Dosing: 3 mg/day
- Case report of improving restricted and repetitive behaviors in a 18-year-old boy who failed aripiprazole, risperidone, and sertraline

Poyraz Fındık OT, Gümüştaş F. Melatonin for restrictive repetitive behaviours in a young adult with autism: A case report. Psychiatr Danub. 2021;33(4):580–582. doi:10.24869/psyd.2021.580

Bipolar Disorder

- Case report of rapidly improving insomnia, aborting mania, and stabilizing bipolar disorder in a boy who failed lithium, carbamazepine, and valproic acid; improvement with melatonin 3 mg at age 8 then, with melatonin 12 mg and alprazolam at age 10
- A negative double-blind, placebo-controlled RCT for hypomania and mania; poor design – patients continued their existing medication and psychiatric teams were free to add or remove medication during the trial (adult data)

Robertson JM, Tanguay PE. Case study: The use of melatonin in a boy with refractory bipolar disorder. J Am Acad Child Adolesc Psychiatry. 1997;36(6):822–825. doi:10.1097/00004583-199706000-00020

N-acetylcysteine (NAC)

- Primarily used in medicine as an antidote for acetaminophen toxicity, as a mucolytic, a renal protectant, to prevent atrial fibrillation, and as an adjunct therapy in HIV
- Psychiatric uses have been studied and in the past decades, clinical studies and reports have begun to emerge in a variety of psychiatric conditions
- NAC may modulate oxidative stress, neurogenesis/neuronal apoptosis, mitochondrial dysfunction, inflammation, and receptors for glutamate and dopamine
- NAC may have a significant role in long-term neuronal adaptation and metaplasticity
- Adverse effects are generally mild, with very few of the studies below having any patients who discontinued due to adverse effects. Common side effects included abdominal discomfort, nausea, headaches, and musculoskeletal pain

Natural Health Products (cont.)

Deepmala, Slattery J, Kumar N, et al. Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. Neurosci Biobehav Rev. 2015;55:294–321. doi:10.1016/j.neubiorev.2015.04.015
Minarini A, Ferrari S, Galletti M, et al. N-acetylcysteine in the treatment of psychiatric disorders: Current status and future prospects. Expert Opin Drug Metab Toxicol. 2017;13(3):279–292. doi:10.1080/17425255.2017.1251580

Substance Use Disorders

- Dosing: 1200 mg twice/day
- In a double-blind RCT, NAC (1200 mg twice/day) for 8 weeks increased rates of abstinence compared to placebo in adolescents seeking treatment for cannabis use disorder; all participants had contingency management and brief weekly cessation counseling
- Two post hoc analyses: One showed no significant difference between NAC and placebo groups, suggesting NAC may work via a mechanism not related to craving. Another showed impulsivity, baseline negative cannabinoid test, and adherence to treatment increased the odds of abstinence
- In contrast to prior findings in adolescents, RCT of NAC 1200 mg twice/day plus contingency management compared to placebo plus contingency management was not more efficacious in terms of abstinence rates in cannabis use disorder in adults
- Small RCTs for other substances of abuse (e.g., cocaine, methamphetamine, nicotine) in adults only – NAC decreased craving compared to placebo

Gray KM, Carpenter MJ, Baker NL, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. Am J Psychiatry. 2012;169(8):805–812. doi:10.1176/appi.ajp.2012.12010055

Anxiety Disorder/ Obsessive-Compulsive Disorder

- Dosing: Initial 600–900 mg/day, gradually increase to 2400–2700 mg/day
- Two positive but low-quality RCTs in children and adolescents – NAC decreased Y-BOCS compared to placebo, but one study was underpowered and the other started various SSRIs at the same time
- Systematic review of adult RCTs for OCD contradictory results
- Case report of benefit as adjunct in SSRI-resistant anxiety in an adolescent

Ghanizadeh A, Mohammadi MR, Bahraini S, et al. Efficacy of N-acetylcysteine augmentation on obsessive compulsive disorder: A multicenter randomized double blind placebo controlled clinical trial. Iran J Psychiatry. 2017;12(2):134–141.
Li F, Welling MC, Johnson JA, et al. N-acetylcysteine for pediatric obsessive-compulsive disorder: A small pilot study. J Child Adolesc Psychopharmacol. 2020;30(1):32–37. doi:10.1089/cap.2019.0041

Excoriation Disorder/ Onychophagia/Trichotillomania

- Dosing: 1200–3000 mg/day
- Statistically significant benefit for excoriation disorder in RCT in adults; case report in a child
- One RCT in children and adolescents for chronic nail biting; NAC increased nail length after first month but no difference after two months compared to placebo
- Three positive case reports for nail biting in adults
- Large, statistically significant benefit for trichotillomania in RCT in adults; a pediatric RCT in trichotillomania showed no benefit

Bloch MH, Panza KE, Grant JE, et al. N-acetylcysteine in the treatment of pediatric trichotillomania: A randomized, double-blind, placebo-controlled add-on trial. J Am Acad Child Adolesc Psychiatry. 2013;52(3):231–240. doi:10.1016/j.jaac.2012.12.020
Ghanizadeh A, Derakhshan N, Berk M. N-acetylcysteine versus placebo for treating nail biting, a double blind randomized placebo controlled clinical trial. Antiinflamm Antiallergy Agents Med Chem. 2013;12(3):223–228. doi:10.2174/1871523011312030003
Grant JE, Chamberlain SR, Redden SA, et al. N-acetylcysteine in the treatment of excoriation disorder: A randomized clinical trial. JAMA Psychiatry. 2016;73(5):490–496. doi:10.1001/jamapsychiatry.2016.0060

ADHD

- Dosing: 1200 mg twice/day / 2400 mg twice/day (adult data)
- One RCT in adults including 24 patients showed ADHD symptoms elevated in patients with systemic lupus erythematosus (SLE) compared to healthy controls and NAC daily for 3 months improved ADHD symptoms compared to placebo

Garcia RJ, Francis L, Dawood M, et al. Attention deficit and hyperactivity disorder scores are elevated and respond to N-acetylcysteine treatment in patients with systemic lupus erythematosus. Arthritis Rheum. 2013;65(5):1313–1318. doi:10.1002/art.37893

Autism Spectrum Disorder

- Dosing: 500–2700 mg/day for monotherapy and 600–1200 mg/day for adjunctive treatment; generally well tolerated

- Meta-analysis of RCTs of NAC (monotherapy or adjunctive to risperidone) for treatment of irritability of autism showed nonsignificant effect of NAC compared to placebo
- In a meta-analysis of same RCTs excluding one RCT that recruited children with less severe conditions there was a significant effect on irritability and hyperactivity
- Several but not all trials used the Aberrant Behavior Checklist Irritability Subscale (ABC-I) as the primary outcome measure

Lee T, Lee K, Lee C, et al. Effectiveness of N-acetylcysteine in autism spectrum disorders: A meta-analysis of randomized controlled trials. Aust N Z J Psychiatry. 2021;55(2):196–206. doi:10.1177/0004867420952540
Liu Y, Yang Z, Du Y, et al. Antioxidant interventions in autism spectrum disorders: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2022;113:110476. doi:10.1016/j.pnpbp.2021.110476

Bipolar Disorder

- Dosing: 1000–3000 mg/day for adjunctive treatment
- Systematic review and meta-analysis suggesting augmentation with NAC for bipolar depression appears superior to placebo with a moderate effect size but a large confidence interval (adult data)
- CANMAT 2018 guidelines recommend NAC as third-line adjunctive treatment for acute bipolar I depression (level 3 evidence) and bipolar II depression (level 4 evidence) (adult data)

Nery FG, Li W, DelBello MP, et al. N-acetylcysteine as an adjunctive treatment for bipolar depression: A systematic review and meta-analysis of randomized controlled trials. Bipolar Disord. 2021;23(7):707–714. doi:10.1111/bdi.13039

Major Depressive Disorder

- Dosing: 1000 mg twice/day (adult data)
- RCT in adults – heterogeneous results: Decrease in some scales of depression at 16 weeks, no changes in others when used as an adjunct or monotherapy; significant for more severe depression

Berk M, Dean OM, Cotton SM, et al. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: A double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2014;75(6):628–636. doi:10.4088/JCP.13m08454

Schizophrenia

- Dosing: 1200–2000 mg/day as adjunctive treatment (adult data)
- Three adult RCTs showed NAC adjunct to usual antipsychotic improved negative PANSS score compared to placebo; conflicting results for positive and overall PANSS scores

Berk M, Munib A, Dean O, et al. Qualitative methods in early-phase drug trials: Broadening the scope of data and methods from an RCT of N-acetylcysteine in schizophrenia. J Clin Psychiatry. 2011;72(7):909–913. doi:10.4088/JCP.09m05741yel
Farokhnia M, Azarkolah A, Adinehfar F, et al. N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. Clin Neuropharmacol. 2013;36(6):185–192. doi:10.1097/WNF.0000000000000001
Sepehrmanesh Z, Heidary M, Akasheh N, et al. Therapeutic effect of adjunctive N-acetyl cysteine (NAC) on symptoms of chronic schizophrenia: A double-blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry. 2018;82:289–296. doi:10.1016/j.pnpbp.2017.11.001

Omega-3 Polyunsaturated Fatty Acids

- Best source for these essential polyunsaturated fatty acids (PUFAs) is fatty fish (e.g., mackerel, halibut, salmon), as this contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
- Other sources are green leafy vegetables, nuts, flaxseed oil, and canola oil; all contain alpha-linolenic acid (ALA), which can be converted (only 5–10%) to EPA and DHA
- May slow nerve signaling and alter cell membrane composition at neuron synapses, normalizing faulty neurotransmission
- Fish oils are also known to have anti-inflammatory properties

ADHD

- Suggested that relative deficiencies in highly unsaturated fatty acids may be implicated in some of the behavioral and learning problems associated with ADHD
- Earlier studies used Efamol (evening primrose oil (contained gamma-linolenic acid (GLA); omega-6 fatty acids) or DHA
- Dosage ranges from 500 mg to 4 g/day depending on age and weight
- Systematic reviews of 2019 and 2021 and meta-analyses suggest no benefit from omega-3 fatty acids on ADHD symptoms compared to placebo
- A 2018 systematic review and recent meta-analysis point to a modest but significant benefit from omega-3 fatty acids on ADHD symptoms with higher doses of EPA (greater than 500 mg/day)
- A 2012 Cochrane review of 13 trials with 1011 patients concluded that there is very little evidence that fish oils alone provide benefit for children/adolescents with ADHD

Natural Health Products (cont.)

- Contradictory results reported in double-blind studies in combination with psychostimulants (d-amphetamine) in children with ADHD; augmentation studies also inconclusive
- In a double-blind, randomized, placebo-controlled trial of 120 children with subthreshold ADHD, omega-3 fatty acids in combination with Korean red ginseng (*Panax ginseng*) for 12 weeks significantly decreased ADHD total score and inattention score (effect sizes 0.4 and 0.5 respectively)

Abdullah M, Jowett B, Whittaker PJ, et al. The effectiveness of omega-3 supplementation in reducing ADHD associated symptoms in children as measured by the Conners' rating scales: A systematic review of randomized controlled trials. J Psychiatr Res. 2019;110:64–73. doi:10.1016/j.jpsychires.2018.12.002
Chang JC, Su KP, Mondelli V, et al. Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder (ADHD): A systematic review and meta-analysis of clinical trials and biological studies. Neuropsychopharmacology. 2018;43(3):534–545. doi:10.1038/npp.2017.160
Gillies D, Sinn JKh, Lad SS, et al. Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Cochrane Database Syst Rev. 2012;(7):CD007986. doi:10.1002/14651858.CD007986.pub2
Händel MN, Rohde JF, Rimestad ML, et al. Efficacy and safety of polyunsaturated fatty acids supplementation in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents: A systematic review and meta-analysis of clinical trials. Nutrients. 2021;13(4):1226. doi:10.3390/nu13041226

Autism Spectrum Disorder

- A 2020 systematic review and meta-analysis of 9 RCTs with 405 patients found low strength of evidence for polyunsaturated fatty acids (DHA with or without EPA) supplementation in autism spectrum disorder, thus they are not recommended
- A 2011 Cochrane review of 2 RCTs with 37 patients showed no benefit of omega-3 fatty acids in autism spectrum disorder
- Data contradictory for irritability associated with autism in RCTs
- In a small, single-blind pilot RCT of toddlers (mean age 27 months) born at $\leq$ 29 weeks of gestation, omega-3-6-9 fatty acids liquid supplementation reduced core symptoms of autism at 90 days compared to placebo. However, follow-up suggests autism spectrum diagnosis or symptoms were not different between the groups at mean age 70 months

De Crescenzo F, D'Alò GL, Morgano GP, et al. Impact of polyunsaturated fatty acids on patient-important outcomes in children and adolescents with autism spectrum disorder: A systematic review. Health Qual Life Outcomes. 2020;18(1):28. doi:10.1186/s12955-020-01284-5
James S, Montgomery P, Williams W. Omega-3 fatty acids supplementation for autism spectrum disorders (ASD). Cochrane Database Syst Rev. 2011;(11):CD007992. doi:10.1002/14651858.CD007992.pub2

Bipolar Disorder

- Monotherapy open-label study with 20 patients: In children and adolescents with bipolar disorder, omega-3 monotherapy showed modest reduction in Young Mania Rating Scale (YMRS) and small response rate
- Adjunct open-label study including 18 patients: In adolescents with bipolar disorder, omega-3 supplementation adjunct to standard pharmacotherapy lowered ratings of mania and depression, and improved global functioning at 6 weeks
- A double-blinded, placebo-controlled trial with 56 patients: In adolescents with depressive disorder and at high risk of developing bipolar I disorder, 12-week fish oil monotherapy produced significant but similar reduction in depression symptom severity compared to placebo; both groups had nonsignificant reduction in YMRS

Clayton EH, Hanstock TL, Hirneth SJ, et al. Reduced mania and depression in juvenile bipolar disorder associated with long-chain omega-3 polyunsaturated fatty acid supplementation. Eur J Clin Nutr. 2009;63(8):1037–1040. doi:10.1038/ejcn.2008.81
McNamara RK, Strawn JR, Tallman MJ, et al. Effects of fish oil monotherapy on depression and prefrontal neurochemistry in adolescents at high risk for bipolar I disorder: A 12-week placebo-controlled proton magnetic resonance spectroscopy trial. J Child Adolesc Psychopharmacol. 2020;30(5):293–305. doi:10.1089/cap.2019.0124
Wozniak J, Biederman J, Mick E, et al. Omega-3 fatty acid monotherapy for pediatric bipolar disorder: A prospective open-label trial. Eur Neuropsychopharmacol. 2007;17(6–7):440–447. doi:10.1016/j.euroneuro.2006.11.006

Depression

- Dosing: 1–4 g/day (EPA + DHA)
- Monotherapy double-blinded RCT including 51 patients: In adolescents/adults aged 12–19, omega-3 supplementation (1.2–3.6 g/day; EPA:DHA ratio 2:1) for 10 weeks was not superior to placebo in reducing depression severity, anhedonia, irritability, or suicidality. Both groups significantly improved depression severity
- Monotherapy double-blinded pilot trial with 20 patients: In children aged 6–12, omega-3 fatty acids at a dose of 600 mg/day (400 mg EPA, 200 mg DHA) significantly reduced scores on the CDRS-R at 16 weeks compared to placebo. Placebo response was uncharacteristically small for a pediatric depression trial

- Adjuvant double-blind RCT with 60 patients: A Slovakian trial of children aged 11–17; omega-3 adjuvant at a dose of 2400 mg/day (1000 mg EPA, 750 mg DHA) to standard antidepressant therapy significantly reduced depression rating scores after 6 and 12 weeks compared to omega-6 adjuvant. Reduction in score was greater in depressive disorder subgroup compared to mixed anxiety and depression disorder subgroup
- A 2021 Cochrane review of 34 trials including 1924 patients concluded that omega-3 supplementation does not have a clinically significant effect on depression compared to placebo (adult data)
- One meta-analysis studied the effects of EPA and concluded that supplements with EPA greater than or equal to 60% showed benefit on standardized mean depression scores (vs. supplements with EPA less than 60%) (adult data)
- CANMAT 2016 guidelines state that omega-3 fatty acids have level 1 evidence of efficacy but, because of the inconsistency in the evidence, are recommended as second-line monotherapy for mild to moderate MDD and adjunctive to antidepressants for moderate to severe MDD (adult data)
- Well tolerated in children and adolescents; mild gastrointestinal effects, foul breath, and unpleasant fishy taste reported; this may be reduced by taking an enteric-coated formulation

Gabbay V, Freed RD, Alonso CM, et al. A double-blind placebo-controlled trial of omega-3 fatty acids as a monotherapy for adolescent depression. J Clin Psychiatry. 2018;79(4):17m11596. doi:10.4088/JCP.17m11596
Nemets H, Nemets B, Apter A, et al. Omega-3 treatment of childhood depression: A controlled, double-blind pilot study. Am J Psychiatry 2006;163:1098–1100. doi:10.1176/appi.ajp.163.6.1098
Ravindran AV, Balneaves LG, Faulkner G, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical guidelines for the management of adults with major depressive disorder: Section 5. Complementary and alternative medicine treatments. Can J Psychiatry. 2016;61(9):576–587. doi:10.1177/0706743716660290
Trebatická J, Hradečná Z, Surovcová A, et al. Omega-3 fatty-acids modulate symptoms of depressive disorder, serum levels of omega-3 fatty acids and omega-6/omega-3 ratio in children: A randomized, double-blind and controlled trial. Psychiatry Res. 2020;287:112911. doi:10.1016/j.psychres.2020.112911

Schizophrenia Prodrome

- Dosing: 1.2–1.4 g/day (EPA + DHA)
- An RCT of omega-3 fatty acids at a dose of 1.2 g/day (as 700 mg EPA, 480 mg DHA, 7.6 mg tocopherol) or placebo for 12 weeks reduced the risk of progression to schizophrenia in adolescents and young adults at ultra-high risk of psychotic disorder at 1 year and after mean 6.7 years of follow-up. (Number needed to treat to prevent progression at 12 months was 5)
- A multicenter RCT of over 300 ultra-high risk psychosis patients (late adolescent/early adult age range) who received omega-3 fatty acids at a dose of 1.4 g/day (as 840 mg EPA and 560 mg DHA) or placebo for 6 months showed no significant difference in reducing conversion to schizophrenia, though patients in both groups received up to 20 sessions of concurrent cognitive behavioral case management
- Significant heterogeneity and competing results, with the larger trial result being clearly non-significant. Omega-3 fatty acids are currently not recommended for psychosis prophylaxis in patients at ultra-high risk for psychotic disorders but minimal harm was associated with their use

Amminger GP, Schäfer MR, Papageorgiou K, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: A randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010;67(2):146–154. doi:10.1001/archgenpsychiatry.2009.192
Amminger GP, Schäfer MR, Schlögelhofer M, et al. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. Nat Commun. 2015;6:7934. doi:10.1038/ncomms8934
McGorry PD, Nelson B, Markulev C, et al. Effect of ω-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: The NEURAPRO randomized clinical trial. JAMA Psychiatry. 2017;74(1):19–27. doi:10.1001/jamapsychiatry.2016.2902
Mossaheb N, Schäfer MR, Schlöglhofer M, et al. Effect of omega-3 fatty acids for indicated prevention of young patients at risk for psychosis: When do they begin to be effective? Schizophr Res. 2013;148(1–3):163–167. doi:10.1016/j.schres.2013.05.027

Schizophrenia

- Dosing: 1–4 g/day (EPA + DHA)
- E-EPA (ethyleicosapentanoate) suggested to inhibit phospholipase A_2, an enzyme found to be overactive in patients with schizophrenia and may be responsible for depletion of arachidonic acid from brain and red cell phospholipids in these patients
- Post hoc analysis of omega-3 use in young patients with schizophrenia suggests delayed onset of action to reduce positive symptoms, negative symptoms, and improve global functioning
- Systematic review of 26 studies concluded effect of omega-3 fatty acids on first-episode schizophrenia and chronic schizophrenia are inconclusive (adult data)
- Cochrane review of 8 studies reported that evidence for omega-3 fatty acids in patients with schizophrenia is inconclusive; reduction in PANSS scores was not clinically significant (adult data)
- Conflicting data for metabolic adverse effects: Omega-3 fatty acids decreased triglycerides level in one RCT, and waist circumference (but not triglycerides level) in another RCT in patients with schizophrenia treated with second-generation antipsychotics (adult data)

Natural Health Products (cont.)

- Conflicting data for tardive dyskinesia: In placebo-controlled RCTs, E-EPA improved tardive dyskinesia, but DHA did not improve tardive dyskinesia (adult data)
- Review of double-blind studies suggests E-EPA (at a dose of 2 g/day) can augment effects of clozapine in treatment-refractory patients (adult data)

Fusar-Poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. J Clin Psychopharmacol. 2012;32(2):179–185. doi:10.1097/JCP.0b013e318248b7bb
Hsu M, Ouyang W. A systematic review of effectiveness of omega-3 fatty acid supplementation on symptoms, social functions, and neurobiological variables in schizophrenia. Biol Res Nurs. 2021;23(4):723–737. doi:10.1177/10998004211020121
Irving CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia. Cochrane Database Syst Rev. 2006;(3):CD001257. doi:10.1002/14651858.CD001257.pub2

St. John's Wort (*Hypericum perforatum*)

- Two most active components thought to be hypericin and hyperforin – standardized products contain 0.3% hypericin and/or 2–5% hyperforin
- Inhibits reuptake of 5-HT, NE, DA, GABA, and L-glutamate
- The half-life of hypericin, pseudohypericin, and hyperforin (the most implicated active ingredients) ranges from 9–30 h
- May cause increase in 5-HT receptors

Depression

- Dosing: 150–300 mg of standardized 0.3% hypericin (or 2–5% hyperforin) 3 times per day (open-label data)
- Two open-label studies in children and adolescents with MDD showed good response, however, one study had a high dropout rate due to continuing depression or noncompliance
- Post-marketing surveillance reports efficacy and good tolerability in 101 children under age 12 with mild to moderate depression
- Effective for major depression: Two independent meta-analyses of 27 and 29 clinical trials suggests that St. John's wort extracts are superior to placebo in patients with major depression, are similarly effective as standard antidepressants, and have fewer side effects/dropouts than standard antidepressants (adult data)
- St. John's wort does not seem to be effective in severe depression according to 2 well-designed trials (adult data)
- Adverse effects are rare and less common than with conventional antidepressants:
  - Most common: GI problems, dry mouth, sedation, fatigue, headache, anxiety or restlessness
  - Others may include: Serotonin syndrome, photosensitivity, increased hepatic enzymes, hepatitis, erythema, and cases of mania and hypomania in bipolar patients, including irritability, disinhibition, agitation, anger, decreased concentration, and disrupted sleep
- **Contraindications:** In pregnancy, lactation, schizophrenia (case reports of inducing psychosis), and bipolar disorder (case reports of hypomania or mania)
- Interactions:
  - Potent inducer of CYP3A4 (and, to a lesser extent, CYP2C9 and CYP1A2) and the p-glycoprotein transporter; case report of decreased plasma level of drugs metabolized by these systems, including cyclosporine (30–70% decrease has resulted in rejection of transplanted organ); also reported to decrease plasma level of indinavir (57% decrease in AUC), digoxin (up to 25% decrease in AUC), theophylline, imatinib, irinotecan, amitriptyline, barbiturates, alprazolam, methadone, opioids, phenytoin, and warfarin; breakthrough bleeding and cases of pregnancy reported in patients taking oral contraceptives; may interact with other drugs metabolized by these enzymes
  - Low-dose hyperforin (less than 4 mg) preparations may not affect p-glycoprotein expression
  - Several cases of serotonin syndrome reported in combination with serotonergic drugs

Findling RL, McNamara NK, O'Riordan MA, et al. An open-label pilot study of St. John's wort in juvenile depression. J Am Acad Child Adolesc Psychiatry. 2003;42(8):908–914. doi:10.1097/01.CHI.0000046900.27264.2A
Hübner WD, Kirste T. Experience with St John's Wort (Hypericum perforatum) in children under 12 years with symptoms of depression and psychovegetative disturbances. Phytother Res. 2001;15(4):367–370. doi:10.1002/ptr.829
Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: An updated systematic review. Drugs. 2009;69(13):1777–1798. doi:10.2165/11317010-000000000-00000
Linde K, Berner MM, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev. 2008;(4):CD000448. doi:10.1002/14651858.CD000448.pub3
Ng QX, Venkatanarayanan N, Ho CY. Clinical use of Hypericum perforatum (St John's wort) in depression: A meta-analysis. J Affect Disord. 2017;210:211–221. doi:10.1016/j.jad.2016.12.048
Pharmacists Letter. Natural Medicines Comprehensive Database. St. John's wort. 2013:1460–1471.

Valerian

- Valerian consists of the roots, rhizomes (underground stems), and stolons from the plant *Valeriana officinalis*
- Active ingredients associated with sedative properties thought to be valepotriates, mono- and sesquiterpenes (e.g., valerenic acid), and pyridine alkaloids
- May enhance GABA release and decrease uptake; alters binding at benzodiazepine receptor and causes CNS depression (mechanism of action unclear)

Anxiety Disorders

- Systematic review and meta-analysis of 7 RCTs: Significant publication bias, missing data in the area of negative outcome, and high heterogeneity. Subgroup analysis of 2 studies revealed positive outcomes for the whole root (adult data)

Sleep Disorders

- Dosing: 200–1200 mg/day; usual dose 400–900 mg taken 2 h before bedtime
- Double-blind placebo-controlled trial in 8 children with various intellectual disabilities (and hyperactivity) demonstrated a decrease in sleep latency and nocturnal wake time, increased total sleep time, and improved quality of sleep
- Preliminary data report benefit on sleep latency and quality in children with hyperactivity
- A 2020 systematic review and meta-analysis: Overall inconsistent outcomes likely due to variable quality of herbal extracts (they lose potency at room temperature). Subgroup analysis for the whole root/rhizome showed it improved sleep quality at 450–1410 mg/day (effect size 0.83), whereas subgroup analysis for valerian extracts produced inconsistent outcomes. Single dose ineffective; repeated administration needed for effect (adult data)
- Several placebo-controlled crossover studies show improvement in sleep quality, decrease in sleep latency, and a decrease in the number of awakenings; response better in females and individuals less than 40 years of age; some studies did not show benefit (adult data)
- Double-blind crossover polysomnographic evaluation of two preparations of valerian (*V. edulis* and *V. officinalis*) over 4 nights showed that both increased REM sleep and decreased stages 1–2; *V. edulis* also decreased the number of waking episodes
- Preliminary data report benefit for stress-induced insomnia
- Adverse effects are rare and include nausea, excitability, blurred vision, headache, morning hangover with higher doses, pruritus, bradycardia, and arrhythmias; reports of vivid dreams, nightmares, visual hallucinations, and abnormal thinking
- Will potentiate the effects of other CNS drugs
- Liver dysfunction reported; use with caution in patients with a history of liver disease – periodic liver function tests recommended
- Four cases of hepatotoxicity reported when valerian combined with herbal product "skullcap"
- Withdrawal symptoms including delirium, visual hallucinations, and cardiac complications reported after abrupt discontinuation of chronic use

Vitamins & Minerals

ADHD

- Iron:
  - Dosing: 80 mg/day or 5 mg/kg/day
  - Meta-analysis on 10 case-control studies of total 2191 children and 1196 ADHD cases indicated that lower serum ferritin but not serum iron is associated with ADHD
  - Iron supplementation (80 mg/day) improved ADHD symptoms (especially inattention) reported by children, parents, and teachers, and restless legs syndrome in RCT of 22 French children with low ferritin and without anemia
  - Iron supplementation (5 mg/kg/day) plus methylphenidate improved inattention, hyperactivity, and impulsivity reported by parents compared to methylphenidate alone in RCT of 42 Iranian children with low ferritin and without anemia
- Zinc:
  - Dosing: 10–40 mg/day
  - Zinc supplementation (40 mg/day) improved hyperactivity, impulsivity, and impaired socialization, but had no effect on inattention in 400 children in a Turkish RCT. Higher improvement in children of older age, higher BMI, and lower baseline zinc and free fatty acid levels
  - Zinc supplementation (15 mg/day) together with methylphenidate produced a marked improvement in Teacher and Parent rating scale over methylphenidate alone in 44 children in an RCT
  - Zinc supplementation (15 mg once or twice/day) together with dextroamphetamine was not superior to dextroamphetamine alone, though did result in reduction in total amphetamine dose requirements in 52 children in a US-based RCT
  - Limited generalizability for studies conducted in countries where zinc deficiency is more common (estimated at 28% and 20% of children in Turkey and Iran, respectively)
  - Zinc generally well-tolerated; most common adverse effect metallic taste

Natural Health Products (cont.)

- Multivitamin with minerals:
  - Improvement with multimineral-vitamin in inattention, emotional regulation, aggression, and general functioning compared to placebo in an RCT involving 93 patients. Dose was 3–15 capsules/day; significant pill burden and cost
  - No relation between the change in serum/plasma nutrient levels and improvement in ADHD, mood, and general functioning. Weak association for decrease in ferritin and increase in copper with greater improvement in overall functioning. Results not clinically significant and monitoring nutrient levels likely not helpful

Akhondzadeh S, Mohammadi MR, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: A double blind and randomized trial [ISRCTN64132371]. BMC Psychiatry. 2004;4:9. doi:10.1186/1471-244X-4-9
Bilici M, Yildirim F, Kandil S, et al. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(1):181–190. doi:10.1016/j.pnpbp.2003.09.034
Cortese S, Angriman M, Lecendreux M, et al. Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. Expert Rev Neurother. 2012;12(10):1227–1240. doi:10.1586/ern.12.116
Konofal E, Lecendreux M, Arnulf I, et al. Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 2004;158(12):1113–1115. doi:10.1001/archpedi.158.12.1113
Konofal E, Lecendreux M, Deron J, et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatr Neurol. 2008;38(1):20–26. doi:10.1016/j.pediatrneurol.2007.08.014
Panahandeh G, Vatani B, Safavi P, et al. The effect of adding ferrous sulfate to methylphenidate on attention-deficit/hyperactivity disorder in children. J Adv Pharm Technol Res. 2017;8(4):138–142. doi:10.4103/japtr.JAPTR_45_17
Rucklidge JJ, Eggleston, MJF, Johnstone JM, et al. Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: A fully blinded, randomized, placebo-controlled trial. J Child Psychol Psychiatry. 2018;59(3):232–246. doi:10.1111/jcpp.12817

Autism Spectrum Disorder

- Vitamin B_6 (pyridoxine):
  - Vitamin B_6 supplementation (100 mg/day for 2 weeks, then 100 mg twice/day for 2 weeks) increased verbal IQ scores compared to placebo in a small Japan RCT involving 9 patients
- Vitamin B_9 (folate):
  - Folinic acid (Leucovorin; reduced form of folic acid) supplementation (2 mg/kg/day, maximum 50 mg/day), adjunctive to risperidone improved inappropriate speech, stereotypic behavior, and hyperactivity/noncompliance scores, but showed no difference in lethargy/social withdrawal and irritability scores, compared to placebo adjunctive in 55 children in an Iranian RCT
  - Folinic acid supplementation (2 mg/kg/day, maximum 50 mg/day) improved verbal communication compared to placebo in an RCT with 48 patients, in patients who were positive for folate receptor α (FRα) autoantibodies
  - In a pilot, single-blinded RCT including 19 patients, folinic acid at a smaller dose (5 mg twice/day; mean dose 0.48 mg/kg/day) improved global, social interaction and communication scores at 12 weeks compared to placebo. Study conducted in France where there is no mandatory food fortification with folic acid
  - Case-control study of folinic acid supplementation (1–3 mg/kg/day) led to partial or complete recovery of autism symptoms after 12 months in patients with low 5-MTHF levels in CSF; better outcome if the autism spectrum disorder diagnosis and treatment were established before age 3
  - Open-label study in China suggests folic acid supplementation (400 micrograms twice/day) improved some autism symptoms: Sociability, cognitive verbal/preverbal, receptive language, affective expression and communication
- Vitamin B_{12}:
  - A meta-analysis suggests significantly lower Vitamin B_{12} levels in patients with autism spectrum disorder compared to healthy controls
  - Methylcobalamin (methyl B_{12}) supplementation (64.5 microgram/kg every third day, subcutaneously) demonstrated no difference in behavior tests compared to placebo in an RCT with 30 patients
  - Methylcobalamin supplementation (75 microgram/kg every third day, subcutaneously) showed improvement in CGI-I score compared to placebo in an RCT involving 50 patients
- Vitamin C (ascorbic acid):
  - Vitamin C supplementation (8 g/70 kg/day) showed reduction in core symptoms of autism compared to placebo in an RCT with 18 patients

- Vitamin D:
  - A meta-analysis of 3 RCTs involving 104 patients showed no improvement in hyperactivity, irritability, or sensory issues with Vitamin D supplementation alone compared to placebo
  - Vitamin D supplementation (300 IU/kg, maximum 6000 IU/day) improved autism symptoms compared to placebo in an Iran RCT with 43 patients. At baseline, all patients had Vitamin D deficiency; 77% had severe deficiency (serum 25-hydroxyvitamin D $\leq$25 nmol/L or $\leq$10 nanogram/mL)

Batebi N, Moghaddam HS, Hasanzadeh A, et al. Folinic acid as adjunctive therapy in treatment of inappropriate speech in children with autism: A double-blind and placebo-controlled randomized trial. Child Psychiatry Hum Dev. 2021;52(5):928–938. doi:10.1007/s10578-020-01072-8
Frye RE, Slattery J, Delhey L, et al. Folinic acid improves verbal communication in children with autism and language impairment: A randomized double-blind placebo-controlled trial. Mol Psychiatry. 2018;23(2):247–256. doi:10.1038/mp.2016.168
Javadfar Z, Abdollahzad H, Moludi J, et al. Effects of vitamin D supplementation on core symptoms, serum serotonin, and interleukin-6 in children with autism spectrum disorders: A randomized clinical trial. Nutrition. 2020;79–80:110986. doi:10.1016/j.nut.2020.11098
Li B, Xu Y, Zhang X, et al. The effect of vitamin D supplementation in treatment of children with autism spectrum disorder: A systematic review and meta-analysis of randomized controlled trials. Nutr Neurosci. 2022;25(4):835–845. doi:10.1080/1028415X.2020.1815332
Prades N, Varela E, Flamarique I, et al. Water-soluble vitamin insufficiency, deficiency and supplementation in children and adolescents with a psychiatric disorder: A systematic review and meta-analysis. Nutr Neurosci. 2022:1–23. doi:10.1080/1028415X.2021.2020402

Depression & Anxiety

- Vitamin B_{12}:
  - A prospective cohort study in Iran including 524 patients reported anxiety, depression, and forgetfulness were related to vitamin B_{12} deficiency in adolescents. Vitamin B_{12} deficiency was also correlated with a low vitamin D level and poor nutritional status. Children and adolescents with vitamin B_{12} level less than 220 pmol/L (less than 300 pg/mL) were treated with parenteral or oral vitamin B_{12}. Patients were also treated with oral iron if they presented with hemoglobin less than 110 g/L (11 g/dL). One month after the treatment, all symptoms resolved

Kazanci SY, Saglam NO, Omar RH. Vitamin B12 < 300 pg/mL in children and especially adolescents may predispose forgetfulness, anxiety, and unhappiness. Iran J Pediatr. 2017;27(4):e4663. doi:10.5812/ijp.4663

Schizophrenia

- Vitamin B_6 (pyridoxine):
  - Schizophrenic and schizoaffective male patients with tardive dyskinesia (TD) reported to have lower pyridoxal-5-phosphate plasma levels than non-TD patients
  - Vitamin B_6 may act as an antioxidant and free radical scavenger
  - Small double-blind study using vitamin B_6 600 mg bid for 5 days reported to improve acute antipsychotic-induced akathisia compared to placebo (adult data)
  - Two adult RCTs: Vitamin B_6 produced greater reduction in TD symptoms compared to placebo
- Vitamin C:
  - Small adult RCT: Vitamin C adjunct to atypical antipsychotics improved Brief Psychiatric Rating Scale (BPRS) scores at week 8 compared to placebo
- Vitamin D:
  - Systematic review and meta-analysis on 3 RCTs: Conflicting results (adult data)
- Vitamin E:
  - Systematic review and meta-analysis of 5 RCTs: Vitamin E decreased TD symptoms compared to placebo, but there was high heterogeneity and possible publication bias (adult data)
  - Cochrane review of 13 poorly reported RCTs: Vitamin E did not improve TD symptoms but prevented deterioration of TD compared to placebo (adult data)

Artukoglu BB, Li F, Szejko N, et al. Pharmacologic treatment of tardive dyskinesia: A meta-analysis and systematic review. J Clin Psychiatry. 2020;81(4):19r12798. doi:10.4088/JCP.19r12798
Cui X, McGrath JJ, Burne THJ, et al. Vitamin D and schizophrenia: 20 years on. Mol Psychiatry. 2021;26(7):2708–2720. doi:10.1038/s41380-021-01025-0
Dakhale GN, Khanzode SD, Khanzode SS, et al. Supplementation of vitamin C with atypical antipsychotics reduces oxidative stress and improves the outcome of schizophrenia. Psychopharmacology (Berl). 2005;182(4):494–498. doi:10.1007/s00213-005-0117-1
Lerner V, Bergman J, Statsenko N, et al. Vitamin B6 treatment in acute neuroleptic-induced akathisia: A randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2004;65(11):1550–1554. doi:10.4088/jcp.v65n1118
Lerner V, Miodownik C, Kaptsan A, et al. Vitamin B6 treatment for tardive dyskinesia: A randomized, double-blind, placebo-controlled, crossover study. J Clin Psychiatry. 2007;68(11):1648–1654.

PHARMACOGENETIC INFORMATION FOR COMMON PSYCHOTROPIC DRUGS

General Comments

- Responses to psychotropic drugs are influenced by an array of factors including age, sex, ethnicity, nutritional status, smoking and alcohol or other drug use. In addition, there is now strong evidence for the role of genetic variability in individual responses to psychotropic drugs.[1] With genetic testing becoming more widely available in the clinical setting (e.g., see [2]), it is important that prescribers have easy access to pharmacogenetic information. Searching available databases often requires specialized knowledge and could be time consuming. This chapter is a brief summary of genetic variations associated with the metabolism, side effects, and effectiveness of commonly prescribed psychotropic drugs. Information was obtained from pertinent publications produced by the US Food and Drug Administration (FDA)[3], the Clinical Pharmacogenetics Implementation Consortium (CPIC)[4, 5], the Dutch Pharmacogenetics Working Group (DPWG)[6], and the Pharmacogenomics Knowledgebase (PharmGKB) database[7]
- In 2021, a consensus on pharmacogenomic testing was published.[8] There is currently support for the use of several pharmacokinetic genes for clinical decisions, which are listed in the below tables. The use of efficacy-related pharmacodynamic genes (e.g., *SLC6A4, COMT, MTHFR,* etc.) is not ready for clinical practice due to lack of clinical support. Some safety-related pharmacodynamic genes (e.g., *human leukocyte antigen (HLA)* genes) are supported for use in clinical practice, these are listed in the below tables
- The American Academy of Child and Adolescent Psychiatry recommends clinicians avoid using pharmacogenetic testing to select psychotropic medications in children and adolescents[9]
- The American Academy of Pediatrics does not recommend pharmacogenetic testing in patients with attention-deficit/hyperactivity disorder due to lack of information demonstrating clinical utility[10]
- Information on pharmacokinetic effects of CYP2C19 and CYP2D6 enzymes responsible for the metabolism of a substantial majority of psychotropic drugs that is provided below pertains to highly polymorphic genes encoding these enzymes. For more details on CYP polymorphisms, refer to the Pharmacogene Variation (PharmVar) Consortium (https://www.pharmvar.org/) and PharmGKB (https://www.pharmgkb.org/) databases
- Patients who are intermediate metabolizers for a CYP enzyme often do not need dosage adjustments per CPIC guidelines, and therefore, recommendations for this phenotype are not described in below tables
- Potential misuse of CYP450 genotype results include dose or drug selection adjustments[5] in patients on stable and effective medications per CPIC guidelines[5]

Genotype Effects on Pharmacokinetic Properties of Psychotropic Drugs*

Biomarkers	CYP2D6				CYP2C19			
Phenotypes	Ultrarapid metabolizer	Normal (extensive) metabolizer	Intermediate metabolizer	Poor metabolizer	Ultrarapid metabolizer	Normal (extensive) metabolizer	Intermediate metabolizer	Poor metabolizer
Phenotype definitions	Duplications of functional alleles	Two functional alleles or two reduced-function alleles; or one functional and one nonfunctional allele; or one functional and one reduced-function allele	One reduced-function allele and one nonfunctional allele	Two nonfunctional alleles	Two gain-of-function alleles or one functional allele and one gain-of-function allele	Two functional alleles	One functional allele and one nonfunctional allele; or one gain-of-function allele and one nonfunctional allele	Two nonfunctional alleles

* Definitions of drug metabolizer phenotypes

Biomarkers	CYP2D6				CYP2C19			
Clinical significance	Drug blood concentration reduced – lower efficacy at normal doses	Drug blood concentration as expected	Risk of phenoconversion[#]	Drug blood concentration increased – side effects increased at normal doses	Drug blood concentration reduced – lower efficacy at normal doses	Drug blood concentration as expected	Risk of phenoconversion[#]	Drug blood concentration increased – side effects increased at normal doses

[#] Substances that inhibit CYP2D6/CYP2D19 activity may convert intermediate metabolizers to poor metabolizers

Pharmacogenomics-Based Dose Adjustment Recommendations and Guidelines*

Drug	Gene	Phenotype	Consequences	Recommendations
Amitriptyline	CYP2D6	Ultrarapid metabolizer	Lower systemic drug concentration	Avoid amitriptyline-lack of efficacy
	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Avoid amitriptyline or consider 50% lower starting dose and check blood levels to guide treatment
	CYP2C19	Ultrarapid metabolizer	Lower systemic drug concentration	Avoid amitriptyline-lack of efficacy
	CYP2C19	Poor metabolizer	Higher systemic drug concentration	Avoid amitriptyline or consider 50% lower starting dose and check blood levels to guide treatment
	Combinations of above genes		May alter systemic drug concentration	Refer to CPIC guideline for tricyclic antidepressants
Amphetamine	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Dosage adjustment should be considered. Refer to FDA labeling for specific dosing recommendations
Aripiprazole	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Administer half the usual dose In patients who also take strong/moderate CYP3A4 inhibitors, administer a quarter of the usual dose
Atomoxetine	CYP2D6	Ultrarapid metabolizer	Lower systemic drug concentration	Consider alternative drug; possible lack of efficacy at normal doses. Initiate at 40 mg/day and increase to 80 mg/day after 3 days. If no response after 2 weeks, consider increase to 100 mg/day and obtain peak plasma concentration to determine further dose adjustments
	CYP2D6	Poor metabolizer	Higher systemic drug concentration	FDA labeling: Increased risk of adverse effects, but also increased efficacy is possible if tolerated. In children and adolescents *under 70 kg* body weight initiate at 0.5 mg/kg/day and only increase to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. Consider obtaining a peak plasma concentration to guide further dosing In children and adolescents *over 70 kg* body weight initiate at 40 mg/day and only increase to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. Consider obtaining a peak plasma concentration to guide further dosing Canadian labeling: No genotyping recommendations, but recommendations for patients taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine) are provided. In children and adolescents *under 70 kg* body weight initiate ~0.5 mg/kg/day and only increase to next subsequent dose (~0.8 mg/kg/day, then ~1.2 mg/kg/day, then maximum 1.4 mg/kg/day or 100 mg, whichever is less) if symptoms fail to improve after 14 days and previous dose is well tolerated. In children and adolescents *over 70 kg* body weight initiate at 40 mg/day and only increase to next subsequent dose (60 mg/day, then 80 mg/day, then maximum of 100 mg/day) if symptoms fail to improve after 14 days and previous dose is well tolerated

* The table shows metabolizer phenotype effects on drug metabolism. Only commonly used psychotropics are included. The recommendations column reflects published dose adjustment guidelines by the US Food and Drug Administration (FDA) and the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Pharmacogenomics-Based Dose Adjustment Recommendations and Guidelines* (cont.)

Drug	Gene	Phenotype	Consequences	Recommendations
Brexpiprazole	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Dosage adjustment should be considered, but not listed in FDA package insert In patients who also take strong/moderate CYP3A4 inhibitors, administer a quarter of the usual dose
Carbamazepine	HLA-A	*31:01 allele positive	Higher adverse reaction risk (severe skin reactions)	Do not start carbamazepine if therapy naïve. Choose alternative agent. Genotyping is not a substitute for clinical vigilance
	HLA-B	*15:02 allele positive	Higher adverse reaction risk (severe skin reactions)	Do not start carbamazepine if therapy naïve. Choose alternative agent. Patients positive for HLA-B*15:02 may be at increased risk of severe skin reactions with other drugs that are associated with a risk of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Screening of patients with ancestry in genetically at-risk populations (patients of Asian descent) for the presence of the *15:02 allele should be carried out prior to treatment. Genotyping is not a substitute for clinical vigilance
Citalopram	CYP2C19	Ultrarapid metabolizer	Lower systemic drug concentration	Consider an alternative drug not predominantly metabolized by CYP2C19
	CYP2C19	Poor metabolizer	Higher systemic drug concentration	Consider 50% lower starting dose
Clomipramine	CYP2D6/2C19			See amitriptyline recommendations, which do not have as high a level of evidence for clomipramine
Clozapine	CYP1A2	Poor metabolizer	Higher systemic drug concentration	Dosage reductions and very slow initial titration may be necessary
Codeine	CYP2D6	Ultrarapid metabolizer	Higher systemic active metabolite concentration and higher adverse reaction risk (life-threatening respiratory depression and death)	Avoid codeine. Consider alternative that is NOT tramadol, such as morphine or non-opioid analgesics, if clinically appropriate
	CYP2D6	Poor metabolizer	Lower systemic active metabolite concentration, may result in reduced efficacy	Avoid codeine. Consider morphine or non-opioid analgesics, if clinically appropriate
Desipramine	CYP2D6/2C19			See amitriptyline recommendations, which do not have as high a level of evidence for desipramine
Divalproex	POLG	Mutations in POLG	Contraindicated in individuals with known mitochondrial disorders caused by mutations in mitochondrial DNA polymerase gamma (POLG), and suspected POLG-related disorders in children under 2 years of age	Genetic testing required
Doxepin	CYP2D6/2C19			See amitriptyline recommendations, which do not have as high a level of evidence for doxepin
Escitalopram	CYP2C19			See citalopram recommendations
Fluvoxamine	CYP2D6	Ultrarapid metabolizer	Lower systemic drug concentration	No recommendation due to lack of evidence
	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Consider a 25–50% reduction of recommended starting dose or use alternative drug
Haloperidol	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Use 60% of standard dose
Imipramine	CYP2D6/2C19			See amitriptyline recommendations, which do not have as high a level of evidence for imipramine
Lamotrigine	HLA-B	*15:02 positive	Higher adverse reaction risk (severe skin reactions)	Risk of lamotrigine-induced SJS/TEN in patients with HLA-B*15:02 is estimated at 0.4%. Carbamazepine carries higher risk and is not a better alternative. Genotyping is not a substitute for clinical vigilance
Nortriptyline	CYP2D6/2C19			See amitriptyline recommendations

Drug	Gene	Phenotype	Consequences	Recommendations
Oxcarbazepine	HLA-B	*15:02 positive	Higher adverse reaction risk (severe skin reactions)	Do not start oxcarbazepine if therapy naïve. Risk of oxcarbazepine-induced SJS/TEN in patients with HLA-B*15:02 is estimated at 0.73%. Carbamazepine carries higher risk and is not a better alternative. Genotyping is not a substitute for clinical vigilance
Paroxetine	CYP2D6	Ultrarapid metabolizer	Lower systemic drug concentration	Select alternative drug not metabolized by CYP2D6
	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Select alternative drug or consider 50% reduction in starting dose
Risperidone	CYP2D6	Ultrarapid metabolizer	Lower systemic drug concentration	Consider alternative drug (e.g., paliperidone) or higher than normal risperidone doses with drug level monitoring
	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Use 67% of standard dose
Sertraline	CYP2C19	Ultrarapid metabolizer	Lower systemic drug concentration	Initiate drug at recommended starting dose. If patient does not respond to dose increase, consider alternative medication
	CYP2C19	Poor metabolizer	Higher systemic drug concentration	Consider 50% lower starting dose and titrate to response or alternative medication
Vortioxetine	CYP2D6	Poor metabolizer	Higher systemic drug concentration	Maximum recommended dose is 10 mg/day (adults). Reduce dose by half if patient concomitantly receives a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine)

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MANAGEMENT OF AGGRESSION IN CHILDREN AND ADOLESCENTS

General Comments

- Aggression is a symptom that can result in psychological harm, injury, and even severe outcomes such as death. It is a common emergency presentation with a diverse etiological background. Virtually every psychiatric diagnosis, as well as many non-psychiatric conditions, can result in behavioral aggression
- In children and adolescents, it's important to note that the likelihood of severe mental illness causing aggression is significantly lower than in the adult population
- Aggression that results from frustration, missed expectations, conflict, and relationship challenges will not be solved pharmacologically
- In any situation of aggression, the intervention chosen can have beneficial or deleterious effects upon the aggression itself, and an important hierarchy of principled management is necessary
- The hierarchy of aggression management methods is outlined below. These must be used with the following principles in mind:
  - When safety is a concern, select an intervention that is appropriately matched to the concern
  - **Whenever possible, move towards Engagement.** This should occur at every opportunity, even if a more intensive method has already been prepared
  - Always use language that indicates the desire to avoid more intensive methods, and the desire for the child or adolescent to return to a non-aggressive state
  - Avoid using threats of more intensive methods to an aggressive child or adolescent; this is punitive and may escalate the fear response
  - Never use anti-aggression measures punitively, or "to teach a lesson." This can only damage the relationship between the treatment provider and the child or adolescent, and escalates fear that may contribute to more aggression
- The first five methods in the table (level 1–5) can be employed in most environments. The last three methods (level 6–8) should only be used in a setting with trained professionals

Method	Hierarchy level	Likelyhood of harm or fear	Definition	Comments and Examples*
Engagement	1	Minimal	Using discussion, empathy, and comfort measures to promote pathways towards more calm or comforted behaviors	Almost always the best option for pediatric aggression. By not meeting the expectation of "fighting back," engagement disarms aggression quickly • Comfort measures: Offering the requested or a comfort thing (food, electronics, extending bedtime, cancellation of planned activity or introduction of something fun) • Discussion: "What's happening for you?" or "How can I help you right now?" • Empathy: "You must be in a lot of distress" or "I can see you're struggling"[1]
Making the environment safer	2	Minimal	Measures designed to improve the safety and calm promotion of the environment around the aggressive child or adolescent	Can be done in concert with Engagement above. Examples include moving to a quieter environment, removing dangerous objects, separating people who are in conflict, or introducing enjoyable environments like offering an activity
Environmental isolation (open)	3	Minimal	Volitional but stronger environmental restrictions	The classic "time out" or "go to your room" response. Children and adolescents, unlike adults, have a strong chance of responding to this, especially if offered constructively. "Why don't you go to your room for a bit and I'll come talk to you when things are calmer"
Recruiting help	4	Minimal to small	Adding a neutral or supportive person who can help with conflict reduction or provide extra safety	At home, this could mean calling for help or enacting an emergency response. In hospital settings, this could mean calling for extra hospital or security staff

Method	Hierarchy level	Likelyhood of harm or fear	Definition	Comments and Examples*
Offer as-needed medications	5	Small	Volitional use of medications that promote sedation or anxiolysis	Best used as early as possible; for the vast majority of children and adolescents, diagnosis-specific medication is unnecessary and general medications with sedative properties are possible (diphenhydramine, lorazepam, low-potency antipsychotic at low dose). If underlying diagnoses are causative, as-needed diagnosis-specific medications may be helpful (antipsychotics, benzodiazepines)
Environmental isolation (closed)	6	Moderate to high	Use of locked/secure rooms to reduce danger of aggression	Policies and procedures relevant to the jurisdiction and setting must be followed. Most children and adolescents require very short durations of seclusion environments (less than 15 min) and regular supervision with offers towards Engagement is necessary
Compelled as-needed medications	7	Moderate to high	Use of compelled medications, including injectable versions, to promote sedation or anxiolysis	Policies and procedures relevant to the jurisdiction and setting must be followed. If using intramuscular agents, likelihood of harm and fear increases significantly. When preparing an intramuscular agent, consider preparing and also offering an oral equivalent so that a less traumatic administration alternative is available
Physical restraints	8	High to severe, including death	Use of physical restraints to restrict dangerous movement	Policies and procedures relevant to the jurisdiction and setting must be followed. Should **always** initiate a review after the event to determine how use of restraints could have been avoided. Minimal durations are necessary. Caution is necessary as soft-tissue, joint, and bone injuries are common. Struggling against restraints is associated with cardiovascular distress, thrombotic events, kidney damage, and death[2]

* Note: Medication doses and selection are at the discretion of the treatment provider. Unfortunately, very little guidance can help with specifics but, in general, benzodiazepines, antihistamines, and low-dose antipsychotic medications appear to be safe and well tolerated.[3]
Typical doses include[1]:
diphenhydramine 1 mg/kg/dose (maximum dose 50 mg);
lorazepam (0.05–0.1 mg/kg/dose (maximum dose 2 mg);
chlorpromazine 0.5–1 mg/kg/dose (maximum dose 50 mg);
olanzapine child 2.5 mg/dose, adolescent 5 mg/dose

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GLOSSARY

ACE	Angiotensin-converting enzyme
ADHD	Attention deficit hyperactivity disorder
ADL	Activities of daily living
Agranulocytosis	Reduction of neutrophil white blood cells to very low levels
AIMS	Abnormal Involuntary Movement Scale
Akathisia	Inability to relax, compulsion to change position, motor restlessness
Akinesia	Absence of voluntary muscle movement
Alopecia	Hair loss
ALT	Alanine aminotransferase
Amenorrhea	Absence of menstruation
ANC	Absolute neutrophil count
Anorexia	Lack of appetite for food
Anterocollis	Forward spasm of the neck
Anticholinergic	Block effects of acetylcholine
Antiemetic	Helps prevent nausea and vomiting
ARB	Angiotensin receptor blocker
Arrhythmia	Any variation of the normal rhythm (usually of the heart beat)
Arteriosclerosis	Hardening and degeneration of the arteries due to fibrous tissue formation
Arthralgia	Pain in the joints
ASD	Autism spectrum disorder
AST	Aspartate aminotransferase
Asterixis	Abnormal tremor consisting of involuntary jerking movements, especially in the hands, frequently occurring with impending hepatic coma and other forms of metabolic encephalopathy; also called flapping tremor
Asthenia	Weakness, fatigue
Ataxia	Incoordination, especially the inability to coordinate voluntary muscular action
Atherosclerosis	Degeneration of the walls of the arteries due to fatty deposits
Atypical depression	As per DSM-5-TR, patient has mood reactivity and at least 2 of the following symptoms: increased appetite or weight, hypersomnia, leaden paralysis and a long-standing pattern of extreme sensitivity to perceived interpersonal rejection
AUC	Area under the concentration vs time curve (on graph depicting drug in the plasma after a single dose) – represents the extent of systemic exposure of the body to the drug
Autonomic	The part of the nervous system that is functionally independent of thought control (involuntary)
BD	Bipolar disorder
Ballismus	Jerking, twisting
Bioavailability	The fraction of an administered dose of unchanged drug that reaches the systemic circulation
Bipolar I disorder	Cyclical mood disorder with depression alternating with mania
Bipolar II disorder	Cyclical mood disorder with depression alternating with hypomania
Blepharospasm	Forceful sustained eye closure
BMI (body mass index)	Weight (in kg) divided by height (in m^2)
BPRS	Brief Psychiatric Rating Scale
Bradycardia	Abnormally slow heart beat
Brugada syndrome	Cardiac conduction disorder that can lead to sudden cardiac death
Bruxism	Teeth clenching, grinding
BUN	Blood urea nitrogen
Cataplexy	Loss of muscle tone and collapse
CBC	Complete blood count
CBT	Cognitive-behavioral therapy
CDRS-R	Children's Depression Rating Scale – Revised
CGI	Clinical Global Impressions. Rating scales for the assessment of symptom severity and treatment response/efficacy in patients with mental disorders. CGI-S = severity scale, CGI-I = improvement scale
CHD	Coronary heart disease
Choreiform	Purposeless, uncontrolled sinuous movements
Choreoathetosis	Slow, repeated, involuntary sinuous movements or twitching of muscles
Chronic brain syndrome	Irreversible damage to brain cells = dementia
CI	Confidence interval
Clearance	Rate at which drug is removed from the body (depends on rate of metabolism by liver and elimination from body)
CNS	Central nervous system
CNS depression	Drowsiness, ataxia, incoordination, slowing of respiration which in severe cases may lead to coma and death
COPD	Chronic obstructive pulmonary disorder
Cortex	The external layer (superficial gray matter) of the brain
Coryza	"Head cold," acute catarrhal inflammation of nasal mucosa
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease

Cycloplegia Paralysis of accommodation of the eye
CYP Cytochrome P450 enzymes, involved in drug metabolism
DA Dopamine
DBPC Double-blind placebo-controlled
DDAVP Desmopressin acetate
Dermatitis Inflammation of the skin
Diaphoresis Perspiration
Diplopia Double vision
DLPFC Dorsolateral prefrontal cortex
DMDD Disruptive mood dysregulation disorder
Dravet syndrome Rare form of intractable epilepsy beginning in infancy or early childhood
DRESS Drug reaction with eosinophilia and systemic symptoms
Dysarthria Impaired, difficult speech
Dysgeusia Unpleasant taste
Dyskinesia Abnormal movements, i.e., twitching, grimacing, spasm
Dyspepsia Pain or discomfort in upper abdomen or chest (gas, feeling of fullness, or burning pain)
Dysphagia Difficulty in swallowing
Dystonia Disordered muscle tone leading to spasms or postural change
ECG Electrocardiogram (tracing of electrical activity of the heart muscle)
ECT Electroconvulsive therapy, "shock therapy"
Edema Swelling of body tissues due to accumulation of fluid
EEG Electroencephalogram (tracing of electrical activity of the brain)
Elimination Excretion or removal of drug (and/or metabolites) from the body, usually by the kidneys
Emesis Vomiting
Endocrine A gland that secretes internally, a ductless gland
Enuresis Involuntary discharge of urine
Enzyme Organic compound that acts upon specific fluids, tissues, or chemicals in the body to facilitate chemical action
Eosinophilia myalgia syndrome (EMS) Connective tissue disease with elevated eosinophil count and muscle pain
Epigastric Referring to the upper middle region of the abdomen
Epistaxis Nose bleed
EPSE/Extrapyramidal syndrome Extrapyramidal side effects/parkinsonian-like effects of drugs
ER Extended release
Exacerbation Increase in severity of symptoms or disease
Extrapyramidal Refers to certain nuclei of the brain close to the pyramidal tract
FAS/FASD Fetal alcohol syndrome/Fetal alcohol spectrum disorder
Fasciculation Twitching of muscles
Fibrosis Formation of fibrous or scar tissue
First-pass effect Drugs absorbed from the intestine first pass through the liver; a portion of the drug is metabolized before it can act on receptors
FSH Follicle-stimulating hormone
GABA Gamma-amino butyric acid; inhibitory neurotransmitter
GAD Generalized anxiety disorder
GAF Global Assessment of Functioning
Galactorrhea Excretion of milk from breasts
GERD Gastroesophageal reflux disease
GFR Glomerular filtration rate
GI Gastrointestinal
Glaucoma Increased pressure within the eye
Glomerular Pertaining to small blood vessels of the kidney that serve as filtering structures in the excretion of urine
Glossodynia Burning mouth syndrome – a persistent tingling or burning sensation in the lips, tongue or entire mouth
GnRH Gonadotropin-releasing hormone
Gynecomastia Increase in breast size in males
Half-life Time required to decrease the plasma concentration of a drug by 50% (depends on drug clearance and volume of distribution)
Histological Pertaining to microscopic tissue anatomy
Hypercalcemia An excessive amount of calcium in the blood
Hyperkinetic Abnormal increase in activity
Hyperparathyroidism Excessive activity of the parathyroid gland
Hyperreflexia Increased action of the reflexes
Hypertension High blood pressure
Hyperthyroid Excessive activity of the thyroid gland
Hypertrophy Enlargement
Hypnotic Inducing sleep
Hypoesthesia Diminished sensitivity to tactile stimuli
Hypospadias Developmental abnormality in males in which the urethra opens on the under surface of the penis or in the perineum
Hypotension Low blood pressure
Hypothyroid Decreased activity of the thyroid gland
ICU Intensive care unit
Induration Area of hardened tissue
INR International normalized ratio; measures coagulation of blood via extrinsic coagulation pathway
IPT Interpersonal therapy
IR Immediate release
Jaundice Yellow skin caused by excess of bile pigment
Kindling Epileptogenesis caused by adaptive changes in neurons producing repeated electrical discharges; phenomenon also observed in bipolar disorder
LAI Long-acting injection
LDH Lactate dehydrogenase (an enzyme)

Lennox-Gastaut syndrome	Rare form of severe, complex childhood-onset epilepsy
LFTs	Liver function tests
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
Libido	Drive or energy usually associated with sexual interest
Limbic system	A system of brain structures common to the brains of all mammals (deals with emotions)
Leukocytosis	Increase in the white blood cells in the blood
Leukopenia	Decrease in the white blood cells in the blood
Macrosomia	Birth weight of infant more than 4 kg
MADRS	Montgomery Åsberg Depression Rating Scale
Manic depressive psychosis	Conspicuous mood swings ranging from normal to elation or depression, or alternating of the two; called bipolar disorder in DSM-5-TR
MAOI	Monoamine oxidase (an enzyme) inhibitor
Metabolic syndrome	An interrelated cluster of CVD risk factors that include abdominal obesity, dyslipidemia, hypertension, and impaired glucose tolerance (also called insulin resistance syndrome, syndrome X, or dysmetabolic syndrome); see p. 186 for diagnostic criteria
MDD	Major depressive disorder
Metabolism	Chemical processes living organisms utilize to maintain life. Drug metabolism is the biochemical process by which living organisms modify pharmaceutical substances. For example, drug metabolism often converts fat-soluble drugs into more water-soluble drugs, which can more readily be excreted by the kidneys. Most psychotropic drugs are metabolized by cytochrome P450 enzymes
Metabolites	Resultant by-products of metabolism; metabolites can be either active substances or inactive agents
MHD	Active 10-monohydroxy metabolite of oxcarbazepine
MI	Myocardial infarction
Micrographia	Decrease in size of hand writing; may be a form of akinesia
Miosis	Constricted pupils
Myalgia	Tenderness or pain in muscles
Mydriasis	Dilated pupils
Narcolepsy	Condition marked by an uncontrollable desire to sleep
Nephritis	Inflammation of the kidneys
nM	Nanomoles – measure of receptor binding affinity
NMDA	N-methyl-D-aspartate
NMS	Neuroleptic malignant syndrome – rare disorder characterized by autonomic dysfunction (e.g., tachycardia and hypertension), hyperthermia, altered consciousness, and muscle rigidity with an increase in creatine phospho – changed therekinase (CPK) and myoglobinuria
NNRTI	Non-nucleoside reverse-transcriptase inhibitor – antiretroviral drug used in the treatment of human immunodeficiency virus (HIV)
NRT	Nicotine replacement therapy
Nystagmus	Involuntary movement of the eyeball or abnormal movement on testing
OC	Oral contraceptive
Occipital	In the back part of the head
OCD	Obsessive-compulsive disorder
Oculogyric crisis	Rolling up of the eyes and the inability to focus
ODT	Orally disintegrating tablets
Onychophagia	Nail biting
Ophthalmoplegia	Paralysis of the extraocular eye muscles
Opisthotonus	Arching (spasm) of the body due to contraction of back muscles
Oral hypoesthesia	Diminished oral sensitivity
OROS	Osmotic-controlled release oral delivery system
Orthostatic hypotension	Faintness caused by suddenly standing erect (leading to a drop in blood pressure)
Osteomalacia	Rickets; softening of the bones caused by defective bone mineralization due to inadequate available phosphorus and calcium, or overactive resorption of calcium from the bone as a result of hyperparathyroidism
Palinopsia	Visual perseveration,"tracking" or shimmering
PANSS	Positive and Negative Syndrome Scale; used in the diagnosis and monitoring of schizophrenia symptoms
Papilledema	Edema of the optic disc
Paresthesia	Feeling of "pins and needles," tingling or stiffness in distal extremities
Parkinsonism	A condition marked by mask-like facial appearance, tremor, change in gait and posture (resembles Parkinson's disease)
PD	Panic disorder (with/without agoraphobia)
PEG 3350	Polyethylene glycol 3350, an osmotic laxative
Perioral	Around the mouth
Peripheral neuropathy	Pathological changes in the peripheral nervous system
Petechiae	Small purplish hemorrhagic spots on skin
P-gp	P-glycoprotein; a protein that transports molecules through cell membranes (e.g., in and out of specific body organs)
Photophobia	Sensitivity of the eyes to light
Photosensitivity	Light sensitive
PI	Protease inhibitor – drug used in the treatment of human immunodeficiency virus (HIV)
Piloerection	"Goose-bumps" or hair standing up
Pisa syndrome	Lateral dystonia of trunk causing individual to lean to one side
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
Polydipsia	Excessive drinking
Polyuria	Excessive urination
"Poop-out" syndrome	Tolerance to effects (tachyphylaxis)
Postural hypotension	Lowered blood pressure caused by a change in position

Priapism Abnormal, continued erection of the penis
Prostatic hypertrophy Enlargement of the prostate gland
Pruritus Itching
Psychomotor excitement Physical and emotional overactivity
Psychomotor retardation Slowing of physical and psychological reactions
Psychosis A major mental disorder of organic or emotional origin in which there is a departure from normal patterns of thinking, feeling and acting; commonly characterized by loss of contact with reality
PTSD Posttraumatic stress disorder
Pyloric Referring to the lower opening of the stomach
QRS prolongation Lengthening of the combination of the Q, R, and S waves in an ECG
Rabbit syndrome Rhythmic vertical-only motion of the mouth/lips, resembling the chewing movements of a rabbit (5 Hz), with no involvement of the tongue
RCT Randomized controlled trial
RDBCT Randomized double-blind controlled trial
Retardation Slowing
Retrocollis Spasm of neck muscles causing the head to twist up and back
Schizophrenia A severe disorder of psychotic depth characterized by a retreat from reality with delusions and hallucinations
Sedative Producing calming of activity or excitement
Serotonin syndrome Hypermetabolic syndrome resulting from serotonergic excess; symptoms include: Disorientation, confusion, agitation, tremor, myoclonus, hyperreflexia, twitching, shivering, ataxia, hyperactivity
SIADH Syndrome of inappropriate secretion of antidiuretic hormone
Sialorrhea Excessive flow of saliva
SIDS Sudden infant death syndrome
SL Sublingual
Social AD Social anxiety disorder
SOFAS Social and Occupational Functioning Assessment Scale
Somnambulism Sleepwalking
SR Sustained release
Stereotypic Rhythmic and repetitive
Stevens-Johnson syndrome Rare, serious hypersensitivity reaction causing blistering of skin and mucous membranes
Syncope A sudden loss of strength or fainting
T2DM Type 2 diabetes mellitus
Tachycardia Abnormally rapid heart rate
Tachyphylaxis Tolerance to effects
Tardive akathisia Persistent physical and mental restlessness that appear late in neuroleptic therapy
Tardive dyskinesia Persistent dyskinetic movements that appear late in neuroleptic therapy
Tardive dystonia Persistent abnormal muscle tone that appears late in neuroleptic therapy
TCAs Tricyclic antidepressants
TD Tardive dyskinesia
THC Tetrahydrocannabinol, the main psychoactive constituent of cannabis
Therapeutic index Ratio of median lethal dose of a drug to its median effective dose: i.e.,

$$\text{therapeutic index} = \frac{\text{median lethal dose}}{\text{median effective dose}}$$

TIA Transient ischemic attack
Tinnitus A noise in the ears (ringing, buzzing, or roaring)
Torticollis Spasm on one side of the neck causing the head to twist
Tortipelvis Twisting of pelvis due to muscle spasm
Tracking A reaction in which the medication leaves the original injection site and moves to another
TRH Thyrotropin-releasing hormone, releases TSH and prolactin
Trismus Severe spasm of the muscles of the jaw resembling tetanus (lock jaw); jaw clenching
TSH Thyroid-stimulating hormone
UGT Uridine diphosphate glucuronosyltransferase, enzyme involved in drug metabolism
Ulceration An open lesion on the skin or mucous membrane
Vasoconstrictor Causes narrowing of the blood vessels
VMAT2 inhibitors Vesicular monoamine transporter 2 inhibitors; agents used in treatment of involuntary body movements
Volume of distribution (Vd) The theoretical volume that a drug would have to occupy to provide the same concentration as it currently is in blood plasma
WBC White blood cell count
Wernicke-Korsakoff syndrome Syndrome characterized by confusion, ataxia, ophthalmoplegia, recent memory impairment, and confabulation
XR Extended release
Y-BOCS Yale–Brown Obsessive Compulsive Scale

DRUG USE IN PREGNANCY AND EFFECTS ON BREAST MILK

Drug labeling

- The FDA requires prescription drug labeling to include the following three detailed subsections, as outlined in the Pregnancy and Lactation Labeling Rule (2014):
  - **Pregnancy:** This subsection provides information relevant to the use of the drug in pregnant women, such as dosing and potential risks to the developing fetus, as well as information about whether there is a registry that collects and maintains data on how pregnant women are affected when they use the drug or biological product
  - **Lactation:** This subsection provides information about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed child
  - **Females and Males of Reproductive Potential:** This subsection includes information about pregnancy testing, contraception, and infertility as it relates to the drug
- The "Pregnancy" and "Lactation" subsections include three subheadings: "risk summary," "clinical considerations," and "data." These subheadings provide more detailed information regarding, for example, human and animal data on the use of the drug, and specific adverse reactions of concern for pregnant or breastfeeding women

Pregnancy exposure registries and studies

- If any psychotropic medication is used during pregnancy, consider patient enrollment or registration in any relevant studies or pregnancy exposure registries (e.g., in the US: FDA list of pregnancy registries at https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm)
- In the US, the National Pregnancy Registry for Psychiatric Medications is dedicated to gathering information on psychotropic medications to improve the evidence base. It maintains registries for antidepressants, atypical antipsychotics, and ADHD medications at https://womensmentalhealth.org/research/pregnancyregistry

Further Reading

Additional Suggested Reading

Print resources

1. American College of Obstetricians and Gynecologists (ACOG). Use of psychiatric medications during pregnancy and lactation. (ACOG practice bulletin no. 92). Obstet Gynecol. 2008;111(4):1001–1020. doi:10.1097/AOG.0b013e31816fd910
2. Betcher HK, Wisner KL. Psychotropic treatment during pregnancy: Research synthesis and clinical care principles. J Womens Health (Larchmt). 2020;29(3):310–318. doi:10.1089/jwh.2019.7781
3. Creeley CE, Denton LK. Use of prescribed psychotropics during pregnancy: A systematic review of pregnancy, neonatal, and childhood outcomes. Brain Sci. 2019;(9):235. doi:10.3390/brainsci9090235
4. Briggs GG, Freeman RK, Towers CV, et al. Briggs drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. (12th ed.) New York, NY: Wolters Kluwer, 2021.
5. Hale TW, Krutsch K. Hale's medications and mothers' milk 2023. (20th ed.) New York, NY: Springer, 2022.
6. Larsen ER, Damkier P, Pedersen LH, et al. Use of psychotropic drugs during pregnancy and breast-feeding. Acta Psychiatr Scand Suppl. 2015;445(1):1–28. doi:10.1111/acps.12479
7. McAllister-Williams RH, Baldwin DS, Cantwell R, et al. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017. J Psychopharmacol. 2017;31(5):519–552. doi:10.1177/0269881117699361
8. Raffi ER, Nonacs R, Cohen LS. Safety of psychotropic medications during pregnancy. Clin Perinatol. 2019;46(2):215–234. doi:10.1016/j.clp.2019.02.004

Online resources (freely accessible)

1. Exposure to psychotropic medications and other substances during pregnancy and lactation: A handbook for health care providers [A Canadian resource developed by the Centre for Addiction and Mental Health in Toronto]. https://www.camhx.ca/Publications/Resources_for_Professionals/Pregnancy_Lactation/index.html
2. LactMed [A US National Library of Medicine database of drugs and other chemicals to which breastfeeding mothers may be exposed. Includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant]. https://www.ncbi.nlm.nih.gov/books/NBK501922/
3. MothertoBaby. Medications & more during pregnancy & breastfeeding – Ask the experts [From the Organization of Teratology Information Specialists (OTIS). This site assesses and evaluates risks to pregnancy and breastfeeding outcomes from medications and other exposures]. https://mothertobaby.org/

Online resources (subscription required)

1. HalesMeds.com [electronic version (online/app) of Hale's medications and mothers' milk]. https://www.halesmeds.com/
2. REPROTOX [A database developed by the Reproductive Toxicology Center in Washington, DC, USA for its members, which contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development]. https://www.reprotox.org
3. TERIS - Teratogen Information System [Developed by the University of Washington, Seattle, WA, USA; provides current information on the teratogenic effects of drugs and environmental agents]. https://depts.washington.edu/terisweb/teris/index.html

PATIENT AND CAREGIVER INFORMATION SHEETS

The Patient and Caregiver Information Sheets contain information that may be passed on to patients and families/caregivers about some of the most frequently used psychotropic medications in children and adolescents as well as two non-pharmacological interventions (electroconvulsive therapy and bright light therapy). The sheets are designed to be easily understood by patients, parents, and caregivers, and give details on such matters as the uses of the drug, how quickly it starts working, how long it should be taken, side effects and what to do if they occur, what to do if a dose is forgotten, drug interactions, and precautions. Information sheets such as these, of course, cannot replace a proper consultation with and advice from a physician or other medical professional, but can serve as a useful tool to increase medication adherence, improve efficacy, and enhance safety.

The authors and the publisher welcome feedback and suggestions from readers (for contact addresses, see the front of the book).

Printable pdf files of Patient and Caregiver Information Sheets on the drugs and classes of drugs listed on the right can be found at the end of this PDF eBook.

The Patient and Caregiver Information Sheets may be reproduced by users of the *Clinical Handbook of Psychotropic Drugs for Children and Adolescents* for their own clinical practice but not for any commercial use.

The following Patient and Caregiver Information Sheets are available:

1. Acamprosate
2. Anticonvulsant Mood Stabilizers
3. Antiparkinsonian Agents for Treating Extrapyramidal Side Effects
4. Antipsychotic Drugs
5. Atomoxetine
6. Benzodiazepines and Anxiolytics
7. Buprenorphine
8. Bupropion
9. Buspirone
10. Clonidine
11. Clozapine
12. Cyclic Antidepressants
13. Disulfiram
14. Electroconvulsive Therapy
15. Guanfacine
16. Hypnotics/Sedatives
17. Lithium
18. MAOI Antidepressants
19. Methadone
20. Mirtazapine
21. Moclobemide
22. Naltrexone
23. Psychostimulants
24. SARI Antidepressants
25. SNRI Antidepressants
26. SSRI Antidepressants
27. Vilazodone
28. Viloxazine
29. Vortioxetine

INDEX OF DRUGS*

* Page numbers in **bold type** indicate main entries.

Patient and Caregiver Information on Acamprosate

What is this drug used for?

Acamprosate is primarily used in the treatment of alcohol dependence, where it reduces alcohol cravings and can prevent relapse.
Acamprosate has been shown to maintain abstinence if taken, as directed, as part of a treatment program that includes counseling and support.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Acamprosate is usually prescribed after an individual has been withdrawn from alcohol use. It is not effective if the person is actively drinking, nor will it treat withdrawal symptoms. It reduces cravings for alcohol.

How long should you take this medication?

Acamprosate is usually prescribed for a set period of time (months) to help the individual remain alcohol-free. Do not increase or decrease your dose of medication without discussing this with your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effect that should be reported to your doctor at the **NEXT VISIT** include:

- Upset stomach, nausea, gas, diarrhea – if these symptoms continue, your doctor may need to adjust your dose.
- Headache – this tends to be temporary and can be managed by taking a pain reliever (e.g., acetaminophen or ibuprofen) as required. If the headache persists or is "troubling," contact your doctor.
- Increased anxiety, sleeping difficulties – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication.
- Itching, skin rash.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- **Severe anxiety, change in your mood or behavior or thoughts of suicide**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you are taking the medication 3 times a day with meals and miss taking your dose by more than 2 hours, skip the missed dose and continue with your next scheduled dose.

Is this drug safe to take with other medication?

Because acamprosate can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking acamprosate.

Precautions/considerations

1. This drug may impair the mental and physical abilities and reaction time required for driving or operating other machinery. Avoid these activities if you feel drowsy or slowed down.
2. Do not change your dose or stop the drug suddenly without discussing this with your doctor.
3. Should you restart drinking during treatment, continue taking the acamprosate but notify your doctor as soon as possible.
4. Report any changes in mood or behavior to your doctor.

What else do I need to know about acamprosate?

1. Swallow the tablets whole – do not cut, crush, or chew acamprosate tablets.
2. Store your medication in a clean, dry area at room temperature. Keep all medication out of reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on Anticonvulsant Mood Stabilizers

The name of your medication is _____.

What is this drug used for?

Anticonvulsants are used to treat seizure disorders as well as certain pain syndromes (e.g., trigeminal neuralgia – carbamazepine; migraines – valproate).
They can also be used to treat symptoms of acute mania and in the long-term control or prevention of bipolar depression.
These drugs have also been found to be useful in the treatment of several other conditions, including: Add-on therapy with antidepressants to treat depression, add-on therapy with antipsychotics to treat schizophrenia, withdrawal reactions from alcohol or sedatives/hypnotics, and in behavior disturbances such as chronic aggression, impulsivity or irritability of autism. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How does your doctor decide on the dosage?

The dose of the medication is different for every patient and is based on the amount of drug in the blood (for some of these drugs) as well as your response to treatment. You may initially take your medication two or three times a day; after several weeks, your doctor may decide to prescribe the drug once daily if extended release forms are available.

How often will you need to have blood levels done with carbamazepine and valproate?

Your doctor will measure the drug level in the blood on a regular basis during the first few months until the dose is stable. Thereafter, drug levels will be done at least once a year or whenever there is a change in drug therapy.

What do the blood levels mean?

The carbamazepine level that is usually found to be effective for most patients is between 17 and 50 micromol/L (4–12 micrograms/mL). The valproate level that is usually found to be effective for most patients is between 350 and 875 micromol/L (50–125 micrograms/mL).
On the morning of your blood test, take the morning dose of your medication **after** the test to avoid inaccurate results.
Blood levels usually do not need to be tested if you are taking lamotrigine, topiramate or gabapentin.

How quickly will the drug start working?

Control of manic symptoms or stabilization of mood may require up to 14 days of treatment or longer. Because these medications need time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor. Improvement in seizures and pain symptoms as well as aggression/impulsivity also occur gradually.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of mania it is usually recommended that these drugs be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms; if none occur, the drug can gradually be stopped. For individuals who have had several or severe episodes of mania or depression, medication may need to be continued indefinitely. Long-term treatment is generally recommended for recurring depression, seizure disorder, and aggression/impulsivity.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy, tired, difficulty concentrating – this problem usually goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Dizziness – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint – then call your doctor.
- Problems with balance or unsteadiness – discuss this with your doctor as this may require a change in your dosage.
- Blurred vision – this usually happens when you first start the drug and tends to be temporary. Reading under a bright light or at a distance may help; a magnifying glass can be of temporary use. If the problem lasts for more than a few weeks, let your doctor know.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sugar-containing drinks as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Nausea or heartburn – if this happens, take the medication with food. If vomiting or diarrhea occur and last for more than 24 hours, call your doctor.
- Muscle tremor – speak to your doctor as this may require a change in your dosage.
- Changes in hair texture, hair loss (valproate).
- Changes in your menstrual cycle (valproate).
- For adolescents: changes in sex drive or sexual performance – discuss this with your doctor.

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- Weight/appetite changes – watch the type of food you eat; avoid foods with high fat or sugar content (e.g., cakes and pastry).
- Periods of hyperventilation or rapid breathing.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat, mouth ulcers or sores
- Skin rash or itching, swelling of the face, skin blistering or crusting (especially with carbamazepine and lamotrigine)
- Severe stomach pain, nausea, vomiting, loss of appetite
- Feeling tired, weak, feverish or like you have the flu
- Feeling confused or disoriented or having trouble finding the right words you want to say
- Easy bruising, bleeding, appearance of splotchy purplish darkening of the skin
- Yellowing of the skin or eyes; dark-colored urine (pee)
- Uncomfortable tingling sensations in fingers or toes
- Unusual eye movements
- Sudden blurring of vision and/or painful or red eyes
- Feeling very dizzy or falling/fainting
- Severe agitation, restlessness, irritability, or thoughts of suicide

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of medication in the morning or at bedtime and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because these drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations . Always inform any doctor or dentist that you see that you are taking this drug.

Precautions/considerations

1. Do not change your dose or stop the drug suddenly without speaking with your doctor, as this may result in withdrawal symptoms such as anxiety, irritability, and changes in mood.
2. These drugs may impair the mental and physical abilities and reaction time required for driving a car or operating other machinery. Avoid these activities if you feel drowsy or slowed down.
3. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
4. Report any changes in mood or behavior to your doctor.

What else do I need to know about anticonvulsants?

1. Avoid drinking grapefruit juice while on *carbamazepine* as it can change the amount of carbamazepine in your body.
2. If you are on *liquid carbamazepine*, do not mix it with any other liquid medication.
3. The liquid form of *valproic acid* should not be mixed with carbonated beverages, such as soda pop; this may cause an unpleasant taste or mouth irritation.
4. Unless you are prescribed a chewable tablet, capsules or tablets should be swallowed whole; do not break, chew or crush them; chewing capsules can cause irritation in the mouth and throat; extended-release capsules can be opened and sprinkled on food.
5. *Gabapentin* should not be taken within 2 hours of an antacid (e.g., Tums, Rolaids, Maalox).
6. If you are taking *topiramate,* drink plenty of fluids before and during activities such as exercise or exposure to warm temperatures. Avoid the regular use of antacids (e.g., Tums, Maalox).
7. To treat occasional pain, avoid the use of ASA (aspirin and related products) if you are taking *divalproex* or *valproic acid*, as it can be harmful to children, and may affect the amount of this drug in your body. Acetaminophen (Tylenol) or ibuprofen (Motrin, Advil) are safer alternatives.
8. On the morning when blood is drawn for an anticonvulsant level, withhold your morning dose of the drug until after the blood draw.
9. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on Antiparkinsonian Agents for Treating Extrapyramidal Side Effects

The name of your medication is _____.

What is this drug used for?

This drug is called an antiparkinsonian drug. It is used to treat a group of side effects, known as extrapyramidal side effects (or EPSE) that can happen when taking antipsychotic drugs. EPSE affect your muscles and can cause:

- Muscle spasms or tightening (this usually happens in the neck – can make your neck tip back or turn to the side; eyes – can make your eyes to roll back up in your head; or tongue – can make your tongue feel bigger than normal, making it hard to swallow). Rarely, muscle spasms from EPSE can lead to difficulty breathing.
- Muscle stiffness, tremors or shaking, and a shuffling walk.
- Feeling restless or unable to sit still.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

When given by injection, this drug works very fast, usually in 10 or 15 minutes. When swallowed as a pill, the drug should make you feel better within 1 hour.

How long should you take this medication?

Many people only take this drug for 2–3 weeks to prevent or treat EPSE when an antipsychotic drug is first started. Your doctor may lower the dose of this drug to see if any signs of EPSE return; if not, you may be able to stop this drug. Do not change the dose of this drug without talking to your doctor first.
Some people may need to take this drug for a longer time because they are more "sensitive" or more likely to get EPSE. Other people only have to take it for short periods from time to time. (e.g., for 1 week after getting an antipsychotic by injection, or just for 1 or 2 doses when they have bothersome EPSE, i.e., as needed).

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. Many side effects get better or go away over time. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects than can occur with antiparkinsonian drugs are:

- Dry mouth – sugarless hard candy or gum, ice cubes or popsicles can help. Do not drink sugar-containing drinks to help your dry mouth as they may give you cavities and increase your weight. Brush your teeth daily and visit your dentist regularly.
- Blurred vision – may happen when you first start to take this drug and may last for 1–2 weeks. Reading under a bright light or moving the book further away to read may help. If the problem lasts for more than a few weeks let your doctor know.
- Constipation – drink water, try to increase the amount of fiber in your diet (like fruits, vegetables or bran), and exercise your abdominal muscles. Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If this does not work or if you go more than 3 days without having a bowel movement, call your doctor or pharmacist.
- Feeling sleepy or tired – this usually goes away over time. Be careful if you are driving or using heavy machinery or during times when you need to be wide awake.
- Nausea or heartburn – try taking your drug with food if this happens.

Less common side effects that you should tell your doctor about **RIGHT AWAY** are:

- Feeling confused, having memory loss or noticing an increase in your psychosis symptoms
- Going more than 3 days without having a bowel movement
- Going more than 12 hours without peeing
- Getting a skin rash

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

Is this drug safe to take with other medication?

Antiparkinsonian drugs can change the effect of other drugs that you are taking or they may be affected by other drugs. Always check with your doctor or pharmacist before taking any drugs, including those that you are taking or plan to take, those you can buy without a prescription (like cold remedies), and herbal medications (like St. John's Wort, ginseng, and many others).

What else do I need to know about antiparkinsonian drugs?

1. Do not change your dose or stop it without talking to your doctor.
2. This drug may increase the effects of alcohol, making you more sleepy and less alert. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
3. This drug may affect your body's ability to control body temperature, so be cautious or avoid places that are very hot and humid, like saunas and hot tubs.
4. Keep your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions about this drug, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on Antipsychotic Drugs

The name of your medication is _____.

What is this drug used for?

The main uses of this class of drug are to treat psychosis and biopolar disorder. Psychosis can be a part of many illnesses like schizophrenia, major depression, and bipolar disorder. In children, studies show that some antipsychotic drugs are effective for reducing irritability in patients with autism, treating tic disorders or Tourette's disorder, and for reducing aggression. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

What symptoms will this drug help control?

Symptoms of psychosis may not be the same for each person. Some symptoms of psychosis that this drug can help with are:

- Hearing voices, seeing things or smelling, tasting or feeling things that are not real (hallucinations).
- Feeling that someone is trying to hurt you or is following you or that people are talking about you or that you have special powers or are famous (delusions).
- Finding it hard to think clearly, having thoughts that are speeded up or feeling like you don't have control of your thoughts.
- Becoming easily upset or overexcited.
- Showing diminished interest in yourself or others.

Your doctor may choose to use this medication for reasons not listed here. If you are not sure why this drug is being prescribed for you, please ask your doctor.

How quickly will this drug start working?

Some symptoms of psychosis may get better before others. Over the first few weeks, you may find that you sleep better and have fewer mood changes (feel too angry, sad or happy or have too much energy). Slowly, over the next 2–8 weeks, hallucinations or delusions fade away and your thoughts become clearer. Because antipsychotics take time to work, do NOT change your dose or stop your medication without talking to your doctor.

How long should you take this medication?

This depends on what type of illness you have and how well you do. If you are taking this medication to treat psychosis for the first time and do well on it, your doctor will likely want you to stay on it for at least 1–2 years. This will help stop you from getting sick again. If you have had symptoms of psychosis for many years or symptoms that go away but then come back, you may need to stay on this drug for a longer time. Talk with your doctor about how long you should stay on this medication.

How do you take this drug?

Antipsychotic drugs come in different forms:

- Fast-acting injection – used to control symptoms quickly.
- Liquid form or oral dissolving tablet – usually used for people who can't swallow tablets easily.
- Tablets or capsules – the most common way to take this drug.
- Sublingual tablets – tablets that dissolve or melt under the tongue without the need to swallow
- Long-acting or depot injection – drug is given in an injection once every 2–13 weeks. This is helpful if you can't remember to take your drug every day.

What side effects may happen?

Side effects may happen with any drug. They do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. Many side effects get better or go away over time. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects of some antipsychotic drugs that you should tell your doctor about **RIGHT AWAY** are:
Extrapyramidal Side Effects (or EPSE): There are different kinds of EPSE. Try not to be scared if these symptoms happen to you because they can be treated.

- One kind of EPSE, called acute dystonia, can make your muscles stiff. This can make your neck tip back or turn to the side or cause your eyes to roll back up in your head or make your tongue feel bigger than normal, making it hard to swallow. This kind of EPSE most often happens in the first week that you start to take an antipsychotc drug. Call your doctor right away if you think you have this reaction and they can give you another medicine that should make you feel better within 10–15 minutes. If you experience difficulty breathing related to this reaction, go to your nearest hospital emergency room or call an ambulance.
- Another kind of EPSE, called akathisia, may make you feel restless, fidgety, or unable to sit or stand still.
- Another kind of EPSE, called parkinsonism, may make your hands shake or your body feel stiff and slow.

Common side effects that you should tell your doctor about at the **NEXT VISIT** include:

- Feeling sleepy or tired – this usually goes away over time. Be careful driving or during times when you need to be wide awake.
- Feeling dizzy – you may find you get dizzy or feel faint when you get up too fast from sitting or lying down. Getting up more slowly or sitting on the side of your bed with your feet on the floor before getting up will help. This side effect usually goes away over time.
- Dry mouth – sugarless hard candy or gum, ice cubes, or popsicles can help. Do not drink sugar-containing soft drinks to help your dry mouth as they may give you cavities and increase your weight. Brush your teeth daily and visit your dentist regularly.
- Blurred vision – may happen when you first start to take this drug and may last for 1–2 weeks. Reading under a bright light or moving the book further away to read may help. If the problem lasts for more than a few weeks, let your doctor know.

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- Constipation – drink water, try to increase the amount of fiber in your diet (like fruits, vegetables or bran), and exercise your abdominal muscles. Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If this does not work or if you go more than 3 days without having a bowel movement, call your doctor or pharmacist.
- Weight gain – the best way to limit weight gain is to watch how much you eat and avoid eating fatty foods (like cakes, ice cream) or foods high in sugar (like soft drinks or energy drinks). Exercise can also help. Your doctor should check your weight, cholesterol (a type of body fat), and sugar levels from time to time.
- Increased thirst or peeing more often – let your doctor know. Your doctor may want to check your blood sugar.
- Nausea or heartburn – try taking your drug with food if this happens.
- For adolescents: changes in sex drive or sexual performance – discuss this with your doctor.
- Effects in women – some antipsychotic drugs may cause changes in how regular your monthly periods are or cause you to miss your period. It may also cause your breasts to leak milk. Talk with your doctor if this happens to you as these effects can be treated.
- Tardive dyskinesia – may occur in people taking antipsychotic drugs (usually the older agents) for many years. Tardive dyskinesia happens when some of your body muscles, usually in your face (lips and tongue), fingers, or toes, move on their own, without you making them do so. Your doctor may periodically examine you for any signs of tardive dyskinesia as picking them up early and taking action (depending on how you are doing, your doctor may decide to stop your drug or change to another drug) can help increase the chance that this side effect will go away.

Rare side effects you should tell your doctor about **RIGHT AWAY** are:

- Skin rash or itching
- Really bad headache
- Constant dizziness or fainting, breathing too fast or feeling like your heart is skipping or missing beats
- Fever, nausea, vomiting, appetite loss or feeling tired, confused, really thirsty, weak or like you have a flu
- Sore mouth, gums or throat
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Going more than 12 hours without peeing
- Going more than 3 days without having a bowel movement
- Fever (temperature above 38 degrees Celsius/100 degrees Fahrenheit) with muscle stiffness
- Sudden weakness or numbing in the face, arms or legs or difficulty seeing or talking
- Thoughts of suicide

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If it is almost time for your next dose, just skip the missed one. Do NOT take two doses at the same time.

Is this drug safe to take with other medication?

Antipsychotic drugs can change the effect of other drugs that you are taking or they may be affected by other drugs. Always check with your doctor or pharmacist before taking any drugs, including those that you are taking or plan to take, those you can buy without a prescription (like cold remedies), and herbal medications (like St. John's Wort, ginseng, and many others).

What else do I need to know about antipsychotic drugs?

1. Do not change your dose or stop it without talking to your doctor.
2. If you take asenapine (Saphris) let the tablet melt under your tongue and do not eat or drink for 10 minutes afterwards. Most other antipsychotic drugs can be taken with meals or with water, milk or orange juice. Do NOT take them with apple juice or grapefruit juice as these may change the amount of drug in your body.
3. If you take ziprasidone (Geodon/Zeldox) or lurasidone (Latuda), make sure you take your tablets with meals. If you take risperidone liquid (Risperdal oral solution), do NOT take it with caffeine-containing soft drinks or with tea.
4. Risperidone, olanzapine, and aripiprazole oral dissolving tablets (Risperdal M-tab, Zyprexa Zydis, and Abilify Discmelt) dissolve rapidly in saliva and can be taken with or without liquid. They can also break easily. Do NOT push tablets through foil backing as this could damage tablets. Use dry hands to remove tablet and immediately place tablet on tongue.
5. Do not split, crush or chew quetiapine (Seroquel XR) or paliperidone (Invega) tablets.
6. If you take paliperidone (Invega), you may see the tablet shell in your stool. This is normal.
7. Do not break or crush your drug unless you have been told to do so by your doctor.
8. This drug may increase the effects of alcohol, making you more sleepy and less alert. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
9. This drug may affect your body's ability to control body temperature, so be cautious or avoid places that are very hot and humid, like saunas and hot tubs.
10. Antacids (like Diovol, Maalox, Amphogel, etc.) may lower the amount of drug in your body. Take your antacid at least 2 hours before or 1 hour after taking your antipsychotic drug to avoid this.
11. Some people who take this drug may get badly sunburnt even without being in direct sun for a long time. Avoid direct sun, wear protective clothes, and use sunscreen.
12. Drinking a lot of caffeine (coffee, teas, caffeine-containing soft drinks, etc.) can cause you to become easily upset or jittery and make it harder for this drug to work.
13. Cigarette smoking can change the amount of this drug in your body, so let your doctor know if you smoke or if you stop smoking or change how much you smoke.
14. Stopping your drug all of a sudden ("cold turkey") may make you ill. Talk to your doctor or pharmacist first about how to stop it safely.
15. Keep your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions about antipsychotic drugs, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on Atomoxetine

What is this drug used for?

Atomoxetine is used primarily in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adults, and may also help treat symptoms of anxiety that may be present along with ADHD.
Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Some response to atomoxetine is usually noted within the first 3–4 weeks of treatment of ADHD.

How does your doctor decide on the dosage?

Atomoxetine comes in a capsule; the dose is based on how you respond to initial low doses and is guided by your body weight. The capsule is usually taken once or twice a day, with or without food. **Do not increase or decrease the dose without speaking to your doctor.**

How long should you take this medication?

Atomoxetine is usually prescribed for a period of several months to years.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Increased anxiety, agitation or excitability – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication.
- Headache – this tends to be temporary and can be managed by taking pain medicine (e.g., acetaminophen or ibuprofen) when required. If the headache persists or is "troubling," contact your doctor.
- Nausea, abdominal pain, vomiting – try taking your medication with food; if symptoms persist, speak to your doctor.
- Loss of appetite, weight loss – eating smaller meals more frequently or drinking liquid nutritional supplements may help.
- Feeling sleepy and tired – the problem usually goes away with time, however, your doctor may suggest you take your medication at bedtime. Use of other drugs that make you drowsy will worsen the problem. Avoid operating machinery or tasks that require alertness if drowsiness persists.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sugar-containing drinks as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Dizziness – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint, then contact your doctor.
- Difficulty remembering things – speak to your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Fast or irregular heart beat
- Skin rash with swelling, itching
- Soreness of the mouth, gums or throat
- Any unusual bruising or bleeding, appearance of splotchy purplish darkening of the skin
- Tenderness on the right side of your abdomen, fatigue, weakness, fever or flu-like symptoms accompanied by nausea, vomiting or loss of appetite
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Going 12 or more hours without peeing
- Severe agitation, restlessness, or irritability
- A persistent or painful erection of the penis that continues for longer than 4 hours
- **Switch in mood to an unusual state of happiness, excitement, irritability, a marked disturbance in sleep, or thoughts of suicide**

Let your doctor know **as soon as possible** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take atomoxetine more than once a day and you forget to take a dose by more than 6 hours, skip the missed dose and continue with your regular schedule. **DO NOT DOUBLE THE DOSE.**

Is this drug safe to take with other medication?

Because atomoxetine can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking atomoxetine.

Precautions/considerations

1. This medication should not be used in patients who have high blood pressure, heart disease or abnormalities, hardening of the arteries or an overactive thyroid.
2. Report to your doctor any changes in sleeping or eating habits or changes in mood or behavior.
3. Do not change your dose or stop atomoxetine without speaking with your doctor.
4. Use caution while performing tasks requiring alertness as atomoxetine can mask fatigue.

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5. This drug may interact with medication prescribed by your dentist, so let him/her know you are taking atomoxetine.

What else do I need to know about atomoxetine?

1. Swallow the capsules whole; do not open the capsules as the powder inside the capsule may irritate your eyes.
2. Take atomoxetine with or after meals to lessen stomach upset, nausea or vomiting.
3. Store your medication in a clean dry area at room temperature. Keep all medication out of reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Benzodiazepines and Anxiolytics

The name of your medication is _____.

What is this drug used for?

This medication is used to **treat symptoms of anxiety.** Anxiety is a normal human response to stress and is considered necessary for effective functioning and coping with daily activities. It may, however, be a symptom of many other disorders, both medical and psychiatric. There are many different types of anxiety and there are many different approaches to treating it. Anxiolytics can help relieve the symptoms of anxiety but will not get rid of its cause. In usually prescribed doses, they help to calm and relax the individual; in high doses, these drugs may be used to induce sleep. Benzodiazepines may also be used as muscle relaxants, to stop seizures, and before some diagnostic procedures. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Anxiolytic drugs can reduce agitation and induce calm or sedation usually within an hour. Sometimes they are given by injection or dissolved under the tongue for a quicker effect.

How long should you take this medication?

Anxiety is usually self-limiting; often when the cause of anxiety is treated or eliminated, symptoms of anxiety will decrease. Therefore, anxiolytics are usually prescribed for a limited period of time. Many individuals take the medication only when needed (during periods of excessive stress) rather than on a daily basis. Tolerance or loss of effectiveness can occur in some individuals if the medication is used continuously beyond 4 months. If you have been taking the medication for a continuous period of time, your doctor may try to reduce the dose of this drug slowly to see if the anxiety symptoms return; if not, the dosage may be further reduced and you may be advised to stop using this medication. **Do not increase the dose or stop the drug suddenly without consulting with your doctor.**
Some patients need to use an anxiolytic drug for longer time periods because of the type of anxiety they may be experiencing. Others require anxiolytic medication only from time to time, i.e., as needed.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. Many side effects get better or go away over time. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy and tired – this problem goes away when the dose is reduced. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Muscle incoordination, weakness or dizziness – inform your doctor; an adjustment in your dosage may be needed.
- Forgetfulness, memory lapses – inform your doctor.
- Slurred speech – an adjustment in your dosage may be needed.
- Nausea or heartburn – if this happens, take the medication with food.
- Nervousness, excitement, restlessness, or any behavior changes – this type of reaction occurs more commonly in young children

Less common side effects that you should report to your doctor **RIGHT AWAY** include:

- Disorientation, confusion, worsening of memory, blackouts, difficulty learning new things or amnesia
- Incoordination leading to falls
- Skin rash

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

Is this drug safe to take with other medication?

Because these drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations . Always inform any doctor or dentist that you see that you are taking these drugs.

Precautions/considerations

1. Do not change your dose or stop the drug suddenly without talking to your doctor, especially if you have a seizure disorder, have been on the medication for a number of months, or have been taking high doses. Anxiolytics need to be withdrawn gradually to prevent withdrawal reactions.
2. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.
3. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.

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What else do I need to know about antianxiety drugs?

1. Take your medication with meals or with water, milk, orange or apple juice. Avoid grapefruit juice as it may change the amount of the drug in your body.
2. If you are taking sublingual lorazepam, dissolve the tablet under your tongue. The tablet will dissolve within 20 seconds, but you should not swallow for 2 minutes so the drug can be absorbed.
3. If you are taking extended-release alprazolam (Xanax XR) or clorazepate (Tranxene SD), do not cut, crush or chew the tablet. Rather, swallow it whole. Take this drug at the same time in relation to your meals (preferably in the morning).
4. Drinking a lot of caffeine (coffee, tea, caffeine-containing soft drinks, etc.) can cause you to become easily upset or jittery and make it harder for this drug to work.
5. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Buprenorphine

What is this drug used for?

Buprenorphine is primarily used as a substitute drug in the treatment of opioid-dependent patients who desire maintenance therapy. It suppresses cravings for opioids and can aid in the withdrawal process. Buprenorphine is part of a complete addiction treatment program that also includes behavior therapy and counseling. It has been demonstrated that buprenorphine is beneficial in helping patients avoid illicit opioid use and helps them become socially stable.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How is it supplied?

Buprenorphine is available as two different preparations: Subutex, which is a sublingual tablet of buprenorphine, and Suboxone, which is a combination of sublingual buprenorphine and sublingual naloxone. Your doctor will determine which preparation is most appropriate for you.
Buprenorphine is an opioid and its dispensing and usage is governed by Federal regulations.

How quickly will the drug start working?

Buprenorphine will be started once you have abstained from opioids for 12–24 hours and are in the early stages of withdrawal. The dose will be determined by your doctor, and will be given once daily. Put the tablets under your tongue and let them melt; this will take 2–10 minutes. Do not chew or swallow the tablets, as this will change the effect of the drug.
Any changes in dosage of buprenorphine will be determined by your response, i.e., a decrease in cravings and no withdrawal symptoms. You should see a response within the first 2 weeks. **Follow your doctor's directions exactly; do not increase or decrease your dose as either severe adverse effects or withdrawal effects could occur.**

How long should you take this medication?

The length of time buprenorphine is prescribed varies among individuals and depends on a number of factors, including how well they do in therapy. Some patients receive buprenorphine for several months, while most may require it for several years. Any decreases in dose should be done very gradually under the direction of your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Energized feeling, insomnia – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication.
- Nausea, stomach pain – if this happens, take the medication after eating.
- Drowsiness – this problem goes away with time. Use of other drugs that make you sleepy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist.
- Sweating – you may sweat more than usual; frequent showering and use of antiperspirants may help.
- Pain in joints, muscles – temporary use of non-opioid pain medicine (e.g., acetaminophen or ibuprofen) may help.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Feeling faint, dizzy, and confused
- Slowed, difficult breathing
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, accompanied by feeling tired, weak, feverish or like you have the flu.

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take two doses at once unless told to do so by your doctor.
Missed doses as well as extra doses can cause withdrawal reactions which include: Nausea/vomiting, diarrhea, muscle aches and cramps, sweating, tearing of the eyes, running nose, dilated pupils, yawning, craving, mild fever, irritability, and insomnia. If you have a combination of these symptoms, call your doctor right away or your local emergency number.

Is this drug safe to take with other medication?

Because buprenorphine can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking this medication.

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It is important to carry a card in your wallet, stating that you are taking buprenorphine, in case of emergency.
DO NOT drink alcohol or take tranquilizers or sedatives while you are taking buprenorphine, as serious reactions can occur.

Precautions/considerations

1. Do not share this medication with anyone and store it out of reach of children (preferably in a locked cupboard or desk); buprenorphine can be poisonous to other individuals.
2. Do not change the dose or stop the drug suddenly without speaking to your doctor. Taking higher doses can precipitate a withdrawal syndrome; misuse/abuse may result in poisoning.
3. You can develop dependence from taking buprenorphine, so withdrawal symptoms can occur if you stop the drug suddenly.
4. Buprenorphine can cause death from overdose or if it is injected.
5. You may feel drowsy while taking buprenorphine; do not drive a car or perform tasks requiring alertness if you feel drowsy or slowed down.

What else do I need to know about buprenorphine?

1. The tablets should not be handled, but placed directly in the mouth; they should be placed (all together) under the tongue until dissolved (this takes 2–10 minutes); drinking fluids prior to taking the tablets may speed up the dissolution process; chewing or swallowing them reduces the effect of the drug; do not drink for at least 5 minutes afterwards so as to allow the drug to be absorbed.
2. Carry an identification card stating the name of the drug you are taking and ensure every doctor and dentist you visit is aware you are taking buprenorphine.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Bupropion

Bupropion belongs to a class of antidepressants called selective norepinephrine dopamine reuptake inhibitors (NDRI).

What is this drug used for?

Bupropion is mainly used in the treatment of major depressive disorder and bipolar depression. It has also been approved for use in the management of smoking cessation.
Though not approved for these indications, bupropion has also been found useful in children and adults with attention-deficit/hyperactivity disorder (ADHD), and has been used as an add-on treatment to increase the effects of other classes of antidepressants. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Bupropion is usually prescribed twice a day, morning and afternoon or once a day if you are using an extended-release tablet. It begins to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.
Improvement in smoking cessation/withdrawal also occurs over a period of 6 weeks.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression, it is usually recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.
Use of bupropion for smoking cessation is recommended as a one-time treatment for a period of 12 weeks.
Long-term treatment is generally recommended for treatment of ADHD.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. Report this to your doctor; he/she may advise you to take the medication in the morning.
- Vivid dreams or nightmares – this can occur at the start of treatment.
- Headache – this can be managed by taking a pain reliever (e.g., acetaminophen or ibuprofen) as required. If the headache persists or is "troubling," contact your doctor.
- Muscle tremor, twitching – speak to your doctor as this may require a change in your dosage.
- Nausea or heartburn – if this happens, take the medication with food.
- Loss of appetite.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Sweating – you may sweat more than usual; frequent showering and use of antiperspirants may help.
- Blood pressure – a slight increase in blood pressure can occur with this drug. If you are taking medication for high blood pressure, tell your doctor, as this medication may have to be adjusted.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Persistent, troubling headache
- Seizures; these may occur with high doses – should you have a seizure, stop taking bupropion and contact your doctor
- Chest pain, shortness of breath
- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, fatigue, weakness, fever or flu-like symptoms
- Muscle pain and tenderness or joint pain accompanied by fever and rash
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Tingling in the hands and feet, severe muscle twitching
- **Severe agitation, restlessness, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If take the sustained-release form of bupropion (Wellbutrin SR, Zyban) and take this medication twice daily, and you forget to take the morning dose by more than 4 hours, skip the missed dose and continue with your schedule for the evening dose. If you

miss the evening dose by more than 4 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE** as seizures may occur.
If you take the extended-release form of bupropion (Aplenza, Forfivo, Wellbutrin XL) and you forget to take the morning dose by more than 4 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE** as seizures may occur.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication, or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Inform your doctor if you have a history of seizure disorder (epilepsy), alcohol abuse, or an eating disorder such as anorexia or bulimia.
3. Do not stop this drug suddenly (without discussing it with your health care advisor), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
4. Report any changes in mood or behavior to your doctor.
5. Inform your doctor of all medications you are taking including all drugs prescribed by any doctor as well as over-the-counter and herbal preparations.
6. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

What else do I need to know about bupropion?

1. If you are taking a sustained-release or extended-release tablet of bupropion, swallow it whole; **do not split, crush or chew the tablet**, as this will affect the action of the medication and may increase the risk for a seizure to occur.
2. It is best not to drink alcohol at all, or to drink very moderately, while taking bupropion. The risk of seizures is increased if you drink a lot of alcohol regularly for an extended period of time (several weeks or longer) and suddenly stop.
3. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
4. Store your medication in a clean, dry area at room temperature and away from high humidity, as tablets can deteriorate. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Buspirone

Buspirone is an anti-anxiety drug (anxiolytic).

What is this drug used for?

Buspirone is used to **treat symptoms of chronic anxiety.** Anxiety is a normal human response to stress and is considered necessary for effective functioning and coping with daily activities. It may, however, be a symptom of many other disorders, both medical and psychiatric. There are many different types of anxiety and there are many different approaches to treating it.
Though not approved for these indications, buspirone has also been found effective in other conditions, including posttraumatic stress disorder, social anxiety disorder, body dysmorphic disorder, agitation, irritability, aggression, and antisocial behavior, and as an aid in smoking cessation and alcohol withdrawal. It has been used alone or in combination with antidepressants in the treatment of depression and obsessive-compulsive disorder. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Buspirone causes a gradual improvement in symptoms of anxiety and can reduce agitation and induce calm usually within 1–2 weeks. The maximum effect is seen after 3–4 weeks. Improvement in symptoms of other disorders for which buspirone may be prescribed occur gradually over several weeks.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Anxiety is usually self-limiting; often when the cause of anxiety is treated or eliminated, symptoms of anxiety will decrease. Therefore, anxiolytics are usually prescribed for a limited period of time. To maintain effectiveness, buspirone cannot be taken only when needed (during periods of excessive stress), but needs to be taken on a daily basis. Your doctor may try to reduce the dose of this drug to see if the anxiety symptoms return; if not, the dosage may be further reduced and you may be advised to stop using this medication. **Do not increase the dose or stop the drug without consulting with your doctor.**
Some patients need to use an anxiolytic drug for longer time periods because of the type of anxiety they may be experiencing. Long-term treatment is generally recommended for certain other indications such as social anxiety disorder, body dysmorphic disorder or antisocial behavior.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy and tired – this problem goes away with time or when the dose is reduced. Avoid driving a car or operating machinery if drowsiness persists.
- Headache – tends to be temporary and can be managed by taking a pain reliever (e.g., acetaminophen or ibuprofen) when required.
- Nausea or heartburn – if this happens, take the medication with food.
- Dizziness, lightheadedness – sit or lie down; if symptoms persist, contact your doctor.
- Energized/agitated feeling – some individuals may feel nervous for a few days after starting this medication. Report this to your doctor.
- Tingling or numbing in fingers or toes – report this to your doctor.

Less common side effects that you should report to your doctor **RIGHT AWAY** include:

- Severe agitation, excitement, or any changes in behavior

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of buspirone at bedtime and you forget to take your medication, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because this drug can change the effect of other medication, or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking this drug.

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What else do I need to know about buspirone?

1. Do not increase your dose without consulting your doctor.
2. Take your medication at the same time each day in relation to your meals (i.e., always with or without food).
3. Take your medication with water, milk orange or apple juice. Avoid grapefruit juice as it may change the amount of the drug in your body.
4. Drinking a lot of caffeine (coffee, tea, caffeine-containing soft drinks, etc.) can cause you to become easily upset or jittery and make it harder for this drug to work.
5. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
6. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Clonidine

Clonidine was originally approved to treat high blood pressure, and is used in the treatment of attention deficit/hyperactivity disorder (ADHD) and tic disorder in children and adults. It has also been found effective for controlling some problematic behaviors in children and adults, including patients with autism, in decreasing symptoms in certain anxiety disorders as well as in schizophrenia, and in increasing patient comfort during heroin and nicotine withdrawal. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Some response to clonidine is usually noted within the first week of treatment of ADHD and tends to increase over the next 3 weeks.

How does your doctor decide on the dosage?

Clonidine comes in both a tablet and a transdermal patch. The dose is based on body weight. The tablet is usually taken once or twice daily (extended-release forms) or several times a day (short-acting form), while the patch is applied to the upper arm or chest and is left there for a period of one week.
Do not increase or decrease the dose without speaking to your doctor. Do not take off the patch mid-week unless you have been told to do so by your doctor.

How long should you take this medication?

Clonidine is usually prescribed for a period of several months or years for ADHD. The length of use for other conditions varies.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy and tired – the problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid activities that require alertness (e.g., driving, operating machinery) if drowsiness persists.
- Dry mouth – sour candy, mints, and sugarless gum help increase saliva in your mouth. Do not drink sugar-containing drinks as they may increase your risk for dental cavities and increase your weight. Drink water and brush your teeth regularly.
- Dizziness – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint, then contact your doctor.
- Headache – this tends to be temporary and can be managed by taking pain medicine (e.g., acetaminophen or ibuprofen) when required. If the headache persists or is "troubling," contact your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Fast, slow or irregular heart beat
- Skin rash with swelling, itching
- Sore mouth, gums or throat
- Any unusual bruising or bleeding, appearance of splotchy purplish darkening of the skin
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Severe agitation, restlessness, or irritability
- Changes in mood or depressed mood

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take clonidine more than once a day and you forget to take a dose by more than 6 hours, skip the missed dose and continue with your regular schedule. **DO NOT DOUBLE THE DOSE.**

Is this drug safe to take with other medication?

Because clonidine can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking clonidine.

Precautions/considerations

1. Report to your doctor any changes in sleeping or eating habits or changes in mood or behavior.
2. Do not change your dose or stop the drug suddenly, without speaking with your doctor, as it may result in withdrawal symptoms including insomnia and changes in blood pressure. If you need to stop taking this medication, your doctor will tell you how to gradually reduce your dosage to prevent changes in blood pressure.
3. Use caution while performing tasks requiring alertness as clonidine can cause fatigue.
4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.

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What else do I need to know about clonidine?

1. If using the clonidine patch and it begins to loosen from the skin after application, apply adhesive tape directly over the patch to make sure it stays on for the rest of the week.
2. Take off the used patch before applying a new patch to the skin. Handle used transdermal patches carefully; fold the patch in half with the sticky sides together, and place inside a baggie prior to discarding. Keep out of reach of children and pets.
3. If you take clonidine extended-release tablets (Kapvay), swallow the tablet whole. Do not crush, split or chew the tablet.
4. Store your medication in a clean dry area at room temperature. Keep all medication out of reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Clozapine

Clozapine belongs to the class of drugs called **antipsychotics**.

What is this drug used for?

The main use of this drug is to treat psychosis. Psychosis can be a part of many illnesses like schizophrenia or bipolar disorder. Clozapine is most often used in people when other antipsychotic drugs don't work well enough. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

What symptoms will this drug help control?

Symptoms of psychosis may not be the same for each person. Some symptoms of psychosis that this drug can help with are:

- Hearing voices, seeing things or smelling, tasting or feeling things that are not real (hallucinations).
- Feeling that someone is trying to hurt you or is following you or that people are talking about you or that you have special powers or are famous (delusions).
- Finding it hard to think clearly, having thoughts that are speeded up or feeling like you don't have control of your thoughts.
- Becoming easily upset or overexcited.
- Showing no interest in yourself or others.

How quickly will the drug start working?

Some symptoms of psychosis may get better before others. Over the first few weeks, you may find that you sleep better and have fewer mood changes (feel too angry, sad or happy or have too much energy). Slowly, over the next 2–8 weeks, hallucinations or delusions fade away and your thoughts become clearer. Other symptoms such as having no interest in socializing with others may get better slowly over 6 months or more.
Because antipsychotics take time to work, **do NOT change your dose or stop your medication without talking to your doctor.**

How long should you take this medication?

People who take clozapine have often had symptoms of psychosis for a long time and may need to stay on this drug long term. Your doctor may change your dose from time to time based on how well you are doing and on the results of blood tests that you have. DO NOT CHANGE the dose or STOP taking clozapine without talking to your doctor first. Stopping clozapine all at once ("cold turkey") may cause you to feel ill.
If you have stopped taking clozapine for more than 2 days, do not re-start taking it on your own. Speak to your doctor or pharmacist about what to do.

Why do I need blood tests with clozapine? Why can I only get a small supply of clozapine at a time?

Clozapine can cause a rare side effect called agranulocytosis. This is when the number of white blood cells (a type of cell in your blood) to drop too low. This makes it harder for your body to fight off an infection. This can happen in 1 out of every 100 people that take clozapine. Blood tests must be done regularly so your doctor can check your white blood cells. Usually, a blood test must be done once a week for the first 26 weeks, then once every 2 weeks for the next 26 weeks, then every four weeks after that, while you stay on clozapine. Sometimes your doctor may want you to get extra blood tests depending on how you feel or if your white blood cells drop in number. It is also very important to call your doctor if you get any signs of infection such as fever, sore throat or mouth sores. Always let your doctor and pharmacist know you are taking clozapine before taking any new drugs. Your pharmacist is only allowed to dispense a supply of clozapine to you that lasts until you are due for your next blood test.

What side effects may happen?

Side effects may happen with any drug. They do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. Many side effects get better or go away over time. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that you should tell your doctor about at the **NEXT VISIT** include:

- Feeling sleepy or tired – this usually goes away over time. Be careful if you are driving or using heavy machinery or during times when you need to be wide awake.
- Feeling dizzy – you may find you get dizzy or feel faint when you get up too fast from sitting or lying down. Getting up more slowly or sitting on the side of your bed with your feet on the floor before getting up will help. This side effect usually goes away over time.
- Dry mouth – sugarless hard candy or gum, ice cubes or popsicles can help. Do not drink sugar-containing drinks to help your dry mouth as they may give you cavities and increase your weight. Brush your teeth daily and visit your dentist regularly.
- Blurred vision – may happen when you first start to take this drug and may last for 1–2 weeks. Reading under a bright light or moving the book further away to read may help. If the problem lasts for more than a few weeks, let your doctor know.
- Constipation – drink water, try to increase the amount of fiber in your diet (like fruits, vegetables or bran), and exercise your abdominal muscles. Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If this does not work or if you go more than 3 days without having a bowel movement, call your doctor or pharmacist.
- Drooling – often occurs at night. Use a towel on the pillow when sleeping. Drooling may occasionally occur while you are awake. If this is bothersome, talk to your doctor or pharmacist about other ways to manage this side effect.

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- Weight gain – the best way to limit weight gain is to watch how much you eat and avoid eating fatty foods (like cakes, ice cream) or foods high in sugar (like soft drinks or energy drinks). Exercise can also help. Your doctor may check your weight, cholesterol, (a type of body fat) and sugar levels from time to time.
- Increased thirst or peeing more often – let your doctor know. Your doctor may want to check your blood sugar.
- For adolescents: changes in sex drive or sexual performance – discuss this with your doctor.
- Episode of urinary incontinence/bladder accidents
- Nausea or heartburn – try taking your drug with food if this happens.

Rare side effects you should tell your doctor about **RIGHT AWAY** are:

- Sore mouth, gums or throat
- Feeling tired or weak, fever or flu-like symptoms or other signs of having an infection
- Feeling like your heart is beating too fast, chest pain or problems breathing
- Having a blackout, fit or seizure
- Skin rash or itching
- Really bad headache
- Constant dizziness or fainting
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Going 12 hours or more without peeing
- Going more than 3 days without having a bowel movement
- New or worsened distressing thoughts or compulsive behaviors
- Thoughts of suicide
- Fever (temperature above 38 degrees Celsius/100 degrees Fahrenheit) with muscle stiffness

Tardive dyskinesia: This is a movement disorder that may occur in people who have taken antipsychotic drugs for many years. Tardive dyskinesia happens when some of your body muscles, usually in your face (lips and tongue), fingers, or toes, move on their own, without you making them do so. The chance of this happening with clozapine is very low and sometimes clozapine may be used to help treat tardive dyskinesia.

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you miss a dose and remember within 2 hours, take the dose right away. Otherwise skip the missed dose. Do NOT take two doses at the same time. If you have stopped taking clozapine for more than 2 days, do not re-start taking clozapine on your own. Speak to your doctor or pharmacist about what to do.

Is this drug safe to take with other medication?

Clozapine can change the effect of other drugs that you are taking or it may be affected by other drugs. Always check with your doctor or pharmacist before taking any drugs, including those that you are taking or plan to take, those you can buy without a prescription (like cold remedies or medications for fever), and herbals (like St. John's Wort, ginseng, and many others).

What else do I need to know about clozapine?

1. Do not change your dose or stop it without talking to your doctor.
2. Take clozapine with meals or with water, milk or orange juice. Do NOT take it with grapefruit juice as this may change the amount of clozapine in your body.
3. Do not break or crush clozapine unless you have been told to do it by your doctor. If you are taking clozapine oral disintegrating tablets (FazaClo), do not push the tablet through the foil blister pack. Remove FazaClo by peeling back the foil and gently removing the tablet. Use dry hands to remove the tablet and immediately place the tablet on your tongue and let it melt. No water is needed to take FazaClo.
4. This drug may increase the effects of alcohol, making you more sleepy and less alert. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
5. Clozapine may affect your body's ability to control body temperature, so avoid places that are very hot and humid like saunas.
6. Antacids (like Diovol, Maalox, Amphogel, etc.) may lower the amount of clozapine in your body. Take your antacid at least 2 hours before or 1 hour after taking clozapine to avoid this.
7. Drinking a lot of caffeine (coffee, teas, caffeine-containing soft drinks, etc.) can cause you to become easily upset or jittery and make it harder for clozapine to work.
8. Cigarette smoking can change the amount of clozapine in your body, so let your doctor know if you smoke or if you stop smoking or change how much you smoke.
9. Stopping clozapine all of a sudden ("cold turkey") may make you ill. Starting to take your regular clozapine dose again after more than 48 hours have passed without taking may also make you ill. Talk to your doctor or pharmacist first about how to stop taking clozapine safely or how to safely restart taking clozapine after not taking it for a period of more than 48 hours.
10. Keep your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions about clozapine, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on Cyclic Antidepressants

The name of your medication is _____.

What is this drug used for?

Cyclic antidepressants are primarily used in the treatment of major depressive disorder and bipolar depression.
Certain drugs in this class have also been found effective in several other disorders including obsessive-compulsive disorder, anxiety disorders, panic disorder, bulimia, social anxiety disorder, and premenstrual dysphoria or depression as well as management of chronic pain conditions (e.g., migraines, neuropathic pain) and treatment of attention-deficit/hyperactivity disorder (ADHD) and persistent bedwetting in children. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Antidepressants begin to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.
Improvement in symptoms of obsessive-compulsive disorder, panic disorder, and bulimia as well as pain management also occur gradually.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression it is usually recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.
Long-term treatment is generally recommended for obsessive-compulsive disorder, anxiety disorders, panic disorder, bulimia, pain management, and persistent bedwetting in children.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling drowsy or tired – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery until you know how the drug affects you. If drowsiness persists your doctor may advise you to take the medication at bedtime.
- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. Report this to your doctor; he/she may advise you to take the medication in the morning.
- Blurred vision – this usually happens when you first start the drug and tends to be temporary. Reading under a bright light or at a distance may help; a magnifying glass can be of temporary use. If the problem lasts more than a few weeks, let your doctor know.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist. Avoid taking laxatives within 2 hours of this medication, as this may reduce the antidepressant effect.
- Headache – this tends to be temporary and can be managed by taking a pain reliever (e.g., acetaminophen or ibuprofen) when required.
- Nausea or heartburn – if this happens, take the medication with food.
- Dizziness – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint, then contact your doctor.
- Sweating – you may sweat more than usual; frequent showering and use of antiperspirants may help.
- Muscle tremor, twitching – speak to your doctor as this may require a change in your dosage.
- For adolescents: changes in sex drive or sexual performance – discuss this with your doctor.
- Nightmares – can be managed by changing the time you take your drug, speak with your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, fatigue, weakness, fever or flu-like symptoms
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Going 12 hours or more without peeing
- Inability to have a bowel movement (for more than 2–3 days)
- Tingling in the hands and feet, severe muscle twitching
- **Severe agitation, restlessness, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

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Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop this drug suddenly (without discussing it with your health care advisor), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
3. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.
4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
5. Report any changes in mood or behavior to your doctor.
6. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

What else do I need to know about cyclic antidepressants?

1. Take your drug with meals or with water, milk orange or apple juice; avoid grapefruit juice as it may change the effect of the drug in your body.
2. Avoid taking high-fiber foods (e.g., bran) within 2 hours of this medication, as this may reduce the antidepressant effect.
3. Avoid exposure to extreme heat and humidity since this drug may affect your body's ability to regulate temperature.
4. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
5. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Disulfiram

What is this drug used for?

Disulfiram is primarily used as a **deterrent to alcohol use/abuse**. Disulfiram has been shown to maintain abstinence if taken, as directed, as part of a treatment program that includes counseling and support.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Disulfiram inhibits the breakdown of alcohol in the body, resulting in a build-up of a chemical called acetaldehyde; this results in an unpleasant reaction when alcohol is consumed. The reaction can occur 10–20 minutes after drinking alcohol and may last up to 2 hours. The reaction may also be delayed up to 24 hours after alcohol exposure.
The reaction consists of: flushing, choking, nausea, vomiting, increased heart rate and decreased blood pressure (dizziness).

How long should you take this medication?

Disulfiram is usually prescribed for a set period of time to help the individual stop the use of alcohol. **Do not decrease or increase the dose** without discussing this with your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy, tired, depressed – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication.
- Headache – temporary use of pain medicine (e.g., acetaminophen or ibuprofen).
- Garlic-like taste.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Sore mouth, gums or throat
- Skin rash, itching or swelling of the face
- Feeling tired, weak, feverish or like you have the flu, associated with nausea, vomiting, and loss of appetite

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of the drug in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**.

Is this drug safe to take with other medication?

Because disulfiram can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking this medication.

Precautions/considerations

1. Do not change your dose or stop the drug without speaking to your doctor.
2. Report to your doctor any changes in sleeping or eating habits or changes in mood or behavior.
3. Avoid all products (food and drugs) containing alcohol, including tonics, cough syrups, mouth washes, and alcohol-based sauces. A delay in the reaction may be as long as 24 hours.
4. Exposure to alcohol-containing rubs or solvents (e.g., after-shave) may trigger a reaction.

What else do I need to know about disulfiram?

1. Carry an identification card or wear an alert bracelet stating the name of the drug you are taking.
2. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on Electroconvulsive Therapy (ECT)

What is ECT used for?

ECT is a procedure used primarily to treat patients with severe depression or severe catatonia. It has also been found effective in the manic phase of bipolar depression and in some patients with schizophrenia.

What is the ECT procedure?

ECT is given to the patient while under a general anesthetic that has put him/her to sleep; a muscle relaxant is also given to prevent injury to the muscles, bones, and joints.
ECT involves passing a small, controlled electric current between two metal discs (electrodes) which are applied on the surface of the scalp. The two electrodes may be placed on one side of the head (called unilateral ECT) or on both sides of the forehead (called bilateral ECT). The electric current passes between the two electrodes and through part of the brain in order to stimulate the brain; that electrical stimulation induces a convulsion or seizure which usually lasts 20–90 seconds.
The procedure takes approximately 10 minutes from the time the anesthetic is given until its effect wears off. Oxygen is given throughout this time and the patient is monitored continuously by the physician. The treatment is not painful and the electric current and seizure are not felt by the patient.

How does ECT work?

As is the case with many medical treatments, the actual way that ECT relieves symptoms of illness is not totally understood. ECT affects some of the chemicals which transfer impulses or messages between nerve cells in the brain, perhaps more strongly and quickly than some medications. The treatment may correct some of the changes in these chemicals which accompany some mental illnesses.

How effective is ECT?

Studies comparing the effectiveness of ECT and drug therapy in depression have consistently shown that ECT is the most effective treatment of depression, especially in patients whose illness does not respond adequately to drug treatment.
The total number of treatments required to get the full benefit from ECT usually ranges from 6 to 20, depending on the patient's diagnosis and response to treatment. In some patients, improvements may be seen after 3 treatments; however, a full course is generally recommended to obtain a full response. Some patients require ongoing periodic ECT treatments to maintain their improvement.

How safe is ECT and what are the potential side effects?

ECT is considered safe when given according to modern standards. It has been given safely to children and adolescents as well as to patients during pregnancy, with proper monitoring.
Side effects that can occur include the following:

- Memory – the most common side effect seen following ECT is some degree of memory loss. Recovery from that memory loss begins a few weeks after treatment and is usually complete in most patients after 6–9 months. There may be a permanent loss of memory for details of some events, particularly those which occurred some time before and during the weeks ECT treatment was given. Also, there may be some difficulty learning and remembering new information for a short period after ECT. However, the ability to acquire and retain new memories recovers completely, usually a few months after treatment. A very small number of patients report severe problems with memory that remain for months or years.
- Confusion – some patients experience a brief period of confusion after waking from the anesthetic.
- Headache – common, but not usually severe.
- Muscle aches – usually most significant after the first ECT treatment session and not usually severe.
- Increased heart rate and blood pressure – this can occur during treatment and last for several minutes. Monitoring of patients during and following ECT includes temperature, pulse, blood pressure, and electrocardiogram (ECG).
- Prolonged seizure – occurs rarely; seizure activity is monitored during the procedure by an electroencephalogram (EEG). Rarely, a patient may have a spontaneous seizure following ECT.
- Dental injury (e.g., broken teeth) or bone fractures – occur very rarely.

The risk of death is very rare (2–4 per 100,000 treatments) and is similar to that seen with any treatment given under a brief general anesthetic.

What else do I need to know about the ECT procedure?

1. Make sure that you understand the information that has been provided to you by your doctor or nurse regarding ECT; ask them to explain anything about the treatment which you do not understand.
2. Do not eat or drink anything for approximately 8 hours before each treatment (and nothing after midnight).
3. Any essential medication (e.g., for high blood pressure) which your doctor has told you must be taken before ECT, should be swallowed only with a very small sip of water.
4. Any other medication which you usually take in the morning should not be taken until after the ECT procedure.

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Patient and Caregiver Information on Guanfacine

What is this drug used for?

Guanfacine was originally approved to treat high blood pressure, and is used in the treatment of attention-deficit/hyperactivity disorder (ADHD) and tic disorders in children and adults. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Some response to guanfacine is usually noted within the first week of treatment of ADHD and tends to increase over the next 3 weeks.

How does your doctor decide on the dosage?

Guanfacine comes in both a short-acting tablet and an extended-release tablet. The dose is based on body weight. The tablet is usually taken once daily (extended-release form) or twice daily (short-acting form). For the extended-release form, swallow the tablet whole. The short-acting and extended-release tablets release drug in different ways. One form of tablet should not be used in place of the other form. **Do not decrease or increase the dose** without speaking to your doctor.

How long should you take this medication?

Guanfacine is usually prescribed for a period of several months or years for ADHD. The length of use for other conditions varies.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy, tired, depressed – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid activites that require alertness (e.g., driving, operating machinery) if drowsiness persists.
- Dry mouth – sour candy, mints, and sugarless gum help increase saliva in your mouth. Do not drink sugar-containing drinks as they may increase your risk for dental cavities and increase your weight. Drink water and brush your teeth regularly.
- Dizziness – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint, then contact your doctor.
- Headache – tends to be temporary and can be managed by taking a pain reliever (e.g., acetaminophen or ibuprofen) when required. If the headache persists or is "troubling," contact your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Fast, slow or irregular heart beat
- Skin rash or itching, swelling of the face
- Sore mouth, gums or throat
- Any unusual bruising or bleeding, appearance of splotchy purplish darkening of the skin
- Nausea, vomiting, loss of appetite, abdominal pain, feeling tired, weak, feverish, or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Severe agitation, restlessness, or irritability
- Changes in mood or depressed mood or thoughts of suicide

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take guanfacine more than once a day and you forget to take a dose by more than 6 hours, skip the missed dose and continue with your regular schedule. **DO NOT DOUBLE THE DOSE**. If you take guanfacine once a day and you forget to take a dose by more than 6 hours, skip the missed dose and continue with your regularly scheduled dose the next day. **DO NOT DOUBLE THE DOSE**.

Is this drug safe to take with other medication?

Because guanfacine can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription, such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking guanfacine.

Precautions/considerations

1. Report to your doctor any changes in sleeping or eating habits or changes in mood or behavior.
2. Do not change your dose or stop the drug sudddenly without speaking to your doctor as it may result in withdrawal symptoms, including insomnia and changes in blood pressure. If you need to stop taking this medication, your doctor will tell you how to gradually reduce your dosage to prevent changes in blood pressure.
3. Use caution when performing tasks that require alterness as guanfacine can cause fatigue.
4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.

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What else do I need to know about guanfacine?

1. If you take guanfacine extended-release tablets (Intuniv/Intuniv XR), swallow the tablet whole. Do not crush, split or chew the tablet.
2. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Hypnotics/Sedatives

The name of your medication is _____.

What is this drug used for?

This medication is used to **treat sleep problems,** such as problems falling asleep or remaining asleep for a reasonable number of hours or waking up often during the night. Sleeping problems occur in most individuals from time to time. If, however, sleeping problems persist, this may be a symptom of some other disorder, either medical or psychiatric.

A person may have difficulty in falling asleep because of stress or anxiety felt during the day, pain, physical discomfort or changes in daily routine (e.g., jet-lag, changes in work shifts, etc.). Any disease that causes pain (e.g., ulcers) or breathing difficulties (e.g., asthma or a cold) can interfere with continuous sleep. Stimulant drugs, including some ADHD treatments and caffeine, may also contribute to problems falling asleep; other medications may change sleep patterns when they are stopped (e.g., antidepressants, antipsychotics). Sleep will improve when these causes have been identified, corrected or treated.

Problems remaining asleep may be due to age, as older people tend to sleep less at night. Certain disorders, including depression, may also affect sleep.

Hypnotics/sedatives are similar to antianxiety (anxiolytic) drugs but tend to cause more drowsiness and incoordination; therefore, antianxiety drugs are sometimes given to treat sleep problems.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Hypnotics/sedatives can induce calmness or sedation usually within an hour. As some drugs act quickly, take the medication just prior to going to bed and relax in bed until the drug takes effect.

How long should you take this medication?

Sleep problems are usually self-limiting; often when the cause of sleep difficulties is treated or eliminated, sleep will improve. Therefore, hypnotic/sedatives are usually prescribed for a limited period of time. Many individuals take the medication only when needed (during periods of insomnia) rather than on a daily basis. It is suggested that once you have slept well for 2 or 3 nights in a row, try to get to sleep without taking the sedative/hypnotic.

Tolerance or loss of effectiveness can occur in some individuals if the medication is used every day for weeks or months. Individuals taking hypnotics for long periods of time have a risk of developing dependence – they may have difficulty stopping the medication and may experience withdrawal symptoms if the medication is stopped suddenly. To stop taking these medications following long-term use, the dosage should be gradually reduced over time, on the advice of your doctor.

If you have been taking the medication every day for a period of time, your doctor may try to reduce the dose of this drug slowly to see if sleeping problems persist; if not, the dosage may be further reduced and you may be advised to stop using this medication. **Do not increase the dose or stop the drug without consulting with your doctor.**

Some patients need to use a sedative/hypnotic drug for longer time periods because of the type of problems they may be experiencing. Others require it only from time to time, i.e., as needed.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that you should report to your doctor at the **NEXT VISIT** include:

- Morning hangover, feeling sleepy and tired – this problem may lessen with time; inform your doctor. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Muscle incoordination, weakness, lightheadedness or dizziness – inform your doctor; a change in your dosage may be needed.
- Forgetfulness, memory lapses – inform your doctor.
- Slurred speech – a change in your dosage may be needed.
- Nausea or heartburn – if this happens, take the medication with food.
- Bitter taste – can occur with certain drugs (e.g., zopiclone (Imovane) and eszopiclone (Lunesta)). Avoid drinking milk in the morning to lessen this effect.

Less common side effects that you should report to your doctor **RIGHT AWAY** include:

- Disorientation, confusion, worsening of your memory, periods of blackouts or amnesia
- Nervousness, excitement, agitation, hallucinations or any behavior changes
- Worsening of depression, suicidal thoughts
- Incoordination leading to falls
- Skin rash
- Rare incidents of sleepwalking, driving, aggression, and food binging while "asleep" have been reported.

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

Is this drug safe to take with other medication?

Because these drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations . Always inform any doctor or dentist that you see that you are taking these drugs.

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Precautions/considerations

1. Do not increase your dose without consulting your doctor.
2. Check with your doctor or pharmacist before taking other drugs, including drugs you can buy without prescription such as cold remedies and herbal preparations.
3. Speak to your doctor if you begin having sleeping problems after starting any new medication (e.g., for a medical condition).
4. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.
5. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
6. Do not stop taking this drug suddenly, especially if you have been on the medication for a number of months or have been taking high doses. Hypnotics/sedatives need to be withdrawn gradually to prevent withdrawal reactions.

What else do I need to know about hypnotics/sedatives?

1. Take your medication about half an hour before bedtime; do not smoke in bed afterwards.
2. If you are prescribed zolpidem (Ambien CR) or ramelteon (Rozerem), do not split, crush or chew the tablet but swallow it whole.
3. If you are taking ramelteon or zaleplon (Sonata), do not consume a high-fat meal within 1 hour of taking this medication.
4. If you are taking sublingual forms of zolpidem (Edluar, Intermezzo, Sublinox) the tablet should be placed under the tongue, where it will disintegrate. The tablet should not be chewed or swallowed and should not be taken with water. The tablet should not be taken with or immediately after a meal.
5. Drinking a lot of caffeine (coffee, tea, caffeine-containing soft drinks, etc.) can cause you to become easily upset or jittery and make it harder for this drug to work.
6. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

Some nondrug methods to help you sleep include:

1. Avoid taking caffeine-containing drinks or foods (e.g., chocolate) or heavy meals within 4 hours before bedtime. A warm glass of milk before bedtime is effective for some people.
2. Napping and sleeping during the day will make restful sleep at night difficult. Keep active during the day and exercise regularly.
3. Engage in relaxing activities prior to bedtime such a reading, listening to music or taking a warm bath. Strenuous exercise (e.g., jogging) immediately before bedtime may make it difficult to get to sleep.
4. Establish a routine or normal pattern of sleeping and waking.
5. Use the bed and bedroom only for sleep and when you are ill.
6. Minimize external stimulation which might disturb sleep. If necessary, use dark shades over windows or wear earplugs.
7. Once in bed, make sure you are comfortable (i.e., not too hot or cold); use a firm mattress.
8. Relaxation techniques (e.g., muscle relaxation exercises, yoga) may be helpful in decreasing anxiety and promoting sleep.
9. If you have problems getting to sleep, rather than tossing and turning in bed, have some warm milk, read a book, listen to music or try relaxation techniques until you again begin to feel tired.
10. Don't worry about the amount of sleep you are getting as the amount will vary from day to day. The more you worry the more anxious you will get and this may make it harder for you to fall asleep.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Lithium

Lithium is classified as a mood stabilizer. It is a simple element, found in nature, and is also present in small amounts in the human body.

What is this drug used for?

Lithium is used primarily to treat symptoms of acute mania and in the long term for control or prevention of bipolar depression and mania.
Though not approved for these indications, lithium has also been found to augment the effects of antidepressants in depression and obsessive-compulsive disorder, and is useful in the treatment of cluster headaches as well as chronic aggression or impulsivity.
Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How does your doctor decide on the dosage?

The dose of lithium is different for every patient and is based on how much lithium is in your blood, as well as the response to treatment. Your doctor will measure the lithium level in your blood on a regular basis during the first few months. The lithium level that is usually found to be effective for most patients is between 0.6 and 1.2 mmol/L (mEq/L).
You may initially take your medication two or three times a day; after several weeks, your doctor may decide to prescribe lithium once daily. It is important to drink 8–12 cups of fluid daily when taking lithium (e.g., water, juice, milk, broth, etc.).
On the morning of your lithium blood test, take the morning dose of lithium **after** the test to avoid inaccurate results.

How quickly will the drug start working?

Control of manic symptoms may require up to 14 days of treatment. Because lithium takes time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.
Improvement in symptoms of depression, obsessive-compulsive disorder, and cluster headaches as well as aggression/impulsivity also occur gradually.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of mania, it is usually recommended that lithium be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of mania or depression, lithium may need to be continued indefinitely.
Long-term treatment is generally recommended for recurring depression, obsessive-compulsive disorder, cluster headaches or aggression/impulsivity.

DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling tired, difficulty concentrating – this problem usually goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Nausea or heartburn – if this happens, take the medication with food. If vomiting or diarrhea occur and persist for more than 24 hours, call your doctor.
- Muscle tremor, weakness, shakiness, stiffness – speak to your doctor as this may require a change in your dosage.
- For adolescents: changes in sex drive or sexual performance – discuss this with your doctor.
- Weight changes – watch the type of food you eat; avoid foods with a high fat or sugar content (e.g., cakes and pastry).
- Increased thirst and increase in how often you pee – discuss this with your doctor.
- Skin changes, e.g., dry skin, acne, rashes.

Side effects you should report RIGHT AWAY, as they may indicate the amount of lithium in the body is higher than it should be, include:

- Loss of balance
- Slurred speech
- Visual disturbances (e.g., double vision)
- Nausea, vomiting, stomach ache
- Watery stools, diarrhea (more than twice a day)
- Abnormal general weakness or drowsiness
- Marked trembling (e.g., shaking that interferes with holding a cup), muscle twitches, jaw shaking.

IF THESE OCCUR CALL YOUR DOCTOR RIGHT AWAY. If you cannot reach your doctor, stop taking lithium until you get in touch with him/her. Drink plenty of fluids and eat some salty foods (e.g., chips, crackers). If symptoms continue to get worse or if they do not clear within 12 hours, go to the Emergency Department of the nearest hospital. A clinical check-up and a blood test may show the cause of the problem.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Swelling of the neck (goiter)

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- Abnormally frequent need to pee and increased thirst (e.g., having to get up in the night several times to pee)
- Thoughts of suicide

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of lithium in the morning or evening and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because lithium can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including over-the-counter medication such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking lithium.

Precautions/considerations

1. Do not change your dose or stop the drug without talking to your doctor.
2. This drug may impair the mental and physical abilities and reaction time required for driving a car or operating other machinery. Avoid these activities if you feel drowsy or slowed down.
3. Do not stop your drug suddenly as this may result in withdrawal symptoms such as anxiety, irritability, and changes in mood.
4. Report any changes in mood or behavior to your doctor.

What else do I need to know about lithium?

1. It is important to drink 8–12 cups of fluids daily (e.g., water, juice, milk, broth, etc.).
2. Limit the number of caffeinated liquids you drink (e.g., coffee, tea, caffeine-containing soft drinks), and avoid excessive alcohol use.
3. To treat occasional pain, avoid the use of nonsteroidal anti-inflammatory drugs (e.g., ibuprofen (Motrin, Advil) or naproxen (Aleve, Naprosyn)) as they can affect the blood level of lithium and may result in toxicity. Acetaminophen (Tylenol) is a safer alternative.
4. Do not change your salt intake during your treatment without first speaking to your doctor (e.g., avoid no-salt or low-salt diets).
5. If you have the flu, especially if vomiting or diarrhea occur, check with your doctor regarding your lithium dose.
6. Use extra care in hot weather and during activities that cause you to sweat heavily (e.g., hot baths, saunas, exercising). The loss of too much water and salt from your body may lead to changes in the level of lithium in your body and increased side effects, some of which may be serious.
7. If you take sustained-release lithium tablets (Lithobid, Lithmax), the tablets should be swallowed whole, and not chewed or crushed. Lithmax tablets may be split in half.
8. On the morning when blood is drawn for a lithium level, withhold your morning dose of lithium until after the blood draw.
9. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on MAOI Antidepressants

The name of your medication is _____.
It belongs to a class of antidepressants called monoamine oxidase inhibitors (MAOI).

What is this drug used for?

This medication is primarily used in the treatment of major depressive disorders and bipolar depression. It has also been approved in the management of atypical depression, phobic anxiety states or social anxiety disorder.
Though not approved for these indications, MAOIs have also been found effective in persistent depressive disorder (dysthymia), panic disorder and obsessive-compulsive disorder. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

MAOIs begin to improve sleep and appetite and to increase energy within about one week; however, feelings of depression may take from 4 to 6 weeks to improve. Because antidepressants take time to work, do not decrease or increase the dose or stop the medication without discussing this with your doctor.
Improvement in symptoms of atypical depression, phobic anxiety or social anxiety disorder, persistent depressive disorder (dysthymia), panic disorder and obsessive-compulsive disorder also occur gradually.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression it is usually recommended that antidepressants be continued for a minimum of one year; this decreases the chance of being ill again. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped. For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor. Long-term treatment is generally recommended for atypical depression, phobic anxiety or social anxiety disorder, persistent depressive disorder (dysthymia), panic disorder or obsessive-compulsive disorder.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy or tired – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery until you know how the drug affects you. If drowsiness persists your doctor may advise you to take the medication at bedtime.
- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. Report this to your doctor; he/she may advise you to take the medication in the morning and afternoon (rather than the evening).
- Headache – this can be managed by taking a pain reliever (e.g., acetaminophen or ibuprofen) as required. If the headache persists or is "troubling", contact your doctor.
- Dizziness – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint – then call your doctor.
- Nausea or heartburn – if this happens, take the medication with food.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Blurred vision – this usually happens when you first start the drug and tends to be temporary. Reading under a bright light or at a distance may help; a magnifying glass can be of temporary use. If the problem lasts more than a few weeks, let your doctor know.
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist.
- Muscle tremor, twitching, jerking – speak to your doctor as this may require a change in your dosage.
- Sweating – you may sweat more than usual; frequent showering and use of antiperspirants may help.
- Loss of appetite.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Persistent, throbbing headache
- Sore mouth, gums, or throat
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish, or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Going 12 hours or more without peeing
- **Severe agitation, restlessness, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be pregnant, plan to become **pregnant**, or are breastfeeding.

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Caution

Certain foods and drugs contain chemicals which are broken down by the enzyme monoamine oxidase. Since this drug blocks the action of that enzyme, these chemicals can increase in the body and may raise the blood pressure and cause a severe reaction called a **hypertensive crisis**.
Listed below are the foods and drugs which should be **avoided** while taking this drug.

Do not eat the following foods:
- All matured or aged cheeses (Cheddar, Brick, Blue, Stilton, Camembert, Roquefort)
- Broad bean pods (e.g., Fava Beans)
- Concentrated yeast extracts ("Marmite," "Vegemite")
- Sausage (if aged, especially salami, mortadella, pastrami, summer sausage), other unrefrigerated fermented meats, game meat that has been hung, aged liver
- Dried salted fish, pickled herring
- Sauerkraut
- Soy sauce or soybean condiments, tofu
- Packet soup (especially miso)
- Tap (draft) beer, alcohol-free beer
- Improperly stored or spoiled meat, poultry, or fish

Wait for 14 days after stopping a MAOI drug before restarting to eat the above foods.

Hypertensive reactions have been reported, by some individuals, with the following foods; try small portions to determine if these foods are safe for you to eat or will cause a reaction:
- Smoked fish, caviar, snails, tinned fish, shrimp paste
- Yogurt
- Meat tenderizers
- Meat extract ("Bovril," "Oxo")
- Homemade red wine, Chianti, canned/bottled beer, sherry, champagne
- Cheeses (e.g., Parmesan, Muenster, Swiss, Gruyere, Mozzarella, Feta)
- Pepperoni
- Overripe fruit, avocados, raspberries, bananas, plums, canned figs and raisins, orange pulp, tomatoes
- Asian foods
- Spinach, eggplant

It is SAFE to use the following foods, in moderate amounts (only if fresh):
- Cottage cheese, cream cheese, farmer's cheese, processed cheese, Cheez Whiz, ricotta, Havarti, Boursin, Brie without rind, Gorgonzola
- Liver (as long as it is fresh), fresh or processed meats, poultry or fish (e.g., hot dogs, bologna)
- Spirits, liquor (in moderation)
- Soy milk
- Sour cream
- Salad dressings
- Worcestershire sauce
- Yeast-leavened bread

Make sure all food is fresh, stored properly, and eaten soon after being purchased. Never touch food that is fermented or possibly "off." Avoid restaurant sauces, gravy and soup.

Do not use the following drugs, which you can buy without a prescription, unless you have spoken to your doctor or pharmacist:
- Cold remedies, decongestants (including nasal sprays and drops), some antihistamines and cough medicine
- Opioid painkillers (e.g., products containing codeine, meperidine, or tramadol)
- All stimulants including pep-pills (Wake-ups, Nodoz), or appetite suppressants
- Anti-asthma drugs (Primatene P)
- Sleep aids and sedatives (Sominex, Nytol)
- Yeast, dietary supplements (e.g., Ultrafast, Optifast)

It is SAFE to use:
- Plain acetaminophen (e.g., Tylenol), or ibuprofen (e.g., Motrin, Advil)
- Antacids (e.g., Tums, Maalox)
- Throat lozenges

If a **hypertensive reaction** (high blood pressure) should occur, the symptoms usually come on suddenly, so be alert for these signs:
- Severe, throbbing headache which starts at the back of the head and radiates forward; often the headache is accompanied by nausea and vomiting
- Stiff neck
- Heart palpitations, fast heart beat, chest pain
- Sweating, cold and clammy skin
- Enlarged (dilated) pupils of the eyes
- Sudden unexplained nose bleeds

If a combination of these symptoms does occur, **contact your doctor IMMEDIATELY**; if you are unable to do so, go to the Emergency Department of your nearest hospital.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication, or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking a MAOI antidepressant.

Precautions/considerations

1. Do not increase or decrease your dose without consulting your doctor.
2. Be aware of foods which you cannot eat while taking this medication.
3. Take no other medication (including those you can buy without a prescription or herbal products) without speaking with your doctor or pharmacist. Avoid all products containing dextromethorphan (DM).
4. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

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5. This drug may impair the mental and physical abilities required for driving a car or operating other machinery. Avoid these activities if you feel drowsy or slowed down.
6. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
7. Do not stop your drug suddenly as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
8. Report any changes in mood or behavior to your doctor.
9. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.
10. If you are to have surgery, tell your surgeon you are taking this medication. You will probably have to discontinue this medication 10 days before your surgery date.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Methadone

What is this drug used for?

Methadone is primarily used as a substitute drug in the treatment of opioid-dependent patients who desire maintenance therapy. It blocks the effect of the highly addicting opioids (e.g., heroin, oxycodone). It suppresses withdrawal symptoms of other opioid analgesics as well as the craving for opioids. Methadone is part of a complete addiction treatment program that also includes behavior therapy and counseling. It has been shown that methadone helps patients avoid illicit opioid use and helps them attain social stability.
On occasion methadone is prescribed for severe chronic pain. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Methadone blocks the "craving" and withdrawal reactions from opioids immediately. Methadone is started at a low dose and increased gradually, based on effectiveness, to a maintenance dose. It is then usually prescribed once daily.

Why is methadone given on a daily basis?

Methadone is an opioid and its dispensing and usage is governed by Federal regulations. It is prepared as a liquid and, in some locations, is dispensed mixed with orange juice. At first, patients receive their methadone from the pharmacy on a daily basis and are required to drink the contents of the bottle in the presence of the pharmacist. After a period where there has been no substance use, patients may receive up to 7 days' supply.

How long should you take this medication?

The length of time methadone is prescribed varies among individuals and depends on a number of factors, including their progress in therapy; some patients receive methadone for several months, while most may require it for several years. Any decreases in dose should be done very gradually under the direction of your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling tired, confusion, depression – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Energized feeling, insomnia – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication.
- Dizziness, lightheadedness, weakness – this should go away with time.
- Joint and muscle pain – temporary use of non-opioid pain medicine may help (e.g., acetaminophen or ibuprofen).
- Nausea and vomiting – if this happens, take the medication after eating.
- Loss of appetite, weight loss – taking the medication after meals, eating smaller meals more frequently or drinking high calorie drinks may help.
- For adolescents: changes in sex drive or sexual performance – though rare, should this problem occur, discuss it with your doctor.
- Changes to the menstrual cycle.
- Sweating, flushing – you may sweat more than usual; frequent showering and use of antiperspirants may help.
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist.
- Small jerks of muscles.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Combination of symptoms that include dizziness, fainting spells, palpitations, nausea, and vomiting
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Slowed difficult breathing
- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Feeling tired, weak, feverish or like you have the flu, associated with nausea, vomiting, and loss of appetite

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

It is important to take methadone at approximately the same time each day. Missing a dose can result in a withdrawal reaction, consisting of restlessness, insomnia, nausea, vomiting, headache, increased perspiration, congestion, "gooseflesh," abdominal cramps, and muscle and bone pain.

Is this drug safe to take with other medication?

Because methadone can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those

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you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking this medication. It is important to carry a card in your wallet, stating that you are taking methadone, in cases of emergency.

Precautions/considerations

1. Do not share this medication with anyone. If you receive "carries" of methadone, store them out of the reach of children (preferably in a lockable compartment in the refrigerator); methadone can be lethally poisonous to individuals who do not take opioids. Misuse/abuse may result in poisoning.
2. Report to your doctor any changes in sleeping or eating habits or changes in mood or behavior.
3. This drug may impair the mental and physical abilities and reaction time required for driving or operating other machinery. Avoid these activities if you feel drowsy or slowed down.
4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.

What else do I need know about methadone?

1. Carry an identification card stating the name of the drug you are taking and ensure every doctor and dentist you visit is aware you are taking methadone.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Mirtazapine

Mirtazapine belongs to a class of antidepressants called noradrenergic agonists/specific serotonergic antidepressants (NaSSA).

What is this drug used for?

Mirtazapine is primarily used in the treatment of major depressive disorder and bipolar depression.
Though not approved for these indications, mirtazapine has also been found effective in several anxiety disorders including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, and posttraumatic stress disorder, and for acute and chronic insomnia. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Mirtazapine begins to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor. Improvement in symptoms of anxiety disorders also occur gradually over several weeks.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression, it is usually recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.
Long-term treatment is generally recommended for anxiety disorders.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy or tired – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery until you know how the drug affects you. If drowsiness persists your doctor may advise you to take the medication at bedtime.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist.
- Increased appetite and weight gain – monitor your food intake and try to avoid foods with a high fat content (e.g., cakes and pastry).
- Joint pain or worsening of arthritis – discuss this with your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat, mouth ulcers
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- **Severe agitation, restlessness, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication at bedtime and you forget to take your medication, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

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Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop this drug suddenly (without discussing it with your health care provider), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
3. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.
4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
5. Report any changes in mood or behavior to your doctor.
6. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

What else do I need to know about mirtazapine?

1. Mirtazapine oral disintegrating tablets dissolve rapidly in saliva and can be taken with or without liquid, chewed or allowed to dissolve.
2. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
3. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on Moclobemide

Moclobemide belongs to a class of antidepressants called reversible inhibitors of monoamine oxidase-A (RIMA).

What is this drug used for?

Moclobemide is primarily used in the treatment of major depressive disorder and bipolar depression. It has also been approved for use in the management of chronic low mood (persistent depressive disorder (also known as dysthymia)). Though not approved for these indications, moclobemide has also been found effective in seasonal affective disorder and social anxiety disorder. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Moclobemide begins to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor. Improvement in symptoms of seasonal affective disorder and social anxiety disorder also occur gradually.

When should I take this medication?

Moclobemide is usually prescribed to be taken twice daily, morning and evening. Take this drug after meals to minimize side effects such as nausea.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression, it is usually recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely. DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.
Long-term treatment is generally recommended for social anxiety disorder, while cyclical therapy may be effective for seasonal affective disorder.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. Report this to your doctor; he/she may advise you to take the medication in the morning and afternoon (rather than the evening).
- Headache – this can be managed by taking a pain reliver (e.g., acetaminophen or ibuprofen) as required. If the headache persists or is "troubling," contact your doctor.
- Dizziness – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint, – then call your doctor.
- Nausea or heartburn – if this happens, take the medication with food.
- Sweating – you may sweat more than usual; frequent showering and use of antiperspirants may help.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Persistent, throbbing headache
- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- **Severe agitation, restlessness, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

Treatment with moclobemide usually does NOT require special diet restrictions as with other MAOIs. However, you should avoid eating excessive amounts of aged, overripe cheeses or yeast extracts. If a **hypertensive reaction** (severe increase in blood pressure) should occur, the symptoms may come on suddenly, so be alert for these signs:

- Severe, throbbing headache which starts at the back of the head and moves toward the front. Often nausea and vomiting occur at the same time
- Stiff neck
- Heart palpitations, fast heart beat, chest pain
- Sweating, cold and clammy skin
- Enlarged (dilated) pupils of the eyes
- Sudden unexplained nose bleeds

If a combination of these symptoms does occur, **contact your doctor IMMEDIATELY**; if you are unable to do so, go to the Emergency Department of your nearest hospital.
Moclobemide should always be taken after meals to avoid any food-related side effects (e.g., headaches).

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What should you do if you forget to take a dose of your medication?

If you take your total dose of antidepressant in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking the antidepressant drug moclobemide.

Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop this drug suddenly (without discussing it with your health care advisor), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
3. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
4. Report any changes in mood or behavior to your doctor.
5. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.
6. Do NOT take other medication (including drugs you buy without a prescription or herbal products) without consulting with your doctor or pharmacist. Avoid all products containing dextromethorphan (DM).

What else do I need to know about moclobemide?

1. Take moclobemide after food to decrease potential side effects; a big meal should not be eaten after taking moclobemide.
2. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
3. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Naltrexone

What is this drug used for?

Naltrexone is mainly used as an aid in the treatment of alcohol dependence or addiction to opioids. Naltrexone has been shown to maintain abstinence if taken, as directed, as part of a treatment program that includes counseling and support. Though not approved for these indications, naltrexone has also been used in the treatment of behavior and impulse-control disorders, obsessive-compulsive disorder, and self-injurious behavior in patients with autism. It is available as an oral tablet and (in the USA) as a monthly injection. Ask your doctor if you are not sure why you are taking this drug.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Naltrexone blocks the "craving" for alcohol and opioids. It does not suppress withdrawal symptoms that can occur in an opioid user and should not be used in anyone who has used opioids in the previous 10 days; these individuals must undergo detoxification programs before starting naltrexone. Naltrexone is started at a low dose and increased gradually based on effectiveness. Onset of response is quick (within the hour). A similar craving for naturally produced opioids (e.g., endorphins) is thought to occur in some autistic patients who deliberately injure themselves. It may take weeks to see a reduction in self-injurious behaviors in these patients.

How long should you take this medication?

Naltrexone is usually prescribed for a set period of time to help the individual discontinue the use of alcohol or opioids. Naltrexone is used for a prolonged period of time in the treatment of behavior and impulse-control problems, obsessive-compulsive disorder, and self-injurious behavior in patients with autism. **Do not decrease or increase the dose** without discussing this with your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling tired, confusion, depression – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery if drowsiness persists.
- Nervousness, anxiety, problems sleeping – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication.
- Headache – temporary use of a pain reliever (e.g., acetaminophen or ibuprofen) may be required; contact your doctor if headaches occur frequently or are "troubling."
- Joint and muscle pain or stiffness – temporary use of pain medicine may be required.
- Stomach pain, cramps, nausea, and vomiting – if this happens, take the medication with food or milk.
- Weight loss.
- Pain, tenderness, itchiness at site of injection; occasionally a lump can be felt.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Nausea, vomiting, loss of appetite, fatigue, weakness, fever or flu-like symptoms
- Shortness of breath, persistent coughing and wheezing

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of the drug in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because naltrexone can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking this medication.

Precautions/considerations

1. Do not change your dose or stop taking naltrexone without speaking to your doctor.
2. Report to your doctor any changes in sleeping or eating habits or changes in mood or behavior.
3. Do NOT use opioid preparations while taking oral or injectable naltrexone as this may cause serious adverse effects including coma and death.

What else do I need to know about naltrexone?

1. Limit the use of nonprescription pain medicine such as acetaminophen (Tylenol) or nonsteroidal anti-inflammatories (e.g., ibuprofen (Motrin)).

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2. Carry an identification card or wear an alert bracelet stating you are taking naltrexone.
3. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Psychostimulants

The name of your medication is _____.

What is this drug used for?

Psychostimulants (also sometimes called "stimulants") are primarily used in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. These drugs are also approved for use in other conditions such as Parkinson's disease and narcolepsy (a sleeping disorder).
Though they are currently not approved for this indication, psychostimulants have been found useful as add-on therapy in the treatment of depression. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Some response to psychostimulants is usually noted within the first week of treatment of ADHD and tends to increase over the next 3 weeks.

How does your doctor decide on the dosage?

Psychostimulants come in various formulations including short-acting and slow-release (i.e., Spansules or extended-release) forms as well as a skin patch (Daytrana – available in the US only). The dose is sometimes based on body weight and is given once daily (for slow-release forms) or several times a day (short-acting forms). Take the drug exactly as prescribed; **do not increase or decrease the dose without speaking to your doctor.**

How long should you take this medication?

Psychostimulants are usually prescribed for a period of several years. Some clinicians may prescribe "drug holidays" to individuals on this medication (i.e., the drug is temporarily not taken at certain times such as vacations, etc.), in situations when side effects may be of concern.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Energizing/agitated feeling, excitability – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. If you are taking the medication in the late afternoon or evening, your doctor may decide to prescribe it earlier in the day.
- Increased heart rate – speak to your doctor.
- Headache – this tends to be temporary and can be managed by taking pain medicine (acetaminophen or ibuprofen) when required. If the headache persists or is "troubling," contact your doctor. Blood pressure should be checked by your doctor before and after starting, and following dose increases.
- Nausea or heartburn – if this happens, take the medication with food or milk.
- Dry mouth – sour candy, mints, and sugarless gum help increase saliva in your mouth. Do not drink sugar-containing drinks frequently as they may increase the risk for dental cavities and increase your weight. Drink water and brush your teeth regularly.
- Loss of appetite, weight loss, decreased growth – taking the medication after meals, eating smaller meals more frequently, switching to use of whole milk, or drinking liquid nutritional supplements may help. Some clinicians may prescribe "drug holidays" to individuals on this medication (i.e., the drug is temporarily not taken at certain times, such as vacations, etc.) to help with appetite and growth.
- Blurred vision – this usually happens when you first start the drug and tends to be temporary. Reading under a bright light or at a distance may help. If the problem lasts for more than a few weeks, let your doctor know.
- Respiratory symptoms including sore throat, coughing or sinus pain.
- Skin irritation and rashes at the application site with topical patch (Daytrana).

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Fast or irregular heart beat
- Dizziness, feeling faint or lightheaded
- Muscle twitches, tics or movement problems
- Persistent throbbing headache
- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face with oral form and topical patch
- Any unusual bruising or bleeding, appearance of splotchy purplish darkening of the skin
- Tiredness, weakness, fever or feeling like you have the flu, associated with nausea, vomiting, loss of appetite
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Severe agitation or restlessness
- A persistent or painful erection of the penis that continues for longer than 4 hours
- **A switch in mood to an unusual state of happiness or irritability; fluctuations in mood or hallucinations (e.g., hearing voices, or seeing persons or things that no-one else sees) or thoughts of suicide**.

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

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What should you do if you forget to take a dose of your medication?

If you take the psychostimulant 2–3 times a day and forget to take a dose by more than 4 hours, skip the missed dose and continue with your regular schedule. **DO NOT DOUBLE THE DOSE**.
If you take an extended-release form of a psychostimulant once daily in the morning and forget to take a dose by more than 4 hours, skip the dose and continue with your regular schedule the next day.
The skin patch (Daytrana) is placed on the body in the morning and removed 9 hours later.

Is this drug safe to take with other medication?

Because psychostimulants can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking a psychostimulant drug.

Precautions/considerations

1. This medication should not be used in patients who have high blood pressure, heart disease or abnormalities, hardening of the arteries or an overactive thyroid. If there is a history of heart problems or sudden or unxplained deaths in your family, tell your doctor before taking this medication.
2. Do not change your dose or stop taking this medication without talking to your doctor.
3. Use caution while driving or performing tasks requiring alertness as these drugs can mask symptoms of fatigue and impair concentration.
4. Report to your doctor any changes in sleeping or eating habits or changes in mood or behavior.
5. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.
6. If using the Daytrana patch, it takes about 8 hours after applying the patch before blood concentrations reach a maximum level. Furthermore, substantial amounts of drug remain in the body for about 6 hours after patch removal.
7. Your doctor should monitor height and weight periodically for children taking psychostimulants to ensure they are growing properly.

What else do I need to know about psychostimulants?

1. Do not chew or crush the tablets or capsules unless specifically told to do so by your doctor.
2. If you have difficulty swallowing medication, your doctor may prescribe a liquid form, an orally disintegrating tablet, a chewable tablet, a capsule that can be opened and the beads from it sprinkled on apple sauce and swallowed without chewing, or a capsule that can be opened and the contents mixed in a glass of plain water, orange juice or yogurt and swallowed.
3. If you are prescribed the skin patch (Daytrana), it should be applied to clean, dry skin on the hip immediately upon removal from the protective pouch; do not apply to skin areas that are inflamed or broken. The patch should not be exposed to external heat sources (e.g., heating pads, hot tubs); used patches need to be discarded carefully, according to package instructions. There may occasionally be some difficulties removing the patch.
4. If you take Concerta, you may notice the tablet shell in your stool. This is normal; the tablet shell does not dissolve but the contents of the tablet are fully absorbed.
5. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on SARI Antidepressants

The name of your medication is _____.
It belongs to a class of antidepressants called serotonin-2 antagonist/reuptake inhibitors (SARI).

What is this drug used for?

SARI antidepressants are used in the treatment of major depressive disorder and bipolar depression. Though currently not approved for these indications, these drugs have also been found effective in several other disorders including persistent depressive disorder, premenstrual dysphoria or depression, social anxiety disorder, posttraumatic stress disorder, and acute and chronic insomnia as well as disruptive and impulsive behavior. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Antidepressants begin to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.
Improvement in symptoms of premenstrual dysphoria or impulsive behavior also occur gradually.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression, it is usually recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling drowsy or tired – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery until you know how the drug affects you. If drowsiness persists your doctor may advise you to take the medication at bedtime.
- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication.
- Headache – this tends to be temporary and can be managed by taking a pain reliever (such as acetaminophen or ibuprofen) when required. If the headache persists or is "troubling," contact your doctor.
- Nausea or heartburn – if this happens, take the medication with food.
- Muscle tremor, twitching – speak to your doctor as this may require a change in your dosage.
- For adolescents: changes in sex drive or sexual performance – though rare, should this problem occur, discuss it with your doctor.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Loss of appetite.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Any unusual bruising or bleeding
- Episodes of dizziness or falling
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Persistent abdominal pain, pale stools
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Tingling in the hands and feet, severe muscle twitching
- A persistent or painful erection of the penis that continues for longer than 4 hours
- **Severe agitation, restlessness, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because SARI antidepressant drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs,

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including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop your drug suddenly (without discussing it with your health care advisor), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
3. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.
4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
5. Report any changes in mood or behavior to your doctor.
6. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

What else do I need to know about SARI antidepressants?

1. Take your drug with water, milk orange or apple juice; avoid grapefruit juice as it may change the effect of the drug in your body.
2. If you are taking an extended-release tablet, do not break, chew or crush the drug but swallow it whole.
3. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
4. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on SNRI Antidepressants

The name of your medication is _____.
It belongs to a class of antidepressants called serotonin and norepinephrine reuptake inhibitors (SNRI).

What is this drug used for?

SNRIs are primarily used in the treatment of major depressive disorder, bipolar depression, generalized anxiety disorder or social anxiety disorder, panic disorder, neuropathic pain, and fibromyalgia in adults.
Though not approved for these indications, some of these drugs have also been found effective in several other disorders including obsessive-compulsive disorder, premenstrual dysphoria or depression, pain syndromes, and in children and adults with attention-deficit/hyperactivity disorder. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

SNRIs begin to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.
Improvement in symptoms of generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, and symptoms of pain also occur gradually over several weeks.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression, it is usually recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.
Long-term treatment is generally recommended for generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, and social anxiety disorder.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. Report this to your doctor; he/she may advise you to take the medication in the morning.
- Headache – this can be managed by taking a pain reliever (e.g., acetaminophen or ibuprofen) as required. If the headache persists or is "troubling," contact your doctor.
- Nausea or heartburn – if this happens, take the medication with food.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist.
- Sweating – you may sweat more than usual; frequent showering and use of antiperspirants may help.
- Blood pressure – a slight increase in blood pressure can occur with this drug. If you are taking medication for high blood pressure, tell your doctor, as this medication may have to be adjusted.
- For adolescents: changes in sex drive or sexual performance – discuss this with your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Persistent, troubling headache
- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Going 12 hours or more without peeing
- Nausea, vomiting, diarrhea, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Sharp or persistent stomach pain or cramps
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Tingling in the hands and feet, severe muscle twitching, tremor, shivering, and loss of balance
- Racing heart/pulse
- **Severe agitation, restlessness, anxiety, panic, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication in the morning and you forget to take it for more than 6 hours, skip the missed dose

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and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop your drug suddenly (without discussing it with your health care advisor), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
3. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.
4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
5. Report any changes in mood or behavior to your doctor.
6. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

What else do I need to know about SNRI antidepressants?

1. If you are taking sustained-release tablets of venlafaxine or desvenlafaxine or extended/delayed-release capsules of duloxetine, levomilnacipran or venlafaxine, swallow the drug whole. Do not break, crush, or chew the tablet/capsule.
2. If you are taking desvenlafaxine, you may notice the empty tablet shell in your stool after a bowel movement. This is normal; the tablet shell does not dissolve but the contents of the tablet are fully absorbed.
3. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
4. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

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Patient and Caregiver Information on SSRI Antidepressants

The name of your medication is _____.
It belongs to a class of antidepressants called selective serotonin reuptake inhibitors (SSRI).

What is this drug used for?

SSRI antidepressants are used in the treatment of a number of disorders including:

- Major depressive disorder, bipolar depression
- Generalized anxiety disorder
- Obsessive-compulsive disorder
- Panic disorder
- Bulimia and other eating disorders
- Social anxiety disorder
- Premenstrual dysphoria or depression
- Posttraumatic stress disorder

These drugs are also used to treat several other disorders. Ask your doctor if you are not sure why you are taking this drug.

Note: These medications may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

SRRI antidepressants begin to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.
Improvement in symptoms related to anxiety disorders such as obsessive-compulsive disorder, panic disorder, social anxiety disorder, and symptoms of bulimia also occurs gradually.

How long should you take this medication?

This depends on what type of illness you have and how well you do. Following the first episode of depression, it is usually recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped.
For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better, without first discussing this with your doctor.
Long-term treatment is generally recommended for obsessive-compulsive disorder, panic disorder, and bulimia.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Feeling sleepy or tired – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery until you know how the drug affects you. If drowsiness persists, your doctor may advise you to take the medication at bedtime.
- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. Report this to your doctor; he/she may advise you to take the medication in the morning.
- Headache – this tends to be temporary and can be managed by taking a pain reliever (such as acetaminophen or ibuprofen) when required. If the headache persists or is "troubling," contact your doctor.
- Nausea or heartburn – if this happens, take the medication with food.
- Muscle tremor, twitching – speak to your doctor as this may require a change in your dosage.
- For adolescents: changes in sex drive or sexual performance – discuss this with your doctor.
- Sweating – you may sweat more than usual; frequent showering and use of antiperspirants may help.
- Blurred vision – this usually happens when you first start the drug and tends to be temporary. Reading under a bright light or at a distance may help; a magnifying glass can be of temporary use. If the problem lasts for more than a few weeks, let your doctor know.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly.
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist.
- Nightmares – can be managed by changing the time you take your drug, speak with your doctor.
- Loss of appetite.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face
- Any unusual bruising or bleeding, increased nosebleeds or blood in your stool
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Going a day or more without peeing
- Tingling in the hands and feet, severe muscle twitching
- **Severe agitation, restlessness, irritability, or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability, or problems sleeping**

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Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant, or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**. If you take the drug several times a day, take the missed dose when you remember, then continue with your regular schedule.

Is this drug safe to take with other medication?

Because SSRI antidepressant drugs can change the effect of other medication, or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription, such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop this drug suddenly (without discussing it with your health care provider), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
3. Take your drug with meals or with water, milk, orange or apple juice; avoid grapefruit juice as it may change the effect of the drug in your body.
4. If you are taking a controlled-release medication (e.g., paroxetine (Paxil CR), fluvoxamine (Luvox CR), fluoxetine/olanzapine combination (Symbyax), or enteric-coated capsules (e.g., fluoxetine (Prozac Weekly)) swallow the drug whole. Do not split, crush or chew the tablet/capsule, as this will affect the action of the medication.
5. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.
6. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
7. Report any changes in mood or behavior to your doctor.
8. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.
9. Oral disintegrating tablets of citalopram (Celexa) or escitalopram (Cipralex Meltz) should be placed under the tongue and may be taken with or without liquid.
10. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
11. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist, or nurse.

Patient and Caregiver Information on Vilazodone

Vilazodone belongs to a class of antidepressants called serotonin-1A partial agonist/serotonin reuptake inhibitor (SPARI).

What is this drug used for?

Vilazodone is used in the treatment of major depressive disorder.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for the above use.

How quickly will the drug start working?

Vilazodone begins to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.

How long should you take this medication?

Following the first episode of depression, it is recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped. For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely. DO NOT STOP taking your medication if you are feeling better without first discussing this with your doctor.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Energizing/agitated feeling – some individuals may feel nervous or have difficulty sleeping for a few days after starting this medication. Report this to your doctor; he/she may advise you to take the medication in the morning.
- Nausea, heartburn – if this happens, take the medication with food.
- Loose stools, diarrhea – a bulking agent, such as psyllium (Metamucil) can help. If diarrhea persists, contact your doctor.
- Dizziness, lightheaded feeling – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint, then contact your doctor.
- Headache – this can be managed by taking pain medicine (e.g., aspirin, acetaminophen) as required. If the headache persists or is "troubling," contact your doctor.
- Feeling sleepy or tired – this problem goes away with time. Use of other drugs that make you drowsy will worsen the problem. Avoid driving a car or operating machinery until you know how the drug affects you. If drowsiness persists, your doctor may advise you to take the medication at bedtime.
- For adolescents: Changes in sex drive or sexual performance – discuss this with your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face, difficulty breathing
- Any unusual bruising or bleeding, increased nosebleeds or blood in your stool
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Going a day or more without peeing
- Tingling in the hands and feet, severe muscle twitching
- **Severe agitation, restlessness, irritability or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop this drug suddenly (without discussing it with your health care provider), as this may result in withdrawal symptoms such as muscle aches, chills, tingling in your hands or feet, nausea, vomiting, and dizziness.
3. This drug may impair the mental and physical abilities required for driving a car or operating machinery. Avoid these activities if you feel drowsy or slowed down.

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4. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
5. Avoid grapefruit juice as it may change the effect of the drug in your body.
6. Report any changes in mood or behavior to your doctor.
7. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

What else do I need to know about vilazodone?

1. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
2. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist or nurse.

Patient and Caregiver Information on Viloxazine

What is this drug used for?

Viloxazine is used in the treatment of attention deficit/hyperactivity disorder (ADHD) in children and adolescents.

How quickly will the drug start working?

Some response to Viloxazine is usually noted within the first 1–2 weeks of treatment of ADHD.

How does your doctor decide on the dosage?

Viloxazine comes in a capsule; the dose is based on your age and how you respond to initial low doses. The capsule is usually taken once a day, with or without food. **Do not increase or decrease the dose without speaking to your doctor.**

How long should you take this medication?

Viloxazine is usually prescribed for a period of several months to years.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Increased agitation or excitability – some individuals may be more irritable or have difficulty sleeping for a few days after starting this medication.
- Headache – this tends to be temporary and can be managed by taking pain medicine (e.g., acetaminophen or ibuprofen) when required. If the headache persists or is "troubling," contact your doctor.
- Nausea, abdominal pain, vomiting – try taking your medication with food; if symptoms persist, speak to your doctor.
- Loss of appetite, weight loss – eating smaller meals more frequently or drinking liquid nutritional supplements may help.
- Feeling sleepy and tired – the problem usually goes away with time, however, your doctor may suggest you take your medication at bedtime. Use of other drugs that make you drowsy will worsen the problem. Avoid operating machinery or tasks that require alertness if drowsiness persists.
- Fast heart beat

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Severe agitation, restlessness or irritability
- **Switch in mood to an unusual state of happiness, excitement, irritability, a marked disturbance in sleep or thoughts of suicide**

Let your doctor know **as soon as possible** if you miss your period or think you may be **pregnant**, plan to become pregnant or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you forget to take a dose by more than 8 hours, skip the missed dose and continue with your regular schedule. **DO NOT DOUBLE THE DOSE.**

Is this drug safe to take with other medication?

Because viloxazine can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking viloxazine.

Precautions/considerations

1. This medication should be used with caution in patients who have personal or family history of suicide, bipolar disorder or depression.
2. Report to your doctor any changes in mood or behavior.
3. Do not change your dose or stop viloxazine without speaking with your doctor.
4. Use caution while performing tasks requiring alertness as viloxazine can cause sedation and fatigue.
5. This drug may interact with medication prescribed by your dentist, so let them know the name of the drug you are taking.

What else do you need to know about viloxazine?

1. Swallow the capsule whole; do not cut, crush or chew the capsule. The capsule may be opened and the contents sprinkled on soft food (e.g., applesauce) before taking.
2. Store your medication in a clean dry area at room temperature. Keep all medication out of reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist or nurse.

From: Elbe D, Black TR, McGrane IR, Choi S. *Clinical Handbook of Psychotropic Drugs for Children and Adolescents*, 5th edition, © 2023 Hogrefe Publishing.

Patient and Caregiver Information on Vortioxetine

Vortioxetine belongs to a class of antidepressants called serotonin modulator and stimulator (SMS).

What is this drug used for?

Vortioxetine is used in the treatment of major depressive disorder. Though not approved for this indication, vortioxetine is also used in the treatment of generalized anxiety disorder.

Note: This medication may not have formal approval by regulatory agencies such as Health Canada or the US Food and Drug Administration (FDA) for use in children or adolescents for some or all of the above uses.

How quickly will the drug start working?

Vortioxetine begins to improve sleep and appetite and to increase energy within 1–2 weeks; however, feelings of depression may take 4–6 weeks to improve. Because antidepressants take time to work, **do not decrease or increase the dose or stop the medication** without discussing this with your doctor.
Improvement in symptoms of anxiety disorders also occur gradually over several weeks.

How long should you take this medication?

Following the first episode of depression, it is recommended that antidepressants be continued for a minimum of 1 year; this decreases the chance of having another episode. Your doctor may then decrease the drug slowly and monitor for any symptoms of depression; if none occur, the drug can gradually be stopped. For individuals who have had several episodes of depression, antidepressant medication should be continued indefinitely.
DO NOT STOP taking your medication if you are feeling better without first discussing this with your doctor.
Long-term treatment is generally recommended for anxiety disorders.

What side effects may happen?

Side effects may happen with any drug. They are not usually serious and do not happen to everyone. Side effects may sometimes occur before beneficial effects of the medication are noticed. If you think you may be having a side effect, speak to your doctor or pharmacist as they can help you decrease it or cope with it.

Common side effects that should be reported to your doctor at the **NEXT VISIT** include:

- Nausea, heartburn – if this happens, take the medication with food. If vomiting occurs regularly, contact your doctor.
- Loose stools, diarrhea – a bulking agent, such as psyllium (Metamucil) can help. If diarrhea persists, contact your doctor.
- Dizziness, lightheaded feeling – get up from a lying or sitting position slowly; dangle your legs over the edge of the bed for a few minutes before getting up. Sit or lie down if dizziness persists or if you feel faint, then contact your doctor.
- Headache – this can be managed by taking pain medicine (e.g., acetaminophen or ibuprofen) as required. If the headache persists or is "troubling," contact your doctor.
- Dry mouth – sour candy and sugarless gum help increase saliva in your mouth. Do not drink sweet drinks like colas as they may give you cavities and increase your weight. Drink water and brush your teeth regularly
- Constipation – drink plenty of water and try to increase the amount of fiber in your diet (like fruit, vegetables or bran). Some individuals find a bulk laxative like psyllium (e.g., Metamucil) or PEG 3350 (e.g., Miralax, Pegalax)) or a stool softener like docusate (e.g., Colace, Surfak) helps regulate their bowels. If these remedies are not effective, speak to your doctor or pharmacist.
- For adolescents: Changes in sex drive or sexual performance – discuss this with your doctor.

Rare side effects you should report to your doctor **RIGHT AWAY** include:

- Sore mouth, gums or throat
- Skin rash or itching, swelling of the face, difficulty breathing
- Any unusual bruising or bleeding, increased nosebleeds or blood in your stool
- Nausea, vomiting, loss of appetite, feeling tired, weak, feverish or like you have the flu
- Yellow tinge in the eyes or to the skin; dark-colored urine (pee)
- Eye pain, vision changes, or swelling or redness in or around the eye
- Going a day or more without peeing
- Tingling in the hands and feet, severe muscle twitching, seizures
- **Severe agitation, restlessness, irritability or thoughts of suicide**
- **Switch in mood to an unusual state of happiness, excitement, irritability or problems sleeping**

Let your doctor know **right away** if you miss your period or think you may be **pregnant**, plan to become pregnant or are breastfeeding.

What should you do if you forget to take a dose of your medication?

If you take your total dose of this medication in the morning and you forget to take it for more than 6 hours, skip the missed dose and continue with your schedule the next day. **DO NOT DOUBLE THE DOSE**.

Is this drug safe to take with other medication?

Because antidepressant drugs can change the effect of other medication or may be affected by other medication, always check with your doctor or pharmacist before taking other drugs, including those you can buy without a prescription such as cold remedies and herbal preparations. Always inform any doctor or dentist that you see that you are taking an antidepressant drug.

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Precautions/considerations

1. Do not change your dose without talking with your health care provider (e.g., doctor, pharmacist, nurse).
2. Do not stop this drug suddenly (without discussing it with your health care provider).
3. This drug may increase the effects of alcohol, making you more sleepy, dizzy, and lightheaded. If taken together with alcohol, this may make it dangerous for you to drive, operate machinery, or perform tasks that require careful attention.
4. Report any changes in mood or behavior to your doctor.
5. This drug may interact with medication prescribed by your dentist, so let him/her know the name of the drug you are taking.

What else do I need to know about vortioxetine?

1. Excessive use of caffeinated foods, drugs or beverages may increase anxiety and agitation and confuse the diagnosis.
2. Store your medication in a clean, dry area at room temperature. Keep all medication out of the reach of children.

If you have any questions regarding this medication, please ask your doctor, pharmacist or nurse.