Clinical Handbook of Psychotropic Drugs for Children and Adolescents

Dean Elbe
Tyler R. Black
Ian R. McGrane
Sabina Choi
(Editors)

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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


Adverse Effects

Contraindications

Discontinuation Syndrome


Precautions


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

Dean Elbe, BScPharm, PharmD, BCPP[A, B, C]
Tyler R. Black, BSc, MD, FRCPC[C]
Ian R. McGrane, PharmD, BCPS, BCPP[D]
Sabina Choi, BScPharm, PharmD[E]
(Editors)

The editors wish to acknowledge the contribution of
Kalyna Z. Bezchlibnyk-Butler, BScPhm, FCSHP, Ric M. Procyshyn, BScPharm, MSc, PharmD, PhD, and Adil S. Virani, BScPharm, PharmD, FCSHP,
editors of previous editions of the Clinical Handbook of Psychotropic Drugs for Children and Adolescents

[A] Healthy Minds Centre, Children's & Women's Health Centre of British Columbia, Vancouver, BC, Canada
[B] Lower Mainland Pharmacy Services and Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
[C] Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada
[D] Skaggs School of Pharmacy, University of Montana, Missoula, MT, USA
[E] Victoria Primary Care Network, Island Health, Victoria, BC, Canada

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Phone +49 551 99950-0, Fax +49 551 99950-111, E-mail publishing@hogrefe.com

SALES & DISTRIBUTION
USA: Hogrefe Publishing, Customer Services Department,
30 Amberwood Parkway, Ashland, OH 44805
Phone (800) 228-3749, Fax (419) 281-6883, E-mail customersupport@hogrefe.com
UK: Hogrefe Publishing, c/o Marston Book Services Ltd.,
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Phone +44 1235 465577, Fax +44 1235 465556, E-mail direct.orders@marston.co.uk
EUROPE: Hogrefe Publishing, Merkelstr. 3, 37085 Göttingen, Germany
Phone +49 551 99950-0, Fax +49 551 99950-111, E-mail publishing@hogrefe.com

OTHER OFFICES
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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.

Dean Elbe
E-mail: DElbe@cw.bc.ca

TABLE OF CONTENTS

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
  - Separation anxiety disorder (p. 14)
  - 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

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

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 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]

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

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]

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

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