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


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

4th edition

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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.

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 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, and differences are seen among countries, specific "indications" listed in this text as "approved" should be viewed in conjunction with 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. Consideration should be given to obtaining informed consent from the caregiver or youth (depending on the patient's age) for use in unapproved indications.

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. 387.

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 some added extras: (1) An auto-completion powered search function, (2) browse features for generic names, trade names, indications, and interacting agents, (3) column-selector enhancement of comparison charts (dosages, side effects, pharmacokinetics, interactions…) that allows you to choose which information is displayed, and (4) 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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TABLE OF CONTENTS

Psychiatric Disorders in Children and Adolescents 2
NEURODEVELOPMENTAL DISORDERS 3
Autism Spectrum Disorder (ASD) 3
Attention-Deficit/Hyperactivity Disorder (ADHD) 4
Tourette's Disorder 5
SCHIZOPHRENIA 6
BIPOLAR DISORDER (BD) 8
DEPRESSIVE DISORDERS 9
Disruptive Mood Dysregulation Disorder (DMDD) 9
Major Depressive Disorder (MDD) 10
ANXIETY DISORDERS 11
Separation Anxiety Disorder 12
Specific Phobia 12
Social Anxiety Disorder 13
Panic Disorder 14
Generalized Anxiety Disorder (GAD) 15
OBSESSIVE-COMPULSIVE DISORDER (OCD) 16
POSTTRAUMATIC STRESS DISORDER (PTSD) 17
DISRUPTIVE, IMPULSE-CONTROL, AND CONDUCT DISORDERS 18
Oppositional Defiant Disorder (ODD) 18
Conduct Disorder (CD) 18
SYNDROME: Catatonia 19

Drugs for ADHD 23
Psychostimulants 23
Atomoxetine 33
Comparison of Drugs for ADHD 36
α_2 agonists 42
Augmentation Strategies in ADHD 45

Antidepressants 48
Selective Serotonin Reuptake Inhibitors (SSRI) 49
Norepinephrine Dopamine Reuptake Inhibitor (NDRI) 62
Serotonin Norepinephrine Reuptake Inhibitors (SNRI) 68
Serotonin-2 Antagonists/Reuptake Inhibitors (SARI) 75
Serotonin-1A Partial Agonist/Serotonin Reuptake Inhibitor (SPARI) 81
Serotonin Modulator and Stimulator (SMS) 85
Noradrenergic/Specific Serotonergic Antidepressants (NaSSA) 89
Nonselective Cyclic Antidepressants 93
Monoamine Oxidase Inhibitors 101
Reversible Inhibitor of MAO-A (RIMA) 102
Irreversible Monoamine Oxidase (A&B) Inhibitors (MAOIs) 105
Irreversible MAO-B Inhibitor 111
Effects of Antidepressants on Neurotransmitters/Receptors 115
Pharmacological Effects of Antidepressants on Neurotransmitters/Receptors 116
Frequency of Adverse Reactions to Antidepressants at Therapeutic Doses 117
Antidepressant Doses and Pharmacokinetics 120
Switching Antidepressants 124
Antidepressant Augmentation Strategies 127

Electroconvulsive Therapy (ECT) 133

Antipsychotics 139
Second-Generation Antipsychotics/SGAs 145
Third-Generation Antipsychotics/TGAs 173
First-Generation Antipsychotics/FGAs 184
Effects of Antipsychotics on Neurotransmitters/Receptors 201
Pharmacological Effects of Antipsychotics on Neurotransmitters/Receptor Subtypes 202
Frequency (%) of Adverse Reactions to Antipsychotics at Therapeutic Doses 203
Antipsychotic Doses and Pharmacokinetics (Oral and Short-Acting Injections) 205
Comparison of Long-Acting IM Antipsychotics 213
Switching Antipsychotics 217
Antipsychotic Augmentation Strategies 219

Antipsychotic-Induced Extrapyramidal Side Effects (EPSE) and Their Management 226
Extrapyramidal Side Effects of Antipsychotics 226
Treatment Options for Extrapyramidal Side Effects 230
Effects on Extrapyramidal Side Effects 235
Comparison of Agents for Treating Acute Extrapyramidal Side Effects 236
Doses and Pharmacokinetics of Agents for Treating Acute Extrapyramidal Side Effects 238

Anxiolytic (Antianxiety) Agents 242
Benzodiazepines 242
Comparison of the Benzodiazepines 251
Buspirone 255

Hypnotics/Sedatives 259
Comparison of Hypnotics/Sedatives 265

Mood Stabilizers 272
Lithium 272
Anticonvulsants 281
Comparison of Anticonvulsants 296
Frequency of Adverse Reactions to Mood Stabilizers at Therapeutic Doses 304

Drugs/Substances of Abuse 307
Alcohol 310
Stimulants 314
Hallucinogens 319
Opioids 327
Inhalants/Aerosols 331
Sodium Oxybate (Gamma-Hydroxybutyrate – GHB) 332
Flunitrazepam (Rohypnol) 335
Nicotine/Tobacco 336

Treatment of Substance Use Disorders 339
Acamprosate 340
Disulfiram 342
Naltrexone 344
Buprenorphine 348
Methadone 352
Pharmacotherapy for Nicotine/Tobacco Use Dependence 357
Comparison of Treatments for Nicotine/Tobacco Use Disorder 359

Unapproved Treatments of Psychiatric Disorders 364
Adrenergic Agents 364
Anti-inflammatory Agents 366
Cholinergic Agents 366
Dopaminergic Agents 367
NMDA Agents 368
Miscellaneous 371

Natural Health Products 372

Glossary 382

Drug Use in Pregnancy and Effects on Breast Milk 386

Patient and Caregiver Information Sheets 387

Index of Drugs 388

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. 3)
  - Attention-deficit/hyperactivity disorder (ADHD) (p. 4)
  - Tourette's disorder (p. 5)
- Schizophrenia (p. 6)
- Bipolar disorder (BD) (p. 8)
- Depressive disorders
  - Disruptive mood dysregulation disorder (DMDD) (p. 9)
  - Major depressive disorder (MDD) (p. 10)
- Anxiety disorders
  - Separation anxiety disorder (p. 12)
  - Specific phobia (p. 12)
  - Social anxiety disorder (p. 13)
  - Panic disorder (p. 14)
  - Generalized anxiety disorder (GAD) (p. 15)
- Obsessive-compulsive disorder (OCD) (p. 16)
- Posttraumatic stress disorder (PTSD) (p. 17)
- Disruptive, impulse-control, and conduct disorders
  - Oppositional defiant disorder (ODD) (p. 18)
  - Conduct disorder (CD) (p. 18)

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

- Catatonia

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. 48–132), antipsychotics (pp. 139–225), α_2 agonists (pp. 42–45), anxiolytics (pp. 242–258), and anticonvulsants (pp. 281–304)

Psychostimulants (cont.)

Generic Name	Trade Name[A]	Dosage Forms and Strengths	Monograph Statement
	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	Not recommended for children and adolescents under age 18
	Cotempla XR-ODT[B]	Extended-release orally disintegrating tablets: 8.6 mg, 17.3 mg, 25.9 mg	Safety and efficacy not established in children under age 6
	Quillichew ER[B]	Extended-release chewable tablets: 20 mg, 30 mg, 40 mg	
	Quillivant XR[B]	Extended-release suspension: 5 mg/mL (after reconstitution)	
Methylphenidate transdermal patch[B]	Daytrana	Transdermal patch: 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]	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]	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
Dextroamphetamine/Amphetamine salts (mixed amphetamine salts)	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	Approved for children (USA: age 3 and above; Canada: age 6 and above)
	Mydayis[B]	Extended-release capsules: 12.5 mg, 25 mg, 37.5 mg, 50 mg	Not recommended for children under age 13
Dextroamphetamine	Dexedrine	Tablets: 5 mg, 10 mg[B] Elixir: 5 mg/5 mL[B]	Approved for children (USA: age 3 and above; Canada: age 6 and above)
	Dexedrine Spansules	Extended-release capsules: 5 mg[B], 10 mg, 15 mg	Not recommended for children under age 3
	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	Vyvanse	Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg[B] Chewable tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg	Not recommended for children under age 6
Methamphetamine[B] (desoxyephedrine)	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. [A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

In children and adolescents:

- Attention-deficit/hyperactivity disorder (ADHD)
- 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

Atomoxetine (cont.)

Patient Instructions

- For detailed patient instructions on atomoxetine, see the Patient and Caregiver Information Sheet (details p. 387)

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
Dextromethorphan (DM)		Competitive inhibition of DM metabolism via CYP2D6, with potential for increased plasma level of either drug
Stimulant	Methylphenidate, amphetamine, and related products	Possible potentiation of hypertension and tachycardia. However, combination use recommended as an option by some ADHD guidelines

Comparison of Drugs for ADHD

	Methylphenidate	**Dexmethylphenidate**	**Amphetamine Salts/Dextroamphetamine/ Lisdexamfetamine/Methamphetamine**	**Atomoxetine**
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

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		over 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		over 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]	over 90	80–85	1.6 (immediate release)	10–14 (parent)[a]	1A2[w], **2B6**[p], 2D6[b], 3A4[w], 2C9[w], 2E1[m]	2D6[w]
Bupropion SR/XL (Wellbutrin SR/XL, Zyban)	Adolescents: 150–300 mg[e]	200[e]				3 (bupropion) 6 (metabolite) (SR)	20–27 (metabolites)		

- Potential interventions may include:
  1) watchful waiting (in some instances, tolerance to the adverse effect may develop)
  2) altering the administration schedule
  3) lowering the antipsychotic dose
  4) switching to an alternate antipsychotic
  5) adding a non-pharmacological or pharmacological agent to treat the adverse effect
  6) changing diet (e.g., eliminating caffeine intake where there is akathisia)
  7) discontinuing the antipsychotic

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)

- 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 levels 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

Concomitant Medications

- TGA metabolism can be affected by inducers or inhibitors of CYP2D6 (no known inducers) and 3A4. For specific drug interactions, see pp. 180–183
- 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. 208. See https://www.pharmgkb.org/ for updated clinical guidelines and dosing recommendations when utilizing pharmacogenetic testing

Pharmacokinetics

- Also see table p. 209

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 $\pm$ 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)

Frequency (%) of Adverse Reactions to Antipsychotics at Therapeutic Doses

Reaction	SECOND-GENERATION AGENTS									THIRD-GENERATION AGENTS		
	Clozapine	Paliperidone	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Asenapine	Iloperidone	Lurasidone	Aripiprazole	Brexpiprazole	Cariprazine
CNS Effects												
Drowsiness, sedation	> 30	> 2	> 10[a]	> 30	> 30	> 30	> 30	> 10	> 30	> 10	> 2	> 2
Insomnia, agitation	> 2	> 10	> 10	> 10	> 10	> 10	> 2	> 10	> 2	> 10	> 2	> 2
Extrapyramidal Effects												
Parkinsonism	> 2	> 2	> 10[i]	> 2	> 2	> 2	> 2	< 2	< 2	> 2	> 2	> 2
Akathisia	> 10	> 2	> 10[i]	> 10	> 2	> 2	> 2	> 2	> 10	> 10	> 2	> 2
Dystonic reactions	< 2	< 2	< 2[i]	< 2	< 2	> 2	> 2	< 2	> 2	< 2	> 2	< 2
Anticholinergic Effects	> 30[k]	> 2	> 2	> 10	> 30	> 10	> 2	> 2	> 2	> 2	> 2	< 2
Cardiovascular Effects												
Orthostatic hypotension	> 10–30[a]	> 2	> 10[a]	> 2	> 10	> 10	> 10	> 10	> 2	> 2	> 2	> 2
Tachycardia	> 10[a]	> 2	< 2	> 10[l]	> 10	< 2	< 2	> 10	—	> 2	< 2	< 2
ECG abnormalities[b]	> 30[c]	< 2	> 2	< 2	< 2	> 2[c]	< 2	< 2	< 2	< 2	< 2	< 2
QTc prolongation (> 450 msec)	< 2[c]	> 2	< 2	< 2	< 2	< 2[c]	9	< 2	–	–	–	–
Endocrine Effects												
Sexual dysfunction[d]	< 2[e]	< 2	> 30[e]	> 30[e]	> 30[e]	< 2[e]	?	> 2	< 2	< 2[e]	< 2[e]	< 2[e]
Galactorrhea	< 2	< 2	> 10	> 2	–	> 2	?	< 2	< 2	< 2	< 2	< 2
Weight gain	> 30	> 10	> 10	> 30	> 10	> 2	> 10	> 10	< 2	> 2[f]	> 2[f]	< 2[f]
Hyperglycemia	> 30	?	> 10	> 30	> 30	> 2	> 10	?	< 2	< 2	< 2	< 2
Hyperlipidemia	> 30	?	> 10	> 30	> 10	< 2	> 10	?	< 2	< 2	< 2	< 2
Ocular Effects[s]												
Lenticular pigmentation	–	?	–	–	< 2	–	?	?	–	–	–	–
Pigmentary retinopathy	–	–	–	–	–	–	?	?	–	–	–	–
Blood dyscrasias	< 2[m]	?	< 2	< 2	–	< 2	< 2	?	< 2	< 2	< 2	< 2
Hepatic disorder	> 2	?	< 2	> 2	> 2	–	> 2	< 2	—	< 2	< 2	< 2
Seizures[h]	> 2[n]	< 2	< 2	< 2	< 2	–	< 2	< 2	< 2	< 2	< 2	< 2
Skin Reactions												
Photosensitivity	> 2	?	> 2	–	–	–	?	?	–	< 2	< 2	< 2
Rashes	> 2	?	< 2	< 2	< 2	> 2	?	?	< 2	> 2	< 2	< 2
Pigmentation[s]	–	?	< 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

Comparison of Anticonvulsants (cont.)

	Second-Generation Agents		Third-Generation Agents			
	Carbamazepine	Valproate	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate
Recommended plasma level	4–12 mg/L = 17–50 micromol/L	50–125 mg/L = 350–875 micromol/L Higher end of dosing range recommended for acute mania[28]	2–20 mg/L = 12–117 micromol/L reported for epilepsy	2.5–15 mg/L = 10–59 micromol/L reported for epilepsy	15–35 mg/L = 59–138 micromol/L (MHD metabolite) reported for epilepsy	5–20 mg/L = 15–59 micromol/L reported for epilepsy[29]
Pharmacokinetics						
Bioavailability	75–85%	78%	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%	13–17%
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	CYP1A2, 2A6, 2B6, 2C8, 2C9, 2E1, 3A4$^{(m)}$; UGT1A3, 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

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