Pediatric Psychopharmacology

FOR PRIMARY CARE

2ND EDITION

Mark A. Riddle, MD

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- Additional information on psychotropic drugs
- Training resources
- Additional resources for assessment and symptom monitoring

To access the digital tool, visit www.aap.org/psychopharmacology.

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Every effort is made to keep *Pediatric Psychopharmacology for Primary Care* consistent with the most recent advice and information available from the American Academy of Pediatrics.

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What People Are Saying

Second Edition

"This concise, practical, informative, and easy-to-read primer on pediatric psychopharmacology in the primary care setting could not have come at a better time. I read the entire book and already applied some of its contents to a recent case.

"A significant new morbidity in the practice of pediatrics is the rising prevalence of mental health disorders in our children and adolescents, coupled with the increasing limited access to mental health specialists and the limited training in behavioral and mental health in primary care residencies. One answer to these issues is for us currently practicing clinicians to read and use this book. *Pediatric Psychopharmacology for Primary Care* is organized in such a way that a quick perusal of its contents delivers much-needed guidance for the initial treatment and eventual management of common and not-so-common psychiatric disorders in children and adolescents. Rationale and resources for initial screening, referral, non-pharmacologic therapy, and pharmacologic therapy are prominently provided. Even better, the book offers advice on how to handle the FDA's Black Box warnings and how to provide behavioral therapy and to prescribe medications when experts in psychiatry and behavioral counseling are not readily available. After reading this book on treating children and adolescents with mental health issues, one should feel more confident in treating this vulnerable population.

"*Pediatric Psychopharmacology for Primary Care,* with its short chapters, tables, appendixes, and links to online resources, provides crucial information for medical students, primary care residents, and practicing primary care clinicians who desire to care for children and adolescents with common psychiatric disorders, who deal with shortages in mental health resources, and who seek reassurance that successful caring for such children and adolescents in the primary care setting is achievable."

Joseph A. Zenel, MD

Editor in Chief, *Pediatrics in Review*

Professor, Pediatrics, and Director,
Pediatric Residency, at Sanford Children's Hospital,
University of South Dakota Sanford School of Medicine

First Edition

"This clear and well-organized volume provides an excellent and useful compendium of advice on the use of psychotropic medications in pediatric primary care. Building on strong work by the AAP over the past 15 to 20 years to develop clinical practice guidelines for primary care management of attention-deficit/hyperactivity disorder and the work of the AAP Task Force on Mental Health, this book offers clear guidance on when to use psychotropics, which to use, and what coexisting conditions and side effects the clinician should monitor."

James M. Perrin, MD, FAAP

John C. Robinson Chair in Pediatrics

MassGeneral Hospital for Children

President (2014), American Academy of Pediatrics

"This guide to pediatric psychopharmacology provides pediatric primary care clinicians, and specialists working with them, with a practical clinical resource that concisely integrates relevant current literature and significant experience. Within a helpful framework that emphasizes safety and efficacy, this book provides clear guidance on dosing, monitoring, and potential adverse reactions. It makes access to and use of the information simple, yet incredibly valuable, for the busy clinician."

Christopher J. Kratochvil, MD

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Introduction

What Is This Book?

Pediatric Psychopharmacology for Primary Care, 2nd Edition, provides primary care clinicians with a practical and coherent approach to initial prescribing and ongoing management of psychotropic medications for children and adolescents.

The book has the following 5 parts:

- Conceptual Framework
- Practical Guidance
- Group 1 Medications for Specific Diagnoses: Attention Deficit/Hyperactivity Disorder, Anxiety, and Depression
- Group 2 (FDA-approved Antipsychotics and Mood Stabilizers) and Group 3 (All Other) Medications
- Advanced Topics

The Table of Contents provides a detailed outline of each part. Each chapter is designed to "stand alone" so that, depending on the reader's knowledge, skills, and experience, relevant chapters and sections may be specifically utilized. Additionally, numerous resources are included in the appendixes, with an emphasis on access to electronic content from the American Academy of Pediatrics (AAP).

Selected Updates in Second Edition

Newly approved medications, changes in regulations and guidelines, and updates in the professional literature are included in the second edition, including:

- Updated AAP guidelines for attention-deficit/hyperactivity disorder (ADHD)
- US Food and Drug Administration (FDA)–approved additional medications for treating children and adolescents
  - Methylphenidate extended release preparation for ADHD for ages 6 years and older.
  - Amphetamine preparation for ADHD for ages 3 years and older.

  - Dextroamphetamine preparation for ADHD for ages 3 years and older.
  - Amphetamine extended-release orally disintegrating tablet for ADHD for ages 6 years and older.
  - Serotonin norepinephrine reuptake inhibitor (SNRI) for generalized anxiety disorder for ages 7 years and older.
  - Second generation antipsychotic for schizophrenia for ages 13 years and older.
- The FDA added "long-term suppression of growth" to Warnings and Precautions for stimulant medications.
- Weight gain and secondary metabolic changes from antipsychotic medications became more prominent concerns as more data emerged regarding monitoring and treatment.
- Commercial marketing increased for genetic testing for pharmacokinetics and pharmacodynamics of psychiatric medications in pediatric primary care.
- Articles were published questioning the efficacy of medications for ADHD and depression; other articles refuted these claims.
- The AAP released several new and relevant clinical reports, technical reports, and policy statements (see Appendix B).
- The AAP published *Mental Health Care of Children and Adolescents: A Guide for Primary Care Clinicians*, with a chapter on psychopharmacology based on the conceptual framework and recommendations described in this book.

Target Audience

This book is written for pediatric primary care clinicians (PCCs) who care for children and adolescents with common psychiatric disorders in their outpatient practices and who prescribe and monitor medications, including

- Primary care pediatricians
- Family physicians
- Pediatric physician assistants
- Pediatric, psychiatric, and family nurse practitioners

Secondary audiences include specialists who provide consultation to pediatric PCCs in performing those roles, including

- Developmental-behavioral pediatricians
- Specialists in neurodevelopmental disabilities

- Child and adolescent psychiatrists
- Specialists in adolescent medicine
- Pediatric neurologists
- Some adult psychiatrists with training in adolescent care

Another secondary audience is allied mental health professionals, who collaborate with medication prescribers and who can provide evidence-based psychotherapies and other care for children and adolescents, including

- Psychologists
- Social workers
- Nurses
- Counselors

The book may also be useful for those who want to understand how clinicians strategize about medication for children and adolescents, including

- Parents, guardians, and caregivers
- Families
- Youth
- Advocates
- Policy makers

Why Now?

The need for a conceptual framework with practical guidance for pediatric psychopharmacology is critical.

- At least 8 million US youth (10%) have an impairing psychiatric disorder.[1]
- A persistent critical shortage of mental health specialists, especially child and adolescent psychiatrists (<8,000 practicing), limits the ability of these youth to access care for their mental health needs.

Pediatric PCCs are ideally suited to meet this need because of their knowledge of child development, their long-term relationships with patients and families, and the frequency with which they evaluate and treat children and teens.

There are about 170,000 US pediatric PCCs.

- Approximately 60,000 primary care pediatricians (AAP Pediatric Workforce)
- More than 80,000 family physicians[2]

- Approximately 2,000 pediatric physician assistants[3]
- Approximately 12,000 pediatric nurse practitioners[4]
- Approximately 12,000 youth-dedicated family nurse practitioners[5]

The AAP[6] recommends that primary care pediatricians achieve competence in initiating care for children and adolescents with ADHD, anxiety, depression, and substance use and abuse. This raises several important considerations.

- Pediatric residency training in psychiatric assessment and psychopharmacology is limited, and requirements are minimal.[7]
- Treatment of 3 of these conditions—ADHD, anxiety, and depression—may include medication.
- Many pediatric PCCs report having insufficient knowledge, skills, and training to prescribe psychotropic medications to youth with these conditions.[8]
- The effectiveness of postgraduate pediatric psychopharmacology courses targeted to pediatric PCCs has not been well studied, and the courses can be difficult and costly to access.
- Child psychiatry consultation programs in many parts of the country (see Appendix B for the National Network of Child Psychiatry Access Programs) address these gaps by providing real-time clinical guidance to pediatric PCCs[9]; it is critical that consultants in these programs apply a framework that recognizes realities of the primary care setting.

Because of limited time and resources for obtaining new knowledge and skills, pediatric PCCs, and those who train or consult with them, need an approach to pediatric psychopharmacology that is coherent, practical, and flexible to meet their needs.

Basic Principles

A few basic principles provide the foundation for all recommendations in this book.

- Evaluation and diagnosis of ADHD, common anxiety disorders, and depression in children and adolescents can be relatively simple and straightforward.
- Whenever possible, psychotropic medications should be prescribed concomitantly with, or following inadequate response to, evidence-based psychotherapies and evidence-informed pragmatic supports.

- Medications that have FDA approval for the patient's diagnosis (or a similar diagnosis) are recommended, whenever possible, because these medications have met a formal standard for efficacy and safety and, generally, more information is available regarding their use in youth.
- There are only a few classes of medications (eg, stimulants, α_2-adrenergic agonists, and selective serotonin reuptake inhibitors) that need to be mastered to effectively treat most presentations of ADHD, common anxiety disorders, and depression.
- Providing clinical and medico-legal informed consent and assent can strengthen the therapeutic alliance with patients and caregivers.
- Prescribing as few psychotropic medications as possible is recommended to improve safety.
- Sequential, not simultaneous, changes in medication are preferred, whenever possible.
- Monitoring for safety is as important as monitoring for effectiveness.
- Use of pragmatic supports can improve efficiency and effectiveness.
- Resources included in this book are derived from the FDA as well as national organizations such as the AAP and the American Academy of Child and Adolescent Psychiatry.
- As an important component of the continuum of mental health care, pediatric PCCs will encounter children who require additional specialty care. Consultative and collaborative relationships with mental health professionals are thus important.

What About the Future?

- The conceptual framework and treatment strategies in *Pediatric Psychopharmacology for Primary Care* are designed to prepare pediatric PCCs for future developments in pediatric psychopharmacology and clinical care of children with common psychiatric disorders. New information about the safety and efficacy of existing psychopharmacologic agents continues to accrue, and safer and more effective medications for children and adolescents will be developed and disseminated. Based on its recent emphasis on pediatric mental health, we can anticipate that the AAP and other professional organizations will provide ongoing and up-to-date educational and training opportunities for interested clinicians (see Appendix C, Training Resources for Clinicians).

- As US health care systems continue to evolve, emphasis on value-based medicine will continue to grow. Accountable care organizations and similar entities that incentivize cost reduction while maximizing quality will be responsible for providing care to specific populations within a fixed total budget. Demonstrating the financial benefit of safe and effective medication prescribing is a key component in the effort to secure funds for necessary evidence-based mental health treatments.

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Part 1—Conceptual Framework

CHAPTER 1

Conceptual Framework for Prescribing Psychotropic Medications

Rationale for the Conceptual Framework

General Rationale

Although many pediatric primary care clinicians (PCCs) are already using medications to treat attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression, there remains a wide range of comfort with, confidence in, and knowledge about how these drugs are initiated, titrated, and monitored across care settings. In addition, the ever-increasing number of psychotropic medications available can be overwhelming, even for experienced mental health specialists. According to an expert task force consisting of representatives from 5 major international organizations, 108 psychotropic medications are available for prescribing (the second edition of the app Neuroscience-based Nomenclature is available at https://www.nbn2.com). Many of these drugs are approved by the US Food and Drug Administration (FDA) only for adults, leaving pediatric PCCs in a quandary when it comes to prescribing for youth.

This chapter offers a unifying approach, grounded in the most up-to-date clinical research, for the prescribing of psychotropic medications by pediatric PCCs. The intention is not to dictate practice but, rather, to offer a framework that can best serve a wide range of clinicians who, after completing a thorough diagnostic assessment in which medication-responsive illness is identified, must then make decisions regarding medication treatment options for youth and families. The conceptual framework is designed to simplify and organize the medications into 3 manageable and targeted groups, in accordance with the American Academy of Pediatrics mental health competencies policy statement.[1]

Group 1 Medications

Group 1, the most important group of psychotropic medications for pediatric PCCs, includes medications for the common pediatric psychiatric disorders: ADHD, major depressive disorder, and anxiety disorders. The best epidemiologic data indicate that more than 80% of psychotropic medications prescribed to youth are for ADHD, anxiety, and depressive disorders.[2]

Group 1 includes all FDA-approved medications for ADHD in youth: 2 stimulants (methylphenidate and amphetamine), 2 α_2-adrenergic agonists (guanfacine and clonidine), and a norepinephrine reuptake inhibitor (NRI) (atomoxetine). It includes the serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine, recently FDA-approved for generalized anxiety disorder. It also includes all FDA-approved medications for depression in children: the 2 selective serotonin reuptake inhibitors (SSRIs) fluoxetine and escitalopram. Also, for anxiety in children, 3 SSRIs are included—fluoxetine, fluvoxamine, and sertraline—which have at least 1 high-quality, positive efficacy study for anxiety disorders commonly occurring in children and have FDA approval for obsessive-compulsive disorder (OCD), an anxiety-related condition.

Ten medications are in group 1 (Table 1-1). It is important to emphasize that these are not a formulary or restricted list of possible medications. However, as described in greater detail in Appendix D, they are the only medications with high-quality scientific evidence supporting their efficacy in youth. These medications are also relatively safe; thus, pediatric PCCs should feel comfortable prescribing them and monitoring their use.

Group 2 Medications

The second group of medications (group 2) includes all FDA-approved medications for youth with other psychiatric disorders (ie, not ADHD, anxiety, or depression). Group 2 includes 7 antipsychotics (aripiprazole, asenapine, lurasidone, olanzapine, quetiapine, risperidone, and paliperidone) and the mood stabilizer lithium. These medications are approved for treatment of youth with psychosis in schizophrenia and/or mania in bipolar disorder, and, for aripiprazole and risperidone, "irritability" in autism spectrum disorder. However, they are most commonly used in youth to treat behavioral problems, particularly aggression (see Chapter 3 and the description of T-MAY in Appendix B for details). Group 2 medications

Table 1-1. Group 1 Medications[a]

Drug (Mode of Action)	Indication[b]	US FDA Approval and Approved Age, y
ADHD		
Methylphenidate (stimulant)	ADHD	Yes; ≥6
Amphetamine (stimulant)[c]	ADHD	Yes; ≥6
Guanfacine (α_2-adrenergic agonist)	ADHD	Yes; ≥6
Clonidine (α_2-adrenergic agonist)	ADHD	Yes; ≥6
Atomoxetine (NRI)	ADHD	Yes; ≥6
Certain Anxiety Disorders[d] and OCD		
Fluoxetine (SSRI)	(Anxiety)	No
	OCD	Yes; ≥7
	MDD	Yes; ≥8
Sertraline (SSRI)	(Anxiety)	No
	OCD	Yes; ≥6
Fluvoxamine (SSRI)	(Anxiety) OCD	No Yes; >10
Major Depressive Disorder		
Fluoxetine (SSRI)	MDD	Yes; ≥8
Escitalopram (SSRI)	MDD	Yes; ≥12

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, Food and Drug Administration; MDD, major depressive disorder; NRI, norepinephrine reuptake inhibitor; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor.

[a] Evidence of efficacy, favorable adverse effect profile, and management of disorder within primary care competencies; for a detailed discussion on pediatric mental health competencies for primary care, see Committee on Psychosocial Aspects of Child and Family Health: Task Force on Mental Health, 2009.[1]

[b] Each of these disorders also has evidence-based psychosocial interventions. See Evidence-Based Child and Adolescent Psychosocial Interventions at https://www.aap.org/en-us/Documents/resilience_anxiety_interventions.pdf.

[c] Some preparations approved down to age 3 years.

[d] Generalized anxiety disorder, social anxiety disorder, separation anxiety disorder.

have a higher risk profile than group 1 medications and are associated with more concerning acute and chronic adverse effects. Pediatric PCCs are ideally suited to monitor adverse effects of group 2 medications. Some pediatric PCCs, for various reasons, will be involved in prescribing them.

Group 3 Medications

The third group of medications (group 3) includes medications not FDA approved for youth and, thus, not included in groups 1 or 2. Of group 3 medications, there are about 10 that pediatric PCCs are most likely to use and encounter in their practices. These are discussed in terms of available efficacy data and adverse effect profile. Other group 3 medications, which are not commonly prescribed, will not be discussed, but their adverse effect profiles can be accessed via electronic media (eg, Drugs@FDA, Epocrates, Micromedex).

Group 1 Medications for Attention-Deficit/Hyperactivity Disorder, Anxiety, and Depression

General Rationale

Inclusion of medications that PCCs might consider basic to the management of ADHD, anxiety, and depression—group 1 medications—was determined by available data regarding efficacy and safety.

Evidence Supporting Efficacy

The evidence base for the treatment of ADHD, common anxiety disorders (ie, generalized, social, and separation), and depression has been demonstrated in several multisite, randomized clinical trials conducted since the mid-1990s.[3–5]

The research procedure used to demonstrate efficacy of a medication is the random assignment, masked ("blinded"), placebo-controlled treatment study (randomized controlled trial [RCT]). Additional design features that improve the quality of RCTs include 1) a predetermined primary outcome variable; 2) a sufficiently large number of participants, usually estimated via a power analysis, to accurately test the efficacy hypothesis; 3) multiple performance sites that use comparable methodology; 4) independent funding to minimize bias (eg, in the United States, the National Institutes of Health [NIH] or another government agency); and 5) use of independent evaluators who do not receive any participant-specific information about medication adverse effects or treatment assignment.

There is no single criterion for determining that a medication is efficacious. In adults, 2 well-designed and well-conducted RCTs that demonstrate

superiority of active medication over placebo are the generally accepted standard used by the FDA as a necessary prerequisite for drug approval. In children and adolescents, because fewer funding resources and studies exist, the FDA sometimes relaxes this standard and approves a medication with just 1 large, high-quality, multicenter RCT along with other supportive data. That approach is also used by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group to evaluate treatments for children and adolescents (www.gradeworkinggroup.org).

One of the widely recognized limitations of this approach to determining efficacy is that, for both ethical and practical reasons, RCTs are short-term studies, while most psychotropic medications are used as long-term treatment for children and adolescents with chronic disorders. Despite this limitation, the well-designed and well-conducted RCT remains the best method currently available for demonstrating efficacy.

Of note, no SSRIs have FDA-approved pediatric indications for an anxiety disorder (except for OCD, an anxiety-related condition), in large part, because of a discrepancy between FDA rules regarding anxiety disorder indications and efficacy studies that have been conducted in children and adolescents with anxiety. The FDA requires that studies used to support an application for an indication focus on a single anxiety disorder, such as social anxiety disorder, separation anxiety disorder, or generalized anxiety disorder. In children, symptoms and diagnoses of these disorders often co-occur and change over time. Thus, several well-designed studies sponsored by the NIH have examined the use of an SSRI, such as fluoxetine,[6] fluvoxamine,[7] or sertraline,[5] to treat children with 1, 2, or 3 of the common childhood anxiety disorders (social, separation, or generalized). Most commonly, participants in these studies met criteria for 2 or 3 disorders, not just 1. Therefore, the FDA did not use data from these studies to support an indication.

For a summary of efficacy data supporting use of group 1 medications, see Appendix D.

Evidence Supporting Safety

There is no single criterion for assessing safety of medications in children and adolescents. We selected 5 parameters for assessing safety.

1. An FDA-approved pediatric indication (a proxy for a minimal standard of research data supporting short-term safety [and efficacy] of a medication for a specified indication)

2. At least 10 years on the market (a proxy for sufficient time to discover rare adverse consequences and rare complications with long-term exposure; rare adverse events typically are detected only after large numbers of individuals have been exposed to treatment [eg, 1 in 100,000])
3. Minimal overdose harm, determined by a review of available literature
4. Lack of clinically significant boxed warnings (a formal FDA proxy for severe, major adverse effects [see Chapter 4, FDA Boxed Warnings, for discussion of clinical significance])
5. Lack of other known or potentially harmful long-term effects, determined by a review of available literature and warnings and precautions in FDA package inserts

Table 1-2 applies these safety parameters to the 4 categories of group 1 medications.

Specific Rationale

Group 1 medications for use in the primary care setting belong to 5 different classes of medications.

Stimulants

Despite numerous products available on the market, there are just 2 distinct stimulant chemical entities: *methylphenidate* and *amphetamine*. The available literature has not shown any advantage for either methylphenidate or amphetamine with regard to efficacy or safety. The *d*-enantiomer of methylphenidate is more pharmacologically active than the *l*-enantiomer; thus, the recommended dose of dexmethylphenidate is half of that of regular (*d*,*l*-) methylphenidate. Available literature has not shown advantages of different racemic mixtures (*d*- vs *l*- vs *dl*-) of amphetamine.

Methylphenidate and amphetamine are available in numerous release preparations that provide a treatment effect ranging from 3 to 12 hours. Those with longer time on the market and lower cost may be preferred, but that is a general comment, not a preparation-specific recommendation.

α_2-Adrenergic Agonists

Guanfacine extended release is approved by the FDA for use in children and adolescents with ADHD. It is relatively specific to the α_{2A}-receptor subtype, which mediates attention and other executive functions. *Clonidine extended release* is approved by the FDA for use in children and adolescents

Table 1-2. Safety Profile of Group 1 Medication Classes in Children and Adolescents

Safety Criteria	Stimulant	α_2-Adrenergic Agonist	NRI	SSRI	SNRI
FDA-approved age, y	≥3	≥6	≥6	≥8	≥7
Time on market, y[a]	>50	>30	≥10	>25	≥10
Overdose harm	Low	Low (hypotension)	Very low	Very low	Very low
Boxed warning (major adverse effects)[b]	Drug abuse potential	None known[c]	Suicidality	Suicidality	Suicidality
Long-term risk to health[d]	None known[e]	None known	None known	None known	None known

Abbreviations: FDA, Food and Drug Administration; NRI, norepinephrine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Measure of exposure in large populations; time to observe potentially harmful events.

[b] Original FDA meta-analysis for suicidality: 2% for placebo and 4% active in forced dose titration studies.[8] More recent analysis[9] shows difference of 0.67%, down from 2%.

[c] Immediate-release (not sustained-release) clonidine is associated with acute drops in blood pressure, syncope, and even death following unintentional or intentional ingestions of more than therapeutic quantities.

[d] Lack of studies to assess long-term risk to health, with the exception of stimulants.

[e] It is not clear that growth deceleration by a stimulant is a risk to health.

with ADHD. It nonspecifically interacts with α_{2A}-, α_{2B}-, and α_{2C}-receptor subtypes. B and C receptors mediate the sedation and hypotension or bradycardia adverse effects. Thus, clonidine may have a less favorable adverse effect profile than guanfacine. There are no direct comparative data regarding this issue. Also, regular (not sustained-release) clonidine is associated with acute drops in blood pressure, syncope, and even death following unintentional or intentional ingestions of more than therapeutic quantities.

Norepinephrine Reuptake Inhibitors

Atomoxetine, an NRI, has an FDA indication for ADHD. It has more concerning FDA warnings and precautions than other medications for ADHD included in group 1 (described in Chapter 5).

Selective Serotonin Reuptake Inhibitors

Six SSRIs are marketed in the United States: fluoxetine, sertraline, escitalopram, paroxetine, citalopram, and fluvoxamine. Comments regarding the 4 SSRIs included in group 1 are

- *Fluoxetine:* FDA indications for depression and OCD in children and adolescents; high-quality, NIH-sponsored study demonstrating efficacy for the 3 common anxiety disorders in youth[6]; first SSRI marketed in the United States; longest half-life, so abrupt discontinuation results in slow, safe fall in plasma and brain levels
- *Sertraline:* FDA indication for OCD in children and adolescents; second SSRI on the market; shorter half-life; best data for the 3 common anxiety disorders in youth,[5] thus offering an alternative to fluoxetine when shorter half-life may be indicated (eg, for a child taking multiple medications with further changes likely) or when fluoxetine cannot be used because of interactions with metabolic isoenzymes (eg, inhibition of CYP2D6)
- *Escitalopram:* FDA indication for depression in children and adolescents; no clinically relevant interactions with hepatic CYP450 isoenzymes
- *Fluvoxamine:* FDA indication for OCD in youth and a high-quality, NIH-sponsored study demonstrating efficacy for the 3 common anxiety disorders in youth[7]

Serotonin and Norepinephrine Reuptake Inhibitors

Duloxetine, an SNRI, has an FDA indication for generalized anxiety disorder. The main clinical difference between duloxetine and SSRIs is the adverse event profile (described in Chapter 5).

Group 2 Medications

General Rationale

In addition to prescribing and monitoring group 1 medications, pediatric PCCs are ideally suited to collaborate with psychiatrists and other mental health specialists in the care of children and adolescents with more severe or uncommon disorders. They may be asked to take on partial responsibility for monitoring therapeutic and adverse effects of various other medications, which are included in groups 2 and 3.

Group 2 medications can be monitored in primary care settings. However, because they generally have a more serious safety profile and more complicated monitoring requirements than group 1 medications, they are generally prescribed by specialists—child and adolescent psychiatrists, developmental-behavioral pediatricians, specialists in neurodevelopmental disabilities or adolescent medicine, pediatric neurologists, or adult psychiatrists with additional training in child and adolescent psychiatry. Depending on the skills and experience of an individual pediatric PCC, as well as (lack of) availability of specialists for referral (especially in rural and underserved areas), some pediatric PCCs with additional training in pediatric psychopharmacology may choose to prescribe group 2 medications.

Group 2 includes all FDA-approved medications for youth with other disorders (ie, not ADHD, anxiety, or depression). Group 2 includes 6 second-generation antipsychotics (asenapine, lurasidone, olanzapine, quetiapine, risperidone, and paliperidone [the active metabolite of risperidone]), one third-generation antipsychotic (aripiprazole), and lithium, a mood stabilizer. The second-generation antipsychotics are approved for treatment of youth with psychosis in schizophrenia (all except asenapine); mania in bipolar disorder (all except paliperidone); and "irritability" in autism spectrum disorder (only risperidone and aripiprazole). However, these medications are most commonly used off-label (ie, outside the FDA-approved indications) in youth to treat behavioral problems, especially aggression. Lithium is approved by the FDA to treat acute mania in youth with bipolar disorder. Lithium is also used off-label to treat nonbipolar mood instability.

Specific Rationale

Antipsychotics

Antipsychotics can reduce severity of various major psychiatric symptoms and have various effects, including

- Antipsychotic effects for hallucinations, delusions, and disorganized thinking
- Mood-stabilizing effects for mania, irritability, and mood instability
- Possible "organizing" or "calming" effects for agitation and aggressive behavior

However, of all psychotropic medications used in children and adolescents, antipsychotics have the most concerning adverse effects, including

- Daytime sedation
- Weight gain
- Elevated glucose and insulin resistance
- Elevated triglyceride and cholesterol levels
- Abnormal movements (neurologic)
- Endocrine (eg, gynecomastia, galactorrhea)

Many major adverse effects of antipsychotics—particularly weight gain, metabolic abnormalities, and involuntary movements—can develop into major health problems (eg, cardiovascular disease and its consequences, tardive dyskinesia) during long-term treatment and may not be reversible. Most disorders treated with antipsychotics are chronic and generally require long-term treatment. Thus, determining risk versus benefit when initiating antipsychotics is difficult.

Mood Stabilizers

Mood stabilizers (excluding antipsychotics) are used to treat mania, depression, irritability, and problematic mood swings in bipolar disorder and other mood disorders. Two groups of mood stabilizers are available: traditional (lithium, valproic acid [divalproex sodium], and carbamazepine) and newer anticonvulsants (eg, lamotrigine).

Lithium is the only mood stabilizer included in group 2. Lithium is approved by the FDA for mania in bipolar disorder for ages 12 years and older. Available data for lithium suggest efficacy for acute mania in bipolar disorder.

Chapter 7 is devoted to a more extensive presentation of group 2 medications, including information about individual medications.

Group 3 Medications

General Rationale

Group 3 includes medications not approved by the FDA for treatment of youth, that is, medications not included in groups 1 or 2. Ten group 3 medications that pediatric PCCs are most likely to encounter in their practices are discussed in Chapter 8 in terms of available efficacy data and adverse effect profile. Other group 3 medications, which are not commonly prescribed, will not be discussed, but their adverse effect profiles (as well as those for groups 1 and 2) can be accessed via electronic media (eg, Drugs@FDA, Epocrates, Micromedex).

Specific Rationale for 10 Medications

The author and editorial advisory group selected 10 medications in group 3 that are commonly encountered in pediatric primary care. This selection was based on expert opinion because data on the safety and efficacy of these medications in youth are insufficient. These medications, which include 4 antidepressants, an antipsychotic, a mood stabilizer, 2 anxiolytics, and 2 sleep aids, are presented in Chapter 8.

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Part 2—Practical Guidance

CHAPTER 2

The Psychosocial Assessment in Primary Care

Pediatric primary care clinicians (PCCs) face challenging yet rewarding tasks related to providing mental health care for youth of different ages, developmental capacities and problems, while working in a range of settings with variable access to services. They must provide preventive care, which involves health promotion, anticipatory guidance, surveillance, and psychosocial screening of patients and their families. Pediatric PCCs often have the opportunity to intervene early, when mental health or social problems first emerge. When problems are severe or impairing or when they persist despite primary care interventions, pediatric PCCs may provide diagnostic assessment and/or treatment services, or they may refer their patients to mental health specialists for these services. No matter who provides the mental health services, pediatric PCCs participate in monitoring patients with mental health concerns and chronic mental health conditions. Ideally, these activities are collaborative, involving the child, family, pediatric PCC, office staff, school personnel, and mental health specialists, as appropriate.

The American Academy of Pediatrics (AAP) has offered guidance related to the performance of these roles. This guidance has included publications of its Task Force on Mental Health (2004–2010); a revision of its policy statement on mental health competencies for pediatrics[1–7]; Web postings of the Mental Health Leadership Work Group at www.aap.org/mentalhealth; contents of the *AAP Textbook of Pediatric Care*, 2nd Edition; and *Pediatric Care Online, Mental Health Care of Children and Adolescents*, and several other publications (see Appendix B), including the first edition of this book.

The AAP Mental Health Leadership Work Group's algorithm[8] describing a primary care approach to mental health care is shown in Appendix B. It highlights the many opportunities pediatric PCCs have to assess the psychosocial well-being of a child and family during routine health supervision

and acute care visits, as well as visits scheduled specifically to address mental health problems. The longitudinal relationship that the pediatric PCC often has with a patient and family can facilitate the identification of strengths and assist in the management of mental health concerns.

Start With Inquiry About Normative Developmental Trajectory

Although it is important to gather information about the symptoms and diagnostic criteria of psychiatric disorders, it may be more productive to start with general inquiries about areas of function—eg, school, home, family, friends, activities, health, and sources of enjoyment. The World Health Organization International Classification of Functioning, Disability and Health organizes these functions into 3 groups: body function/structure, activities and participation, and environmental factors. (See www.who.int/classifications/icf/icfbeginnersguide.pdf?ua=1.) Talking about quality of sleep, appetite, energy, or interest in and pleasure from activities is usually easier than talking about upsetting thoughts. Anger and irritability may be more noticeable and important concepts to a patient and caregiver than "depression." Physical discomfort, such as an upset stomach or restlessness, may be more salient than "anxiety." Once a dialogue is established, it is easier to progress to more challenging topics, including problematic thoughts, feelings, and behaviors.

Triage for Psychiatric and Social Emergencies

Triage for psychiatric and social emergencies is an essential part of the evaluation for any mental health concern. Psychiatric and social emergencies that require immediate attention, and usually a referral for emergency evaluation and treatment, are listed in Box 2-1.

Significant parent or child concerns, while not true emergencies, may require urgent attention. An example is a child or adolescent presenting with severe panic symptoms or a first panic attack. Symptoms of a panic attack, such as palpitations; feelings of choking, chest pain, or discomfort; fear of losing control; or fear of dying, can be frightening to a child and caregiver. Pediatric

Box 2-1. Psychiatric and Social Emergencies in Pediatric Primary Care

Psychiatric Emergencies
• Suicidality • Serious threat of violence by the child or adolescent • Psychosis • Acute alcohol or substance intoxication or withdrawal
Social Emergencies
• Sexual or physical abuse • Threat of violence to the child • Family or social circumstances that threaten safety of the child/adolescent (eg, domestic violence) • Inadequate family resources that pose urgent health or safety risks

PCCs and their office staff must therefore consider not only the type and severity of symptoms but also the level of distress and impairment when defining emergency and urgent situations.

If the initial evaluation reveals that the presenting problem is not an emergency, it is usually appropriate to proceed with an evaluation that follows the sequence described as follows.

Emphasize Function

Assessment of functioning is typically part of primary care screening and initial assessment and can be applied and/or enhanced as part of a full diagnostic assessment. Determining the type and severity of functional impairment is essential for guiding treatment goals. Primary care–friendly tools in the AAP mental health toolkit include the performance section on the NICHQ Vanderbilt Assessment Scale and the Strengths and Difficulties Questionnaire (see Appendix A). In general, a child with a mental health disorder and severely impaired functioning will need care in the mental health specialty system. For children who are less impaired, the pediatric PCC and family can decide whether to engage a specialist or other services within the mental health system or to provide treatment within the primary care setting (or both). Medication usually is not recommended for a child who has symptoms but does not have *clinically significant functional impairment*.

Assess Sleep Pattern

Disrupted sleep can be the result of a mental health disorder. Conversely, disrupted sleep can lead to or exacerbate a mental health disorder. Sleep problems can be secondary to various environmental stressors (particularly family turmoil or school examinations), excessive responsibilities and activities (eg, job, athletics, homework), procrastination, or socializing (actual or virtual). Inadequate sleep can cause distractibility, restlessness, worry, irritability, and low mood—all symptoms that can masquerade as symptoms of mental health conditions. Assessment of sleep includes determining a change from baseline in the child's quantity and quality of sleep, satisfaction with sleep, sleep hygiene (including electronic screen use before bedtime), sleep schedule, and daytime somnolence. An important element of the history is asking about the ability to sleep when they want to sleep. *Inability* to sleep—as opposed to *resistance* to sleep or poor sleep hygiene—more likely suggests a psychiatric origin or a sleep disorder. Table 2-1 summarizes sleep requirements at various ages during childhood and adolescence.

If there are sleep concerns, a sleep log completed over a 2-week period can be helpful in determining patterns or areas for improvement. A convenient, single-page pediatric sleep log is available at www.brightfutures.org/mentalhealth/pdf/families/ec/diary.pdf. This information, combined with other elements of the psychosocial assessment, can assist the clinician in determining whether to prioritize the sleep problem as a primary or secondary concern.

Table 2-1. How Much Sleep Do You Need?

Age Group		Recommended Hours of Sleep Per 24 hours
Infant	4–11 mo	12–16 (including naps)
Toddler	1–2 y	11–14 (including naps)
Preschool	3–5 y	10–13 (including naps)
School age	6–12 y	9–12
Teen	13–18 y	8–10
Adult	19–60 y	≥7 h

From Centers for Disease Control and Prevention, National Center for Chronic Disease and Prevention and Health Promotion, Division of Population Health. CDC features: are you getting enough sleep? http://www.cdc.gov/Features/Sleep. Updated March 13, 2018. Accessed April 11, 2018.

Identify Environmental Stressors

A growing body of literature suggests that environmental and family-level factors can have short- and long-term negative effects on childhood mental health and can contribute to a decline in both physical and mental health into adulthood. These adverse childhood experiences (ACEs) include exposure to poverty, abuse, family disruption, domestic violence, parental mental health disorders, and substance abuse. Mental and physical effects of ACEs appear to be cumulative, especially in the absence of protective factors and with prolonged exposure, with higher numbers of ACEs associated with more significant impairment. The Adverse Childhood Experiences Questionnaire can be found at www.ncjfcj.org/sites/default/Finding%20Your%20ACE%20Score.pdf.

In addition to the potential for long-terms effects, ACEs and other significant stressors can cause more immediate symptoms that may mimic those of ADHD, anxiety, and depression. These stressors may include single incidents (eg, car crash), ongoing trauma (eg, exposure to domestic violence), or a combination of single and ongoing stresses (none of which alone would be considered "trauma").[9]

Simple surveillance questions can be incorporated into a standard visit.

> "Since the last time I saw you, has anything really scary or upsetting happened to you or your family?"
>
> Are there ever times that you worry you won't have enough food to eat or a safe place to stay?"

For children younger than 8 years, analogous questions should be asked to parents.

> "Since the last time I saw your child, has anything really scary or upsetting happened to your child or anyone in your family?"

The Safe Environment for Every Kid (SEEK) questionnaire, available at www.ncbi.nlm.nih.gov/books/NBK117231/bin/appc-fm1.pdf, can be used to screen for many types of environmental stressors.

The pediatric PCC's clinical judgment, combined with the history provided by a patient and family, is essential in determining whether a response qualifies as a clinically relevant stressor. Any compromise of the child's safety indicates an urgent need for intervention.

Screen for Substance Use

Substance use and experimentation are very common among youth. According to the Centers for Disease Control and Prevention, approximately 25% of high school–aged youth report buying, selling, or being given drugs on school grounds in the past 6 months.[10] Thus, for preteens and adolescents, screening for substance use is recommended. The CRAFFT (car, relax, alone, forget, friends, trouble) substance use questionnaire is a validated, brief pediatric assessment tool recommended for use in the primary care setting (www.ceasar-boston.org/clinicians/crafft.php).

Substance use and posttraumatic stress disorder (PTSD) may co-occur with other mood or behavioral disorders (eg, anxiety, depression, ADHD). Complex psychopathology may require further mental health consultation for diagnostic evaluation or incorporation of specific psychosocial treatments (or both). It is important to note that, with the exception of naltrexone for opioid addiction or alcohol dependence for ages 16 to 17 years, there are no US Food and Drug Administration–approved pediatric medications for either substance abuse disorder or PTSD; however, there are evidence-based psychosocial interventions (eg, motivational interviewing and trauma-focused cognitive behavioral therapy [TF-CBT]). There is some evidence supporting the use of selective serotonin reuptake inhibitors (SSRIs) and α-adrenergic agonists for PTSD.[11]

Differentiate New Problems From Exacerbation of Old or Chronic Problems

The breadth and depth of an initial evaluation of a mental health problem depends on the type of problem or presentation. Any new problem generally requires a thorough evaluation and diagnostic assessment, with consideration of symptom severity, functional impairment, family support, and available resources. An exacerbation of a previously diagnosed and generally stable problem will rarely require the same extent of assessment as a newly presenting problem.

Recurrences or exacerbations are often associated with some change in the child's environment or a transition to a new developmental stage. Identifying these issues is a good start to a problem-focused approach to treatment.

Understanding how the present episode differs from past episodes can provide a clue as to how much new assessment is required or if a different treatment is needed.

Inquire About Prior Evaluations and Prior and Current Treatments

Obtaining information about previous evaluations and interventions can be useful in understanding what has and what has not been helpful for the child in the past. The child and family's understanding of prior evaluations and diagnoses, as well as prior and current medications, may also influence their response to the evaluation process and subsequent treatment approaches. Prior positive experience usually makes the current clinician's work easier. Prior negative treatment experiences may lead to the child and family's reluctance to seek specialty professional help, which can be managed when the pediatric PCC is aware of this in the history. Inquiry about prior and current treatments should include over-the-counter and complementary medication approaches, in part because some of these medications (eg, nutritional supplements that include the stimulant β-methylphenylethylamine or St John's wort) may interact with prescription medications.

Provide Initial Primary Care Intervention for Problems That Are Not Disorders

Many children have mild symptoms or impaired functioning but no diagnosable disorder. Through the use of empathy, support, and simple behavioral interventions, clinicians can be effective in decreasing the child and family's distress, and can improve the child's functioning, even in the absence of a formally diagnosed disorder.[12] Clinicians can also provide brief interventions in the office using "common elements," or components of evidence-based psychosocial therapies that are effective across classes of related symptoms and disorders.[13] These clinical skills can be particularly useful in primary care, either as primary treatment for mild symptoms or to help bridge treatment until the patient can be referred to a specialty mental health professional. Lack of response is an indication for further assessment. For more information, see HELP mnemonic in Appendix B.

Provide Extended Evaluations and Interim Check-ins, if Needed

It is not always possible to spend enough time to complete an initial evaluation that results in sufficient clarity regarding diagnosis and safety to facilitate a coherent treatment plan. In such situations, it is useful to schedule a follow-up evaluation appointment relatively soon and, in the interim, to have a staff member conduct brief phone check-ins with the parents and the patient. Check-ins should include review of symptoms, functioning, monitoring, and safety. Collateral information from child care or school may be useful. Even if a referral to a child and adolescent psychiatrist or other specialist is initiated at the first evaluation visit, interim check-ins should be done until the time of the child's first appointment with a specialist.

Preparing the Practice

Standardizing office procedures for the iterative primary care assessment and for the management of common mental health concerns (eg, inattention, anxiety, low mood, behavioral problems) can be helpful in addressing most mental health concerns that present in the primary care setting. These procedures will likely include psychosocial screening tools to identify symptoms of mental health disorders, processes for responding to positive findings on screening tools, informational materials for patients and families, and referral guidelines for mental health services in the community

Additional information on "preparing the practice" to successfully care for children with mental health concerns is available.[6] The AAP practice readiness inventory (see Appendix B) also serves as an assessment tool for practices to identify strengths and gaps in the care they provide to children with mental health concerns.

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CHAPTER 3

Assessment of Disorders, Formulation, and Feedback

Overview

Pediatric primary care clinicians (PCCs) have extensive training and experience in assessing medical problems and proficiency in assessing children's and adolescents' chronic health problems and disorders. This chapter focuses on additional knowledge and skills needed to conduct a mental health diagnostic evaluation.

This chapter has 5 sections.

- Assessment: describes various psychiatric disorders, including *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) diagnostic criteria.
- Medication: describes 5 simple concepts that support a decision to recommend medication.
- Referral: describes findings from the assessment that would support the need for referral to a specialist.
- Formulation: describes a simple approach to organizing the patient's story in a way that guides treatment.
- Feedback: describes a stepwise approach emphasizing partnering with a patient and family in the decision-making process.

Assessment

Assessment of Common Disorders: Attention-Deficit/Hyperactivity Disorder, Anxiety, Depression

The complexity of a mental health assessment depends on several factors, including (1) the salient symptoms that can be described by a patient and/

or observed by caregivers and other informants; (2) other disorders in the differential diagnosis; (3) effect of environmental stressors, particularly in families affected by social determinants of health; and (4) contributing and confounding problems, such as substance use and medical illness.

Attention-deficit/hyperactivity disorder (ADHD) may seem straightforward to diagnose because the symptoms are generally observable by multiple informants (eg, parents, teachers) in multiple settings (eg, school, home). Nonetheless, ADHD can be confused with intellectual, language, and learning difficulties and may be confused with anxiety or the effects of adverse life experiences (or both). Underlying medical concerns such as insomnia or absence seizures may contribute to attention problems. Similarly, differentiating normal activity and attention issues from ADHD in preschoolers can be challenging.

For the evaluation of internalizing disorders (eg, anxiety and depression), separate interviews of the child and caregiver(s) are recommended as part of the assessment. This is not only because the child may not want to disclose to or worry the caregiver, but also because the caregiver may not be aware of the child's worries or negative cognitions. Using separate child and caregiver rating forms is recommended.

Although anxiety and depression are both considered internalizing conditions, some symptoms of anxiety can be observed or elicited easily. Physical symptoms (eg, abdominal pain, muscle tension) are common in children with anxiety[1] and are familiar to pediatric PCCs. Other symptoms—such as avoiding social situations or phobic stimuli, or entering the parents' bedroom or bed at night in response to separation concerns—are either reported to the parent(s) by the child or are readily observed by parents. To elicit a patient's worries or internal distress, asking open-ended questions, such as "Everyone worries; what do you worry about?" is likely to yield more information than "Do you worry?" Useful follow-up questions might include "Tell me more about that" or "What makes that hard for you?" Similarly, when asking about a patient's mood, starting with open-ended questions, such as "Everyone feels sad or grouchy or angry sometimes; how have you been feeling lately?" can often lead to a more informative dialogue.

The differential diagnosis for a specific anxiety disorder (eg, generalized anxiety disorder) includes all other anxiety disorders (eg, panic disorder, social anxiety disorder, separation anxiety disorder, simple phobia), as well as posttraumatic stress disorder, obsessive-compulsive disorder, bereavement,

depression, and oppositional defiant disorder (ODD). In addition, personality traits, such as introversion or neuroticism, may be salient.

Differential diagnosis for depression includes demoralization, grief, and "adjustment disorder," which are common in children and adolescents. Parsing depression from these other conditions requires time and patience. Low mood and worry often co-occur. Sometimes worrying can make a youngster feel sad and grouchy; sometimes feeling sad heightens preexisting worries.

Parent reports and self-reports can provide important information about a child's symptoms and their severity, can be useful in determining diagnostic threshold, and can be useful during "watchful waiting." Also, disease (or symptom)–specific rating scales can help assess severity and can be used to monitor symptoms and track response to primary care interventions. Among the many available reporting tools, the following generally incorporate current *DSM-5* criteria and are available as open-access tools:

- *Attention-deficit/hyperactivity disorder:* National Institute for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale for parents and teachers at www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales (see Appendix A)
- *Anxiety:* Screen for Child Anxiety Related Disorders (SCARED), parent and child versions, at http://pediatricbipolar.pitt.edu/resources/instruments (see Appendix A)
- *Depression:* Patient Health Questionnaire-9 (PHQ-9) Modified for Teens (see Appendix A)

Beyond documentation of the total score on an assessment tool, the pediatric PCC can ask about the level of impairment and distress associated with symptoms to help decide whether medication should be part of the treatment plan.

Anxiety, ADHD, and depression often co-occur. Thus, assessment of each of these 3 common disorders is recommended, even when the presenting concern or the results of initial screening indicates that 1 of the 3 is prominent.

Symptoms of ADHD usually first manifest during preschool or early elementary school years. Onset of anxiety disorders ranges from preschool age (separation), to elementary school age (specific phobias, social), to adolescence (social, generalized, panic). Onset of depression is usually during adolescence and is rare during the prepubertal period.

Attention-Deficit/Hyperactivity Disorder

A conservative estimate of point prevalence of ADHD in children is 5%,[1] but estimates range up to 10%. Prevalence is lower in adolescents. Boys are about twice as likely as girls to have ADHD.

Children with attentional and activity-related concerns can present to pediatric PCCs in outpatient settings, often at the urging of school personnel. Pediatric PCCs are generally skilled and experienced in the evaluation and diagnosis of a child with possible ADHD.

In the American Academy of Pediatrics (AAP) clinical practice guideline "ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents," the first key action statement is "The primary care clinician should initiate an evaluation for ADHD for any child 4 through 18 years of age who presents with academic or behavioral problems or symptoms of inattention, hyperactivity, or impulsivity (quality of evidence B/strong recommendation)."[2] This includes collecting information directly from school and child care personnel who have observed the child, as well as family members (including a noncustodial parent) and youth, using a validated tool such as the NICHQ Vanderbilt Assessment Scale.

The AAP ADHD toolkit includes a wealth of useful information to facilitate the evaluation process for the child with suspected ADHD (see Appendix B). The American Academy of Family Physicians provides information and continuing medical education on ADHD evaluation and diagnosis through its official journal, *American Family Physician* (see www.aafp.org/afp/topicModules/viewTopicModule.htm?topicModuleId=68).

Because most pediatric PCCs are familiar with ADHD and have access to an abundance of high-quality information about evaluation, this section will focus on a just a few selected topics regarding ADHD.

Important data for diagnosing ADHD in a child are caregivers' and teachers' observations that are recorded and organized by structured rating scales. This is because many children can attend and behave well in an office setting with a parent and the clinician; thus, examination room observations may be different from those in the child's "natural" settings of home and school. Obtaining symptom information from informants over at least a week and during various times of day strengthens the validity of the diagnosis, because symptom severity waxes and wanes over short periods.

Symptoms of inattention in ADHD described in *DSM-5* are listed in Box 3-1. Of note, all 9 symptoms start with the word *often*. Obviously, the meaning of often will vary among informants. Thus, it is the clinician's task to work with caregivers and teachers to clarify if a symptom is different from normal developmental expectations.

Symptoms of hyperactivity and impulsivity in ADHD described by *DSM-5* are listed in Box 3-2. Again, it is noteworthy that all 9 symptoms start with the word *often*. Differentiating normal developmental levels of activity and impulsivity can be challenging, particularly in young children (ie, 3- to 5-year-olds). Differentiating can be challenging for caregivers as

Box 3-1. Simplified *DSM-5* Symptoms of Inattention in ADHD[a]

a. Often fails to give close attention to details or makes careless mistakes
b. Often has difficulty sustaining attention in tasks or play activities
c. Often does not seem to listen when spoken to directly
d. Often does not follow through on instructions and fails to finish tasks
e. Often has difficulty organizing tasks and activities
f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
g. Often loses things necessary for tasks or activities
h. Often easily distracted by extraneous stimuli
i. Often forgetful in daily activities

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

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Box 3-2. Simplified *DSM-5* Symptoms of Hyperactivity and Impulsivity in ADHD[a]

Hyperactivity
a. Often fidgets with or taps hands or feet or squirms in seat.
b. Often leaves seat in situations when remaining in seat is expected.
c. Often runs about or climbs in situations where it is inappropriate.
d. Often unable to play or engage in leisure activities quietly.
e. Often "on the go," acting as if "driven by a motor."
f. Often talks excessively.
Impulsivity
g. Often blurts out an answer before a question has been completed.
h. Often has difficulty waiting his or her turn.
i. Often interrupts or intrudes on others.

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

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well. For example, first-time parents may not recognize that high levels of activity and impulsivity in a young child are outside the range of normal, or conversely, that a child's level of activity is within the normal range for her/his age.

Box 3-3 lists *DSM-5* diagnostic criteria for ADHD. Several criteria—addressing impairment and function—are noteworthy. Symptoms need to

- Have persisted for at least 6 months
- Have a negative impact directly on social and academic functioning
- Be present in 2 or more settings
- Interfere with, or reduce the quality of, social, academic, or occupational functioning

Box 3-3. Simplified *DSM-5* Diagnostic Criteria for ADHD[a]

Symptom and Duration Criteria
A. A persistent pattern of inattention, hyperactivity, or both that interferes with functioning or development and is characterized by (1), (2), or both **1. Inattention** • **Six or more inattention symptoms (see Box 3-1).** • **Symptoms have persisted for at least 6 months.** • **Degree is inconsistent with developmental level.** • **Negatively directly affects social and academic functioning.** **2. Hyperactivity and Impulsivity** • **Six or more hyperactivity-impulsivity symptoms (see Box 3-2).** • **Symptoms have persisted for at least 6 months.** • **Degree is inconsistent with developmental level.** • **Negatively directly affects social and academic functioning.**
Onset, Setting, and Quality of Functioning Criteria
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years. **C. Several inattentive or hyperactive-impulsive symptoms are present in 2 or more settings (eg, at home or school, with friends or relatives, in other activities).** **D. There is clear evidence that the symptoms interfere with, or reduce quality of, social, academic, or occupational functioning.**
Exclusion Criteria
E. Symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder.

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

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Presence of 6 or more inattentive symptoms that meet the aforementioned criteria supports a diagnosis of ADHD, inattentive subtype. Presence of 6 or more hyperactive/impulsive symptoms that meet these criteria supports a diagnosis of ADHD, hyperactive/impulsive subtype. Presence of 6 or more symptoms in both groups that meet these criteria supports a diagnosis of ADHD, combined subtype.

The risk of underdiagnosis (and therefore not starting treatment when it is indicated) is the negative effect of ongoing and untreated symptoms on functioning and development. The risks of overdiagnosis (and therefore starting treatment when it is not indicated) include the potential stigma associated with diagnosis and the potential adverse effects of treatment. Reevaluation at regular intervals can greatly reduce both of these risks.

Fortunately, treatment of ADHD is rarely an emergency—though teachers or parents may press the clinician to consider it as one. Taking time to explore issues related to anxiety, trauma, learning problems, and substance use that can co-occur (or cause similar symptoms) is recommended. Also, response, or lack of response, to primary care–initiated interventions to manage problem behaviors at home or in the classroom can contribute to the ongoing assessment.

When multiple diagnoses are possible, a family and pediatric PCC together may be able to choose the order in which they are treated.

Anxiety Disorders

Anxiety disorders are the most common psychiatric disorders of childhood and adolescence.[3] Rigorous and specific prevalence data for preteen children are sparse and estimates vary; the best available data are for 13- to 17-year-old teens in the United States, with a 12-month prevalence rate of 25% and lifetime prevalence rate of 32% for all anxiety disorders.[3]

The core symptoms of anxiety disorders are fears or phobias, worries, and somatic concerns. A common response to these symptoms is avoidance of situations that generate fear or worry.

Children with anxiety can present to the pediatric PCC in various ways. Children may share their worries, fears, or somatic concerns with their caregivers, who then describe them during an office visit. In other cases, a caregiver may report that a child is excessively shy or is avoiding social or other situations (eg, coming close to dogs, being alone). Sometimes, however, children keep their fears or worries to themselves and do not share them

with others. Thus, a general inquiry regarding concerns, worries, and sources of discomfort may elicit previously unidentified anxiety. A common presentation in the primary care setting is recurrent abdominal pain, without any reported concerns about worry or fear. The general inquiry can also elicit parental responses to the child's anxiety, which may be fueling or facilitating the anxiety or providing excessive shielding and protection.

Anxiety and depression frequently co-occur, with one set of symptoms and related behaviors potentially exacerbating the other. When one condition is suspected, it is necessary to ask about the other condition as well.

Box 3-4 lists the types of symptoms associated with common pediatric anxiety disorders. *Fear* (or phobia) is the primary symptom of separation anxiety disorder (fear of being alone), social anxiety disorder (fear of embarrassment or discomfort in social situations), and specific phobia (fear of a specific stimulus [eg, heights, snakes, needles]). *Worry* is the primary symptom of generalized anxiety disorder and may focus on personally relevant topics such as homework or friendships, as well as on topics that can seem less relevant, such as weather events or national "what if" questions (eg, terrorist attacks or nuclear war). *Somatic* concerns can occur with any anxiety disorder and may be the presenting concern at an office visit. Table 3-1 lists the reported frequency of common somatic concerns seen in pediatric anxiety disorders.[4] Avoidance of social situations or phobic stimuli is considered a secondary symptom.

Box 3-5 lists *DSM-5* diagnostic criteria for separation anxiety disorder, social anxiety disorder, and generalized anxiety disorder. All have core symptom and duration criteria, all have additional diagnosis-specific diagnostic criteria, and all require clinically significant distress or impairment in social, academic, and occupational, or other important areas of functioning.

The Screen for Child Anxiety Related Emotional Disorders provides information about the symptoms of all common anxiety disorders as well as severity of each symptom. Parent and child versions are available (see Appendix A). Review and discussion of the SCARED symptom ratings with the child and caregiver together may be educational and can clarify differences in understanding what is or is not a symptom and what distress and impairment may be associated with various symptoms.

Although establishing a specific diagnosis is important for helping a patient and family understand formulation and feedback, the treatment approach for all common anxiety disorders (separation anxiety disorder, social anxiety

Box 3-4. Types of Symptoms in Common Pediatric Anxiety Disorders[a]

Disorders With Fear or Phobia as Primary Symptom
• Separation anxiety disorder • Social anxiety disorder • Specific phobia
Disorders With Worry as Primary Symptom
Generalized anxiety disorder
Symptoms That May Be Present in Any Anxiety Disorder
• Somatic concerns • Avoidance

[a] In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* obsessive-compulsive disorder and posttraumatic stress disorder are not anxiety disorders.

Table 3-1. Ten Most Common Somatic Symptoms in Pediatric Anxiety Disorders[a]

Symptom	Percent, %	Sex or Age Differences (P <.01)
Restlessness	74	NA
Feeling sick to stomach	70	Less common in girls
Blushing	51	NA
Palpitations	48	NA
Muscle tension	45	NA
Sweating	45	More common in 12- to 17-year-olds
Trembling and shaking	43	More common in 12- to 17-year-olds
Easily fatigued	35	NA
Feeling paralyzed	32	NA
Chills and hot flashes	31	NA

Abbreviation: NA, not applicable.

[a] Patients studied (N = 128) were girls (n = 63) and boys (n = 65) aged 6–11 years (n = 86) and 12–17 years (n = 42).

Data were derived from Ginsburg GS, Riddle MA, Davies M. Somatic symptoms in children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry.* 2006;45(10):1179–1187 and The Research Units on Pediatric Psychopharmacology Anxiety Study Group. The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. *J Am Acad Child Adolesc Psychiatry.* 2002;41(9):1061–1069.

disorder, generalized anxiety disorder), simple phobias, and panic attacks is fundamentally the same: cognitive behavioral therapy and, sometimes, medication. The specific technique a cognitive behavioral therapist uses may vary by specific diagnosis, but the basic strategy is the same.

Box 3-5. *DSM-5* Diagnostic Criteria for Common Anxiety Disorders[a]

Core Symptoms
Separation: **Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the youngster is attached as manifested by >3 of 8 symptoms.**
Social: **Marked fear or anxiety about >1 social situation in which the individual is exposed to possible scrutiny by others (adults or peers).**
Generalized: **Excessive anxiety and worry (apprehensive expectation), occurring more days than not, about a number of events or activities.**
Additional Disorder-Specific Diagnostic Criteria
Separation: **Refer to Appendix F for a list of 8 ways in which core separation symptoms can manifest; as noted above, 3 or more are required.**
Social • **Fears will act in a way or show anxiety symptoms that will be negatively evaluated.** • **Social situations almost always provoke fear or anxiety.** • **Social situations are avoided or endured with intense fear or anxiety.** • **Fear or anxiety are out of proportion to actual threat posed by the social situation.**
Generalized • **Youngster finds it difficult to control worry.** • **Anxiety and worry are associated with 1 or more of 6 somatic symptoms: restless, keyed up, or on edge; easily fatigued; difficulty concentrating or mind goes blank; irritability; muscle tension; sleep disturbance.**
Impairment/Distress
All 3: **Symptoms cause clinically significant distress or impairment in social, academic, occupational, or other important areas of functioning.**
Duration
Separation: **Rarely presents clinically with <6 months' duration, but criterion is >4 weeks.**
Social: **6 months.**
Generalized: **6 months.**
Exclusions
All 3: **Physiologic effects of a substance(s), another medical condition (eg, hyperthyroidism), or another mental disorder.**

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

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The assessment should include consideration of other medical, developmental, and mental health conditions. For example, repetitive or rigid behavior may be a feature of obsessive-compulsive disorder or autism spectrum disorder. A communication disorder may better explain failure to speak in specific social situations rather than separation anxiety disorder. Traumatic

reminders may precipitate the symptoms of generalized anxiety disorder for some youth with a significant trauma history. Anxiety symptoms and panic attacks may occur in response to ingestion of some substances, such as methamphetamine, cocaine, or an inhalant. Certain medications, such as some decongestants, may lead to agitation, and rarely, medical conditions, such as hyperthyroidism, may lead to nervousness or excessive worry, though other physical signs and symptoms usually are present.

Major Depressive Disorder

Data on the point prevalence of depressive disorders in prepubertal children are limited; the best data suggest a prevalence of 1% to 2% in the United States.[5] For adolescents, the 12-month and lifetime prevalence of depression is estimated at 7.5% and 11.0%, respectively.[6] Starting in adolescence, there is about a 3:1 female predominance of depression.

The evaluation of depression in a child or adolescent may be more complex and nuanced than the evaluation of ADHD or anxiety. Many of the core symptoms of depression involve emotions and thoughts that youth can keep private. Caregivers may view a clinical episode of depression as a "normal phase of growing up," or a normal effect of the angst and turmoil associated with stress, loss, interpersonal difficulties, or various other problems that are common life challenges. Shame or concerns about stigma may impede help-seeking or disclosure of symptoms of depression, particularly by adolescents.

The PHQ-9 Modified for Teens rating scale and Guidelines for the Management of Adolescent Depression in Primary Care (GLAD-PC) (see Appendix A) may be helpful in eliciting symptoms of depression. However, there is no available shortcut to the accurate diagnosis of an episode of major depressive disorder (MDD).

DSM-5 Symptoms and Diagnostic Criteria

The 9 symptoms of MDD in *DSM-5* are organized into 3 domains: mood, neurovegetative, and cognitive (Box 3-6). In children and adolescents with MDD, depressed mood usually occurs alone or in combination with irritability; rarely, irritability is the only mood symptom. Three of the 5 neurovegetative symptoms may present in the following ways: appetite and weight may be increased or decreased, sleep may be increased or decreased, and there may be psychomotor agitation or retardation.

Box 3-6. *DSM-5* Symptoms of Major Depression Organized by Major Domains[a]

Mood
Depressed or irritable
Neurovegetative
• **Diminished interest or pleasure** • **Weight loss or gain of >5% in a month** • **Insomnia or hypersomnia** • **Psychomotor agitation or retardation** • **Fatigue or loss of energy**
Cognitive
• **Decreased concentration or indecisiveness** • **Worthlessness or guilt** • **Suicidal ideation**

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

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Criterion A in the *DSM-5* diagnostic criteria (Box 3-7) is quite specific and detailed. The episode must include all of the following:

- Five or more of the 9 symptoms in Box 3-6 must be present during the same 2-week period and must represent change from previous functioning.
- Symptoms must be present nearly every day (except weight change and suicidal ideation).
- At least 1 of the symptoms must be either depressed or irritable mood, or loss of interest or pleasure.
- In addition, the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Taken together, these diagnostic criteria make it clear that an episode of MDD is a discrete and relatively specific clinical entity.

Although the minimum duration for an episode of depression is just 2 weeks, children or adolescents may present with symptoms that have been present for many weeks or even months. Such a chronic presentation can make it more challenging to accurately delineate a discrete episode of depression.

Box 3-7. Simplified *DSM-5* Diagnostic Criteria for Major Depressive Disorder[a]

A. Episode must include
- **Five or more of the 9 symptoms in Box 3-6**
- **Symptoms that present during the same 2-week period**
- **Symptoms that represent change from previous functioning**
- **Symptoms that present nearly every day (except weight change and suicidal ideation)**
- **At least one symptom that is depressed or irritable mood or loss of interest or pleasure**

B. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. Episode is not attributable to the physiologic effects of a substance or to another medical condition.

D. Episode is not better explained by another major psychiatric disorder, such as a psychotic disorder.

E. There has never been a manic episode or a hypomanic episode.

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

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Differential Diagnosis

Differential diagnosis of MDD in youth can be a challenge. A child who is demoralized by various family, social, medical, peer, academic, or other problems can exhibit many of the symptoms of MDD. Demoralized children often have mood and cognitive symptoms identical to those in children with MDD, but neurovegetative symptoms are less likely to be present. Grief can also mimic MDD. The prominent affect in grief is feelings of emptiness or loss, in contrast to depressed mood or the inability to anticipate happiness or pleasure in MDD. Trauma- and stress-related disorders, such as adjustment disorder with depressed mood, may also mimic MDD. The essential distinguishing feature of adjustment disorder is an identifiable stressor that precedes the mood symptoms.

Safety Assessment and Monitoring

It is important to ask about suicidal ideation and other types of self-harm. Questions about potential suicide can start with asking about passive death wishes, such as, "Are you feeling that life is not worth living? Would it be OK if you fell asleep and never woke up?" If there is a positive response, or additional concern, ask about vague thoughts of suicide, such as, "Have you thought about ending your life? What would you do?" Additional questions

can elicit details of a suicide plan, such as, "How long have you been thinking about this plan? Have you talked to anyone about your suicidal thoughts and plan?" Although this chapter is not about treatment, positive responses to these questions require a treatment plan that ensures a patient's safety, as described in Chapter 2.

Other types of self-harm, such as superficial cutting or hitting oneself, may not be associated with suicidal ideation. Youth often describe these behaviors as relieving tension and providing short-term sense of comfort. These self-harm behaviors may be associated with mood dysregulation and severe anxiety. Treatment of these behaviors requires skill and time that typically is beyond that of a primary care staff and setting. Thus, identification and referral are usually indicated.

Safety of the home needs to be established, including limiting access to weapons, potentially lethal medications, and other objects and substances that could facilitate a suicide attempt.

The parent's ability to monitor a patient needs to be carefully evaluated; suicide attempts usually occur when the child is not being monitored. Evaluation of safety needs to include inquires such as, "What would you do if you had thoughts or urges to make a suicide attempt? Whom would you inform of such thoughts or urges?" A child's inability or unwillingness to provide reassuring responses to these questions may indicate that it is not safe to send the child home.

Recovery From an Episode

Recovery from an episode of depression often starts with improvement in neurovegetative symptoms, such as sleep, appetite, and energy. Improvement in cognitive symptoms—feelings of worthlessness or guilt and suicidal ideation—usually occurs later. The period between improvement of neurovegetative symptoms and improvement of cognitive symptoms is considered a period of high risk for suicide attempts because a patient may have more energy and vitality to act on lingering suicidal thoughts. Thus, it is important to inform a patient and family about the risk of emergence of suicidal thoughts and behaviors during recovery, whether (or not) medication is part of the treatment.

Assessment of Common Comorbidities

The presence of other comorbidities typically makes feedback, treatment, and monitoring of outcome more complex. The presence of comorbidities may also increase the need for specialty consultation and comanagement. Common comorbid disorders include the following.

Disruptive Behavioral Problems and Disorders

Disruptive behaviors, except for severe aggression and major antisocial acts, rarely occur without the presence of other mental health conditions. Maladaptive aggression/disruptive behavior is to mental health professionals what a fever is to primary care clinicians. It is a symptom suggesting there is a problem that requires further assessment to discover the underlying cause, likely another mental health disorder, such as ADHD, depression, other mood disorders, and adjustment disorders. In addition, children with disruptive behaviors often receive negative attention from caregivers, siblings, peers, and others; the result is a feedback loop that unintentionally reinforces and sustains the disruptive behaviors.

Clinicians often see children with disruptive behavior as their chief complaint, before a mental health diagnosis has been identified. In these instances, it is important to get a detailed assessment to understand why the behavior is occurring. The first step is to ensure there are no safety concerns. It is then important to be specific in defining the actual behavior that is causing distress. Further questions about the behavior should include what triggers it, what the consequences are after the behavior, where the behavior occurs (ie, school, home, playground), how long it lasts, what worsens it, and if there is anything that relieves it. Clinicians can provide first-line guidance by suggesting parenting interventions that use positive reinforcement strategies instead of responding in ways that reinforce the disruptive behavior.

There is considerable controversy about the validity of "pure" disruptive behavioral diagnoses. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), included a diagnosis that was commonly used to codify mild-to-moderate disruptive behaviors: *disruptive behavior disorder not otherwise specified* (NOS). In *DSM-5*, disruptive behavior disorder NOS was eliminated and replaced with 2 diagnostic options for youth with mild-to-moderate disruptive behaviors: 1) *other specified disruptive, impulse-control, and conduct disorder,* and 2) *unspecified disruptive, impulse-control, and conduct disorder*. The former (*other*) is used when a specific reason for not meeting diagnostic criteria can be or is provided

(eg, recurrent behavioral outbursts of insufficient frequency) (*DSM-5,* page 479)[1]; the latter (*unspecified*) is used when a specific reason cannot be or is not provided. The names of these diagnoses are long and cumbersome. More problematic is that these "default" diagnoses provide no specific diagnostic criteria appropriate to children. Further, they are the default diagnoses for conduct disorder and intermittent explosive disorder, which are severe, rare in children, and relatively uncommon in adolescents. For more information on the assessment and treatment of aggression, refer to T-MAY (see Appendix B).

Behavioral and Mood Disorders

Oppositional defiant disorder has a pejorative name that highlights "bad" behavior. However, ODD has 3 domains: angry or irritable mood (3 symptoms), argumentative or defiant behavior (4 symptoms), and vindictiveness (1 symptom). At least 4 symptoms lasting at least 6 months are required to meet diagnostic criteria. A diagnosis of ODD can be useful in helping parents and caregivers understand this pattern of negative behavior that can result in significant parenting stress. However, the diagnosis does not absolve the caregivers from taking responsibility for supporting and participating in treatment to reduce the symptoms of ODD. The NICHQ Vanderbilt Assessment Scales (see Appendix A) include items that can serve as a screener for ODD, which occurs commonly in children with ADHD.

In an extreme example of primarily mood symptoms, a child could receive a diagnosis of ODD by having 3 mood symptoms and only 1 behavioral symptom, such as "*often* blames others for his or her mistakes or behaviors." At the other extreme, a child could receive a diagnosis of ODD with 4 behavioral symptoms and no mood symptoms. Thus, it is important for the clinician and caregivers to focus on the specific problematic symptoms when developing a plan for treatment. The symptoms and diagnostic criteria for ODD are in Boxes 3-8 and 3-9.

The estimated prevalence of ODD is about 3%, indicating that it is a common disorder.[1] Of note, symptom severity in children with ODD is reduced considerably in response to treatment of comorbid disorders, particularly ADHD.[7] Behavioral management training for caregivers—training parents in behavioral principles so that they can alter their interactions and change reinforcers that happen in daily living—is almost always effective.

Box 3-8. Simplified *DSM-5* Symptoms of Oppositional Defiant Disorder[a,b]

Angry or Irritable Mood
• **Loses temper** • **Touchy or easily annoyed** • **Angry and resentful**
Argumentative or Defiant Behavior
• **Argues with adults** • **Actively defies or refuses to comply with requests from authority figures or with rules** • **Deliberately annoys others** • **Blames others for his or her mistakes or misbehavior**
Vindictiveness
Spiteful or vindictive

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] Frequency of symptoms must be *often*, except for vindictiveness, which is at least twice within the past 6 months.

[b] For the full *DSM-5* diagnostic criteria, see Appendix F.

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Disruptive mood dysregulation disorder (DMDD), a new diagnosis in *DSM-5,* has an estimated 6- to 12-month prevalence of 2% to 5% (Box 3-10).[1] Before *DSM-5*, there was considerable controversy about how to diagnose bipolar disorder in children and adolescents who did not meet criteria for bipolar disorder but did have mood instability or irritability and behavioral outbursts. Mood disorder NOS in *DSM-IV* became the default diagnosis for these youth. At the same time, there was concern about excessive and inappropriate diagnosis of bipolar disorder in youth, especially preteens. Subsequent research identified a group of children and adolescents with chronic irritability and intermittent disruptive behaviors. The proposed label for this group was severe mood dysregulation.[8,9] Disruptive mood dysregulation disorder is based, largely, on research about severe mood dysregulation.

The core features of DMDD are chronic, severe, and persistent irritability and frequent temper outbursts. The outbursts can be verbal or physical (or both), including aggression against property or individuals. Chronic DMDD is defined as "persistently irritable or angry most of the day, nearly every day" (*DSM-5,* page 156).[1] The chronicity of irritability is what differentiates DMDD from ODD, MDD, or bipolar disorder, all of which can include irritability that is episodic or periodic but not chronic.

Box 3-9. Simplified *DSM-5* Diagnostic Criteria for Oppositional Defiant Disorder[a]

Symptom and Duration Criteria[b]
• **Persistent pattern of angry or irritable mood, argumentative or defiant behavior, or vindictiveness**
• **Lasting at least 6 months**
• **With at least 4 symptoms from Box 3-8**
• **Exhibited during interaction with at least one individual who is not a sibling**
Functional Impairment Criteria
• **Distress in the child or others in his or her immediate social context (eg, family, peer group, fellow students)**
• **Negatively affects social, educational, or other important areas of functioning**
Exclusion Criteria
• **Behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder.**
• **Criteria are not met for disruptive mood dysregulation disorder.**
Severity
• ***Mild:* Symptoms confined to only one setting (eg, at home, at school, with peers).**
• ***Moderate:* Symptoms present in at least 2 settings.**
• ***Severe:* Symptoms present in 3 or more settings.**

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

[b] Persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 years, the behavior should occur on most days for a period of at least 6 months, except for vindictiveness. For children 5 years or older, the behavior should occur at least once per week for at least 6 months, except for vindictiveness.

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Children and adolescents with DMDD are at risk of developing depression or anxiety disorders (or both) in adulthood. Risk of later development of bipolar disorder is small. Because *DSM-5* first appeared in 2013, research on evidence-based treatments is not widely available.

Other Comorbid Disorders

Adjustment disorders with depressed mood, anxiety, disturbance of conduct, or any combination of these 3 symptoms are common in children and adolescents. The core feature of an adjustment disorder is the development of clinically significant emotional or behavioral symptoms within 3 months of an identifiable stressor. Of note, a recent identifiable stressor does not preclude another diagnosis instead of or in addition to an adjustment disorder

Box 3-10. Simplified *DSM-5* Diagnostic Criteria for Disruptive Mood Dysregulation Disorder[a]

Symptom Criteria
Severe recurrent temper outbursts • **Manifested verbally (eg, verbal rages), behaviorally (eg, physical aggression toward people or property), or both** • **Grossly out of proportion in intensity or duration to the situation or provocation** **Temper outbursts** • **Are inconsistent with developmental level** • **Occur, on average, ≥3 times per week** **Mood between temper outbursts** • **Persistently irritable or angry** • **Most of the day** • **Nearly every day** • **Observable by others (eg, parents, teachers, peers)**
Duration, Setting, and Onset Criteria
Symptom criteria (above) have been present • **Twelve or more months** • **Without a period of ≥3 consecutive months without symptom criteria met** **Symptom criteria are** • **Present in at least 2 of 3 settings (ie, at home, at school, with peers)** • **Severe in at least 1 of these settings** **Diagnosis should *not* be made** • **First time before age 6 years or** • **After age 18 years** **Age of onset is before 10 years by history or observation.**
Exclusion Criteria
• **Manic or hypomanic episode** • **Not exclusively during major depressive episode** • **Not better explained by another mental disorder** • **Not attributable to substances or medical or neurologic conditions**

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

[a] For the full *DSM-5* diagnostic criteria, see Appendix F.

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(eg, ADHD, an anxiety disorder, MDD, ODD, DMDD). Adjustment disorders are common and can accompany any medical condition, but prevalence estimates are inconsistent.

Substance use disorders are common in adolescents. Estimated 12-month prevalence of alcohol use disorder is about 5% in 12- to 17-year-olds.[1] Estimated 12-month prevalence of cannabis use disorder is 3.4% in

12- to 17-year-olds.[1] Prevalence of use disorders for other drugs in adolescents is much lower.

As noted previously, for preteens and adolescents, substance use screening is recommended. The CRAFFT (car, relax, alone, forget, friends, trouble) substance abuse assessment questionnaire is a validated, brief pediatric screening tool (www.ceasar-boston.org/clinicians/crafft.php).

Successful assessment and treatment of any psychiatric disorder is difficult, if not impossible, if there is significant ongoing substance use. These situations may require referral to a substance use specialist or program. Of note, successful treatment of ADHD reduces the risk of substance use.[10]

Learning disabilities or disorders, mild intellectual disability, and *communication disorders* may be identified and diagnosed during health supervision visits or by caregivers or school personnel. Confirmation of these conditions requires formal testing, which should be provided by the child's school system. For further evaluation of a child with suspected learning disability or disorder, intellectual disability, or a communication disorder, consultation and collaboration with specialists in neurodevelopmental disorders is recommended. The prevalence of specific learning disorders across the academic domains of reading, writing, and mathematics ranges from 5% to 15%.[1] The prevalence of intellectual disability is about 1%.[1]

Sleep disorders include insomnia, sleep apnea, narcolepsy, and restless legs syndrome. Insomnia is the most common pediatric sleep disorder. The core symptom of insomnia is an inability to fall or stay asleep that can result in functional impairment throughout the day (www.cdc.gov/features/sleep). Insomnia cannot be attributable to the physiologic effects of a substance or coexisting mental disorders or medical conditions. Insomnia is one of the 9 core symptoms of an MDD. Insomnia, especially difficulty falling asleep, is a common symptom of anxiety disorders. Insomnia often abates when depression and anxiety are treated. Thus, a primary diagnosis of insomnia is usually made if sleep disruption continues after treatment of medical and mental disorders. Consultation with a pediatric sleep specialist is recommended when primary insomnia is suspected.

Assessment of Less Common Comorbidities

Less common disorders, which have a prevalence of less than about 1% in children and adolescents, are usually severe and quite impairing and can be recognized, or at least suspected, because of unique characteristic symptoms.

Some of these less common disorders and characteristic symptoms are

- Autism spectrum disorder: Social communication deficits and restricted repetitive behaviors or interests
- Schizophrenia: Hallucinations, delusions, disordered thinking
- Bipolar disorder: Manic episodes
- Eating disorders: Weight loss, food restriction, bingeing, purging
- Conduct disorder: Behavior violating others' rights and social norms
- Posttraumatic stress disorder: Intrusive memories, dissociative experiences, and avoidance or arousal symptoms in response to exposure to actual or threatened death, serious injury, or sexual violation
- Obsessive-compulsive disorder: Obsessions or compulsions (or both)
- Gender dysphoria: Incongruence between experienced/expressed gender and assigned gender

If these or similar comorbidities are suspected, referral to a specialist for a full evaluation and treatment is recommended.

Determine if Medication Is Indicated

Medication-responsive disorders are those for which there is sufficient empirical evidence of a clinically meaningful reduction of symptom severity in response to medication. It is critical to ensure that a child who may benefit from medication is offered a trial and to ensure that a child who will not benefit from medication is not offered a needless trial.

Even with an accurate diagnosis and evidence-based treatments, there is no completely sensitive and specific way to determine which individual child will respond to which medication or any other evidence-based therapy for psychiatric disorders; nor is there a way to predict what type of adverse effect may emerge and who will experience any adverse effects.

Uncertainty underlying these issues presents clinical challenges for the prescribing pediatric PCC. A relatively simple approach to assessing whether to recommend medication is outlined in Box 3-11. It emphasizes symptom severity and duration, impairment and distress, differentiation from "normal," and prior or concurrent evidence-based behavioral therapies. This approach approximates the American Psychiatric Association *DSM-5* in essential components or criteria, and practice guidelines for behavioral therapies.

Box 3-11. Assessing Whether to Prescribe Medication

1. **Does the child have sufficient symptoms to support a syndrome or disorder?**
2. **Have the symptoms been present for a sufficient period?**
3. **Is the child experiencing sufficient impairment, distress, or both from the symptoms in ways that negatively affect academic development, family life, interactions with peers, participation in activities, or emotional well-being?**
4. **Is this disorder sufficiently different from normal levels of activity and impulsivity (in contrast with ADHD), worry and concern (in contrast with an anxiety disorder), or demoralization or grief (in contrast with an episode of depression)?**
5. **Have evidence-based therapies (eg, behavioral management training with parents for ADHD; cognitive-behavioral therapy for anxiety or depression) been sufficient in quality and duration, if available?**

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

The term *sufficient* (or *sufficiently*) appears in each of the criteria or components in Box 3-11. Thus, the pediatric PCC must judge whether symptoms cross a threshold of severity that warrants a recommendation for medication.

In addition, age is an important consideration when deciding whether to recommend medication. In general, the younger a patient, the more important it is to consider and prescribe behavioral therapies and other psychosocial interventions before medication (see Chapter 4). This is particularly relevant for any child aged 5 years and younger.

Recognize Need for Referral

There are situations in which referral to a range of specialists (eg, child and adolescent psychiatrist, developmental behavioral pediatrician, school psychologist, licensed clinical social worker) could be beneficial, including

- Children with diagnoses for which specialized treatment in the mental health system of care is generally available, such as autism, schizophrenia, and bipolar spectrum disorders, and which often require Group 2 and/or Group 3 medications
- Children with undiagnosed intellectual disabilities, communication disorders, or learning disabilities with significant mood or behavioral problems
- Children with complex differential diagnoses
- Children who have parents or caregivers with mental health or substance use issues, cognitive impairment, or significantly impaired parenting skills
- Children who have been maltreated or exposed to significant childhood adversities

Youth with undiagnosed learning disabilities or cognitive impairment may also present with significant mood or behavioral problems. These problems may be related to school maladjustment (eg, symptoms occur primarily in a school setting, not at home, because of a mismatch between the educational setting and the child's learning needs). Parents may benefit from referral to family advocacy programs or support programs in their school system for information on obtaining evaluations for learning disabilities and advocating for disability services. It can be very difficult to obtain formal cognitive testing, because waiting times may be long, schools may be reluctant to certify the need for testing, and consultations in the community may be prohibitively expensive for some families. In the meantime, pediatric PCCs may be able to help by providing referral to appropriate advocacy organizations, destigmatizing academic difficulties, troubleshooting homework habits, and identifying opportunities for additional academic support (family, peer, or school-based coaching or tutoring).

When differential diagnosis is complex, the pediatric PCC and family may choose to involve a mental health specialist in the assessment process. In most communities, licensed nonmedical mental health specialists (eg, licensed clinical social workers, psychologists) are more accessible than child and adolescent psychiatrists. Such nonmedical mental health specialists are qualified to assist in assessment and diagnosis of children and adolescents with mental health problems, and may be integrated into the primary care clinical team. In addition to confirming a diagnosis, this nonmedical specialist can provide psychosocial treatment and may be able to facilitate the pediatric PCC's consultation with a child and adolescent psychiatrist, as needed, to assist with medication decisions.

Some children have parents with mental health or substance use issues, cognitive impairment, or significantly impaired parenting skills; others have been maltreated or exposed to significant childhood adversities. Those youth may need a more thorough evaluation by a mental health professional or resources and support from the mental health system (or both). If a parent's mental illness is affecting the child's mental health, referral of the parent, for his or her own care, is typically warranted. Pediatric PCCs may want to think about how to approach these situations, including 1) finding time to talk with the parent alone, 2) making sure that the parent knows a motivation of the inquiry is to help the parent to optimize her/his well-being to help the child do her/his best, and 3) being able to offer some practical first-line advice as well as concrete suggestions about how to approach finding care.

Formulation

Formulation refers to how the clinician "puts the case together." Reminiscent of math teachers who say "show your work," the written formulation should show the reader what elements of the history you have extracted as important and how you are connecting them. The reader (another clinician or the family) can then follow your reasoning and understand how you arrived at your diagnosis and treatment plan.

A clear formulation tells a story about why this specific patient (including temperamental strengths and vulnerabilities) is presenting at this specific moment in time (including stressors and life events) in this specific way (including signs, symptoms, and concerns).

A brief formulation might highlight these elements as follows:

> *The patient is a 9-year-old girl with a family history notable for reported yet untreated maternal anxiety, a personal history notable for a shy temperament and high intelligence, who now presents with persistent worries, difficulty falling asleep, school avoidance, upset stomach, and worsening concentration in the context of a family move into a new setting and more competitive school. Her presentation appears most consistent with a diagnosis of generalized anxiety disorder superimposed on a mildly anxious temperament in a household in which anxious behaviors are frequently modeled.*

Feedback

Presenting feedback about your mental health assessment to a youth and family requires skill and practice. The trusting and often longitudinal relationship between pediatric PCCs and their patients is an important factor in reducing the stress and discomfort that families often experience when discussing these types of sensitive topics. Key points in the feedback process are described as follows.

Emphasize Positive Attributes

The pediatric PCC can strengthen engagement with the caregiver(s) and child by reviewing positive attributes of the child and family and highlighting these as protective factors for the child. It is worth noting that both short- and long-term outcome are greatly influenced by positive attributes.

Review Key Points of the History

A brief review of the history can be helpful in allowing the family to feel heard and knowing that the PCC has "gotten it right" before embarking on a formulation, diagnosis, and subsequent treatment plan. This can also help reduce resistance going forward as potentially sensitive diagnoses or interventions are presented.

Normalize the Feedback Experience

Families should be aware that mental health problems are common in children and are not the result of character flaws or bad parenting. If medication is being considered, presenting the disorder as similar to other medical illnesses that respond well to medication (eg, asthma, strep throat) helps normalize the feedback experience and minimize blame and guilt.

If there is another family member(s) who has the same diagnosis as the identified child, and particularly if this family member has responded well to treatment, reviewing his or her experience can help normalize the diagnosis and offer real hope regarding outcome. Conversely, if a family member has not responded well to treatment, it may be helpful to differentiate that family member's experience from the present circumstances.

Several facts cannot be stated too often: common disorders are common; many children and adolescents have them; most do well; and the prognosis, especially for ADHD, anxiety, and depression, is generally positive.

Prioritize Problems and Diagnoses

If more than 1 problem or diagnosis will benefit from treatment, it is important to discuss which to address first and why. Prioritization can be influenced by multiple factors, such as 1) safety concerns, (eg, suicidal thinking), 2) family preference, 3) ease of treatment, and 4) risk of not treating. Treatment prioritization is an ongoing and collaborative process and may change over time depending on a patient's response to the initial treatment plan. Thus, treatment targets should be updated over time.

Discuss Prognosis

Partnering with the child and family is the first step in the discussion of prognosis. For most children, and for most common disorders, the prognosis is positive with treatment. When the initial treatment is not effective, reconsideration of prognosis will be easier if the family knows the clinician is partnering for "the long haul." Response to short-term treatment can improve the validity of long-term prognostication.

Emphasize Success of Treatments

Emphasize that evidence-based treatments, both medication and psychotherapy, are highly effective. Most patients who adhere to treatment improve substantially. Defining goals that are important to the child and family will also help improve engagement and treatment. Rating scales can be useful for monitoring goals. Similarly, when several treatment options are present, presenting a brief "menu of options" can allow for individualized treatment plans tailored to the needs and preferences of the family. Introducing the concept of shared decision-making can also be helpful.

Clarify Plans

If there is a need for additional evaluation, whether by the pediatric PCC or a specialist, or both, that need should be explained. Knowing that other professionals will be involved in the evaluation process (and treatment) may be reassuring to the family. Even if other professionals will be involved, families are often reassured to know that the pediatric PCC is available to provide support throughout the evaluation and treatment process.

Patient(s) and caregiver(s) will want to know who will be in the circle of communication (eg, school personnel, mental health specialists, other family members). It is important to describe the nature of the communications and confidentiality and to address any concerns. Communication between the pediatric PCC and mental health specialist is recommended so that a patient's care can be best coordinated between the medical and mental health systems.

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CHAPTER 4

Before Prescribing

Pediatric primary care clinicians (PCCs) have knowledge, skills, and experience in pediatric pharmacology, and, to varying degrees, pediatric psychopharmacology. Primary care clinicians may find pediatric psychopharmacology more challenging than general pharmacology for a few different reasons, all of which can be addressed. These reasons include 1) the need to know and utilize, usually through referral, effective nonmedication interventions, 2) chronicity of care necessitating regularly updated informed assent and consent, and 3) impact of the patient and family's ideas, concerns, and expectations about mental disorders and medication. This chapter focuses on these potential challenges and includes a summary of important considerations for safe and effective prescribing of psychotropic medications.

Nonmedication Interventions

Nonmedication interventions include 1) relationship building and psychoeducation, 2) brief interventions in the primary care office, 3) pragmatic support, and 4) evidence-based psychotherapy by mental health professionals. In many cases, nonmedication interventions may be preferred by both the family and clinician over the use of medication. For example, guidelines recommend at least 2 trials of psychosocial treatment before starting medication for preschool-aged children.[1] Many children and adolescents present to pediatric PCCs with mild symptoms (ie, they meet diagnostic criteria, but their impairment is minimal) or subthreshold symptoms (ie, they do not meet diagnostic criteria for the disorder but report more than minimal impairment). In general, such a child is likely to benefit from an evidence-based psychosocial intervention and may not need medication. Mental health specialists (psychologists, social workers, counselors, etc) often provide these services, either in their own office after a referral is made or increasingly through integrated mental health services within the primary care office. Given their clinical expertise, pediatric PCCs are often able to

adapt successful strategies used by mental health specialists to use in their own practice, either to address mild symptoms that do not require referral or to address more severe symptoms while the family is waiting for their first mental health appointment.

Relationship Building and Psychoeducation

For pediatric PCCs, nonmedication interventions—before and during medication treatments—are important across multiple aspects of care. Patients and their families need to feel comfortable sharing their concerns about the child's diagnosis and potential interventions to develop an effective treatment plan. This *relationship building* between the PCC and the patient/family allows for important and sensitive conversations to occur. For example, the family may have beliefs and worries about mental disorders and medication treatments, possibly heightened because of stigma; the potential for negative impact of psychotropic medication on the developing brain; and controversy and confusion about medication that abound on social and other media. The Common Factors approach[2] recognizes that certain characteristics of care, common to almost all conditions, support this relationship.[3] The American Academy of Pediatrics (AAP) has developed the mnemonic HEL^{2}P^3 to illustrate these characteristics: hope, empathy, language, loyalty, partnership, permission, and plan.

Given their role as a trusted member of the care team, PCCs also have a unique opportunity to provide information about mental health conditions, often referred to as psychoeducation. Important messages include that mental disorders are common (normalization), that effective and safe treatments are available, and that healthy habits, like good nutrition, sleep and exercise, and reducing overall stress, are all important in promoting overall health and wellness. Psychoeducation about the assessment process and the meaning of diagnoses such as attention-deficit/hyperactivity disorder (ADHD), an anxiety disorder, or major depressive disorder (as described in Chapter 3) can be helpful to caregivers. Also useful are resources and guidance to help caregivers (and teachers) understand basic information about medications that are considered and/or prescribed.[4]

Brief Interventions in the Primary Care Office

A number of evidence-based practices (EBPs) have been found to be effective in the treatment of pediatric mental health conditions, including anxiety, depression, and disruptive behavior. While the delivery of these interventions

is likely out of the scope of many PCCs, some elements of EBPs can be easily adapted for use in primary care for children whose conditions do not yet rise to the level of a disorder or whose families are not yet ready to seek care from a therapist. For example, *common elements*[2] useful in the treatment of anxiety and depression come from the field of cognitive behavioral therapy, including coping skills and relaxation techniques. Behavioral management strategies, derived from evidence-based parent training programs, can also be implemented in primary care. Examples include teaching the use of descriptive praise to increase desirable behaviors and planned ignoring to discourage minor misbehavior.

Pragmatic Supports

Pragmatic supports refer to social, economic, and academic resources that enhance the likelihood that the overall treatment plan will succeed. Examples include academic tutoring, parent-to-parent support groups, funds for transportation to psychotherapy sessions, and assistance in addressing other environmental and socioeconomic issues that influence mental health, such as poor-quality child care, food insecurity, poverty, and unsafe housing. For more information on evidence-informed pragmatic supports, see Appendix C.

Evidence-Based Psychotherapy by Mental Health Professionals

Evidence-based psychotherapies are administered by trained therapists using detailed treatment manuals to guide regularly scheduled sessions (usually weekly) over 8 to 12 weeks or more. The most relevant and commonly prescribed evidence-based psychotherapies for common pediatric disorders (ADHD, anxiety, and depression) are behavior management training for parents or caregivers and cognitive behavioral therapy for the child or adolescent.

In general, psychotherapies are labor and time intensive. They require commitment from the parent or caregiver and specific training and availability of the therapist. An extensive listing of virtually all known psychotherapies for youth is provided by PracticeWise to the AAP (www.aap.org/mentalhealth) and is updated at regular intervals; it does not reflect AAP policy. (See Appendix D.) For clinical practice purposes, the level 1 column (Best Support) is most relevant. It is important to be aware of the therapies in level 4 (Minimal Support) and level 5 (No Support), because these are still commonly used and are of no or very minimal documented benefit.

Evidence from large, multisite studies sponsored by the National Institute for Mental Health demonstrates the advantage of combining psychotherapy and medication treatment, over medication or therapy alone, for ADHD (ages 7–9 years),[5] common anxiety disorders (separation anxiety disorder, social phobia, generalized anxiety disorder; ages 7–17 years),[6] and depression (ages 12–17 years).[7] The additional effect of combined treatment over only medication or psychotherapy is clinically meaningful and ranges in impact across individual children and families. Psychotherapy alone may be preferred over medication or combination treatment for initial care of mild symptoms.

Despite clear effectiveness of various evidence-based psychotherapies and the pressing need for them, too few mental health clinicians—including clinical psychologists, social workers, nurse practitioners, certified counselors, and some child and adolescent psychiatrists—have training and experience to provide high-quality evidence-based psychotherapy. Families also face many administrative and financial barriers to access, including insurance constraints and missed time from work or school.

Unfortunately, there are no quick, brief, effective, evidence-based psychotherapies designed for primary care practice that have been successfully disseminated and broadly implemented. Among the best currently available is the Triple P, Positive Parenting Program, which offers a brief, evidence-based intervention aimed at primary care, though dissemination has been limited.[8–10] Web-based therapies are options when "live" therapy is not accessible or when preferred by patients/families.[11,12]

Because of these potential challenges, pediatric PCCs may be faced with the dilemma of whether to prescribe medication without the provision of psychotherapy. In these situations, it is important to have a frank discussion about the risks and benefits of treatment with the child and family. Pediatric PCCs can join with families and mental health specialists in their communities to advocate for evidence-based psychotherapies in both public and private systems of care, including schools. Information and resources about evidence-based and commonly used nonmedication interventions are in Appendix D.

Informed Consent

Medications indicated for common psychiatric disorders—ADHD, anxiety, and depression—are usually prescribed long term (up to 1 year or more). Thus, in addition to the initial consent process, informed consent should be an ongoing process that unfolds over time as the patient and caregiver(s) develop new questions and concerns about medication(s). Attention-deficit/hyperactivity disorder is a chronic disorder that may require years of medication treatment, though drug holidays may be possible, eg, during the summer or weekends. Anxiety is usually chronic, with a waxing and waning course, and usually requires treatment over several months or longer. Depression is an episodic disorder. To prevent relapse, medication treatment is usually recommended for at least 1 year.

Informed consent and assent have 2 aspects: the medicolegal consent document and the clinical consent process.

Medicolegal consent documentation appears to vary widely, including such practices as[13]

- Use of a specific required form that must be completed (a practice that is likely to expand with increased use of electronic records, particularly in large health care systems)
- Required written documentation without a specific required form
- No documentation of consent

The American Academy of Child and Adolescent Psychiatry practice parameters on the use of psychotropic medication in children and adolescents"[14] provides detailed information about the process of consent but is silent regarding documentation.

For clinical consent, the basic *process* of obtaining informed consent and assent is the same, regardless of the psychotropic medication recommended. A description of domains to cover in the consent process is in Box 4-1. Completing this process requires considerable time and effort and is clearly a challenge, given the time and payment limitations in primary care. However, the course of treatment is likely to be easier if the initial consent process is clinically sound and comprehensive.

Box 4-1. A Clinical Approach to the Process of Informed Consent for Psychotropic Medication

1. Preparation
- Conceptualization of signs and symptoms as illness.
- Think job performance (home, school, friends).
- Think development (emotional, behavioral, social, cognitive).
- What are the risks of not treating with medication?

2. Take the patient's and family's pulse
- Discuss beliefs and concerns.
- Include stigma as part of discussion.

3. Evidence supporting short-term efficacy and effectiveness
- A level: 2 (or 1 if sufficiently worthy) placebo-controlled, random-assignment studies[a]
- B level: 1 placebo-controlled, random-assignment, properly implemented study
- C level: information from open-label studies, case reports, etc

4. Alternative or additional treatments
- Evidence-based psychotherapies
- Community, family, and school-system support
- Other medications

5. Adverse effects and potential effects during pregnancy
(see subsection below)

Severity	Change needed	Examples
Mild	Requires no change	Dry mouth, transient nausea
Moderate	Requires dose change	Sedation
Severe	Requires stopping drug	Real suicidal ideation or attempt

6. Potential long-term adverse effects
- Examples: Growth deceleration (stimulants), diabetes mellitus, or tardive dyskinesia (antipsychotics)
- Unknown

7. Pharmacokinetic issues
- Convenience: Once-daily dosing preferred, no laboratory monitoring preferred
- Drug-drug interactions: especially involving hepatic CYP450 isoenzymes

8. Adherence
Importance of establishing a convenient daily routine for taking the medication

9. Cost
- Generic versus brand
- Insurance coverage
- This drug versus others in class

10. Family preferences and questions
Given the information listed here, what are the family's preference(s) and questions?

Bottom Line: Your Opinion About Benefit-to-Risk Ratio for This Patient
- Taking into consideration all of the above, what do you recommend?
- Why?
- Think: If this were your child, what would you do?

[a] This applies to all Group 1 medications for attention-deficit/hyperactivity disorder, anxiety, and depression.

It is important to establish a timeline for reevaluating medication efficacy and adverse effects and to note that consent can, and will, be revisited in light of the patient's initial and ongoing responses to and experiences with the medication, both positive and negative. Thus, consent is an ongoing component of an evolving clinical process.

Specific Consent Issues

Pregnancy

It is important to determine whether the patient is pregnant, as well as future plans regarding pregnancy. This can be done as part of the informed consent process and may also involve laboratory testing for pregnancy. Primary care clinicians routinely manage the risks that pregnancy and potential pregnancy may play in all aspects of their work with youth, ranging from advocacy and education to counseling and prescribing. How they handle those discussions with patients and with families will vary from clinician to clinician and patient to patient but typically should include discussions about safety and options. When working with youth with mental disorders, additional issues are worth noting. Some disorders, such as substance use disorders and bipolar disorder, may increase the likelihood of high-risk/low-caution behaviors. The chronicity of many mental health disorders means that medication may be taken for longer periods, thereby increasing the likelihood of lapses in caution around becoming pregnant. Age at onset of different disorders can also contribute to a mismatch between risk and protection: early-onset anxiety may not require a discussion, but that same child may initiate sexual activity and thus the informed assent/consent will need to be updated to include the discussion of pregnancy risk. Regardless of these specifics, it is important for all PCCs to have a basic understanding of the current knowledge base regarding the use of psychotropics in pregnancy and to work with psychiatrists and obstetricians regarding specific decisions. The information that follows is based on adult data but may be a useful framework for opening the dialogue with youth and families.

The following "rules of thumb" in designing a treatment plan for pregnant women with mental disorders are from a recent review article: 1) all changes to drugs should be carried out before pregnancy, if possible; 2) ideally the patient should be stable psychiatrically for at least 3 months before trying to get pregnant; 3) use drugs that we know something about, such as

Group 1 medications—fewer data are available for recently approved drugs; 4) minimize the number of exposures for the infant; 5) use a team approach that includes the psychiatrist and obstetrician, if possible; and 6) be supportive if the patient goes against the team's recommendations.[15]

About 15% of pregnant women have a mental disorder and 10% to 13% of fetuses are exposed to a psychotropic (psychiatric or neurologic) medication. Women with mental disorders can experience relapse during pregnancy, especially if their medications for mental disorders are discontinued. The rate of major birth defects in the general population is about 3%. Less than 1% of these defects are considered secondary to exposure to medication of any type or class.[15]

In June 2015, the US Food and Drug Administration (FDA) initiated a new format for the label (or package insert) with new subsections on pregnancy and lactation. These subsections have the following 3 components: a risk summary, clinical considerations, and a data section. The third subsection is entitled "Females and Males of Reproductive Potential." The new labeling applies to all new medications and is being phased in for older medications.

Antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), are the most commonly prescribed psychotropic medications during pregnancy. Selective serotonin reuptake inhibitors have by far the most available data regarding risk to the fetus. The potential complications of SSRIs include modest increased risk of spontaneous abortion or preterm birth and low birth weight, no confirmed risk of birth defects except possibly for paroxetine in the first trimester, poor neonatal adaptation syndrome with third-trimester exposure, and probably no risk of persistent pulmonary hypertension with third-trimester exposure. However, large studies that attempt to control for the underlying mental disorder generally suggest no increased risk.[15]

Fewer data are available for stimulant medications. A recent large and innovative study that included data from 6 countries found a 28% increase in cardiac malformations in infants born to mothers who had filled prescriptions for methylphenidate during pregnancy, and no increase in infants of mothers who filled prescriptions for amphetamine preparations. No increase was found in overall congenital malformations for either medication.[16]

Even fewer data are available for other psychotropic medications, including the Group 2 and 3 medications described in subsequent chapters. Medications to be avoided, if possible, include lithium, valproate, carbamazepine, and benzodiazepines.

Adherence

Pediatric PCCs can set the stage for recurring discussions during treatment regarding adherence by providing information about adherence and nonadherence in a nonjudgmental manner before prescribing a medication. Emphasizing the importance of "tracking" medication adherence (ie, "Just keep me informed about how often [Jane] did or didn't get or take her medication; then we can work together to make decisions about [Jane's] care"), rather than emphasizing actual adherence (eg, "She needs to take the medicine at least 90% of the time") can facilitate openness about medication adherence. Asking about what barriers may interfere with taking medication may facilitate problem-solving. Although not always easy, it is important to establish a therapeutic approach in which children and parents understand that assessing adherence is part of the therapeutic process and will not lead to negative judgment.

Medications that are not ingested are not effective.[17] Unfortunately, rate of nonadherence in pediatric psychopharmacology is not well studied or documented, except for stimulants, for which data suggest high levels of nonadherence.[18] Parent reports of adherence to sustained-release stimulant preparations indicate nonadherence rates of about 10% to 25%. Even more concerning, a retrospective analysis of the Multimodal Treatment Study of ADHD[5] found that only 3% of parents reported that their child did not receive prescribed stimulant medication on the day of a study visit, whereas saliva samples indicated that 25% of children were nonadherent.[19] Higher levels of adherence were associated with greater improvement in ADHD symptoms. Taken together, studies of parent reports and salivary samples indicate that nonadherence to stimulant medication is an important clinical issue.

When the pediatric PCC strongly suspects nonadherence but cannot elicit a history confirming this suspicion, it is important to avoid confrontation and criticism. Improving adherence is not a simple or easy task.[18] Specific interventions for improving adherence,[20–25] referral to a specialist, or both may be useful. Continuing to increase dose in these situations is not recommended.

Off-label Prescribing

Before the mid-1990s, very few psychotropic medications had been approved by the FDA for pediatric indications (ie, approved for use in children younger than 18 years). Those approved included stimulants for ADHD, tricyclic antidepressants for enuresis, a few antipsychotics for psychosis, and lithium for mania in bipolar disorder. Thus, to treat psychiatric disorders in children and adolescents, it was often necessary to prescribe off-label medication.

Although many medications still lack FDA-approved pediatric indications across the age span, the number of pediatric indications has increased markedly over the past 20 years. This has occurred in response to federal legislation, including the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Also, the National Institute for Mental Health began funding large, multisite treatment studies in the mid-1990s.

Currently, a number of medications are available with indications for psychiatric disorders in children, including ADHD, depression, generalized anxiety disorder, obsessive-compulsive disorder, mania in bipolar disorder, psychosis in schizophrenia, and "irritability" in children with autism spectrum disorder. When prescribing these medications for other indications, and especially when prescribing a medication that is not indicated for any psychiatric disorder in children and adolescents, the pediatric PCC should carefully justify and document the rationale in the medical record.

US Food and Drug Administration Boxed Warnings

Two potential adverse effects of some medications used to treat ADHD, anxiety, and depression—suicidal thoughts or behaviors and drug abuse or dependence—can be concerning to pediatric patients and caregivers and have received boxed warnings from the FDA. Some context is provided later in this section for these boxed warnings, which need to be discussed during the initial informed consent process as well as in any ongoing dialogues about treatment. It is important to keep in mind that all adverse effects described in boxed warnings listed here occur infrequently and may never be seen by an individual pediatric PCC.

Antidepressants and Suicidal Thoughts and Behaviors

The FDA boxed warning about suicidality for all antidepressants is a perceived obstacle for many pediatric PCCs who consider prescribing SSRIs for anxiety, depression, or both. The boxed warning stating that all antidepressants pose significant risk of suicidality (suicidal ideation or suicide attempts, not completed suicides) in children and adolescents was issued in October 2004. The warning recommended close monitoring for increased suicidality. Specific recommendations for monitoring were described in a medication guide provided by the FDA. The medication guide is a descriptive handout provided by pharmacists to inform parents or patients of indications, proper administration, and potential adverse effects of or concerns about a prescribed medication.

The medication guide included specific guidelines for monitoring, as follows: "Your child should generally see his or her healthcare provider" weekly for the first 4 weeks, every 2 weeks for the next 4 weeks, at 12 weeks, and at the "health-care provider's advice" after 12 weeks. This prescriptive monitoring mandate presented a major barrier to the use of SSRIs in the primary care setting because this level of intense monitoring is not compatible with most primary care practices.

In May 2007, the FDA issued a revised medication guide that no longer includes specific mandates for monitoring (www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/ucm100211.pdf). Instead, it focuses on information parents need to know regarding suicidality and antidepressants. Thus, the boxed warning should be regarded as just a warning, not a restriction.

Antidepressant-induced suicidality is rare. The original FDA estimate, based solely on data from more than 4,300 research participants in 23 studies, was that 2% of children and adolescents receiving placebo and 4% receiving an antidepressant developed suicidal thoughts or attempted suicide.[26] Thus, the risk difference was 2%. A subsequent analysis, based on data from 27 randomized controlled trials involving more than 5,300 participants, found a significant risk difference of just 0.7%.[27] The most recent estimate, which was based on data from 35 randomized controlled trials involving more than 6,000 participants, found a risk difference of 0.9%, just missing statistical significance.[28]

The most recent, and presumably best, analyses suggest that there may be a very slight increased risk of suicidality with antidepressants in children and adolescents. Clinical prudence indicates the need to educate patients and parents about suicidality and to monitor carefully for suicidality and other adverse effects during the initial phase of treatment (when risk of suicidality is generally greatest from both depression and medication) and throughout treatment.

Stimulants and Concerns About Abuse and Dependence

The boxed warnings for amphetamines and methylphenidate state that they have a high potential for abuse and that prolonged administration may lead to dependence. Fortunately, there are no reports of children who were treated with therapeutic doses of stimulants developing dependence. Available data suggest that children with ADHD who are treated with stimulants are not more likely than those who did not receive stimulants to develop substance abuse later in life.[28–30] A related problem is diversion—that is, patients selling their prescription stimulants to be used as drugs of abuse.[31,32]

Important Considerations for Safe and Effective Prescribing

Box 4-2 provides an "ideal" list of important considerations for safe and effective prescribing of psychotropic medications by pediatric PCCs. Of note, not all of these considerations can be met in all primary care settings (eg, adequate reimbursement, access to expert consultation).

Box 4-2. Important Considerations for Safe and Effective Prescribing of Psychotropic Medications by Pediatric Primary Care Clinicians

The *prescribing physician* needs to have • **Competence and confidence in diagnosing common psychiatric disorders** • **Knowledge of available psychosocial treatments** • **Knowledge of medications prescribed** • **Procedures for monitoring medication effects and adherence**
The *disorder* for which medication is prescribed needs to be • **Sufficiently common to be seen regularly by a pediatric PCC** • **Efficiently and accurately diagnosable by a pediatric PCC**
The *medication* needs to • **Have demonstrated efficacy for the disorder** • **Be relatively safe, as assessed by several parameters (see Table 1-2)** • **Have adverse effects that are reasonably predictable, readily detected, and readily managed**
The *dosing and monitoring* of the medication need to **Generally follow FDA or AAP/AACAP guidelines**
The *system of care* needs to provide • **Access to pediatric psychopharmacology expertise for consultation on issues beyond the expertise of the pediatric PCC** • **Adequate payment for services rendered** • **Minimal administrative and regulatory barriers**

Abbreviations: AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; PCC, primary care clinician.

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Part 3—Group 1 Medications for Specific Diagnoses: Attention-Deficit/Hyperactivity Disorder, Anxiety, and Depression

CHAPTER 5

Group 1 Medications for Attention-Deficit/ Hyperactivity Disorder

General Guidance

Medications

Group 1 medications for attention-deficit/hyperactivity disorder (ADHD) belong to 3 different classes: stimulants, α_2-adrenergic agonists, and a norepinephrine reuptake inhibitor. The rationale for using specific medications from this class is presented in Chapter 1.

Stimulants

Despite numerous products available on the market, there are only 2 distinct stimulant chemical entities approved by the US Food and Drug Administration (FDA): *methylphenidate* and *amphetamine*. Both, in various preparations, are approved for treatment of ADHD in children and adolescents. The available literature has not shown advantages of different racemic mixtures (D- vs DL-). Thus, different racemic preparations are considered interchangeable, except for dose (eg, dexmethylphenidate preparations). Methylphenidate and amphetamine are available in various preparations that provide a treatment effect ranging from 3 to 12 hours. Products that have been on the market longer and have lower cost may be preferred.

α_2-Adrenergic Agonists

Guanfacine is FDA approved for treatment of ADHD in children and adolescents. It is relatively specific to the α_{2A}-receptor subtype, which is involved in attention regulation and impulse control. *Clonidine* is FDA approved for ADHD in children and adolescents. It interacts nonspecifically with α_{2A}-,

α_{2B}-, and α_{2C}-receptor subtypes. Given that B and C receptors mediate sedation, hypotension, and bradycardia adverse effects, clonidine may have a less favorable adverse effect profile than guanfacine; however, there are no direct comparative data regarding this issue. In addition, immediate-release (IR; not sustained-release) clonidine is associated with acute drops in heart rate and blood pressure, syncope, and even death following unintentional or intentional ingestions of more than therapeutic quantities.

Norepinephrine Reuptake Inhibitor

Atomoxetine, a norepinephrine reuptake inhibitor, is also FDA approved for ADHD treatment. It has more concerning FDA warnings and precautions than other medications for ADHD included in Group 1.

Reminder About Psychotherapy

Evidence-based and effective behavioral therapies for youth with ADHD include behavioral management training for parents or caregivers and school personnel and social skills training for patients with problems in social interactions.[1] In addition, consultation with school personnel is recommended.

In the United States, medication for ADHD is relatively common, whereas behavioral treatment is not. Recent data from the Centers for Disease Control and Prevention, focused on youth with special health needs,[2] indicate that 74% of youth with ADHD received medication *in the past week*, whereas only 44% received behavioral treatment *in the past year*. Only 31% received both past-week medication and past-year behavioral treatment, despite convincing research data indicating that a combination of medication and behavioral treatment leads to better outcomes.[3]

Choosing a Medication

Clinical guidance from the American Academy of Pediatrics (AAP)[4] and practice parameters from the American Academy of Child and Adolescent Psychiatry[5] recommend initiating medication with either of the stimulants, methylphenidate or amphetamine. The magnitude of improvement (relative to placebo) is greater for stimulants than other medications approved for ADHD. If there are concerns about starting with a stimulant (eg, specific potential adverse effects or parental preferences), guanfacine, clonidine, or atomoxetine are all secondary options with generally comparable therapeutic effect sizes.

For preschool-aged children, when medication is chosen, methylphenidate is recommended as the first medication for ADHD. To date, there is 1 National Institutes of Health–funded randomized, placebo-controlled study of any psychotropic medication for treatment of ADHD in preschool-aged children, the Preschool ADHD Treatment Study (PATS).[6] The PATS results indicate that, after a 10-week course of parent management training, IR methylphenidate, given 3 times a day in relatively low doses (optimal total daily dose ranged from 7.5–30 mg/day), was safe and effective in reducing symptoms of ADHD in 3- to 5-year-old preschoolers. A 10- to 20-week trial of parent management training, parent-child interaction therapy, or both is recommended before considering methylphenidate for preschoolers with ADHD.[7] An amphetamine preparation is recommended if methylphenidate is ineffective or needs to be discontinued because of adverse effects. A follow-up of PATS participants found that most continued to receive medications for ADHD, primarily stimulants, over a 6-year follow-up period.[8]

Adverse Effects: Boxed Warnings, Warnings and Precautions, and Adverse Reactions

Adverse effects can be evaluated based on either severity or frequency. FDA–required package inserts emphasize severity ranging from the most severe "Boxed Warnings" to the "Warnings and Precautions" followed by "Adverse Reactions." In addition, package inserts include contraindications and drug interactions.

Comprehensive prescribing information about adverse effects can be found in FDA-required package inserts. They are available in various formats and locations, including

- Medication packaging
- *The Physician's Desk Reference*
- Online at Drugs@FDA (www.accessdate.fda.gov)

Since the FDA modified the format a few years ago, each label, or package insert, has a 1-page "Highlights of Prescribing Information" that includes essential information about boxed warnings, warnings and precautions, adverse reactions, contraindications, and drug interactions. These highlights can be accessed and reviewed quickly and conveniently and are recommended as useful resources.

Cost and Affordability

Historically, generic medications for ADHD, particularly stimulants, have been inexpensive. Recently, this has changed, and ADHD medications are a significant factor influencing cost of care for many pediatric populations. In an effort to control medication costs, many Medicaid programs and some private health plans provide formularies from which prescribing clinicians must select medications. Each plan's cost per prescription for the medications on these formularies depends on its contracts with the pharmaceutical suppliers. Generic medications may be in the same price range as—or even more expensive than—branded medications for which the plan has negotiated a favorable contract.

For uninsured and underinsured children, and for children whose families must make a copayment at the time prescriptions are filled, the family's cost is a critical determinant of adherence. Responsibility falls to the prescriber to determine whether the family will experience financial barriers to filling prescriptions. Prescribers should inquire about the family's ability to purchase prescribed medications and should maintain an inventory of community resources for families unable to make copays or to purchase prescription medications. The staff of pediatric primary care clinicians (pediatric PCCs) can gather information about eligibility criteria and contact information for these resources. In some states, it may be necessary to refer the child to the behavioral health specialty system for the child to qualify.

Information for Caregivers About Specific Medications

There are numerous sources of information about medications for patients, parents, and caregivers(s), as well other professionals, such as teachers and school nurses, who may have questions about medications. It is important for pediatric PCCs to be aware that many Web-based sources are supported, at least in part, by the pharmaceutical industry. The FDA "Patient Counseling Information or Medication Guide" is a useful and potentially less biased document located at the end of each package insert (available online at Drugs@FDA [www.accessdate.fda.gov]). This document may be given to the family by the pharmacist for all dispensed prescriptions, including those filled via mail order. In addition, the prescribing clinician can print the document and review it with the caregiver or patient. This review may be most helpful if the pediatric PCC emphasizes the most concerning issues and most likely potential problems.

Methylphenidate

Available Methylphenidate Preparations

Table 5-1 contains detailed information for the 16 methylphenidate preparations available on the US market, including

- Type of preparation
- Estimated duration of action
- Trade name
- Recommended initial dose
- Recommended maximum dose
- Available forms of the medication

Information in the table relies on FDA-approved package inserts or, when specific information is not available, on the author's and contributing editors' recommendations.

The table is formatted to be relatively easy to use when seeking to gather comprehensive information about a specific medication: one can scan across the relevant row to find duration, initial dose, maximum dose, and available forms.

Dexmethylphenidate (Focalin) and dexmethylphenidate XR (Focalin XR) deserve additional consideration because recommended dosages are about one-half those of all other methylphenidate preparations.

Because all methylphenidate preparations are controlled substances in the United States, a written (or approved electronic) prescription can be issued for a maximum of a 30-day supply with no refills.

Onset of Effect

Onset of effect for all methylphenidate preparations is generally 30 to 45 minutes. Appetite suppression occurs concurrently with therapeutic effect. Thus, timing of morning medication and breakfast needs to be coordinated.

Duration of Effect

Four types of oral tablets and capsules are available. On average, IR preparations have a 3- to 5-hour duration of effect. The other 3 types have longer durations of effect, depending on technology used in the formulation:

Table 5-1. Methylphenidate Preparations

Formulation	Duration[a] of effect, h	Trade Name	Initial Dose, mg[b]	Max Daily Dose, mg	Available Unit Dose Forms
Immediate-release (tablet)	3–5	Ritalin Focalin[d]	5 and 5[c] 2.5 and 2.5[c]	60 20	5, 10, or 20 mg 2.5, 5, or 10 mg
Pulse[e] (capsule)	7–8	Ritalin SR Metadate ER Methylin ER Aptensio XR[g]	10[f] 10 10[f] 10	60[f] 60 60[f] 60	20 mg 10 or 20 mg 10 or 20 mg 10, 15, 20, 30, 40, 50, 60
Pearls (capsule)	8–12	Metadate CD Ritalin LA Focalin XR[d]	20 20 5	60 60 30	10, 20, 30, 40, 50, or 60 mg 10, 20, 30, 40, or 60 mg 5, 10, 15, 20, 25, 30, 35, or 40 mg
Pump (capsule)	≤12	Concerta	18	54	18, 27, 36, 54 or 72mg
Non-tablet or Non-capsule Formulations					
Chewable	3–5	Methylphenidate	5 and 5[c]	60	2.5, 5, or 10 mg
Chewable	8–12	Quillichew ER	20	60	20, 30 or 40 mg
Oral disintegrating	8–12	Cotempla XR-ODT	17.3	51.8	17.3 or 25.9 mg
Liquid (solution)	3–5	Methylin	5 and 5[c]	60[d]	5 mg/5 mL and 10 mg/5 mL

Liquid (solution)	**8–12**	**Quillivant XR[g]**	**20**	**60**	**25 mg or 5 mL (in reconstituted form)**
Transdermal patch	**≤12**	**Daytrana[g]**	**10**	**60[f]**	**10, 15, 20, or 30 mg (each has about a 9-hour effect)**

Abbreviation: max, maximum.

[a] Durations listed are based on the author's interpretation of available data, as well as the package insert, and are dose dependent, ie, higher dose may increase duration.

[b] Lower initial dose is recommended for children younger than 6 years, ranging from about one-quarter to one-half of the initial doses in Table 5-1.

[c] Immediate-release methylphenidate preparations are generally dosed at least twice a day, before breakfast and lunch.

[d] Focalin is a dexmethylphenidate preparation; all others are racemic mixtures. Thus, dosing of Focalin is generally about one-half that of other methylphenidate preparations.

[e] Pulse preparations are capsules containing a mixture of immediate-release and delayed-release beads. For children who cannot swallow capsules, they can be opened and the beads can be sprinkled into food such as applesauce.

[f] Author's recommendation, when information is not available in the package insert.

[g] Trade name only (no generic available).

Classified using US Food and Drug Administration. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed April 17, 2018.

pulse or bead (7–8 hours), pearls (8–12 hours), or pump (≤12 hours). However, duration of effect varies from child to child, and most estimates are based on aggregate group data. Also, increased dose can lead to increased duration of effect. Familiarity with at least 1 preparation representing each type is recommended.

An obvious advantage of longer-acting preparations is once-daily dosing. This removes the stigmatizing effect of taking medication at school and the convenient dosing improves adherence. If medication needs to be given very early (eg, 6:00 am or before the bus arrives), duration of effect of 7 to 8 hours may not be adequate for treating symptoms at school; a bus ride home or after-school child care may pose additional challenges for controlling symptoms. Duration of effect approximating 12 hours may be preferred in these instances and for children whose symptoms are a problem at home after the school day. Two potential problems with longer duration of effect are suppression of appetite and interference with sleep onset.

Initial Dose

Table 5-1 presents recommended initial dose for all methylphenidate preparations. In general, the initial dose is 10 to 20 mg/day, once in the morning for long-acting preparations or two 5-mg doses of IR preparation separated by about 4 hours. Exceptions are dexmethylphenidate (Focalin) preparations, which require one-half the dose (ie, 5 mg once in the morning for the long-acting preparation or 2.5 mg twice a day for the IR preparation).

Lower initial dose is recommended for children younger than 6 years, ranging from about one-quarter to one-half of the initial doses in Table 5-1.

Dosage Adjustments

Generally, dose can be increased weekly by an amount equivalent to the starting dose. An advantage of weekly adjustments is that parent and teacher ratings can be collected across school days and weekend days, for parents who opt to use medication on weekends, between dose adjustments. If there is a clear and positive response to the medication and no or minimal adverse effects, dose adjustments may be more frequent, as long as more frequent communication occurs with the caregiver(s) and school personnel.

Monitoring Therapeutic Response During Dose Adjustments

During dose adjustment, a weekly phone check-in or appointment is preferred. Parent and teacher National Institute for Children's Health Quality

(NICHQ) Vanderbilt Assessment Scale reports can facilitate the tracking of changes in severity of symptoms.

Safety Monitoring

Monitoring for contraindications, adverse effects, and potential drug interactions starts before the medication is prescribed and continues throughout drug administration. As with all medications, safety monitoring for methylphenidate depends on a targeted history and physical examination.

Specific contraindications, boxed warnings, warnings and precautions, adverse reactions, and drug interactions vary from preparation to preparation in the methylphenidate FDA labels. The safety information below is most relevant to children and adolescents, taken from the FDA labels with minor modifications. An example of a contraindication that would not be included is "advanced atherosclerosis."

Contraindications include

- Known hypersensitivity or idiosyncrasy to methylphenidate products.
- Marked anxiety, tension, or agitation.
- Glaucoma.
- Tics or a family history or diagnosis of Tourette syndrome (this contraindication is controversial).
- Currently using, or within 2 weeks of using, a monoamine oxidase inhibitor (MAOI).

Boxed warnings include concerns about abuse and dependence. A boxed warning for methylphenidate preparations states that it has a high potential for abuse and that prolonged administration may lead to dependence. Fortunately, there are no reports of children who were treated with therapeutic doses of stimulants developing dependence. Available data suggest that children with ADHD who are treated with stimulants are not more likely than those who did not receive stimulants to develop substance abuse later in life.[9–11] A related problem is diversion—that is, patients selling their prescription stimulants to be used as cognitive enhancers or drugs of abuse.[12]

Warnings and precautions: Most warnings and precautions rarely occur in children and adolescents treated with stimulants. Those most relevant to youth taking methylphenidate preparations include

- Increase in blood pressure and heart rate.

- Serious cardiovascular reactions can result in sudden death (generally only in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems).
  - A detailed personal and family cardiac history is important, with emphasis on the presence of structural heart defects, syncope, sudden unexplained death, and arrhythmias, particularly long QT syndromes, before prescribing any ADHD medication, including stimulants.
  - A recent policy statement from the AAP[13] provides specific recommendations, including a "targeted cardiac history" plus a "physical examination, including careful cardiac examination," "without obtaining routine electrocardiograms or routine subspecialty cardiology evaluations" for most children.
- Psychiatric events (primarily emergence of psychotic, manic, or aggressive symptoms [or a combination of those]).
- Long-term suppression of growth. (Recently, the FDA has added specific information about suppression of growth. The following is an example.)

> Central nervous system (CNS) stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.
>
> Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of patients newly treated with methylphenidate and nonmedication-treated pediatric patients over 36 months (to the ages of 10–13 years), suggests that consistently medicated pediatric patients (ie, treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.
>
> Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Cotempla XR-ODT. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted (verbatim from Cotempla XR-ODT label June 9, 2017).

- Peripheral vasculopathy, including Raynaud phenomenon (rare in children and adolescents).
- Seizures.
- Exacerbation of tics.
- Priapism.

Adverse reactions: The package inserts across different methylphenidate preparations vary in the adverse effects listed. Those reported most consistently are

- Abdominal pain
- Appetite suppression
- Insomnia

Drug interactions: Because methylphenidate is metabolized by an esterase enzyme in the blood, its metabolism and blood levels are not affected by inhibition or induction of hepatic cytochrome P450 isoenzymes. Drug interactions may occur with MAOIs (current use or within the past 2 weeks causes hypertensive crises); vasopressors (causes increased blood pressure); or warfarin anticoagulants, some anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors [SSRIs]; methylphenidate may inhibit their metabolism).

Vital Signs, Physical Examination, and Laboratory Monitoring

For all stimulants, monitoring blood pressure, heart rate, height, and weight is recommended. In addition, patients taking stimulants should be observed for, and parents should be questioned about, tics. No specific laboratory monitoring is recommended.

Optimizing Dose

A general recommendation for optimizing dose—if confident that the child has adhered to the previously prescribed dose—is to continue to increase the dose until the benefit-to-risk ratio is optimized. Treatment response, assessed systematically using information from parent and teacher reports (eg, NICHQ Vanderbilt Assessment Scale ratings), should be considered alongside reported and observed adverse effects during dose escalation. Satisfaction of the caregiver, teacher, and child regarding the child's response can also be useful. Ideally, a consensus will emerge about the preferred dose that maximizes the benefit-to-risk ratio.

Maintenance

Once an optimal dose is determined, maintenance treatment begins. Frequency of monitoring can be reduced, usually to follow-ups every 1 to 3 months, depending on the patient's needs. Consideration of dose adjustments is recommended annually or more often if the patient's clinical status changes significantly.

Medication Holidays

Particularly for patients with methylphenidate-induced growth suppression, medication "holidays" may be beneficial. Discontinuation of medication during a summer school recess may be sufficient to allow a growth "rebound." Input from the patient and family regarding perceived value of additional height, concerns about impact of no medication on relationships with friends and peers, and concerns about success in camps and other activities, is important in informing this decision.

What if a Methylphenidate Preparation Is Ineffective or Not Tolerated?

If adverse effects limit dose escalation or if the initial medication is not considered sufficiently beneficial, discontinuation is recommended. If continued medication treatment is clinically indicated, consideration of another ADHD medication may be warranted. Available data suggest that a methylphenidate or an amphetamine preparation is effective in almost all children, so switching from one to the other is generally indicated if the first is ineffective.

Discontinuing Methylphenidate and Possible Withdrawal Adverse Effects

For some patients, particularly those receiving extended-release (ER) preparations at recommended dosages, methylphenidate can be discontinued abruptly. To minimize withdrawal adverse effects, particularly for patients receiving high doses, staggered discontinuation of methylphenidate over a few days to weeks is recommended. Potential withdrawal adverse effects include anxiety, irritability, insomnia, and increased blood pressure.

Switching From a Methylphenidate to an Amphetamine Preparation

Switching from a methylphenidate preparation to a comparable amphetamine can be done abruptly, as long as the total daily dose is clinically comparable (ie, the amphetamine dose is about one-half the methylphenidate dose).

When to Consult or Refer

In general, consultation with, or referral to, a child and adolescent psychiatrist or other prescribing specialist may be considered when there is lack of clarity about diagnosis or after several medications have been tried and discontinued because of lack of effect or tolerability. Chapter 9 offers a more extensive discussion regarding what to do when interventions fail.

Amphetamine

Available Amphetamine Preparations

Table 5-2 contains detailed information for the 12 amphetamine preparations available on the US market, including

- Type of preparation.
- Estimated duration of action.
- Trade name.
- Recommended initial dose.
- Recommended maximum dose.
- Available dosage forms of the medication.

Information in the table relies on FDA-approved labels (package inserts) or, when specific information is not available, on the author's recommendation.

Vyvanse deserves additional consideration because of several characteristics. The amount of *d*-amphetamine in each Vyvanse capsule is not available in the package insert. Thus, it is difficult to convert to comparable doses of other stimulants. In addition, onset of the effects of Vyvanse may be delayed by about 30 to 60 minutes compared with other stimulants because absorption of the lysine-dextroamphetamine molecule is slower than absorption of regular *d*-amphetamine, which is rapidly absorbed via an active transporter in the gastrointestinal tract. Almost immediately after reaching the bloodstream, the lysine-dextroamphetamine bond is cleaved in the red blood cells, releasing regular d-amphetamine. Claims regarding lack of abuse potential for Vyvanse compared with other amphetamine preparations are somewhat correct because there is less "drug liking" if taken intravenously or by nasal snorting (see Vyvanse package insert, page 18); this may be an important consideration in instances when there is a risk of diversion of the prescribed medication to substance abusers but may not be important to most pediatric patients.

Mydayis also deserves additional consideration. It has a long duration of effect, up to 16 hours, and has an FDA indication for ages 13 years and older only. Patients age 12 years and younger "experienced higher rates of adverse reactions, mainly insomnia and decreased appetite" (FDA label, June 2017).

Because all amphetamine preparations are controlled substances in the United States, a written (or approved electronic) prescription can be issued for a maximum of a 30-day supply with no refills.

Onset of Effect

Onset of effect for all amphetamine preparations (except possibly Vyvanse) is generally 30 to 45 minutes. In addition to therapeutic effects, appetite suppression occurs concurrently. Thus, timing of morning medication and breakfast needs to be coordinated.

Duration of Effect

Four types of oral tablets and capsules are available. On average, IR preparations have a 4- to 8-hour duration of effect. The other 3 types have longer durations of effect, depending on the technology used in the formulation: pulse or bead (7–8 hours), pearls (8–12 hours), or prodrug (≤12 hours). However, duration of effect varies from child to child; most estimates are based on aggregate group data. Also, increased dose can lead to increased duration of effect. Familiarity with at least 1 preparation representing each type is recommended.

An obvious advantage of longer-acting preparations is once-daily dosing; this removes the stigmatizing effect of taking medication at school and the convenient dosing improves adherence. If medication needs to be given very early (eg, 6:00 am or before the bus arrives), duration of effect of less than about 8 hours may not be adequate for treating symptoms at school; a bus ride home or after-school child care may pose additional challenges for controlling symptoms. Duration of effect approximating 12 hours may be preferred in these instances and for children whose symptoms are a problem at home after the school day.

Initial Dose

Table 5-2 presents recommended initial dose for all amphetamine preparations. In general, dosing of amphetamine preparations is about one-half

that of methylphenidate. In general, the initial dose is 5 to 10 mg/day, once in the morning for long-acting preparations and two 2.5-mg or 5-mg doses separated by about 4 to 6 hours for IR preparations.

Lower initial dose is recommended for children younger than 6 years, ranging from about one-quarter to one-half the initial doses in Table 5-2.

Dosage Adjustments

Generally, the dose can be increased weekly by an amount equivalent to the starting dose. An advantage of weekly adjustments is that parent and teacher ratings can be collected across school days and weekend days, for parents who opt to use medication on weekends, between dose adjustments. If there is a clear and positive response to the medication and no or minimal adverse effects, dose adjustments may be more frequent, as long as more frequent communication occurs with the caregiver(s) and school personnel.

Monitoring Therapeutic Response During Dose Adjustments

During dose adjustment, a weekly phone check-in or appointment is preferred. Parent and teacher NICHQ Vanderbilt Assessment Scale reports can facilitate the tracking of changes in severity of symptoms.

Safety Monitoring

Monitoring for contraindications, adverse effects, and potential drug interactions starts before medication is prescribed and continues throughout drug administration. As with all medications, safety monitoring for amphetamine depends on a targeted history and physical examination.

Specific contraindications, boxed warnings, warnings and precautions, adverse reactions, and drug interactions vary from preparation to preparation in the amphetamine FDA labels. The safety information below is most relevant to children and adolescents, taken from the FDA labels with minor modification. An example of a contraindication that would not be included is "advanced atherosclerosis."

Contraindications include

- Known hypersensitivity or idiosyncrasy to amphetamine products
- Symptomatic cardiovascular disease
- Moderate-to-severe hypertension

Table 5-2. D-Amphetamine and DL-Amphetamine (Mixed-Salt) Preparations

Formulation	Form	Duration[a] of Effect, h	Trade Name	Initial Dose, mg[b]	Max DD, mg	Available Unit Dose Forms
Immediate Release[c]	D- tablet	4–8	Zenzedi	5 and 5[c]	40	2.5, 5, 7.5, 10, 15, 20, 30 mg
Immediate Release[c]	DL- tablet	4–8	Adderall Evekeo	5 and 5[c]	40	5, 7.5, 10, 12.5, 15, 20, 30 mg 5 and 10 mg
Pulse[d]	D- capsule with 2 types of beads	6–9	Dexedrine Spansule	5	40	5, 10, 15 mg
Pulse (3 beads)	D- capsule with 3 types of beads	<16	Mydayis Note: For ages 13–17 only	12.5	25	12.5, 25, 37.5, 50 mg
Pearl	DL- capsule	8–12	Adderall XR	10 (5[e])	30	5, 10, 15, 20, 25, 30 mg
Modified IR ("prodrug")	D- capsule	8–12	Vyvanse[f]	20	70	10, 20, 30, 40, 50, 60, 70 mg
Non-tablet or Non-capsule Formulations						
IR[c]	D- liquid	≤8	ProCentra	5	40	5 mg/5 mL
Modified IR	D- chewable	8–12	Vyvanse[f]	30	70	10, 20, 30, 40, 50, 60 mg

Oral disintegrating	**D- tablet**	**8–12**	**Adzenys XR-ODT[f]**	**6.3**	**18.8**	**3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg**
Liquid	**D- liquid**	**8–12**	**Adzenys ER[f]**	**6.3**	**18.8**	**6.3 mg/5 mL**
			Dyanavel XR[f]	**2.5 or 5**	**20**	**2.5 mg/1mL**

Abbreviations: IR, immediate-release; max DD, maximum daily dose.

[a] Durations listed are based on the author's interpretation of available data as well as the package insert.

[b] Lower initial dose is recommended for children younger than 6 years, ranging from about one-quarter to one-half of the initial doses in Table 5-2.

[c] Recommended starting dose is twice daily, about 4–6 hours apart.

[d] Pulse preparations are capsules containing a mixture of immediate-release beads and delayed-release beads. For children who cannot swallow capsules, they can be opened and the beads can be sprinkled into foods such as applesauce.

[e] Author's recommendation.

[f] Trade brand only (no generic available).

Classified using US Food and Drug Administration. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed April 17, 2018.

- Hyperthyroidism
- Glaucoma
- Agitated states
- History of drug abuse
- Currently using, or within 2 weeks of using, an MAOI

Boxed warnings include concerns about abuse and dependence. The boxed warnings for amphetamines state that they have a high potential for abuse and that prolonged administration may lead to dependence. Fortunately, there are no reports of children who were treated with therapeutic doses of stimulants developing dependence. Available data suggest that children with ADHD who are treated with stimulants are not more likely than those who did not receive stimulants to develop substance abuse later in life.[9–11] A related problem is diversion—that is, patients selling their prescription stimulants to be used as cognitive enhancers or drugs of abuse.[12]

Warnings and precautions: Most warnings and precautions rarely occur in children and adolescents treated with stimulants. Those most relevant to youth taking amphetamine preparations include the following.

- Serious cardiovascular reactions can result in sudden death (generally only in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems).
  - A detailed personal and family cardiac history is important, with emphasis on the presence of structural heart defects, syncope, sudden unexplained death, and arrhythmias, particularly long QT syndromes, before prescribing any ADHD medication, including stimulants.
  - A recent policy statement from the AAP[13] provides specific recommendations, including a "targeted cardiac history" plus a "physical examination, including careful cardiac examination," "without obtaining routine electrocardiograms or routine subspecialty cardiology evaluations" for most children.
- Blood pressure and heart rate increases.
- Psychiatric adverse reactions (primarily emergence of psychotic, manic, or aggressive symptoms [or a combination of those]).
- Long-term suppression of growth. (Recently, the FDA added specific information about suppression of growth. The following is an example.)

> Central nervous system stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

> Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including MYDAYIS. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted (verbatim from MYDAYIS label, June 2017).

- Peripheral vasculopathy, including Raynaud phenomenon (rare in children and adolescents).
- Seizures.
- Exacerbation of tics.

Adverse reactions: Across the package inserts for various amphetamine preparations, there is variation in the adverse effects listed. Those reported most consistently are

- Abdominal pain
- Appetite suppression
- Insomnia
- Weight loss
- Nervousness

Drug interactions include

- Monoamine oxidases (current or within 14 days) *may potentiate* the effects of amphetamine.
- Alkalinizing agents *may increase* blood levels of amphetamine.
- Acidifying agents *may reduce* blood levels of amphetamine.
- Effects of α-adrenergic blocking agents, antihistamines, antihypertensives, phenobarbital, phenytoin, Veratrum alkaloids, and ethosuximide *may be reduced* by amphetamine.
- Effects of tricyclic antidepressants, norepinephrine, and meperidine *may be potentiated* by amphetamine.

Vital Signs, Physical Examination, and Laboratory Monitoring

For all amphetamine preparations, monitoring blood pressure, heart rate, height, and weight is recommended. In addition, patients taking stimulants should be observed for, and parents should be questioned about, tics. No specific laboratory monitoring is recommended.

Optimizing Dose

A general recommendation for optimizing dose—if confident that the child has adhered to the previously prescribed dose—is to continue to increase the dose until the benefit-to-risk ratio is optimized. Treatment response, assessed systematically using information from parent and teacher reports (eg, NICHQ Vanderbilt Assessment Scale ratings), should be considered alongside reported and observed adverse effects during dose escalation. Satisfaction of the caregiver, teacher, and child regarding the child's response can also be useful. Ideally, a consensus will emerge about the preferred dose that maximizes the benefit-to-risk ratio.

Maintenance

Once an optimal dose is determined, maintenance treatment begins. Frequency of monitoring can be reduced, usually to follow-ups every 1 to 3 months, depending on the patient's needs. Consideration of dose adjustments is recommended annually, or more often if the patient's clinical status changes significantly.

Medication Holidays

Particularly for patients with amphetamine-induced growth suppression, medication "holidays" may be beneficial. Discontinuation of medication during a summer school recess may be sufficient to allow a growth "rebound." Input from the patient and family regarding perceived value of additional height, concerns about impact of no medication on relationships with friends and peers, and concerns about success in camps and other activities is important in informing this decision.

What if an Amphetamine Preparation Is Ineffective or Not Tolerated?

If adverse effects limit dose escalation or if the initial medication is not considered sufficiently beneficial, discontinuation is recommended. If continued medication treatment is clinically indicated, consideration of another ADHD medication may be warranted. Available data suggest that a methylphenidate or an amphetamine preparation is effective in almost all children, so switching from one to the other is generally indicated if the first is ineffective.

Discontinuing Amphetamine and Possible Withdrawal Adverse Effects

For some patients, particularly those receiving ER preparations at recommended dosages, amphetamine can be discontinued abruptly. To minimize withdrawal adverse effects, particularly for patients receiving high doses, staggered discontinuation of amphetamine over a few days to weeks could be considered if withdrawal effects are anticipated or occur. Potential withdrawal adverse effects include anxiety, irritability, insomnia, and increased blood pressure.

Switching From an Amphetamine to a Methylphenidate Preparation

Switching from an amphetamine preparation to a comparable methylphenidate preparation can be done abruptly, as long as the total daily dose is clinically comparable (ie, the methylphenidate dose is about twice the amphetamine dose).

When to Consult or Refer

In general, consultation with, or referral to, a child and adolescent psychiatrist or other prescribing specialist may be considered when there is lack of clarity about diagnosis or after several medications have been tried and discontinued because of lack of effect or tolerability. Chapter 9 offers a more extensive discussion regarding what to do when interventions fail.

Guanfacine

Available Guanfacine Preparations

Guanfacine is an α_{2A}-adrenergic agonist. Guanfacine preparations available in the United States are listed in Table 5-3 along with

- Type of preparation
- Estimated duration of action
- Trade name
- Recommended initial dose
- Recommended maximum dose
- Available forms of the medication

Table 5-3. Guanfacine Preparations

Drug	Formulation	Duration[a] of effect, h	Trade Name	Initial Dose	Max DD, mg	Available Unit Dose Forms
Guanfacine	IR	4–8	Tenex	0.5–1.0[b]	4 (divided)[b]	1 or 2 mg tablets
Guanfacine	ER[c]	≤24	Intuniv	1	7	1, 2, 3, or 4 mg tablets

Abbreviations: ER, extended-release; IR, immediate-release; max DD, maximum daily dose.

[a] Durations listed are based on the author's interpretation of available data, as well as the package insert.

[b] Author's recommendation.

[c] For extended-release guanfacine, once-daily dosing is recommended.

Classified using US Food and Drug Administration. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed April 20, 2018.

Information in the table relies on FDA-approved labels (package inserts) or, occasionally, the author's and contributing editors' recommendations when specific information is not available.

Extended-release guanfacine (generic and Intuniv) is FDA approved for ADHD in children, adolescents, and adults, age 6 years and older. Immediate-release guanfacine (generic and Tenex) is approved for management of hypertension in adults. Because all guanfacine preparations have the same active agent and are used to treat ADHD in youth, they are included here.

An advantage of the ER preparation is its "flatter" pharmacokinetic profile (ie, the peak level is relatively lower and thus may be associated with fewer or less severe adverse effects than comparable IR preparations; see Figure 1 in Intuniv package insert).[14]

Several points in the ER guanfacine package insert regarding administration are noteworthy (see page 1).[14]

- "Do not crush, chew, or break tablets before swallowing."
- "Do not administer with high-fat meals, because of increased exposure."
- "Do not substitute for immediate-release guanfacine tablets on a mg-per-mg basis, because of differing pharmacokinetic profiles."

Onset of Effect

Precise data regarding onset of effect of guanfacine preparations are not available. Clinical experience suggests that therapeutic effects occur within 1 to 2 hours after administration.

Duration of Effect

Immediate-release guanfacine has a 4- to 8-hour duration of effect. Duration of effect of ER guanfacine is up to 24 hours. The higher the dose, the longer are the potential effects, both therapeutic and adverse. Duration of effect varies from child to child; the estimates in Table 5-3 are based on groups.

An obvious advantage of longer-acting preparations is once-daily dosing; this removes the stigmatizing effect of taking medication at school and improves adherence.

Initial Dose

The recommended starting dose of ER guanfacine is 1 mg, either in the morning or evening. Because IR guanfacine is approved only for hypertension in adults, no relevant dosing recommendations for youth with ADHD are in the package insert. Clinical experience and expert opinion suggest starting with 0.5 mg (one-half of 1-mg tablet) or 1 mg in the morning.

Guanfacine, in any formulation, is not FDA approved for use in youth younger than 6 years. In these young patients, if stimulants are ineffective or not tolerated, low doses of guanfacine may be considered. When possible, consultation with a specialist regarding reconsideration of diagnosis and next steps in treatment is recommended.

The lowest dose available of ER guanfacine is 1 mg.

Dosage Adjustments

Generally, the dose can be increased weekly by an amount equivalent to the starting dose (1 mg). An advantage of weekly adjustments is that parent and teacher ratings can be collected across school days and weekend days between dose adjustments. If there is a clear and positive response to the medication and no or minimal adverse effects, dose adjustments may be more frequent, as long as more frequent communication with the caregiver(s) and school personnel occurs.

In monotherapy clinical trials of ER guanfacine,

> There was dose- and exposure-related clinical improvement as well as risks for several clinically significant adverse effects (hypotension, bradycardia, sedative events). To balance the exposure-related potential benefits and risks, the recommended target dose range depending on clinical response and tolerability for Intuniv is 0.05 to 0.12 mg/kg per day (total daily dose between 1 and 7 mg). … In an adjunctive trial, which evaluated Intuniv treatment with psychostimulants, the majority of patients reached optimal doses in the 0.05–0.12 mg/kg per day range. Doses above 4 mg/day have not been studied in adjunctive trials (see page 2 of package insert).[14]

Because IR guanfacine is approved only for hypertension in adults, there are no relevant dosing recommendations for youth with ADHD in the package insert. Doses higher than 4 mg should be used with caution given

that 4 mg/day is the maximum dose recommended for the treatment of hypertension in adults.

Monitoring Therapeutic Response During Dose Adjustments

During dose adjustment, a weekly phone check-in or appointment is preferred. Parent and teacher NICHQ Vanderbilt Assessment Scale reports can facilitate the tracking of changes in severity of symptoms.

Safety Monitoring

Monitoring for contraindications, adverse effects, and potential drug interactions starts before the medication is prescribed and continues throughout drug administration. As with all medications, safety monitoring for guanfacine depends on a targeted history and physical examination. The following information is based on the package insert for Intuniv,[14] which is derived, in part, from clinical trials involving youth aged 6 to 17 years.

Specific contraindications, boxed warnings, warnings and precautions, adverse reactions, and drug interactions presented below are those most relevant to children and adolescents, taken from the FDA labels with minor modification. An example of a contraindication that would not be included is "advanced atherosclerosis."

The only contraindication is history of hypersensitivity to ER guanfacine or other guanfacine products.

Boxed warnings: There are no boxed warnings.

Warnings and precautions[14] are

> *Hypotension, bradycardia, syncope:* Titrate slowly and monitor vital signs frequently in patients at risk for hypotension, heart block, bradycardia, syncope, cardiovascular disease, vascular disease, cerebrovascular disease, or chronic renal failure. Measure heart rate and blood pressure before initiating therapy, following dose increases, and periodically during therapy. Avoid concomitant use of drugs with additive effects unless clinically indicated. Advise patients to avoid becoming dehydrated or overheated.
>
> *Sedation and somnolence:* Occur commonly with Intuniv. Consider the potential for additive effects with CNS-depressant drugs. Caution patients against operating heavy equipment or

driving until they know how they respond to Intuniv. (Examples of CNS depressants: alcohol, barbiturates, benzodiazepines.)

Cardiac conduction abnormalities: May worsen sinus node dysfunction and atrioventricular block, especially in patients taking other sympatholytic agents. Titrate slowly and monitor vital signs frequently.

Rebound hypertension: Abrupt discontinuation of Intuniv can lead to clinically significant and persistent rebound hypertension. Subsequent hypertensive encephalopathy was also reported. To minimize the risk of rebound hypertension on discontinuation, the total daily dose should be tapered by decrements of no more than 1 mg every 3 to 7 days.

Adverse reactions: Most common (>5% and at least twice the placebo rate) in Intuniv fixed-dose monotherapy ADHD trials in 6- to 17-year-olds are[14]

- Hypotension
- Somnolence
- Fatigue
- Nausea
- Lethargy

Additional adverse effects in Intuniv flexible dose–optimization ADHD trials were abdominal pain, insomnia, dizziness, dry mouth, irritability, vomiting, and bradycardia.

Drug interactions include[14]

- "Strong and moderate CYP3A4 inhibitors increase guanfacine exposure. (Examples of 'strong' [clarithromycin, ketoconazole, nefazodone] and 'moderate' [doxycycline, fluvoxamine, grapefruit juice] CYP3A4 inhibitors.)"
- "Strong and moderate CYP3A4 inducers decrease guanfacine exposure. (Examples of CYP3A4 inducers: barbiturates, carbamazepine, glucocorticoids, phenytoin, St John's wort.)"

Vital Signs and Laboratory Monitoring

For all guanfacine preparations, monitoring blood pressure and heart rate is recommended. No specific laboratory monitoring is recommended.

Optimizing Dose

A general recommendation for optimizing dose—if confident that the child has adhered to the previously prescribed dose—is to continue to increase the dose until the benefit-to-risk ratio is optimized. Treatment response, assessed systematically using information from parent and teacher reports (eg, NICHQ Vanderbilt Assessment Scale ratings), should be considered alongside reported and observed adverse effects during dose escalation. Satisfaction of the caregiver, teacher, and child regarding the child's response can also be useful. Ideally, a consensus will emerge about the preferred dose that maximizes the benefit-to-risk ratio.

Specifics regarding optimizing dose were presented in the previous Dosage Adjustments section.

Maintenance

Once an optimal dose is determined, maintenance treatment begins. Frequency of monitoring can be reduced, usually to follow-ups every 1 to 3 months, depending on the patient's needs. Consideration of dose adjustments is recommended annually, or more often, if the patient's clinical status changes significantly.

What if a Guanfacine Preparation Is Ineffective or Not Tolerated?

If adverse effects limit dose escalation or if the maximal recommended dose is ineffective, discontinuation is recommended. If continued medication is clinically indicated, consideration of another class of ADHD medication may be warranted.

Discontinuing Guanfacine and Possible Withdrawal Adverse Effects

To minimize withdrawal adverse effects, it is recommended that IR and ER guanfacine be tapered in daily dose decrements of 1 mg every 3 to 7 days. Blood pressure and pulse monitoring is recommended during taper and discontinuation. Potential withdrawal adverse effects include small increases in blood pressure and heart rate.

Switching From One Guanfacine Preparation to Another

The following text is taken verbatim from the Intuniv package insert (page 2)[14]:

> If switching from immediate-release guanfacine, discontinue that treatment, and titrate Intuniv following the above recommended schedule. [See summary in the previous Optimizing Dose section.] … Do not substitute for immediate-release guanfacine tablets on a mg-per-mg basis, because of differing pharmacokinetic profiles. Intuniv has significantly reduced Cmax [maximum serum concentration] (60% lower), bioavailability (43% lower) and a delayed Tmax [time of maximum serum concentration] (3 hours later) compared to those of the same dose of immediate-release guanfacine.

Adjunct Treatment to Stimulants

Extended-release guanfacine is FDA approved for adjunctive treatment to stimulants. This may be considered when the stimulant dose cannot be optimized because of adverse effects in the context of persisting ADHD symptoms. Recommendations for using adjunctive guanfacine preparations are the same as when guanfacine is used alone. It is important to note that combination treatment may be prone to a higher likelihood of adverse effects and that, in general, treatment with 1 medication is preferable, when possible.

When to Consult or Refer

In general, consultation with, or referral to, a child and adolescent psychiatrist or other prescribing specialist may be considered when there is lack of clarity about diagnosis or after several medications have been tried and discontinued because of lack of effect or tolerability. Chapter 9 offers a more extensive discussion regarding what to do when interventions fail.

Clonidine

Available Clonidine Preparations

Clonidine is an α_2-adrenergic agonist. Clonidine is available in the United States in 3 forms: IR tablets (Catapres and generic), ER tablets (Kapvay and generic [ER clonidine]), and transdermal patch (Catapres-TTS). Kapvay and ER clonidine are the only clonidine formulations approved for treatment of ADHD in youth aged 6 to 17 years. Catapres and generic formulations

are approved for treatment of hypertension in adults. Because all clonidine preparations have the same active agent and are used to treat ADHD in youth, they are included here (Table 5-4).

Extended-release clonidine is FDA approved for ADHD in children and adolescents. Clonidine nonspecifically interacts with α_{2A}-, α_{2B}-, and α_{2C}-receptor subtypes. The 2B receptor mediates, via baroreceptors, hypotension, and bradycardia adverse effects. Thus, clonidine may have a less favorable adverse effect profile than guanfacine. There are no direct comparative data regarding this issue. In addition, IR clonidine is associated with acute drops in blood pressure, syncope, and even death following unintentional or intentional ingestions of more than therapeutic quantities.

Clonidine preparations available in the United States are listed in Table 5-4 along with

- Type of preparation
- Estimated duration of action
- Trade name
- Recommended initial dose
- Recommended maximum dose
- Available forms of the medication

Information in the table relies on FDA approved package inserts or, occasionally, the author's and contributing editors' recommendations when specific information is not available.

An advantage of the ER preparation is its "flatter" pharmacokinetic profile (ie, the peak level is relatively lower and thus may be associated with fewer or lesser adverse effects than comparable IR clonidine; see Figure 1 in the Kapvay package insert).[15]

Several points in the Kapvay package insert regarding administration are noteworthy (see page 1).[15]

- "Do not crush, chew, or break tablets before swallowing."
- "Do not substitute for other clonidine products on a mg-per-kg basis, because of differing pharmacokinetic profiles."
- "When discontinuing, taper the dose in decrements of no more than 0.1 mg every 3 to 7 days to avoid rebound hypertension."

These points are discussed in the Dosage Adjustments section.

Table 5-4. Clonidine Preparations

Drug	Formulation	Duration[a] of Effect, h	Trade Name	Initial Dose	Max DD, mg	Available Unit Dose Forms
Clonidine	IR	3–5	Catapres	0.05[b]	0.4 (divided)	0.1, 0.2, or 0.3 mg tablets
Clonidine	ER[c]	12–24[b]	Kapvay	0.1 hs	0.4 (divided)	0.1 or 0.2 mg tablets
Non-tablet or Non-capsule Formulations						
Clonidine	Patch	7 days	Catapres	0.05[b]	0.3[b]	0.1, 0.2, or 0.3 mg/day

Abbreviations: ER, extended-release; hs, at bedtime; IR, immediate-release; max DD, maximum daily dose.

[a] Durations listed are based on the author's interpretation of available data, as well as the package insert.

[b] Author's recommendation.

[c] For extended-release clonidine, twice-a-day dosing is recommended.

Classified using US Food and Drug Administration. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed April 20, 2018.

Onset of Effect

Precise data regarding onset of effect of clonidine preparations is not available. Clinical experience suggests that therapeutic effects occur within 30 to 60 minutes after administration.

Duration of Effect

Immediate-release clonidine has a 3- to 5-hour duration of effect. The duration of effect of ER clonidine is 12 to 24 hours. Potentially, higher doses are correlated with longer effects, both therapeutic and adverse effects. Duration of effect varies from child to child; the estimates in Table 5-4 are based on aggregate estimates.

Advantages of the ER preparation are improved adherence and removal of the stigmatizing effect of taking medication at school.

Initial Dose

The recommended starting dose of ER clonidine is 0.1 mg at bedtime. Because IR clonidine is approved only for hypertension in adults, there are no relevant dosing recommendations for youth with ADHD in the package insert. Clinical experience and expert opinion suggest starting with 0.05 mg in the morning or at bedtime.

Clonidine, in any formulation, is not FDA approved for use in youth younger than 6 years. In these young patients, if stimulants are ineffective or not tolerated, low doses of clonidine may be considered. When possible, consultation with a specialist regarding reconsideration of diagnosis and next steps in treatment is recommended.

Dosage Adjustments

Generally, the dose can be increased weekly, by an amount equivalent to the starting dose (0.1 mg), to the optimal dose of the maximum daily dose of 0.4 mg. An advantage of weekly adjustments is that parent and teacher ratings can be collected across school days and weekend days between dose adjustments. If there is a clear and positive response to the medication and no or minimal adverse effects, dose adjustments may be more frequent, as long as more frequent communication occurs with the caregiver(s) and school personnel.

> The dose of Kapvay [ER clonidine], administered either as monotherapy or as adjunctive therapy to a psychostimulant,

> should be individualized according to the therapeutic needs and response of the patient. Dosing should be initiated with one 0.1-mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime (see page 2, section 2.2, in Kapvay package insert).[15]

Because IR clonidine is approved only for hypertension in adults, there are no relevant dosing recommendations for youth with ADHD in the package insert. Clinical experience and expert opinion suggest a maximum total daily dose of 0.4 mg, which is the recommended maximum for treatment of hypertension in adults. Dosing may be up to 4 times a day, depending on patient need; no single dose should exceed 0.2 mg.

Monitoring Therapeutic Response During Dose Adjustments

During dose adjustment, a weekly phone check-in or appointment is preferred. Parent and teacher NICHQ Vanderbilt Assessment Scale reports can facilitate the tracking of changes in severity of symptoms.

Safety Monitoring

Monitoring for contraindications, adverse effects, and potential drug interactions starts before medication is prescribed and continues throughout drug administration. As with all medications, safety monitoring for clonidine depends on a targeted history and physical examination. The following information is based on the package insert for Kapvay.[15] Safety data for this package insert are derived, in part, from clinical trials involving youth aged 6 to 17 years.

Specific contraindications, boxed warnings, warnings and precautions, adverse reactions, and drug interactions presented below are those most relevant to children and adolescents, taken from the FDA labels with minor modification. An example of a contraindication that would not be included is "advanced atherosclerosis."

The only contraindication is a history of hypersensitivity reaction to clonidine.

Boxed warnings: There are no boxed warnings.

Warnings and precautions (verbatim from package insert, page 1)[15] are

> *Hypotension/bradycardia/syncope:* Titrate slowly and monitor vital signs frequently in patients at risk for hypotension, heart block, bradycardia, syncope, cardiovascular disease, vascular disease, cerebrovascular disease, or chronic renal failure. Measure heart rate and blood pressure before initiating therapy, following dose increases, and periodically during therapy. Avoid concomitant use of drugs with additive effects unless clinically indicated. Advise patients to avoid becoming dehydrated or overheated.
>
> *Somnolence/sedation:* Has been observed with Kapvay. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to Kapvay.
>
> *Cardiac conduction abnormalities:* May worsen sinus node dysfunction and atrioventricular block, especially in patients taking other sympatholytic agents. Titrate slowly and monitor vital signs frequently.

Adverse reactions **(from package insert with minor modifications)**[15]: Most common (>5% and at least twice the placebo rate) in monotherapy trials of ADHD in 6- to 17-year-olds are

- Somnolence
- Fatigue
- Irritability
- Nightmares
- Insomnia
- Constipation
- Dry mouth

Most common (>5% and at least twice the placebo rate) as adjunct therapy to psychostimulants in ADHD in 6- to 17-year-olds are

- Somnolence
- Fatigue
- Decreased appetite
- Dizziness

Drug interactions include

- Sedating drugs (alcohol, barbiturates, others)
- Drugs known to affect sinus node function or atrioventricular node conduction (eg, digitalis, calcium channel blockers, β-blockers) because of potential additive effects, such as bradycardia and atrioventricular block
- Antihypertensive drugs

Vital Signs and Laboratory Monitoring

For all clonidine preparations, monitoring blood pressure and heart rate is recommended. No specific laboratory monitoring is recommended.

Optimizing Dose

A general recommendation for optimizing dose—if confident that the child has adhered to the previously prescribed dose—is to continue to increase the dose until the benefit-to-risk ratio is optimized. Treatment response, assessed systematically using information from parent and teacher reports (eg, NICHQ Vanderbilt Assessment Scale ratings), should be considered alongside reported and observed adverse effects during dose escalation. Satisfaction of the caregiver, teacher, and child regarding the child's response can also be useful. Ideally, a consensus will emerge about the preferred dose that maximizes the benefit-to-risk ratio.

Maintenance

Once an optimal dose is determined, maintenance treatment begins. Frequency of monitoring can be reduced, usually to follow-ups every 1 to 3 months, depending on the patient's needs. Consideration of dose adjustments is recommended annually, or more often, if the patient's clinical status changes significantly.

What if a Clonidine Preparation Is Ineffective or Not Tolerated?

If adverse effects limit dose escalation or if the maximal recommended dose is not effective, discontinuation is recommended. If continued medication is clinically indicated, consideration of another class of ADHD medication may be warranted.

Discontinuing Clonidine and Possible Withdrawal Adverse Effects

To minimize withdrawal adverse effects, it is recommended that ER clonidine be tapered in daily dose increments of 0.1 mg every 3 to 7 days. Blood pressure and pulse monitoring is recommended during taper and discontinuation.

Potential withdrawal adverse effects include rebound increases in blood pressure and heart rate.

Switching From One Clonidine Preparation to Another

The following text is taken verbatim from the Kapvay package insert (page 2)[15]: "Due to lack of controlled clinical trial data and differing pharmacokinetic profiles, substitution of Kapvay for other clonidine products on a mg-per-mg basis is not recommended." Thus, cross-tapering should be done cautiously.

Adjunct Treatment to Stimulants

Extended-release clonidine is FDA approved for adjunctive treatment to stimulants. This may be considered when the stimulant dose cannot be optimized because of adverse effects in the context of persisting ADHD symptoms. Recommendations for using adjunctive clonidine preparations are the same as when clonidine is used alone. It is important to note that combination treatment may be prone to a higher likelihood of adverse effects and that, in general, treatment with 1 medication is preferable, when possible.

When to Consult or Refer

In general, consultation with, or referral to, a child and adolescent psychiatrist or other prescribing specialist may be considered when there is lack of clarity about diagnosis or after several medications have been tried and discontinued because of lack of effect or tolerability. Chapter 9 offers a more extensive discussion regarding what to do when interventions fail.

Atomoxetine

Available Atomoxetine Preparations

Atomoxetine, a selective norepinephrine reuptake inhibitor, is available in branded and generic preparations.

Atomoxetine has a therapeutic effect on ADHD symptoms comparable to that of guanfacine and clonidine but less than the stimulants. Much of the information in this section is from the Strattera package insert.[16]

Onset of Effect

The time to initial and full effect of atomoxetine is much longer than for stimulants and α_2-adrenergic agonists: about 1 to 2 *weeks* for initial effect and 4 to 6 weeks for full effect. Patients and their families should be advised of this delayed response to minimize premature discontinuation of treatment.

Duration of Effect

Once atomoxetine reaches peak effect after about 2 to 4 weeks on a stable therapeutic dose, its therapeutic effect is continuous.

Initial Dose

Up to 70 kg body weight: 0.5 mg/kg per day in the morning or in 2 divided doses.

More than 70 kg body weight: 40 mg/day in the morning or in 2 divided doses.

Dosage Adjustments

NOTE: Patients known to be CYP2D6 poor metabolizers should be treated with lower doses than described herein.

Up to 70 kg body weight: After the initial dose for a minimum of 3 days, atomoxetine can be increased to a target daily dose of approximately 1.2 mg/kg, administered as a single daily dose or as evenly divided doses in the morning and late afternoon or evening. No additional benefit has been demonstrated for doses greater than 1.2 mg/kg/day, though the maximum daily dose is listed as 1.4 mg/kg per day or 100 mg/day, whichever is less.

More than 70 kg body weight: After the initial dose for a minimum of 3 days, atomoxetine can be increased to a target daily dose of approximately 80 mg, administered as a single daily dose or as evenly divided doses in the morning and late afternoon or evening. After 2 to 4 additional weeks, the daily dose may be increased to a total daily dose of 100 mg in patients who have not achieved an optimal response. No additional benefit has been demonstrated for higher doses.

Monitoring Therapeutic Response During Dose Adjustments

Although only 1 or 2 dosage adjustments are recommended after the initial dose, a weekly phone check-in or appointment for the first few weeks to monitor for safety and effectiveness is preferred. Parent and teacher NICHQ Vanderbilt Assessment Scale reports can facilitate the tracking of changes in severity of symptoms.

Safety Monitoring

Monitoring for contraindications, adverse effects, and potential drug interactions starts before the medication is prescribed and continues throughout drug administration. As with all medications, safety monitoring for atomoxetine depends on a targeted history and physical examination. The information that follows is based on the package insert for Strattera.[16] Safety data for this package insert are derived, in part, from clinical trials involving youth aged 6 to 17 years.

Contraindications include

- Hypersensitivity to atomoxetine or other constituents of the product
- Atomoxetine use within 2 weeks after discontinuing an MAOI or other drugs that affect brain monoamine concentrations
- Narrow angle glaucoma
- Pheochromocytoma or history of pheochromocytoma
- Severe cardiovascular disorders that may deteriorate with clinically important increases in heart rate and blood pressure

Boxed warning: Increased risk of suicidal ideation in children and adolescents.

Warnings and precautions include

- *Suicidal ideation:* Monitor for suicidal ideation, clinical worsening, and unusual changes in behavior.
- *Severe liver injury:* Should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury.

- *Serious cardiovascular events:* Sudden death, stroke, and myocardial infarction have been reported in association with atomoxetine treatment. Patients should have a careful history and physical examination to assess for presence of cardiovascular disease.
  - Strattera generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to its noradrenergic events.
- *Emergent cardiovascular symptoms:* Patients should undergo prompt cardiac evaluation.
- *Effects on blood pressure and heart rate:* Increase in blood pressure and heart rate, orthostasis, and syncope may occur. Use with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.
- *Emergent psychotic or manic symptoms:* Consider discontinuing treatment if such new symptoms occur.
- *Bipolar disorder:* Screen patients to avoid possible induction of a mixed or manic episode.
- *Aggressive behavior or hostility:* Should be monitored.
- *Possible allergic reactions:* Including anaphylactic reactions, angioneurotic edema, urticaria, and rash.
- *Effects on urine outflow:* Urinary retention and hesitancy may occur.
- *Priapism:* Prompt medical attention is required in the event of suspected priapism.
- *Growth:* Height and weight should be monitored in pediatric patients.
- *Concomitant use of potent CYP2D6 inhibitors (eg, fluoxetine, paroxetine, quinidine):* Dose adjustment may be necessary.
- *Use in patients known to be CYP2D6 poor metabolizers:* Dose adjustment may be necessary.

Adverse reactions: Most common (>5% and at least twice the placebo rate) adverse reactions in child and adolescent trials of ADHD (6- to 17-year-olds) are

- Nausea
- Vomiting
- Fatigue
- Decreased appetite
- Abdominal pain
- Somnolence

Drug interactions include

- Monoamine oxidase inhibitors.
- CYP2D6 inhibitors (concomitant use may increase atomoxetine steady-state plasma concentrations in extensive metabolizers).
- Antihypertensive drugs and pressor agents (possible effects on blood pressure).
- Albuterol or other β_2-adrenergic agonists (action of albuterol on the cardiovascular system can be potentiated).

Vital Signs and Laboratory Monitoring

Monitoring blood pressure, heart rate, height, and weight is recommended. No specific laboratory monitoring is recommended.

Optimizing Dose

A general recommendation for optimizing dose—if confident that the child has adhered to the previously prescribed dose—is to continue to increase the dose until the benefit-to-risk ratio is optimized. However, with atomoxetine, it is recommended to not go above 1.4 mg/kg per day if body weight is 70 kg or less, or 100 mg/day if body weight is more than 70 kg. Treatment response, assessed systematically using information from parent and teacher reports (eg, NICHQ Vanderbilt Assessment Scale ratings), should be considered alongside reported and observed adverse effects during dose escalation. Satisfaction of the caregiver, teacher, and child regarding the child's response can also be useful. Ideally, a consensus will emerge about the preferred dose that maximizes the benefit-to-risk ratio.

Maintenance

Once an optimal dose is determined, maintenance treatment begins. Frequency of monitoring can be reduced, usually to follow-ups every 1 to 3 months, depending on the patient's needs. Consideration of dose adjustments is recommended annually, or more often, if the patient's clinical status changes significantly.

What if Atomoxetine Is Ineffective or Not Tolerated?

If adverse effects limit dose escalation or if the maximal recommended dose is not effective, discontinuation is recommended. If continued medication is clinically indicated, consideration of another class of ADHD medication may be warranted.

Discontinuing Atomoxetine

Atomoxetine can be discontinued without tapering. There are no reported withdrawal-induced adverse effects.

Adjunct Treatment to Stimulants

There is limited information regarding concomitant use of a stimulant and atomoxetine, though no data indicate a problem with this combination. The only relevant comment in the Strattera package insert is in Section 7.7: "Co-administration of methylphenidate with Strattera did not increase cardiovascular effects beyond those seen with methylphenidate alone."[16]

Adjunctive treatment may be considered when the stimulant dose cannot be optimized because of adverse effects, yet clinically impairing ADHD symptoms persist. Recommendations for using adjunctive atomoxetine are the same as when it is used alone. It is important to note that combination treatment may be prone to a higher likelihood of adverse effects and that, in general, treatment with 1 medication is preferable, when possible.

When to Consult or Refer

In general, consultation with, or referral to, a child and adolescent psychiatrist or other prescribing specialist may be considered when there is lack of clarity about diagnosis or after several medications have been tried and discontinued because of lack of effect or tolerability. Chapter 9 offers a more extensive discussion regarding what to do when interventions fail.

Summary

Five medications—the stimulants methylphenidate and amphetamine, the α_2-adrenergic agonists guanfacine and clonidine, and the selective norepinephrine inhibitor atomoxetine—are FDA approved for treatment of ADHD in children and adolescents. The AAP and American Academy of Child Adolescent and Psychiatry guidelines and practice parameters suggest starting treatment with 1 of the stimulants. Multiple preparations of methylphenidate and amphetamine are available, with the major difference between these being their duration of effect. It is recommended that pediatric PCCs develop familiarity with stimulant preparations with various durations of

effect. Available data suggest that a methylphenidate or an amphetamine preparation is effective in almost all children, so switching from one to the other is generally indicated if the first is not effective.

Guanfacine, clonidine, and atomoxetine are secondary options, with lower effectiveness than stimulants; they can be used independently or as adjunctive treatment if stimulants cannot be tolerated or are only partially or not effective. An advantage of guanfacine over clonidine is once-daily dosing in contrast to twice-daily dosing with clonidine. In contrast to the stimulants and α_2-adrenergic agonists, atomoxetine has a much-delayed onset of effect (about 4–6 weeks).

Medication should be part of a comprehensive treatment plan that includes, when indicated, appropriate behavioral therapy and school consultation.

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CHAPTER 6

Group 1 Medications for Anxiety and Depression

General Guidance

Medications

Although the medications described in this chapter are called "antidepressants," research data show that they are also effective for treating anxiety in children and adolescents.[1,2] Children and adolescents with depression have a larger response to placebo medication than children with anxiety. In other words, children and adolescents with depression or anxiety respond to antidepressants at similar rates (about 50%–60%), but respond to placebo differently, about 30% for anxiety and 40% to 50% for depression. Anxiety and depression frequently co-occur in youth, especially adolescents, and are both included in this chapter, because the medications used to treat them are very similar.

Recommendations for pharmacologic treatment of *depression* are straightforward: *fluoxetine* and *escitalopram* have US Food and Drug Administration (FDA) indications for treatment of major depressive disorder (MDD) in children (fluoxetine) and adolescents (fluoxetine and escitalopram).

Recommendations for pharmacologic treatment of anxiety have a more complex rationale. The FDA has not approved any selective serotonin reuptake inhibitor (SSRI) for treatment of any anxiety disorder in youth other than obsessive-compulsive disorder (OCD), an anxiety-like disorder. (See Evidence Supporting Efficacy section in Chapter 1 for an explanation of technical reasons.) However, high-quality, National Institutes of Health (NIH)–sponsored, multisite studies have demonstrated the efficacy and safety of fluoxetine, sertraline, and fluvoxamine for the 3 common anxiety disorders in youth: generalized anxiety disorder, social anxiety disorder, and

separation anxiety disorder. These 3 selective serotonin reuptake inhibitors (SSRIs) have FDA indications for use in youth with OCD (as well as various anxiety disorders in adults) and are recommended as Group 1 medications for treatment of common anxiety disorders in youth.

Throughout this chapter, escitalopram, fluoxetine, fluvoxamine, and sertraline (SSRIs) will be treated the same, unless differences are worthy of comment.

Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has an FDA indication for *generalized anxiety disorder* in children age 7 years and older. The main difference between duloxetine and SSRIs is the adverse event profile. Duloxetine has more concerning "warnings and precautions" than the SSRIs.

The 4 SSRIs and the SNRI duloxetine in group 1 that are recommended for treatment of anxiety or depression are presented in Table 6-1.

Reminder About Psychosocial Interventions

Evidence-based and effective psychotherapies for youth with anxiety or depression are considered first-line treatment; these are discussed in the Nonmedication Interventions section in Chapter 4. Cognitive-behavioral therapy (CBT), with a caregiver and family component, has the most supporting evidence and is the most effective psychotherapy for youth with anxiety. Cognitive behavioral therapy and interpersonal psychotherapy have the most supporting evidence and are the most effective psychotherapies for youth with depression. A substantial body of evidence indicates that combining psychotherapy with medication can enhance effectiveness of medication.

Importance of Combined Treatment

For depression, the largest study to date of moderate-to-severe depression in adolescents (the Treatment for Adolescents With Depression Study) suggests that time to remission is quicker and risk of suicidality is lower with combined treatment compared with medication-only treatment.[3] A 2017 Agency for Healthcare Research and Quality review of pediatric anxiety treatments concluded that "combined SSRI and CBT reduced primary anxiety symptoms and reduced clinical response compared to either approach alone" (page 40).[4]

Table 6-1. Group 1 Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitor for Anxiety and Depression

Generic Name	Trade Name	FDA Youth Indication(s), y	Initial Dose, mg	Max DD, mg	Dosing Frequency	Available Unit Dose Forms
Fluoxetine	Prozac	MDD; 8–17 OCD; 7–17	10–20 (5–10[a])	60	Daily	Capsules and tablets: 10, 20, and 40 mg Weekly capsules: 90 mg Oral solution: 4 mg/mL
Escitalopram	Lexapro	MDD; 12–17	10 mg (2.5–10[a])	20	Daily	Tablets: 5, 10 (scored), and 20 (scored) mg Oral solution: 1 mg/mL
Sertraline	Zoloft	OCD; 6–17	6–12 years: 25 (12.5–25[a]) 13–17 years: 50	200	Daily	Scored tablets: 25, 50, and 100 mg Oral solution: 20 mg/mL
Fluvoxamine	NA in United States	OCD; 8–17	25 (12.5–25[a])	8–11 years: 200 12–17 years: 300	Twice a day[b]	Tablets: 25, 50, and 100 mg
Duloxetine[c]	Cymbalta	GAD; 7–17	30	120 (60[a])	Daily	Delayed-release capsules: 20, 30 and 60 mg The capsule should not be opened, crushed, or chewed.

Abbreviations: FDA, US Food and Drug Administration; GAD, generalized anxiety disorder; max DD, maximum recommended daily dose based on FDA-approved package insert; MDD, major depressive disorder; NA, not available; OCD, obsessive-compulsive disorder.

[a] Author's recommendation.

[b] Divided doses (twice a day) if total daily dose is over 50 mg.

[c] Serotonin norepinephrine reuptake inhibitor.

Classified using US Food and Drug Administration. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed April 20, 2018.

Young Children

Children younger than 6 years are increasingly being treated with medication for anxiety and depression.[5] However, there are minimal data regarding the safety and efficacy of treatment of children under age 6 years with anxiety or depression.[6] Thus, the use of medications to treat young children with these disorders should be approached with caution, and referral to a specialist with appropriate expertise is recommended.

Choosing a Medication

No guidance regarding the selection of a specific SSRI to treat either depression or anxiety is available from the American Academy of Pediatrics or American Academy of Child and Adolescent Psychiatry.

For depression, SSRIs with FDA approval for treatment of MDD in youth are preferred (ie, fluoxetine and escitalopram). For anxiety, SSRIs with FDA approval for treatment of OCD in youth, and supporting efficacy and safety data for the common anxiety disorders in youth, are preferred (ie, fluoxetine, sertraline, and fluvoxamine). Duloxetine (SNRI) is generally recommended as a secondary medication for anxiety because of its adverse event profile.

Other issues that may influence selection of an SSRI include half-life, once-daily dosing, and potential drug-drug interactions. Fluoxetine, which has a much longer half-life (days to weeks) than other SSRIs, may be advantageous for patients with sporadic adherence but disadvantageous if intolerable side effects were to emerge. Fluvoxamine may be less convenient than other SSRIs because it needs to be taken twice a day, in contrast with other SSRIs that can be dosed once a day. Escitalopram may be advantageous when there are concerns about drug-drug interactions because it has less effect on CYP450 isoenzymes compared with other SSRIs.

Adverse Effects, Contraindications, and Drug Interactions

Adverse effects can be evaluated based on either severity or frequency. Package inserts required by the FDA emphasize severity, ranging from the most severe "Boxed Warnings," followed by "Warnings and Precautions," to "Adverse Reactions." In addition, package inserts describe contraindications and drug interactions.

The most comprehensive and least potentially biased prescribing information about adverse effects can be found in FDA-required package inserts. These inserts are available in various formats and locations, including in

medication packaging and the *Physician's Desk Reference*. They are available online at Drugs@FDA (www.accessdata.fda.gov), where they are referred to as 'labels'. Since the FDA modified the format for package inserts a few years ago, each insert has a 1-page "Highlights of Prescribing Information" that includes relatively complete and essential information about boxed warnings, warnings and precautions, adverse effects, contraindications, and drug interactions. These highlights can be accessed and reviewed quickly and conveniently and are recommended as useful resources.

Cost and Affordability

Generic medications are available for all 4 Group 1 SSRIs and duloxetine and are typically less expensive than brand medication. Please refer to the Cost and Affordability section in Chapter 5 for a discussion of cost and affordability of psychotropic medications.

Information for Caregivers About Specific Medications

There are numerous sources of information about medications for patients, parents, and caregivers(s), particularly on various Web sites. It is important for pediatric primary care clinicians (PCCs) to be aware that many, if not all, of these sources are supported, at least in part, by funds from the pharmaceutical industry. Potentially the least biased source is the FDA. At the end of each package insert (available online at Drugs@FDA [www.accessdata.fda.gov]) is a user-friendly document entitled "Medication Guide" or "Patient Counseling and Information." This document should be given to the patient (or caregiver) by the dispensing pharmacist (including mail-order pharmacies). In addition, the prescribing clinician can print the document and go over it with the caregiver or patient.

Group 1 Selective Serotonin Reuptake Inhibitors

Available Preparations

Group 1 SSRIs—fluoxetine, escitalopram, sertraline, and fluvoxamine—are listed in Table 6-1 along with

- Trade name
- Indications for use in youth
- Recommended initial dose

- Recommended maximum dose
- Dosing frequency
- Available unit dose forms of each medication

Information in the table relies on FDA-approved package inserts or, occasionally, the author's recommendation when specific information is not available.

Initial Dose

Table 6-1 presents recommended initial dose for each SSRI. In general, the younger the patient, the smaller is the recommended initial dose. Prepubertal children are particularly sensitive to hyperkinesis, insomnia, and restlessness (sometimes called "activation"), and these adverse effects appear to be dose-responsive.

Onset of Effect

Onset of effect for all Group 1 SSRIs generally occurs after 3 to 4 weeks at an effective dose. This 3- to 4-week delay is not from the time of *initial dose* but from the time of *effective dose*, which may occur several weeks after initial dose, depending on speed and extent of dose titration. Onset of some adverse effects, such as abdominal pain or discomfort, can occur within days of the initial dose and may worsen during dose titration. In addition, some therapeutic effects, such as improved sleep, may occur before more global improvement is seen in anxiety or depression symptoms.

Duration of Effect

The effect of an SSRI is continuous as long as the medication is taken as recommended.

Dosage Adjustments

Dosage adjustment for SSRIs requires balancing the desire to reach a therapeutic dose as quickly as possible with the reality that an effect of a dose change may not be observable for 2 to 4 weeks. A practical approach to dose escalation that balances this desire and reality is to increase the dose about every 1 or 2 weeks by an amount approximately equivalent to the initial dose while observing for adverse effects. If no or minimal adverse effects occur, dose increases may continue, as long as there is consistent communication between the patient and pediatric PCC and the pediatric PCC is confident

of adherence. Dose increases can be delayed or reversed, depending on the clinical situation. Gastrointestinal and activation adverse effects may resolve spontaneously if dose escalation is slowed temporarily. This process can be continued until an optimal dose or the recommended maximum daily dose is reached.

Monitoring Therapeutic Response During Dose Adjustments

During dose adjustment, a weekly phone check-in or appointment is preferred, when possible. Standardized rating scales, such as the Patient Health Questionnaire-9 (PHQ-9) Modified for Teens for depression and the Screen for Child Anxiety Related Disorders (SCARED) for anxiety, may be helpful in systematically assessing symptom change from the patient and caregiver (see Appendix A).

Talking With Patients and Families About Safety

Information in the following section, Safety Monitoring, is detailed and thorough regarding all potential contraindications, boxed warnings, warnings and precautions, adverse reactions, and potential drug interactions of SSRIs. This is more information than a child and family can absorb and remember. It is important that the family know the pharmacy will provide this information and that the pediatric PCC can answer questions that may arise.

Some suggestions about topics for discussion with patients and families about SSRIs are as follows:

- Many healthy children do not have side effects of SSRIs.
- Side effects of SSRIs are reversible if the medicine is decreased or, if necessary, discontinued.
- The most common side effects are upset stomach and/or nausea, which occur soon after the medicine is initiated, or soon after the dose is increased. Often, these side effects subside over a few days.
- Another common side effect that usually occurs with dosage increases is agitation or behavioral activation. It may subside over a few days.
- Less common side effects are disrupted sleep, daytime sleepiness, fatigue, or tremor.
- Adolescents may have increased sweating, decreased sexual desire, or delayed orgasm.
- Suicidal thoughts or behaviors can emerge during recovery from depression. About 1 in 100 to 150 patients taking antidepressants (compared with placebo) develop suicidal ideas or behaviors. It is important to

educate the patient and family about this potential side effect and develop a plan for monitoring and safety.
- If any of these or other possible side effects occur, the patient and family need to know that the pediatric PCC is available to respond.
- Remember, many children do not have side effects of this medication. If side effects occur, they may go away or can be eliminated by discontinuing the medicine.

Safety Monitoring

Monitoring for contraindications, adverse effects, and potential drug interactions starts before the medication is prescribed and continues throughout drug administration. As with all medications, safety monitoring for SSRIs depends on a targeted history and physical examination. The following information is derived from FDA-approved package inserts for the 4 Group 1 SSRIs.

Contraindications: Most warnings and precautions are related to findings that are relatively rare in children and adolescents treated with SSRIs, and include

- Known hypersensitivity to SSRI or any active ingredients.
- Interactions with monoamine oxidase inhibitors (MAOIs) (eg, serotonin syndrome).
  - Do not use SSRIs (*all 4 Group 1 SSRIs)* and MAOIs concomitantly, or within 14 days of stopping an MAOI.
  - Do not start SSRI (*escitalopram, fluvoxamine, sertraline*) within 14 days of stopping an MAOI.
  - Do not start MAOI within 5 weeks of stopping (does not apply to other SSRIs).
- Pimozide: Do not use. Risk of QT interval prolongation. Do not use concomitantly (*all 4 Group 1 SSRIs*).
- Thioridazine: Do not use. Risk of QT interval prolongation. Do not use concomitantly (*fluoxetine and fluvoxamine only*), or within 5 weeks of stopping *fluoxetine*.
- Coadministration of tizanidine or alosetron (*fluvoxamine only*).
- Concomitant use of disulfiram (*sertraline oral solution only*).

Boxed warnings address findings that are relatively rare in children and adolescents treated with SSRIs and include suicidal thoughts and behaviors (*all 4 Group 1 SSRIs*). Monitor for worsening or emergence of suicidal

thoughts and behaviors (see Chapter 3 section entitled "Safety Assessment and Monitoring" for details).

Warnings and precautions: Most warnings and precautions are related to findings that are relatively rare in children and adolescents treated with SSRIs. Warnings and precautions listed herein are derived from package inserts, with minor modifications by the author. Those in the package insert of all 4 Group 1 SSRIs are at the top; those for just 1 SSRI are at the bottom. Below each warning or precaution are recommendations for monitoring.

- *Clinical worsening and suicide risk (all 4 Group 1 SSRIs):* Monitor for clinical worsening, suicidal thinking and behavior, and unusual change in behavior during first few months of therapy and during dosage changes.
- *Serotonin syndrome (all 4 Group 1 SSRIs):* Can occur with SSRI alone. Avoid administering or monitor carefully when coadministering other serotonergic agents, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines and St John's wort. If such symptoms occur, discontinue the SSRI and initiate supportive treatment.
- *Activation of mania or hypomania (all 4 Group 1 SSRIs):* Screen for bipolar disorder and monitor for mania or hypomania.
- *Seizures (all 4 Group 1 SSRIs):* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.
- *Abnormal bleeding (all 4 Group 1 SSRIs):* Use with nonsteroidal anti-inflammatory drugs (eg, aspirin, ibuprofen, naproxen, celecoxib), warfarin, or other drugs that affect coagulation (eg, trazodone) may potentiate the risk of gastrointestinal or other bleeding.
- *Angle-closure glaucoma (all 4 Group 1 SSRIs).* Avoid administering to patients with known and untreated anatomically narrow angles.
- *Hyponatremia (all 4 Group 1 SSRIs).* Consider discontinuing if symptomatic hyponatremia occurs (eg, in patients with syndrome of inappropriate antidiuretic hormone).
- *Potential for cognitive and motor impairment (fluoxetine, escitalopram, sertraline):* Advise using caution when operating machinery.
- *Discontinuation of treatment (escitalopram, sertraline, fluvoxamine):* A gradual reduction in dose rather than abrupt cessation is recommended.
- *Use in patients with concomitant illness (escitalopram, sertraline, fluvoxamine):* Use caution in patients with diseases or conditions that produce altered metabolism or hemodynamic reactions.

- *Altered appetite, weight, or both (fluoxetine, sertraline):* Monitor weight, primarily for potential weight loss.
- *Allergic reactions and rash (fluoxetine):* Discontinue on appearance of rash or allergic phenomena.
- *QT prolongation (fluoxetine, sertraline):* Use caution in conditions that predispose to arrhythmias or increased fluoxetine exposure. Use cautiously in patients with risk factors for QT prolongation.
- *Anxiety and insomnia (fluoxetine):* Be aware that these reactions may occur.
- *Long half-life (fluoxetine):* Be aware that dose changes will not be reflected in plasma for several weeks.
- *Other potentially important drug interactions (fluvoxamine):* Coadministration with a benzodiazepine is generally not advisable. Use with caution in patients taking clozapine, methadone, mexiletine, ramelteon, theophylline, warfarin, or other drugs affecting homeostasis.

Adverse reactions: Across the package inserts for the 4 Group 1 SSRIs, there is considerable variability in the adverse reactions listed. All 4 package inserts list the reactions in adults that were observed in placebo-controlled clinical trials with an incidence greater than or equal to 5% and an incidence at least twice that of placebo. The package inserts also state that adverse effects observed in pediatric studies were similar to those in adult studies. Data from relatively small numbers of pediatric study participants are also presented. The most consistently reported adverse effects are listed herein. More details may be found in the specific package insert for each SSRI.

- Dyspepsia (more common in preteens)
- Nausea
- Agitation or behavioral activation (more common in preteens)
- Insomnia
- Somnolence
- Fatigue
- Sexual (decreased libido, anorgasmia, ejaculatory delay; more common in adolescents)
- Sweating increased (more common in adolescents)
- Tremor

Drug interactions: Drug interactions listed in package inserts vary across the 4 Group 1 SSRIs and, in many instances, overlap with warnings and precautions. The most salient drug interactions are listed herein. More details may be found in the specific package insert for each SSRI.

- SSRIs, serotonin-norepinephrine reuptake inhibitors, or tryptophan
- Drugs that affect homeostasis (nonsteroidal anti-inflammatory drugs, aspirin, warfarin)
- MAOIs
- Drugs that prolong the QT interval (eg, pimozide or thioridazine)
- *For fluoxetine and sertraline:* Drugs metabolized by CYP2D6
- *For fluvoxamine:* Drugs inhibiting or metabolized by CYP1A2, CYP2C9, CYP3A4, and CYP2C19

Vital Signs and Laboratory Monitoring

For all SSRIs, monitoring height and weight is recommended. Routine screening of thyroid functioning is recommended as part of the baseline evaluation of depression and may be repeated at a follow-up assessment for youth with treatment-refractory symptoms.

Optimizing Dose

A general recommendation for optimizing dose—if confident that the child has adhered to the previously prescribed dose—is to continue to increase the dose until the benefit-to-risk ratio is optimized. Treatment response, assessed systematically using information from the parent and the patient's self-reports (eg, PHQ-9 Modified for Teens for depression and SCARED for anxiety) should be considered alongside reported and observed adverse effects during dose escalation. The caregiver's and child's satisfaction with the child's response can also be useful. Ideally, a consensus will emerge about the preferred dose that maximizes the benefit-to-risk ratio.

Maintenance

Once an optimal dose is determined, maintenance treatment begins. Frequency of monitoring can be reduced, usually to follow-ups every 1 to 3 months, depending on the patient's needs. Consider dose adjustments annually, or more often, if the patient's clinical status changes significantly.

What if the First Selective Serotonin Reuptake Inhibitor Is Ineffective or Not Tolerated?

If adverse effects limit sufficient dose escalation or if the initial SSRI is not sufficiently beneficial, discontinuation of the SSRI is recommended.

Discontinuing a Selective Serotonin Reuptake Inhibitor and Possible Withdrawal Adverse Effects

To minimize withdrawal adverse effects, a gradual reduction in dose over a few weeks, rather than abrupt discontinuation, is recommended, except for fluoxetine. Because of the long half-life of fluoxetine (and its active metabolite), it can be discontinued abruptly and will "self-taper." Withdrawal adverse effects, particularly with abrupt discontinuation, may include dysphoric mood, irritability, agitation, insomnia, anxiety, headache, emotional lability, and flulike symptoms.

Switching From One Selective Serotonin Reuptake Inhibitor to Another

The best available research on depression in adolescents indicates that, if the initial SSRI "fails," the next-best medication option is another SSRI.[7]

Switching from one SSRI to another can be staggered and overlapping, as long as the combined total daily dose remains equivalent and comparable. A staggered switch can usually be completed over a few weeks. If fluoxetine is discontinued abruptly, dose escalation of the new SSRI can be based on an approximate half-life of fluoxetine and its active metabolite of 1 to 2 weeks.

When to Consult or Refer

It is important to assess if a child has had adequate duration and dose of medication before concluding that a child is refractory to treatment with that medication. The wait time for symptom improvement can be frustrating for parents and children, so it is helpful to provide clear expectations for treatment and also to convey factors that can accelerate treatment response (eg, taking a medication consistently; cotreatment with therapy). Medications can be beneficial; however, most youth have residual symptoms after acute treatment, so it is also helpful to convey that multiple options can be pursued (eg, with specialist consultation) for youth who do not have a robust response to standard treatment.

In general, consultation with, or referral to, a child and adolescent psychiatrist or other prescribing specialist may be considered when there is a lack of clarity about diagnosis or after more than 1 medication has been tried and discontinued because of lack of effect or tolerability. Chapter 9 offers a more extensive discussion regarding what to do when interventions fail.

Group 1 Serotonin and Norepinephrine Reuptake Inhibitor: Duloxetine

Duloxetine is an SNRI that is FDA approved for treatment of generalized anxiety disorder in children and adolescents aged 7 to 17 years and adults. Because duloxetine is associated with more adverse events than SSRIs, a pediatric PCC may prefer to start treatment of anxiety with an SSRI.

Available Duloxetine Preparations

Generic and branded duloxetine preparations are available and are listed in Table 6-1. Of note, the capsule should not be opened, crushed, or chewed.

Information in the table relies on the FDA-approved package insert and the author's recommendation when specific information is not available.

Initial Dose

Table 6-1 presents recommended initial dose of duloxetine in children and adolescents: 30 mg once a day.

Onset of Effect

Onset of effect of duloxetine is similar to that of the SSRIs. Improvement generally occurs after 3 to 4 weeks at an effective dose. This 3- to 4-week delay is not from the time of *initial dose* but from the time of *effective dose*, which may occur several weeks after the initial dose, depending on speed and extent of dose titration. Onset of some adverse effects, such as abdominal pain or discomfort, can occur within days of the initial dose and may worsen during dose titration. In addition, some therapeutic effects, such as improved sleep, may occur before more global improvement is seen in anxiety symptoms.

Duration of Effect

The effect of duloxetine is continuous as long as the medication is taken as recommended.

Dosage Adjustments

The FDA package insert is very specific about dosage adjustments.

> "Initiate Cymbalta [duloxetine] at a dose of 30 mg once daily for 2 weeks before considering an increase to 60 mg. The recommended dose range is 30 to 60 mg once daily. Some patients may benefit from doses above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day. The safety of doses above 120 mg once daily has not been evaluated" (see page 3 of package insert).[8]

Monitoring Therapeutic Response During Dose Adjustments

During dose adjustment, a weekly phone check-in or appointment is preferred, when possible. A standardized rating scale, such as SCARED, may be helpful in systematically assessing symptom change (see Appendix A).

Safety Monitoring

Monitoring for contraindications, adverse effects, and potential drug interactions starts before the medication is prescribed and continues throughout drug administration. As with all medications, safety monitoring for SSRIs depends on a targeted history and physical examination. The following information is derived from the FDA-approved package insert for duloxetine (Cymbalta).

Contraindication: *"Serotonin Syndrome and MAOIs*: Do not use MAOIs intended to treat psychiatric disorders with Cymbalta or within 5 days of stopping treatment with Cymbalta. Do not use Cymbalta within 14 days of stopping an MAOI intended to treat psychiatric disorders" (see page 1 of package insert).[8]

Boxed warning: "*Increased risk of suicidal thinking and behavior:* Monitor for worsening or emergence of suicidal thoughts and behaviors" (see page 1 of package insert).[8]

Warnings and precautions: Most warnings and precautions are related to findings that are relatively rare in children and adolescents treated with duloxetine. Duloxetine has 6 warnings and precautions described herein for the SSRIs: *serotonin syndrome, abnormal bleeding, discontinuation of treatment, activation of mania or hypomania, angle-closure glaucoma, seizures, and*

hyponatremia. In addition, duloxetine has the following additional warnings and precautions, presented verbatim from the package insert (see page 1)[8]:

- *Hepatotoxicity:* Hepatic failure, sometimes fatal, has been reported in patients treated with [duloxetine]. [Duloxetine] should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction … should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.
- *Orthostatic hypotension, falls, and syncope:* Cases have been reported with [duloxetine] therapy.
- *Severe skin reactions:* Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, can occur with [duloxetine]. [Duloxetine] should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.
- *Blood pressure:* Monitor blood pressure before initiating treatment and periodically throughout treatment.
- *Inhibitors of CYP1A2 or Thioridazine:* Should not administer with [duloxetine].
- *Glucose control in diabetes:* In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, and hemoglobin A1c have been observed.
- *Conditions that slow gastric emptying:* Use cautiously in these patients.
- *Urinary hesitation and retention.*

Adverse reactions: The most common adverse reactions in adults (≥5% and at least twice the incidence of placebo patients) include *nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis*. The most common (≥5% and twice that of placebo) adverse reactions observed in pediatric clinical trials include *nausea, diarrhea, decreased weight, and dizziness*.

Drug interactions: Because both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism

- Potent inhibitors of CYP1A2 should be avoided (eg, fluvoxamine, cimetidine, and quinolone antimicrobials such as ciprofloxacin and enoxacin).
- Potent inhibitors of CYP2D6 may increase duloxetine concentrations (eg, fluoxetine, paroxetine, quinidine).

Vital Signs and Laboratory Monitoring

Monitoring blood pressure, pulse, and weight is recommended. Routine screening of thyroid functioning is recommended as part of the baseline evaluation of depression and may be repeated at a follow-up assessment for youth with treatment-refractory symptoms.

Optimizing Dose

A general recommendation for optimizing dose—if confident that the child has adhered to the previously prescribed dose—is to continue to increase the dose until the benefit-to-risk ratio is optimized. Treatment response, assessed systematically using information from the parent and the patient's self-reports on the SCARED should be considered alongside reported and observed adverse effects during dose escalation. The caregiver's and child's satisfaction with the child's response can also be useful. Ideally, a consensus will emerge about the preferred dose that maximizes the benefit-to-risk ratio.

Maintenance

Once an optimal dose is determined, maintenance treatment begins. Frequency of monitoring can be reduced, usually to follow-ups every 1 to 3 months, depending on the patient's needs. Consider dose adjustments annually, or more often, if the patient's clinical status changes significantly.

What if Duloxetine Is Ineffective or Not Tolerated?

If adverse effects limit sufficient dose escalation or if duloxetine is not sufficiently beneficial, discontinuation is recommended.

Discontinuing Duloxetine and Possible Withdrawal Adverse Effects

To minimize withdrawal adverse effects, a gradual reduction in dose over a few weeks, rather than abrupt discontinuation, is recommended. Withdrawal adverse effects, particularly with abrupt discontinuation, may include dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue (see page 1 of package insert).[8]

Switching From Duloxetine to a Selective Serotonin Reuptake Inhibitor

There is no guidance from the FDA in the package insert for duloxetine regarding switching from duloxetine to an SSRI. Because both drugs

share serotonin reuptake inhibition, a staggered and overlapping approach should be well-tolerated. A staggered switch can usually be completed over a few weeks.

When to Consult or Refer

It is important to assess if a child has had adequate duration and dose of medication before concluding that a child is treatment refractory to a medication. The wait time for symptom improvement can be very frustrating for parents and children, so it is helpful to provide clear expectations for treatment and also to convey factors that can accelerate treatment response (eg, taking a medication consistently; cotreatment with therapy). Although medications can be very beneficial, most youth have residual symptoms after acute treatment, so it is also helpful to convey that multiple options can be pursued (eg, with specialist consultation) for youth who do not have a robust response to standard treatment.

In general, consultation with, or referral to, a child and adolescent psychiatrist or other prescribing specialist may be considered when there is lack of clarity about diagnosis or after more than 1 medication has been tried and discontinued because of lack of effect or tolerability. Chapter 9 offers a more extensive discussion regarding what to do when interventions fail.

Summary

Medication should be part of a comprehensive treatment plan that includes, when indicated and available, evidence-based psychotherapy.

Four Group 1 SSRIs are recommended for treatment of anxiety or depression. No guidance regarding selection of a specific SSRI is available from the American Academy of Pediatrics or the American Academy of Child Adolescent Psychiatry. For depression, SSRIs with FDA approval for treatment of MDD in youth are preferred: fluoxetine and escitalopram. For anxiety, SSRIs with FDA approval for treatment of OCD in youth, and supporting efficacy and safety data for common anxiety disorders, are preferred: fluoxetine, sertraline, and fluvoxamine. Duloxetine, an SNRI, can be considered for anxiety instead of, or after inadequate response to, an SSRI. Duloxetine has more potentially concerning warnings and precautions—hepatotoxicity, severe skin reactions, and blood pressure changes—but does not have the potential sexual adverse reactions of the SSRIs.

References

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Part 4—Group 2 (FDA-Approved Antipsychotics and Mood Stabilizers) and Group 3 (All Other) Medications

CHAPTER 7

Group 2 Medications: Antipsychotics and Mood Stabilizers

Rationale

In addition to prescribing and monitoring Group 1 medications, pediatric primary care clinicians (pediatric PCCs) are ideally suited to collaborate with psychiatrists and other mental health specialists in the care of children with more severe or uncommon disorders. Thus, they may be asked to take on partial responsibility for monitoring therapeutic and adverse effects of various other medications that are included in Groups 2 and 3.

Group 2 medications can be monitored in primary care settings, but because they have a more concerning safety profile and more complicated monitoring requirements than Group 1 medications, they are generally prescribed by specialists—child and adolescent psychiatrists, developmental-behavioral pediatricians, specialists in neurodevelopmental disabilities or adolescent medicine, pediatric neurologists, and adult psychiatrists with additional training in adolescent psychiatry.

Some pediatric PCCs, due to their own interests and additional training or their limited community resources or some combination of the 2, may choose to prescribe Group 2 medications. For example, the pediatric PCC may prescribe an antipsychotic medication to serve as a bridge while a child is in transition to specialty care, ideally after consultation with the specialist. Alternatively, the pediatric PCC may choose to prescribe an antipsychotic medication to a child with autism and irritability due to long wait times for the child to see an appropriate specialist. Fortunately, low doses of the antipsychotic medication are usually sufficient to reduce symptom severity.

Group 2 includes all US Food and Drug Administration (FDA)–approved medications for youth with other disorders (ie, not attention-deficit/hyperactivity disorder, anxiety, or depression). Group 2 includes 6 second-generation

antipsychotics (SGAs; asenapine, lurasidone, olanzapine, quetiapine, risperidone, and paliperidone), 1 third-generation antipsychotic (TGA; aripiprazole), and lithium, a mood stabilizer.

The SGA/TGAs are approved for treatment of youth with psychosis in schizophrenia (all except asenapine); mania in bipolar disorder (all except paliperidone and lurasidone); and "irritability" in autism (only risperidone and aripiprazole). However, these medications are most commonly used off-label (outside FDA indications) in youth to treat behavioral problems, especially aggression that can cause harm to self or others (see later in the chapter for details).

Lithium is FDA approved for treatment of acute mania in bipolar disorder in adolescents. Lithium is also used off-label to treat nonbipolar mood instability.

Antipsychotics

Antipsychotics can be both beneficial and problematic. They are effective in reducing the severity of a wide range of symptoms, but they also are associated with various major adverse effects.

There are 3 "generations" of antipsychotics, based on their mechanisms of action. First-generation antipsychotics (FGAs), approved for use in adults starting in the 1950s, are potent dopamine D_2 receptor blockers. Second-generation antipsychotics, approved starting in the late 1980s, block dopamine D_2 and serotonin $5HT_{2A}$ receptors. Third-generation antipsychotics, approved starting in the early 2000s, have partial agonist activity at dopamine D_2 and serotonin $5HT_{1A}$ receptors and antagonist activity at serotonin $5HT_{2A}$ receptors.

Currently FGAs are prescribed less frequently to youth in the United States compared with the newer agents. Haloperidol, molindone, perphenazine, pimozide, and thioridazine have, or have had, FDA indications in children and/or adolescents for various disorders (eg, schizophrenia, Tourette disorder) and symptoms (eg, severe behavioral problems, psychosis). None of these pediatric indications is based on data from studies of the size and quality required by the FDA starting in the 1990s for SGAs and TGAs. Thus, FGAs are not included in Group 2 medications. Also of note, FGAs generally have more neurologic adverse effects than SGAs and TGAs. Children are

more sensitive than adults to some of these neurologic effects. Haloperidol is still used in emergency departments and inpatient care settings to manage acute agitation and aggression.

Compared with FGAs, SGAs/TGAs are less likely to be associated with neurologic adverse effects in youth, but they are associated with weight gain and secondary metabolic effects. A 2013 systematic review and meta-analysis was conducted of double-blind, placebo-controlled, randomized pediatric SGA trials that reported metabolic adverse effects.[1] That study indicated that SGAs/TGAs vary in their propensity to cause weight gain during initial short-term treatment (6–8 weeks). Mean weight gain compared with placebo was 3.45 kg for olanzapine (95% confidence interval [CI] 2.93–3.98), 1.77 kg for risperidone (95% CI 1.35–2.20), and 0.94 kg for aripiprazole (95% CI 0.65–1.24). A 2015 systematic review and meta-analysis of randomized trials of antipsychotic treatment specifically for psychotic disorders among children, adolescents, and young adults[2] reported that weight gain greater than 7% of baseline weight was very common (relative risk 3.62, 95% CI 1.29–10.17) over a median treatment period of 8 weeks. The authors concluded that youth are more vulnerable than adults to antipsychotic medication–induced weight gain.

Effects, Indications, Ages, Equivalencies, and Dosages

Specific *therapeutic effects* of antipsychotics include

- Antipsychotic effects for hallucinations, delusions, and disorganized thinking
- Mood-stabilizing effects for mania, irritability, and mood instability
- Possible "organizing" or "calming" effects for agitation and aggressive behavior

The 10 SGAs and 2 TGAs *available* in the United States are presented in Table 7-1. The table also includes the 6 SGAs and 1 TGA indicated in children or adolescents, and thus, are included in Group 2.

Table 7-2 lists the *indications* by disorder and age range for the 7 SGA/TGAs on the US market.

Table 7-3 lists *drug equivalencies* for the 7 FDA-approved SGA/TGAs, using risperidone as the comparator, with an equivalency of 1. Also included for comparison are ziprasidone (Geodon), which is one of the Group 3 medications described in Chapter 8, and haloperidol, an FGA. The equivalencies in Table 7-3 are based on the best available data.[3] These data are based on the

Table 7-1. Second- and Third-Generation Antipsychotics

Medication	Brand Name	Initial FDA Approval for Adults
Clozapine	Clozaril	1989
Risperidone[a]	Risperdal	1993
Olanzapine[a]	Zyprexa	1996
Quetiapine[a]	Seroquel	1997
Ziprasidone	Geodon	2001
Aripiprazole[a,b]	Abilify	2002
Paliperidone[a]	Invega	2006
Iloperidone	Fanapt	2009
Asenapine[a]	Saphris	2009
Lurasidone[a]	Latuda	2010
Brexpiprazole	Rexulti	2015
Cariprazine[b]	Vraylar	2015

Abbreviation: FDA, US Food and Drug Administration.

[a] US Food and Drug Administration approved for use in some youth younger than 18 years as of January 10, 2018.

[b] Third-generation antipsychotic.

Table 7-2. SGA/TGAs With Pediatric FDA Indications

Drug	FDA-Approved Disorder and Ages, y		
	Psychosis in Schizophrenia	Bipolar Mania	"Irritability" in ASD[a]
Risperidone	>13	>10	>5
Aripiprazole[a]	>13	>10	>6
Quetiapine	>13	>10	NA
Olanzapine	>13	>13	NA
Paliperidone	>12	NA	NA
Asenapine	NA	>10	NA
Lurasidone	>13	NA	NA

Abbreviations: ASD, autism spectrum disorder; FDA, US Food and Drug Administration; NA, not applicable; SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

[a] Also has indication for Tourette disorder for ages 6 years and older.

Classified using US Food and Drug Administration. Drugs@FDA Web site. https://www.accessdata.fda.gov/scripts/cder/daf/Accessed April 19, 2018.

minimal necessary dose for treatment of psychosis in schizophrenia in adults. No such comparative data are available for children and adolescents or for symptoms and disorders other than psychosis in schizophrenia. Thus, these equivalencies are meant to serve as a general guide, not as a definitive conversion factor.

Table 7-3. Dose Equivalency of Selected Antipsychotic Medications[a]

Medication	Dose Equivalency, mg
Risperidone	1
Aripiprazole	5
Quetiapine	75
Olanzapine	4
Paliperidone	1.5
Ziprasidone	20
Haloperidol	2

[a] Data from adults with schizophrenia; no data available in children and adolescents.

Classified using Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. *Schizophr Bull.* 2014;40(2):314–326.

Table 7-4 lists initial, recommended, and maximal *doses* for various indicated disorders for the 7 FDA-approved SGA/TGAs. These doses were taken directly from the first page of the drug label for each drug at the Web site Drugs@FDA (www.accessdata.FDA.gov). Again, they are meant as guides, not only for clinicians who are prescribing these medications but also for those who are participating in monitoring their appropriateness, effectiveness, adverse effects, and related laboratory measures. Of note, if the pediatric PCC confirms that a child has not taken her/his antipsychotic for a month or longer, retitration from the recommended initial dose is recommended.

Adverse Effects and Monitoring

Of all psychotropic medications used in children and adolescents, SGA/TSAs generally have the most concerning adverse effects, including

- Sedation
- Weight gain
- Elevated glucose
- Insulin resistance
- Elevated triglyceride and cholesterol levels
- Irreversible involuntary movements (tardive dyskinesia)
- Gynecomastia
- Galactorrhea

Three relatively common adverse effects of SGAs are listed in Box 7-1. Also, for the 3 SGAs and TGA for which data are available, the frequency of each type of adverse effect is displayed from left (most common) to right (least

Table 7-4. FDA-Recommended Dosing for Group 2 SGA/TGAs in Youth

Medication	Indication	Ages, y	Initial Dose, mg	Recommended Dose, mg	Maximum Dose, mg
Risperidone	Psychosis in SCZ Mania in BP Irritability in autism	13–17 10–17 5–17	0.5 0.5 0.25 (<20 kg) 0.5 (≥20 kg)	3 1.0–2.5 0.5 (<20 kg) 1.0 (≥20 kg)	6 6 3 3
Aripiprazole	Psychosis in SCZ Mania in BP Irritability in autism	13–17 10–17 6–17	2 2 2	10 10 5–10	30 30 15
Quetiapine	Psychosis in SCZ Mania in BP	13–17 10–17	25 twice a day 25 twice a day	400–800 400–800	800 600
Olanzapine	Psychosis in SCZ Mania in BP Augmentation of fluoxetine for depression in BP I	13–17 13–17 10–17	2.5–5 2.5–5 2.5	10 10 5[a]	NA NA NA
Paliperidone	Psychosis in SCZ	12–17	3 (<51 kg) 3 (>51 kg)	3–6 (<51 kg) 3–12 (>51 kg)	6 (<51 kg) 12 (>51 kg)
Asenapine	Mania in BP	10–17	2.5 twice a day	2.5–10 twice a day	10 twice a day
Lurasidone	Psychosis in SCZ	13–17	40	40–80	NA

Abbreviations: BP, bipolar; FDA, US Food and Drug Administration; NA, not applicable; SCZ, psychosis in schizophrenia; SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

[a] No recommended dose is listed; author's recommendation.

Classified using US Food and Drug Administration. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 20, 2018.

common). Sedation and anticholinergic effects, such as dry mouth or constipation, can be troubling for both patients and their parents and can lead to reduced adherence to or discontinuation of medication. If problematic, these adverse effects can be reduced or alleviated by lowering dose (especially for sedation) or switching to an SGA further to the right in Box 7-1. Tremor, which is usually mild in youth taking clinically appropriate doses, may also be reduced or alleviated by lowering the dose or switching medication.

Three types of major potential adverse effects of SGAs/TGA are presented in Box 7-2. Many of the major adverse effects of SGAs, particularly weight gain, metabolic abnormalities, and delayed involuntary movements, can

Box 7-1. Three Relatively Common Adverse Effects Associated With Group 2 SGAs and TGA (from more severe adverse effect on the left to less severe adverse effect on the right)

Sedation Olanzapine > quetiapine > risperidone ≥ aripiprazole
Anticholinergic (eg, dry mouth, constipation) Olanzapine > quetiapine > risperidone = aripiprazole
Tremor Generally mild and not impairing

Abbreviations: SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

Box 7-2. Three Major Potential Adverse Effects Associated With Group 2 SGA/TGAs

Weight Gain Olanzapine > quetiapine > risperidone > aripiprazole.
Metabolic Abnormalities (eg, elevated glucose, cholesterol, or triglyceride level) • Similar sequence because metabolic effects are secondary to weight gain. • In addition, olanzapine has direct hepatic effect.
Persistent Involuntary Movements • Tardive dyskinesia. • Transient dyskinesia (during drug withdrawal). • Differences among medications are unclear because these are rare in children.

Abbreviations: SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

Classified using Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA.* 2009;302(16):1765–1773, and Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord.* 2010;12(2):116–114.

develop into major health problems (eg, cardiovascular disease and its long-term sequelae, tardive dyskinesia) during long-term treatment and may not be reversible.

There are individual differences in vulnerability to weight gain and the effect of metabolic changes. Some children will experience minimal, if any, weight or metabolic changes, while others may experience substantial increases in weight or changes in metabolism, even in response to treatment with relatively low doses. Unfortunately, there are no valid and reliable predictors beyond, perhaps, family history and antipsychotic naiveté, of the extent of weight gain or metabolic changes in an individual child.

Most disorders treated with SGAs/TGAs are chronic and generally require long-term treatment. Thus, determining risk versus benefit, both before and during treatment, can be challenging and needs to be reassessed at regular intervals.

Box 7-3 *presents 3 other important adverse effects or laboratory findings* associated with SGAs. Acute dystonia is relatively rare in children and occurs almost exclusively during the first few days of treatment or soon after a dose increase. Acute dystonia can be quickly and effectively treated with benztropine or diphenhydramine (severe dystonia may require intramuscular diphenhydramine). Once a child or adolescent starts receiving a stable dose of an SGA, acute dystonia is very rare, so the benztropine or diphenhydramine can be discontinued. Several side effects, such as gynecomastia and galactorrhea, which are relatively uncommon, and salivary hypersecretion and associated drooling that can be very annoying to patients, may be alleviated by lowering the dosage or switching medications. Salivary hypersecretion appears to be more common with risperidone.

Box 7-3. Three Additional Important Adverse Events Associated With Group 2 SGA/TGAs

Acute Dystonia Unclear differences among medications
Gynecomastia, Galactorrhea, or Both More commonly associated with risperidone; may be related to elevated prolactin level
Salivary Hypersecretion and Drooling More commonly associated with risperidone; generally concerning to patients

Abbreviations: SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

Severity of adverse effects associated with SGA/TGAs can vary depending on the drug selected, dose, and duration of treatment (Box 7-4).

Monitoring for adverse effects of SGA/TGAs includes a targeted history and physical examination and a few laboratory studies (Box 7-5). There is no formal, widely accepted protocol that specifies the content and frequency of monitoring in youth receiving SGA/TSAs. Monitoring at baseline, 12 weeks,

Box 7-4. Treatment Variables—the 3 Ds—That Can Intensify Severity of Adverse Effects

Drug SGAs vary regarding severity of various adverse effects (see Boxes 7-1, 7-2, and 7-3).
Duration of SGA/TGA Treatment Longer-term exposure is generally associated with more weight increase, metabolic adverse effects, and possible tardive dyskinesia.
Dose • Particularly relevant to weight-related and metabolic adverse effects. • Only replicated data available are for risperidone.

Abbreviations: SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

Box 7-5. Monitoring SGA/TGA Adverse Effects[a]

Sedation History and physical examination
Gynecomastia, Galactorrhea, or Both History and physical examination (if positive, prolactin level)
Anticholinergic (eg, dry mouth, constipation) History and physical examination
Neurologic History and physical examination (including AIMS and Barnes Akathisia Rating Scale; see Appendix A)
Other • Hepatic function (ALT, AST, alkaline phosphatase) • Cardiac (baseline and therapeutic ECG for ziprasidone or for any SGA/TGA if significant cardiac history)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; ALT, alanine transaminase; AST, aspartate transaminase; ECG, electrocardiography; SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

[a] Excluding weight-related and metabolic effects.

12 months, and then annually is a general (minimal) suggestion that hopefully will be supported by (or need to be modified by) outcome data as more evidence becomes available. Some US states have antipsychotic monitoring programs for youth, which may include specific monitoring guidelines or protocols.

Management of individual adverse effects often starts with lowering the dose or changing medication. Further evaluation by a specialist may be indicated (eg, for gynecomastia and diabetes mellitus). Additional interventions are generally not medication specific and call on general medical management skills. The American Academy of Child and Adolescent Psychiatry is planning to issue a more detailed clinical practice guideline on antipsychotic medication based on the upcoming review by the US Department of Health and Human Services Agency for Healthcare Research and Quality (available at www.aacap.org).

Weight and potential metabolic adverse effects also need to be monitored. The only available formal published guidance is for adults (Table 7-5). These published adult guidelines serve as a general framework for pediatric practice and are endorsed in the American Academy of Child and Adolescent Psychiatry practice parameters. The American Academy of Pediatrics has not issued formal guidelines or recommendations for monitoring antipsychotics.

The pediatric PCC can serve a strong collaborative role in supporting safe pediatric antipsychotic treatment, by providing expertise in metabolic monitoring for youth with signs of adverse medication effects and universal healthy lifestyle interventions to minimize potential unhealthy weight gain over the course of treatment. The American Academy of Pediatrics has issued a helpful 2017 policy statement on obesity primary prevention and a 2015 clinical report to issue guidance on managing the stigma related to obesity (see Appendix B). The guidance supports simple healthy lifestyle changes, which may be feasible for youth with special mental health needs (eg, reduce sugary beverage intake), and careful attention to psychological aspects of obesity-related health problems (eg, educational approach to obesity health concerns).

A survey, based on Vermont Medicaid data, of prescribers of antipsychotics to patients younger than 18 years found that "physicians follow 'best practice' guidelines when prescribing antipsychotics to children and adolescents only about half the time, with failure to monitor cholesterol and blood sugar levels their main misstep."[4]

Table 7-5. Monitoring Protocol for (Adult) Patients Taking SGA/TGAs[a]

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X[b]

Abbreviations: BMI, body mass index; SGA, second-generation antipsychotic; TGA, third-generation antipsychotic.

[a] More frequent assessments may be warranted based on clinical status.

[b] Most proposed guidelines for children suggest annual monitoring of lipids, rather than every 5 years.

Adapted from American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care.* 2004;27(2):596–601. Copyright © 2004 American Diabetes Association.

Involuntary Movements

The recommended method for assessing severity of abnormal involuntary movements[5] is to use a structured instrument, such as the Abnormal Involuntary Movements Scale (AIMS).[6] (See Appendix A.) It is important to obtain a baseline AIMS score before starting an SGA/TGA. Training in administration and scoring of the AIMS is recommended.[7]

Akathisia involves characteristic restless movements of the limbs, subjective awareness of restlessness, or both. Especially when mild, akathisia can be difficult to differentiate from fidgety movements. For eliciting subjective awareness, prompts such as "feeling like you have ants in your pants" or "feeling like you just swallowed some jumping beans" can be helpful. The Barnes Akathisia Rating Scale[8] is the most commonly used structured instrument for rating severity of akathisia (see Appendix A for more information on this scale).

Switching Second- and Third-Generation Antipsychotics

Switching SGA/TGAs in children and adolescents can be challenging and difficult, even in the hands of experienced specialists. Staggered switching is recommended to minimize symptomatic relapse. Because core psychiatric symptoms and adverse effects may emerge or increase during crossover of SGA/TGAs, monitoring requires extra vigilance. When possible, involving a child and adolescent psychiatrist or other experienced expert in switching SGAs is recommended.

Comparing Second- and Third-Generation Antipsychotics

The following comments regarding differences among various Group 2 SGA/TGAs is offered as a general guide. It is not meant to be a protocol for, or restrict prescribing of, any medication. An individualized decision regarding an individual medication for an individual patient is always the final responsibility of the individual prescriber.

No useful data exist comparing efficacy of the 6 Group 2 SGAs and 1 TGA in youth. Paliperidone is the active metabolite of risperidone and appears similar to risperidone in efficacy and adverse effect profile. Perhaps the major difference is that risperidone has been in use longer (since 1993) than paliperidone (since 2006); both are available as generic formulations.

Generally, clinically meaningful differences among SGA/TGAs focus on adverse effects. Only a few relevant differences will be highlighted here.

Olanzapine, in contrast to other Group 2 SGA/TGAs, is associated with more weight gain and metabolic adverse effects. Aripiprazole, the TGA, is associated with the least weight gain and less severe metabolic adverse effects. Among the 3 SGAs (risperidone, quetiapine, olanzapine) and TGA (aripiprazole) with available data, risperidone is most likely to increase prolactin levels and is more frequently associated with gynecomastia and amenorrhea (though there is not a consistent direct relationship between prolactin levels and these adverse effects). Quetiapine appears to be the most sedating. Detailed information regarding each Group 2 SGA/TGA is presented in Table 7-6.

The Mood Stabilizer Lithium

Mood stabilizers are used to treat mania, depression, irritability, and problematic mood swings or instability in bipolar disorder, as well as other mood disorders. There are 2 groups of mood stabilizers.

- Traditional (lithium, valproic acid [divalproex sodium], and carbamazepine)
- Newer anticonvulsants (eg, lamotrigine)

Lithium is included in Group 2 medications. Lithium has an FDA indication for mania in bipolar disorder starting at age 12 years; available data for lithium, although limited, suggest efficacy for acute mania in bipolar disorder.[11,12] Detailed information regarding lithium is presented in Table 7-7.

Common adverse effects associated with lithium are presented in Box 7-6. Gastrointestinal problems (nausea, vomiting, diarrhea) and increased urination are common and are generally responsive to dose reduction. It is important to provide guidance to families on the need to maintain stable fluid status, especially during warm/hot weather. Dosage may need to be decreased during gastrointestinal illness or dehydration.

Lithium has a narrow therapeutic window, and, as noted in the FDA boxed warning, toxicity is closely related to serum levels and can occur at doses close to therapeutic dosages.

As shown in Table 7-8, monitoring of lithium includes a targeted history, targeted physical examination, vital signs, and blood sampling. There is no formal schedule for monitoring. Generally, frequent serum lithium level monitoring (approximately 12 hours after the last dose) during dose

Table 7-6. Group 2 Medications: Second- and Third-Generation Antipsychotics

Medication	Warnings, Precautions, and Adverse Effects	Comments
Risperidone ***Indications in children and adolescents:*** Schizophrenia (13–17 years), acute manic or mixed episodes (10–17 years), "irritability" associated with autism spectrum disorder (5–16 years). ***Uses:*** Schizophrenia spectrum disorder, bipolar spectrum disorder, "irritability" in autism; also, many off-label uses, acute aggression, chronic irritability, tics, and other disorders not responsive to other medications. ***Monitoring:*** See Box 7-5 and Table 7-5 and Adverse Effects and Monitoring section of text.	***Boxed warnings:*** None for nonelderly patients. ***Warnings and precautions:*** Neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, hyperprolactinemia, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, potential for cognitive and motor impairment, seizures. ***Adverse reactions:*** "The most common adverse reactions in clinical trials (>5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain. The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in >1% of adults and/or >2% of pediatrics) were nausea, somnolence, sedation, vomiting, dizziness, and akathisia" (see package insert, page 21).	Risperidone was the first SGA (other than clozapine, which is rarely used in children) approved by the FDA (in 1993) for marketing in the United States. It is generally effective and safe for short-term use, but there are concerns about adverse effects of long-term use, such as obesity, diabetes, metabolic syndrome, and tardive dyskinesia. It can increase prolactin levels and is associated with gynecomastia and amenorrhea.

Aripiprazole (TGA) ***Indications in children and adolescents:*** Schizophrenia (13–17 years), manic or mixed episodes (10–17 years), "irritability" associated with autism spectrum disorder (6–17 years), Tourette disorder (6-17 years). ***Uses:*** Same as risperidone. ***Monitoring:*** Same as risperidone.	***Boxed warning*****:** Increased risk of suicidal thinking and behavior (see Chapter 2 for details). ***Warnings and precautions*****:** Same as risperidone, plus pathological gambling and other compulsive behaviors, but not hyperprolactinemia. ***Adverse reactions*****:** "Pediatric patients (13–17 years) with schizophrenia: Extrapyramidal disorder, somnolence, and tremor. **Pediatric patients (10–17 years) with bipolar mania:** Somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness. **Pediatric patients (6–17 years) with autistic disorder:** Sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy. **Pediatric patients (6–18 years) with Tourette disorder:** Sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite" (see package insert, page 1).	Marketed since 2002, aripiprazole, a TGA, has a somewhat different mechanism of action than SGAs. It is associated with less weight gain and related metabolic effects than the SGAs, except for ziprasidone. It also lowers prolactin levels.

continued on next page

Table 7-6. Group 2 Medications: Second- and Third-Generation Antipsychotics (*continued*)

Medication	Warnings, Precautions, and Adverse Effects	Comments
Quetiapine ***Indications in children and adolescents:*** Schizophrenia (13–17 years), manic episodes associated with bipolar I disorder (10–17 years). ***Uses:*** Same as risperidone. ***Monitoring:*** Same as risperidone.	***Boxed warning*:** Increased risk of suicidal thinking and behavior (see Chapter 2 for details). ***Warnings and precautions*:** Same as risperidone, plus increased blood pressure and cataracts, but not hyperprolactinemia, seizures, and motor and cognitive impairment. ***Adverse reactions*:** "Most common adverse reactions (incidence ≥5% and twice placebo): Children and adolescents: Somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight increased" (see package insert, page 1).	Marketed since 1997, quetiapine is associated with more somnolence than other SGAs.
Olanzapine ***Indications in children and adolescents:*** Schizophrenia (13–17 years), manic or mixed episodes of bipolar I disorder (13–17 years). ***Uses:*** Same as risperidone. ***Monitoring:*** Same as risperidone.	***Boxed warnings:*** None for nonelderly patients. ***Warnings and precautions*:** Same as risperidone, plus suicide (see Chapter 2 for details), drug reaction with eosinophilia and systemic symptoms. ***Warnings and precautions:*** Suicide, neuroleptic malignant syndrome, hyperglycemia, hyperlipidemia, tardive dyskinesia, orthostatic hypotension, leukopenia, neutropenia and agranulocytosis, seizures, potential for cognitive and motor impairment, hyperprolactinemia. ***Adverse reactions:*** In adolescent clinical trials "(incidence ≥5% and at least twice that for placebo): Sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth…dizziness, abdominal pain" (see package insert, page 2).	Marketed since 1996, olanzapine is associated with more weight gain and related metabolic side effects in adolescents than the other SGAs (risperidone, aripiprazole, and quetiapine).[9,10]

Paliperidone ***Indications in children and adolescents:*** Schizophrenia (12–17 years). ***Uses:*** Same as risperidone. ***Monitoring:*** Same as risperidone.	***Boxed warnings:*** None for nonelderly patients. ***Warnings and precautions*:** Same as risperidone, plus QT prolongation, gastrointestinal narrowing, suicide. ***Adverse reactions:*** "Commonly observed adverse reactions (incidence ≥ 5% and at least twice that for placebo) were: Adolescents with schizophrenia: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia" (see package insert, page 1).	Marketed since 2006, paliperidone is the major active metabolite of risperidone; it is very similar to risperidone.
Asenapine ***Indications in children and adolescents:*** Manic or mixed episodes of bipolar I disorder (10–17 years). ***Uses:*** Same as risperidone. ***Monitoring:*** Same as risperidone.	***Boxed warnings:*** None for nonelderly patients. ***Warnings and precautions*:** Same as risperidone, plus QT prolongation, but not hyperprolactinemia. ***Adverse reactions:*** "The most commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were: bipolar I disorder pediatric patients (monotherapy): Somnolence, dizziness, dysgeusia, oral paresthesia, nausea, increased appetite, fatigue, increased weight" (see package insert, page 1).	Marketed since 2009, asenapine is available as a sublingual tablet only.
Lurasidone ***Indications in children and adolescents:*** Schizophrenia (13–17 years). ***Uses:*** Same as risperidone. ***Monitoring:*** Same as risperidone.	***Boxed warning*:** Increased risk of suicidal thinking and behavior (see Chapter 2 for details). ***Warnings and precautions*:** Same as risperidone, *but with no* potential for cognitive and motor impairment, seizures. ***Adverse reactions*:** "Commonly observed adverse reactions (incidence ≥5% and at least twice the rate for placebo) were: Adolescent patients (13–17 years) with schizophrenia: Somnolence, nausea, akathisia, EPS (non-akathisia), rhinitis/rhinorrhea (80 mg only), and vomiting" (see package insert, page 1).	Marketed since 2010, lurasidone has an indication in adults for treatment of bipolar depression. Lurasidone should be taken with food, which substantially increases absorption.

Abbreviations: FDA, US Food and Drug Administration; SGA, second-generation antipsychotic, TGA, third-generation antipsychotic.

Table 7-7. Group 2 Medications: Mood Stabilizer

Medication	Warnings, Precautions, and Adverse Effects	Comments
Lithium ***Class:*** Element of the alkali-metal group (salt). ***Indications in children and adolescents:*** Mania in bipolar disorder (age >12 years). ***Uses:*** Acute mania and maintenance therapy in bipolar disorder, mood stabilization. ***Monitoring:*** Pregnancy testing; ECG; laboratory tests: Serum lithium levels, CBC, electrolyte level, thyroid functions, and renal function.	***Boxed warnings:*** Toxicity closely related to serum lithium levels; can occur close to therapeutic dose levels ***Warnings:*** Very high risk of toxicity, including significant cardiovascular or renal disease, severe debilitation, dehydration, sodium depletion. Taking diuretics or ACE inhibitors. Chronic use may lower renal-concentrating ability and can present as nephrogenic diabetes insipidus, with polyuria or polydipsia. Encephalopathic syndrome (ie, weakness, lethargy, fever, tremulousness and confusion, leukocytosis, extrapyramidal symptoms, and elevated serum enzyme levels, BUN, and fasting blood glucose) may occur with lithium and a neuroleptic. ***Precautions:*** Hypothyroidism, impaired mental or physical abilities, any concomitant medications (ie, diuretics, ACE inhibitors, carbamazepine, fluoxetine). ***Adverse effects:*** **Mild:** <1.5 mEq/L **Mild to moderate:** 1.5–2.5 mEq/L **Moderate to severe:** ≥2.0 mEq/L **< 2.0 mEq/L:** Early signs of toxic diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination; at higher levels, giddiness, ataxia, blurred vision, tinnitus, large output of dilute urine **> 3.0 mEq/L:** Complex clinically, with multiple organs and organ systems	Introduced in the United States in the early 1960s, it was the original mood stabilizer. Clear, documented evidence of effectiveness for acute and maintenance treatment for mania and bipolar disorder in adults. No well-powered, placebo-controlled study for mania in children and adolescents, in large part, because of ethical and practical difficulties associated with conducting placebo-controlled studies. Evidence from several smaller studies is positive but the effect is relatively small.[11,12] Unpopular with children and adolescents because of common adverse effects and need for repeated venipunctures for serum level monitoring. **Note:** A concomitant NSAID may increase lithium level. **Note:** Concomitant use of lithium and an SSRI is associated with symptoms such as diarrhea, confusion, tremor, dizziness, and agitation.

Abbreviations: ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; CBC, complete blood count; ECG, electrocardiography; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Box 7-6. Common Adverse Effects and Laboratory Changes Associated With Lithium

Weight Gain
Gastrointestinal Nausea, vomiting, diarrhea
Central Nervous System Slowing, tremor, ataxia
Dermatologic Acne, rash
Endocrine Thyroid dysfunction
Renal Increased urination, renal function changes

Table 7-8. Lithium Monitoring

History focused on adverse effects (baseline and at each follow-up visit)		
Physical examination focused on adverse effects, central nervous system, thyroid (baseline and at each follow-up visit)		
Vital signs (baseline, 3 months, 6 months, then annually): Height, weight, blood pressure, and pulse		
Laboratory Tests		
System	**Measure**	**Schedule**
Lithium	**12-hour serum trough level (≥5 days' stable dose)**	**Baseline, during dose escalation, then every 3 months**
General health	**CBC**	**Baseline, then annually**
Thyroid	**TSH test**	**Baseline, 6 months, 12 months, then annually**
Renal	**Electrolyte, BUN, creatinine levels**	**Baseline, 3 months, 6 months, 12 months, then annually**
Reproductive	**HCG test**	**Baseline, then as indicated**
Cardiac	**ECG**	**Baseline, 3 months, 12 months, then annually**

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; ECG, electrocardiography; HCG, human chorionic gonadotropin; THS, thyroid-stimulating hormone.

Adapted from Ng F, Mammen OK, Wilting I, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar Disord.* 2009;11(6):559–595, and Thomas T, Stansifer L, Findling RL. Psychopharmacology of pediatric bipolar disorders in children and adolescents. *Pediatr Clin North Am.* 2011; 58(1):173–187.

escalation (generally no more frequently than 5 days after the most recent change in dose so that a steady state level has been reached) is optimal, until a stable and therapeutic blood level is reached. For consistent and valid lithium monitoring, trough levels (approximately 12 hours after the last dose) are essential.

During maintenance treatment, monitoring, including serum blood levels, is generally recommended every 3 months. The target therapeutic level for bipolar disorder is generally in the 0.8 to 1.2 mEq/L range. Therefore, safe prescribing of lithium necessitates an intensive monitoring regimen to ensure patient safety.

Summary

Unifying characteristics of Group 2 medications are that they 1) are used to treat serious and chronic disorders that cause significant disruption in youth and families, 2) are associated with substantial and potentially long-term adverse effects, and 3) need extensive monitoring protocols. Pediatric PCCs are ideally trained and skilled to provide this monitoring because they can integrate knowledge about the child's full health history to assess vulnerability to long-term adverse effects. For example, the pediatric PCC will likely know if the child has a family history of diabetes and if the body mass index percentile of the child has changed over time. The pediatric PCC, perhaps in collaboration with a child and adolescent psychiatrist, is likely to be comfortable with, and equipped to carry out, extensive monitoring protocols associated with Group 2 medications.

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CHAPTER 8

Group 3 Medications

In general, Group 3 includes medications that are not approved for youth by the US Food and Drug Administration (FDA).

A few medications included in Group 3 have FDA indications for youth, but these are based on premodern data (if any) and were grandfathered in by the FDA many years ago. Although the FDA has removed most of these grandfathered indications, a few remain. The author and contributing editors have excluded these approvals from this conceptual framework because they were not subject to the same modern standards of evidence for safety and efficacy as medications included in Groups 1 and 2.

Ten Group 3 medications were selected by the author and contributing editors for description because they are commonly used and pediatric primary care clinicians (PCCs) are likely to have patients for whom they have been prescribed. Table 8-1 summarizes available efficacy data and adverse effect profiles for these 10 medications. Adverse effect data are taken from package inserts and are based on data from adult studies, because the FDA has not provided any applicable data for children younger than 18 years. Several other medications were considered, including buspirone (used for anxiety), lamotrigine (used for depression in patients with bipolar disorder), and prazosin (used, off label in adults, to treat nightmares and posttraumatic stress disorder).

Other Group 3 medications, which are less commonly prescribed, will not be discussed, but their adverse effect profiles can be accessed via electronic media (eg, Drugs@FDA [www.accessdata.fda.gov], Epocrates, Micromedex).

Other Antidepressants

Group 3 contains 4 antidepressants commonly prescribed in children and adolescents: bupropion, citalopram, venlafaxine, and mirtazapine. None has an FDA indication for use in children or adolescents.

Table 8-1. Group 3 Medications

Medication	Warnings, Precautions, and Adverse Effects	Comments
Antidepressant		
Bupropion ***Class:*** Atypical antidepressant; chemical structure like phenylethylamine, which is a stimulant. ***Indications*** Adults: MDD. Children and adolescents: None. ***Uses:*** Depression. ***Monitoring:*** BP, heart rate, height, weight, suicidality.	***Boxed warnings:*** Suicidal thinking and behavior ***Warnings and precautions:*** Seizure risk, agitation, hypertension, mania/hypomania, psychosis and confusion, angle-closure glaucoma. ***Adverse effects:*** "Agitation, dry mouth, constipation, headache/migraine, nausea/vomiting, dizziness, excessive sweating, tremor, insomnia, blurred vision, tachycardia, confusion, rash, hostility, cardiac arrhythmias, and auditory disturbance" (see package insert, page 1).	Because of its structural similarity to stimulants, bupropion is sometimes used to treat both depression and symptoms of ADHD.
Citalopram ***Class:*** SSRI. ***Indications*** Adults: MDD. Children and adolescents: None. ***Uses:*** MDD. ***Monitoring:*** Same as other SSRIs plus ECG (see Group 1).	***Boxed warnings:*** Suicidal thinking and behavior. ***Warnings and precautions:*** Similar to other SSRIs, plus QT prolongation. ***Adverse effects:*** Similar to other SSRIs.	Offers no benefit over escitalopram, which is the Group 1 therapeutically effective (S)-enantiomer of citalopram. Also, citalopram has an FDA warning regarding maximum dose in adults because of the risk of QTc prolongation; relevant dosage maximum is not known in children and adolescents. Thus, the potential need to monitor with ECGs complicates treatment.
Venlafaxine ***Class:*** NRI. ***Indications*** Adults: MDD, GAD, SoAD, PD. Children and adolescents: None.[1,2] ***Uses:*** MDD. ***Monitoring:*** BP, heart rate, height, weight, suicidality.	***Boxed warnings:*** Suicidal thinking and behavior. ***Warnings and precautions:*** Serotonin syndrome, elevations in blood pressure, abnormal bleeding, activation of mania/hypomania, angle closure glaucoma. ***Adverse effects:*** Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision.	Venlafaxine was compared with an SSRI in children and adolescents with depression who had not responded to initial treatment.[3] The second SSRI and venlafaxine showed comparable efficacy; however, venlafaxine was associated with more adverse effects and discontinuations.

Mirtazapine ***Class:*** Tetracyclic. ***Indications*** Adults: MDD. Children and adolescents: None. ***Uses:*** MDD. ***Monitoring:*** BMI, WBC count, lipid panel, transaminase level.	***Boxed warnings:*** Suicidal thinking and behavior. ***Warnings:*** Activation of mania and hypomania, agranulocytosis, serotonin syndrome, angle-closure glaucoma, QT prolongation. ***Precautions:*** Discontinuation symptoms, akathisia, hyponatremia, somnolence, dizziness, increased appetite and weight gain, cholesterol and triglyceride levels, ALT elevation, seizures. ***Adverse effects:*** Somnolence, increased appetite, weight gain, dizziness.	Mirtazapine has both serotonergic and noradrenergic actions and is different from other antidepressants in its mechanism of action. It is generally more sedating and causes more weight gain than other antidepressants. Because of its sedating effect, sometimes it is used as a sleep aid.
Second-Generation Antipsychotic		
Ziprasidone ***Class:*** SGA. ***Indications*** Adults: Schizophrenia, manic or mixed episodes associated with bipolar I disorder, adjunctive maintenance therapy of bipolar I disorder, agitation in schizophrenic patients (intramuscular injection). Children and adolescents: None. ***Uses:*** Same as risperidone (see Group 2 SGAs). ***Monitoring:*** Same as risperidone, plus QTc on ECG.	***Boxed warnings:*** None in nonelderly. ***Warnings and precautions:*** QT interval prolongation, neuroleptic malignant syndrome, severe cutaneous adverse reactions (including DRESS and Stevens-Johnson syndrome), tardive dyskinesia, hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, rash, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures, potential for cognitive and motor impairment, suicide. ***Adverse effects:*** Most common adverse effects in clinical trials (incidence ≥5% and twice placebo): Somnolence, respiratory tract infection, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, asthenia, vomiting, headache, nausea.	Marketed since 2001, ziprasidone is associated with less weight gain than other SGAs. Because of potential to prolong the QT interval, ECG monitoring is needed.

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Table 8-1. Group 3 Medications (*continued*)

Medication	Warnings, Precautions, and Adverse Effects	Comments
Mood Stabilizer		
Valproic acid (divalproex sodium) ***Class:*** Anticonvulsant mood stabilizer. ***Indications*** Adults: Mania in bipolar disorder; prophylaxis of migraines, therapy of complex partial seizures and simple and complex absence seizures. Children and adolescents: None psychiatric (approved for epilepsy). ***Uses:*** Mood stabilizer. ***Monitoring:*** Pregnancy testing, serum levels, CBC, liver function tests.	***Boxed warnings:*** Hepatotoxicity—can be fatal, usually in first 6 months of use in children <2 years; teratogenic, including neural tube defects (eg, spina bifida, malformations, decreased IQ; pancreatitis—can be fatal, hemorrhagic cases. ***Warnings and precautions:*** Hepatotoxicity, birth defects, and decreased IQ following in utero exposure, pancreatitis, suicidal behavior or ideation, bleeding and thrombocytopenia, hypothermia, hyperammonemia, hyperammonemic encephalopathy, DRESS/multiorgan hypersensitivity reaction. ***Adverse effects:*** "Most common adverse effects in clinical trials of mania (incidence ≥5%): Abdominal pain, alopecia, amblyopia and blurred vision, amnesia, anorexia, asthenia, ataxia, bronchitis, constipation, depression, diarrhea, diplopia, dizziness, dyspepsia, dyspnea, ecchymosis, emotional lability, fever, flu syndrome, headache, increased appetite, infection, insomnia, nausea, nervousness, nystagmus, peripheral edema, pharyngitis, rhinitis, somnolence, abnormal thinking, thrombocytopenia, tinnitus, tremor, vomiting, weight gain, weight loss" (see package insert, page 1).	Valproic acid (divalproex sodium) for treatment of mania in adults is supported by substantial data. Supportive data are lacking in youth. An industry-funded, multisite RCT in youth with mania in bipolar disorder did not show efficacy of valproic acid versus placebo.[4] In a comparison of valproic acid, lithium, and risperidone for bipolar disorder in youth,[5] valproic acid had the lowest response rates; they were comparable to those for placebo in the industry-funded study.

Anxiolytics		
Lorazepam ***Class:*** Benzodiazepine. ***Indications*** Adults: Acute anxiety. Children and adolescents: None. ***Uses:*** Acute anxiety; for panic attacks, as needed, especially while waiting for an SSRI to become effective. ***Monitoring:*** Pregnancy testing.	***Boxed warnings:*** Concomitant use with opioids. ***Warnings and precautions:*** Physical and psychological dependence, worsening or emergence of depression, suicidal thoughts or behaviors, respiratory depression, interference with cognitive and motor performance, risk of use in pregnancy, withdrawal symptoms, paradoxical reactions (ie, behavioral disinhibition), should not be used with alcohol. ***Adverse effects:*** "In a sample of about 3,500 adult patients treated for anxiety, the most frequent adverse effect was sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%)" (see package insert, page 6).	Lorazepam is a short-acting benzodiazepine with a duration of effect of about 4–8 hours. Primarily because of the possibility of physical and psychological dependence with prolonged use of benzodiazepines, lorazepam is generally recommended only for short-term use (days to a few weeks) for treatment of acute and severe anxiety after a trauma, before a medical procedure, or while waiting for an SSRI or other anxiolytic to become effective.
Clonazepam ***Class:*** Benzodiazepine. ***Indications*** Adults: Panic disorder and seizure disorders. Children and adolescents: None. ***Uses:*** Acute anxiety. ***Monitoring:*** Pregnancy testing.	***Boxed warnings:*** Concomitant use with opioids. ***Warnings:*** Interference with cognitive and motor performance, suicidal behavior and ideation, physical and psychological dependence, withdrawal symptoms. ***Precautions:*** Worsening of seizures, paradoxical reactions (ie, behavioral inhibition) hypersalivation, porphyria; should not be used with alcohol. ***Adverse effects:*** Somnolence, abnormal coordination, ataxia, depression.	Clonazepam is similar to lorazepam, except for its longer half-life and once-daily dosing.

continued on next page

Table 8-1. Group 3 Medications (*continued*)

Medication	Warnings, Precautions, and Adverse Effects	Comments
Sleep Aids		
Trazodone ***Class:*** SSRI with other unclear specific mechanism of action. ***Indications*** Adults: MDD. Children and adolescents: None. ***Uses:*** Insomnia. ***Monitoring:*** Pregnancy testing.	***Boxed warnings:*** Suicidal thoughts and behaviors. ***Warnings and precautions:*** Serotonin syndrome, increases QT interval, angle closure glaucoma, activation of mania and hypomania, QT prolongation, orthostatic hypotension and syncope, increased risk of bleeding, priapism, potential for cognitive and motor impairment. ***Adverse effects:*** Edema, blurred vision, syncope, drowsiness, fatigue, diarrhea, nasal congestion, weight loss.	Trazodone is sometimes used as a sleep aid in low doses, generally 25 or 50 mg. Because of reports of priapism, its use in adolescent boys is limited.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ALT, alanine transaminase; BMI, body mass index; BP, blood pressure; CBC, complete blood cell count; DRESS, drug reaction with eosinophilia and systemic symptoms; ECG, electrocardiography; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NRI, norepinephrine reuptake inhibitor; PD, panic disorder; RCT, randomized controlled trial; SGA, second-generation antipsychotic; SoAD, social anxiety disorder; SSRI, selective serotonin reuptake inhibitor; WBC, white blood cell.

Bupropion has a chemical structure similar to that of phenylethylamine, which is a stimulant. It is marketed for major depressive disorder, seasonal affective disorder, and smoking cessation in adults and is sometimes used for off-label pediatric treatment of depression (especially when comorbid with attention-deficit/hyperactivity disorder [ADHD]).

Although *citalopram*, a selective serotonin reuptake inhibitor (SSRI), is sometimes used for depression, anxiety, or both in youth, it offers no benefit over escitalopram, a Group 1 medication that is the therapeutically effective (*S*)-enantiomer of citalopram. Citalopram has an FDA warning regarding maximum dose in adults because of the risk of QTc prolongation; however, a relevant dosage maximum is not known in children and adolescents. Thus, the need to monitor with electrocardiography complicates treatment in pediatric patients.

Venlafaxine is a norepinephrine reuptake inhibitor that "behaves" like an SSRI at lower doses. It is used for anxiety, depression, or both in youth.[1,2] In children and adolescents, venlafaxine is associated with more adverse effects than SSRIs.[3] Industry-sponsored efficacy studies for depression and anxiety in youth, although almost reaching statistical significance, have not demonstrated clear efficacy.[1,2]

Mirtazapine has a tetracyclic chemical structure that distinguishes it from other antidepressants. It is marketed for depression in adults. Mirtazapine is associated with more sedation and weight gain than other antidepressants.

Other Antipsychotics

Ziprasidone is a second-generation antipsychotic (marketed since 2001) that is approved in adults only for treatment of psychosis in schizophrenia and mania in bipolar disorder. Ziprasidone has the advantage of generally being associated with less weight gain and fewer metabolic adverse effects than other second-generation antipsychotics. However, it is associated with risk of prolongation of QTc so electrocardiographic monitoring (at baseline and at therapeutic dose) is recommended.

Other Mood Stabilizers

Divalproex sodium, an anticonvulsant, is also prescribed to youth as a mood stabilizer. Unfortunately, efficacy data for divalproex sodium for mania in bipolar disorder suggest no difference from placebo[4] and less efficacy than comparators.[6] Adverse effect burden is considerable, and drug level monitoring requires regular venipuncture.

Anxiolytics

Two benzodiazepine anxiolytics—*lorazepam* (short acting) and *clonazepam* (long acting)—are sometimes prescribed to children and adolescents. Because dependence may develop with long-term benzodiazepine treatment, they are recommended for short-term use *only*.

Benzodiazepines may be used before painful or stressful medical procedures. For any treatment using benzodiazepines, the supply of medication and duration of treatment should be very limited to prevent the development of physical dependence.

Benzodiazepines are generally well tolerated. Sedation is the most common concerning adverse effect. Daytime drowsiness can be dangerous when operating a motor vehicle or machinery. In children, benzodiazepines, especially at relatively low doses, can cause generalized verbal and physical disinhibition, which appears to be most common in children with intellectual and neurodevelopmental disorders. Other concerning adverse effects are unlikely if benzodiazepines are used short term and at appropriately low doses.

Sleep Aids

Insomnia is a common concern in youth with ADHD, anxiety, depression, and other disorders. Sleep problems can be secondary to various environmental stressors (particularly family turmoil or school examinations), excessive responsibilities and activities (eg, job, athletics, homework), procrastination, or socializing (actually or virtually). Inquiries should be made about the child's sleeping arrangements (security, consistency, lack of disturbance) before considering medication. In general, treatment of the

primary psychiatric disorder(s), plus counseling, environmental changes, and/or behavioral approaches to improve sleep hygiene will relieve insomnia. If not, further evaluation is recommended. See Assess Sleep Pattern section in Chapter 2 for more information.

Although research data are lacking, various medications are used to treat insomnia in children and adolescents, especially those with ADHD or autism spectrum disorder associated with sleep problems. Two potential sleep aids, which are among the most commonly used in youth, are included here.

Trazodone is a sedating antidepressant approved for treatment of major depressive disorder in adults. It is sometimes used in low doses for off-label treatment of insomnia in adolescents (and adults). Trazodone's mechanism of action is not well understood; its major effect is thought to be on the serotonergic system. Trazodone's adverse effects profile is similar to that of the SSRIs, but it is also associated with priapism, which may limit its use in male adolescents. When trazodone is used in conjunction with an SSRI, potential drug interactions need to be identified and monitored.

Melatonin is a hormone produced in the pineal gland and is available over the counter but not by prescription (and therefore is not included in Table 8-1). This is a problem because the FDA does not monitor quality control of such over-the-counter preparations; thus, the actual dose in an over-the-counter melatonin preparation may not be the same as the dose on the label. Melatonin is effective in reducing time to sleep onset in adults (and, based on considerably less data, in children) with initial insomnia. This effect appears to last for days to weeks but not long term. It may be helpful for short-term alleviation of initial insomnia, which is relatively common following severe trauma, during an episode of depression, or following travel that crosses multiple time zones. Sustained-release preparations, used for sleep maintenance in adults, can disrupt the circadian rhythm, and are not recommended in children and adolescents. Melatonin's primary adverse effect is sedation. Melatonin is not recommended for long-term use. There are no long-term safety data in children. It has effects on the reproductive systems of primates, as well as effects on cardiovascular, immune, and metabolic systems.[7]

Future Considerations

The medications included in Groups 1, 2, and 3 were based on data available as of February 2018. Medications included in Groups 1 and 2 will change as new medications receive FDA approval for children and adolescents.

Medications included in Group 3 will change as medications without FDA approval in youth become more commonly used or if a medication included in Group 3 gains FDA approval and moves to Groups 1 or 2. A potential example is the antipsychotic ziprasidone, which, if approved by the FDA in youth, would move from Group 3 to Group 2.

A potential example of a medication that could move to the Group 3 list if it becomes commonly used in children or adolescents is ramelteon. Ramelteon is a recently FDA-approved sleep aid (for adults only) that is the first in a new class of sleep aids that are melatonin receptor agonists with high affinity for melatonin 1 and melatonin 2 receptors. At this time, though, ramelteon is too new to allow an informed assessment of its appropriateness for children and adolescents.

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Part 5—Advanced Topics

CHAPTER 9

What to Do When Treatment Is Not Successful

Even when treated by seasoned clinicians using evidence-based protocols, not all patients get better. This can be frustrating for patients, families, and clinicians alike. This chapter addresses the dilemma of unsuccessful treatment.

Understand the Limits of Evidence-Based Treatments and Protocols

The evidence-based psychosocial and medication treatments described in this book can be expected to substantially reduce symptoms and improve function for most children and adolescents. Unfortunately, there are gaps in our current understanding of mental health conditions and their treatment. Thus, nonresponse to or partial response to treatment is not unusual. Placebo-controlled studies indicate that many (about 20%–40%) of patients do not respond to an initial medication intervention, depending on the specific diagnosis and treatment. As noted before, treatment that combines medication and evidence-based therapy leads to higher response rates in attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression. Thus, whenever possible, it is important to recommend both medication and evidence-based therapy. If symptoms have not improved after an adequate course of psychotherapy, pragmatic supports, and/or medication, it is likely time to reassess the diagnosis, treatment approaches, and environmental factors that may result in limited improvement or partial response to treatment.

Reassess Diagnoses

The diagnostic approaches described in Chapter 3 should result in correct diagnoses for most patients. However, complex psychosocial presentations, multiple potential diagnoses, or both can complicate the assessment

process. The patient, family, and pediatric primary care clinician (PCC) can all reasonably expect that treatment will relieve or resolve the identified disorders. When treatment does not appear to be working, however, things may have gone awry in a number of ways that should be reviewed.

Incomplete or Inaccurate Reports

Examples of incomplete or inaccurate reporting that can make correct diagnosis difficult include:

- Misinterpretation of normal behavior (ie, behavior within the range of typical behavior for youngsters of that age) as symptomatic behavior
- Fear of the possible consequences of revealing symptoms or key features of the history (eg, physical, psychological, or sexual abuse)
- Reluctance to reveal, or minimization of, symptoms because of desire to be or appear "normal"
- Differing reports or interpretation of symptoms among multiple reporters (eg, the patient, family members, teachers)

Rating scales completed by both parents and teachers can be helpful in clarifying symptom type and severity. When considering whether behavior is normal, it may be helpful to remember that in 1 study, 13% of parents of school-aged children and 10% of parents of preschool-aged children with normal functioning reported concerns about their child's behavior.[1,2] Many teens are more comfortable reporting symptoms on paper or electronic forms than in individual or family interviews. Rating scales can also help begin an open conversation about the child's strengths and challenges, which is especially important when differences between various reporting sources are present. Inconsistencies between clinical evaluation and rating-scale data may also indicate that a parent or teacher's expectation may not be consistent with the child's skill level. Having the rating scales completed by multiple teachers who see the child throughout the school day is often beneficial to identify which problems have a global effect on academic functioning.

When using rating scales, however, it is important to remember that responses can vary depending on how the scales are introduced, who introduces them, and the setting in which they are completed. Respondents are more likely to respond accurately when they understand who will see their information and how their answers may be used in the diagnostic process. Ensuring privacy and the opportunity to clarify questions about the scales are both important to consider whenever such tools are used.

Phenomenological or Diagnostic Issues

Examples of phenomenological or diagnostic issues that may make diagnostic clarity difficult include

- Impaired concentration may be a symptom of anxiety or depression, or secondary to trauma, rather than ADHD.
- Feelings associated with anxiety (eg, frustration, defeat) may be accompanied by more active symptoms, such as anger, aggression, and oppositional behavior that may be more noticeable to caretakers than anxiety symptoms.
- Demoralization (ie, loss of hope, confidence, courage) may be mistaken for depression or "defiance."

Attention-Deficit/Hyperactivity Disorder (ADHD)

As a reminder, the most important data for diagnosing ADHD are caregivers' and teachers' observations that can be recorded and organized using structured rating scales. Some children with ADHD will exhibit hyperactivity, impulsivity, distractibility, or a combination of those in the examination room; however, many will not. Obtaining symptom information from informants over at least 1 week and during various times of day strengthens validity of the diagnosis, as symptom severity waxes and wanes over short periods. It is always important to remember that many symptoms noted on ADHD rating scales are nonspecific; ADHD is a diagnosis not better explained by other conditions.

Anxiety Disorders

As a reminder, the core symptoms of anxiety disorders are

- Fears or phobias
- Worries
- Somatic concerns

Children with anxiety can present to the pediatric PCC in various ways. A common response to anxious feelings is to avoid situations that generate fear or worry. Children may share their worries, fears, or somatic concerns with their caregivers, who will describe them during an office visit. In other cases, a caregiver may report that a child is avoiding social or other situations. Some children keep their fears or worries to themselves and do not share them with others and some, in the face of perceived threats, may

become oppositional, aggressive, or angry. Anxiety and depression frequently co-occur, with one set of symptoms and related behaviors exacerbating the other. When 1 of the 2 conditions is suspected, it is important to ask about the other as well. Anxiety rating scales such as the Screen for Child Anxiety Related Disorders can be useful in helping children express the extent to which their anxiety interferes with their thinking and function.

Depression

Differential diagnosis of major depressive disorder (MDD) in youth can be challenging. Children who are demoralized by various family, social, medical, peer, academic, or other problems can exhibit many of the symptoms of MDD. Demoralized children often have mood and cognitive symptoms identical to those in children with MDD, but loss of interest/pleasure and neurovegetative symptoms are less likely to be present. Grief can also mimic MDD. The prominent affect in a grieving child is a feeling of emptiness or loss, in contrast to the child with MDD, whose prominent affect is depressed mood/irritability, the inability to anticipate happiness or pleasure, or both. Trauma- and stress-related disorders, such as adjustment disorder with depressed mood, may also mimic MDD. The essential distinguishing feature of adjustment disorder is an identifiable stressor that precedes mood symptoms.

Reassess Psychosocial Risks and Protective Factors

In addition to reassessing diagnoses, it is important to reassess for relevant new information regarding:

- History of present illness
- Past personal history
- Family history
- Family stressors and conflicts
- School stressors or problems
- Adverse childhood experiences
- Substance use
- Treatment adherence

Comments or questions that may be useful in reassessment include:

- "Let's review and think about some of the topics we discussed before."
- "Has anything happened since the initial evaluation that might help us understand what is happening right now?"
- "How challenging has it been for you and/or your child to engage in therapy?"
- "Are there any problems with medication? How many doses during a typical week do you think you are missing for any reason?"
- "Are you having any problems with insurance or Medicaid when purchasing medication?"
- "Is there anything else we should be talking or thinking about?"

Reevaluate Psychotherapies

If a patient is not improving and the treatment plan does not include evidence-based psychotherapy, adding therapy is recommended. Evidence-based psychotherapies are described and discussed in the Nonmedication Interventions section in Chapter 4. Generally, patients or families that have been reluctant to try psychotherapy will be more motivated if an initial treatment without evidence-based psychotherapy was unsuccessful.

If the patient is not improving and the treatment plan includes psychotherapy but not medication, it is important to reevaluate the effectiveness of psychotherapy and whether the intensity of the treatment or therapist's approach is working for this patient before considering additional medication. In addition to reevaluating with the patient and caregiver(s), discussing and reevaluating the treatment plan with the therapist can provide useful information about both the type of psychotherapy and the therapist's approach with the child and family.

If the patient is not improving and the treatment plan includes medication and therapy, both need reevaluation. Changing only one or the other is recommended. Changing medication and therapy simultaneously makes it difficult to determine which treatment is having what effect.

Reconsider Medication

When Medication Is Ineffective

If the first medication is not effective, research evidence supports switching to a second medication. For ADHD, when the initial stimulant fails, available evidence supports switching from an amphetamine to a methylphenidate preparation or vice versa. About 70% of children with ADHD respond to either methylphenidate or amphetamine. Evidence suggests that almost all children with ADHD respond to the other type or class of stimulant if the first is ineffective.[3]

For depression, available evidence in adolescents suggests that if the first selective serotonin reuptake inhibitor (SSRI) is not effective, the optimal choice for a second medication is another SSRI.[4]

For anxiety, there are no data from rigorous studies regarding the best choice for a second medication, though extrapolation from the depression data[4] would support trying a second SSRI for anxiety.

No data support decisions about switching or adding medication if the first 2 medications (prescribed sequentially) have failed for ADHD, anxiety, or depression. Treatment algorithms have been published for various disorders,[5–7] but beyond the second medication, they are based on expert opinion, not rigorous clinical research data. Thus, if 2 sequential medication trials have failed to yield a positive therapeutic response and adherence is consistent, consideration of consultation with a specialist or expert is recommended.

When the First Medication Is Partially Effective

If the first medication is partially effective, addition of a second or "augmenting" medication may be indicated in some circumstances. However, for many psychotropic medications, proper titration of medication (eg, maximizing treatment benefit while minimizing side effects) is the preferred approach. The only available data supporting safe and effective combined medication treatment in youth are for guanfacine extended release (ER) or clonidine ER with a psychostimulant (methylphenidate or amphetamine preparation) for ADHD.[8–10] No such studies are available for youth with anxiety or depression. Of note, increasing rates of polypharmacy (ie, using multiple classes of psychotropic medications simultaneously) have raised concerns about increased likelihood of adverse effects in the absence of clear data on efficacy.[11]

When Adverse Effects Lead to Discontinuation of a Medication

If the first medication needs to be stopped because of adverse effects, deciding which medication to recommend next may be more complicated. In this situation in particular, consideration of psychotherapy—either adding or intensifying it—may be a first choice.

For ADHD, trying the other type or class of stimulant, as described previously, is a viable option. Bypassing a second type or class of stimulant and recommending guanfacine or clonidine may be considered if, for example, the patient or caregiver(s) objects to a second stimulant.

For anxiety or depression, switching to another SSRI, as described previously, is generally recommended. However, especially if the patient or caregiver(s) objects, trying another class of antidepressant, such as duloxetine, may be the next best option. See "When to Consider Group 3 Medications Without FDA Approval for Use in Youth" section later in this chapter for a discussion of such Group 3 medications.

Discontinuing Group 1 Medications

Fluoxetine can be discontinued abruptly because of the long half-life of fluoxetine and its major metabolite. Stimulants can be discontinued abruptly if the dose is low to moderate—generally less than 0.75 mg/kg.

Gradual discontinuation is recommended for all other Group 1 medications. Discontinuation of guanfacine ER and clonidine ER, as described in the US Food and Drug Administration (FDA) package inserts, are by 1 mg per week for guanfacine ER and 0.1 mg per week for clonidine ER. For higher doses of stimulants, atomoxetine, SSRIs, and duloxetine, reducing the dose on a weekly basis by one-third to one-half will generally avoid withdrawal adverse effects.

Switching Group 1 Medications

There are no specific protocols for switching from one Group 1 medication to another. The following are some recommended approaches.

Stimulants can be switched from the current medication to the new medication the next day, as long as methylphenidate-equivalent total daily doses are

generally the same. For switching from a methylphenidate preparation to another methylphenidate preparation, the total daily dosage should stay about the same, unless the preparation is longer acting (the total dosage will need to be increased) or shorter acting (decreased). The same is true for amphetamine to amphetamine switches. Note that dosage of dexmethylphenidate preparations (Focalin) should always be half of the regular methylphenidate dosage. When switching from a methylphenidate preparation to an amphetamine preparation, the total daily dosage should be reduced by one-half. When switching from an amphetamine preparation to a methylphenidate preparation, the total daily dosage should be doubled.

The package inserts for guanfacine ER (Intuniv) and clonidine ER (Kapvay) recommend that the current medication be stopped before the other medication is started.

Among SSRIs, if fluoxetine is being discontinued and escitalopram, fluvoxamine, or sertraline started, the initial dose of the new SSRI can be started the same day the fluoxetine is stopped. Other switches between SSRIs can be overlapping—the current SSRI can be tapered while the dosage of the new SSRI is titrated up to the optimal dose.

Switches involving atomoxetine or duloxetine should generally follow the recommendations listed earlier for SSRIs, that is, overlapping dose escalation and dose decrease.

When to Consider Group 2 Antipsychotics or Lithium

As described in Chapter 7, several antipsychotics have FDA approval for short-term treatment of youth with psychosis in schizophrenia, mania in bipolar disorder, and "irritability" in autism spectrum disorder. Generally, they are prescribed by specialists with experience in treating these relatively uncommon disorders.

When a pediatric PCC is unable to obtain an appropriate consultation with, or referral to, a specialist, there may be circumstances when it is necessary for the pediatric PCC to prescribe an antipsychotic. In these circumstances, the National Network of Child Psychiatry Access Programs, a group of support programs in more than one-half of US states that provide consultations, may be helpful in providing relatively quick consultation and information about available resources (www.nncpap.org/existing-programs). They will usually

provide these consultations by phone and at no charge. Specific information regarding antipsychotics approved by the FDA for use in youth is available in Chapter 7.

Lithium is FDA approved for short-term treatment of mania in bipolar disorder in adolescents. Previous statements about antipsychotics also apply to lithium.

Primary care monitoring of Group 2 medications ideally requires close collaboration between the pediatric PCC and a mental health specialist, much like the collaboration that takes place between the pediatric PCC and pediatric subspecialists, such as pulmonologists and cardiologists. Significant barriers to collaboration between pediatric PCCs and mental health specialists exist, including the misperception that the Health Information Portability and Accountability Act (HIPAA) prevents them from exchanging information without explicit patient consent. Although HIPAA allows exchange of information, without the patient's consent, between clinicians who are simultaneously treating a common patient (except psychotherapy notes per se and certain information regarding substance use treatment services), pediatric PCCs may prefer to obtain signed release of information forms for the exchange of mental health–related information between the pediatric PCC and specialty provider. When possible, communication within an electronic health record is highly desirable, giving both the pediatric PCC and specialist access to all relevant clinical information in real time. Developing relationships between a primary care office staff member and a staff member in the mental health specialist's office can also improve collaboration. The American Academy of Pediatrics *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* includes sample letters that can be used by pediatric PCCs to introduce their practice to mental health professionals in their community, obtain information from mental health professionals about services that they provide, and exchange feedback about their patient's progress.

Antipsychotics are used to treat youth with dysregulated (ie, erratic, rapidly changing) behavior or aggression more frequently than they are used to treat youth with disorders for which antipsychotics are indicated. Generally, a child or adolescent who needs an antipsychotic for dysregulated behavior and aggression also needs the resources of the mental and behavioral health care system. Thus, it is recommended that, whenever possible, this off-label prescribing be done by specialists embedded in the mental and behavioral care system and experienced in treating these often complex problems.

When to Consider Group 3 Medications Without FDA Approval for Use in Youth

As described in Chapter 8, Group 3 medications are not FDA approved for use in youth with psychiatric disorders. Generally, they are prescribed by specialists for disorders other than ADHD, anxiety, and depression. When a pediatric PCC is unable to obtain an appropriate consultation with, or referral to, a specialist, there may be circumstances when it is necessary to prescribe a Group 3 medication. In these circumstances, as noted earlier, consultation with a child and adolescent psychiatrist by phone or telemedicine link should be considered.

Information regarding 10 of the more commonly prescribed Group 3 medications is available in Chapter 8.

When to Consider Drug Levels or Genetic Testing

When Is a Drug Level Test Indicated?

Most children and adolescents' psychotropic medication can be effectively and safely managed without obtaining drug levels (except for lithium and valproate).

Although relatively rare, the most common indications for considering drug level testing are

- Inadequate response at maximum recommended total daily dose
- Worrisome adverse effects that persist at therapeutic doses
- Suspected nonadherence

Some psychotropic medications (eg, fluoxetine, risperidone) have active metabolites that are usually included in a "drug level" obtained from a reputable laboratory. Although there is no established therapeutic blood level for most psychotropic medications, levels that are undetectable, low, or high can be helpful in guiding treatment.

An "undetectable" drug (and, when applicable, active metabolite) level usually indicates nonadherence. A low drug level may indicate inconsistent adherence. Specific interventions to improve adherence,[12–16] referral to a specialist, or both may be useful. Continuing to increase the dose in these situations is not recommended.

A low drug level may also indicate that the patient is an ultrarapid or extensive metabolizer of the drug. Increasing the dose above the recommended total daily maximum may be necessary to achieve a therapeutic response. Consistent and systematic monitoring for clinical response and adverse effects (or referral to a specialist) is important in such situations.

A very high drug (and, when applicable, active metabolite) level in a patient taking a total daily dose in the recommended dosing range may indicate that the patient is a poor metabolizer of the drug. Such patients frequently have concerning and persistent adverse effects. Lowering the total daily dose until adverse effects are manageable or nonexistent is the recommended intervention for these patients.

For medications with active metabolites reported by the laboratory, the ratio of the levels of the parent drug and active metabolite can be informative. Before making changes in dose based on ratios, consultation with an expert at the laboratory or an appropriate specialist is recommended.

When Is Genotyping of CYP450 Isoenzymes Indicated?

Commercial vendors are increasingly promoting genotyping of CYP450 isoenzymes to assist in management of medication. Of particular concern is telling families that treatment can be personalized based on genotyping. In pediatric psychopharmacology, clinical genotyping of CYP450 isoenzymes is rarely indicated.

If dosage adjustment and use of drug levels does not result in an adequate outcome, it may be useful to establish the patient's metabolizer status (eg, poor, intermediate, extensive, ultrarapid) by genotyping the isoenzyme(s) (eg, CYP2D6 for fluoxetine) involved primarily in metabolism of the particular medication.

Can Genotyping Improve Medication Response?

Commercial vendors are also increasingly promoting genotyping to improve medication response. Variants of various receptors, transporters, enzymes, and ion channel subunits or proteins can be identified by commercial laboratories because they may have a role in the effectiveness of a medication. Although this approach, which is relatively expensive, offers hope for the future, it is not considered useful for clinicians at this time.[17,18]

When to Consider Consultation or a Second Opinion

It is appropriate to seek consultation anytime a pediatric PCC has doubts or questions about an evaluation, treatment plan, or a patient's clinical status. Positing specific questions and concerns may improve quality of the consultative feedback. Pediatric PCCs are encouraged to establish relationships with mental health specialists in their community or with their regional medical center so that these issues can be addressed when concerns arise.

When to Consider Referral for All or Part of the Patient's Ongoing Behavioral Health Care

Whenever a pediatric PCC feels that a patient's evaluation or treatment will require knowledge or skills beyond her or his repertoire, a referral to another clinician for part or all of the patient's mental and behavioral health care is recommended. Even when such a referral is for all mental and behavioral care, the pediatric PCC can play an important role in the patient's overall care, especially in monitoring medication adverse effects, encouraging the patient and family to continue the mental and behavioral health treatment, providing preventive services, and coordinating care of any comorbid medical conditions.

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Appendixes

APPENDIX A

Assessment and Symptom Monitoring Tools

Pediatric Symptom Checklist

The Pediatric Symptom Checklist (PSC) is a general screening tool for identifying emotional and behavioral concerns in youths aged 4 to 16 years. It is reproduced here and is available online at http://brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf. An abbreviated 17-item scale and a self-report version, for youths aged 11 years and older, are also available.

BRIGHT FUTURES TOOL FOR PROFESSIONALS

INSTRUCTIONS FOR USE

Pediatric Symptom Checklist

The Pediatric Symptom Checklist is a psychosocial screen designed to facilitate the recognition of cognitive, emotional, and behavioral problems so that appropriate interventions can be initiated as early as possible. Included here are two versions, the parent-completed version (PSC) and the youth self-report (Y-PSC). The Y-PSC can be administered to adolescents ages 11 and up.

INSTRUCTIONS FOR SCORING

The PSC consists of 35 items that are rated as "Never," "Sometimes," or "Often" present and scored 0, 1, and 2, respectively. The total score is calculated by adding together the score for each of the 35 items. For children and adolescents ages 6 through 16, a cutoff score of 28 or higher indicates psychological impairment. For children ages 4 and 5, the PSC cutoff score is 24 or higher (Little et al., 1994; Pagano et al., 1996). The cutoff score for the Y-PSC is 30 or higher. Items that are left blank are simply ignored (i.e., score equals 0). If four or more items are left blank, the questionnaire is considered invalid.

HOW TO INTERPRET THE PSC OR Y-PSC

A positive score on the PSC or Y-PSC suggests the need for further evaluation by a qualified health (e.g., M.D., R.N.) or mental health (e.g., Ph.D., L.I.C.S.W.) professional. Both false positives and false negatives occur, and only an experienced health professional should interpret a positive PSC or Y-PSC score as anything other than a suggestion that further evaluation may be helpful. Data from past studies using the PSC and Y-PSC indicate that two out of three children and adolescents who screen positive on the PSC or Y-PSC will be correctly identified as having moderate to serious impairment in psychosocial functioning. The one child or adolescent "incorrectly" identified usually has at least mild impairment, although a small percentage of children and adolescents turn out to have very little or no impairment (e.g., an adequately functioning child or adolescent of an overly anxious parent). Data on PSC and Y-PSC negative screens indicate 95 percent accuracy, which, although statistically adequate, still means that 1 out of 20 children and adolescents rated as functioning adequately may actually be impaired. The inevitability of both false-positive and false-negative screens underscores the importance of experienced clinical judgment in interpreting PSC scores. Therefore, it is especially important for parents or other laypeople who administer the form to consult with a licensed professional if their child receives a PSC or Y-PSC positive score.

For more information, visit the Web site: http://psc.partners.org.

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BRIGHT FUTURES TOOL FOR PROFESSIONALS

Pediatric Symptom Checklist (PSC)

Emotional and physical health go together in children. Because parents are often the first to notice a problem with their child's behavior, emotions, or learning, you may help your child get the best care possible by answering these questions. Please indicate which statement best describes your child.

Please mark under the heading that best describes your child:

		Never	Sometimes	Often
1. Complains of aches and pains	1	_____	_____	_____
2. Spends more time alone	2	_____	_____	_____
3. Tires easily, has little energy	3	_____	_____	_____
4. Fidgety, unable to sit still	4	_____	_____	_____
5. Has trouble with teacher	5	_____	_____	_____
6. Less interested in school	6	_____	_____	_____
7. Acts as if driven by a motor	7	_____	_____	_____
8. Daydreams too much	8	_____	_____	_____
9. Distracted easily	9	_____	_____	_____
10. Is afraid of new situations	10	_____	_____	_____
11. Feels sad, unhappy	11	_____	_____	_____
12. Is irritable, angry	12	_____	_____	_____
13. Feels hopeless	13	_____	_____	_____
14. Has trouble concentrating	14	_____	_____	_____
15. Less interested in friends	15	_____	_____	_____
16. Fights with other children	16	_____	_____	_____
17. Absent from school	17	_____	_____	_____
18. School grades dropping	18	_____	_____	_____
19. Is down on him or herself	19	_____	_____	_____
20. Visits the doctor with doctor finding nothing wrong	20	_____	_____	_____
21. Has trouble sleeping	21	_____	_____	_____
22. Worries a lot	22	_____	_____	_____
23. Wants to be with you more than before	23	_____	_____	_____
24. Feels he or she is bad	24	_____	_____	_____
25. Takes unnecessary risks	25	_____	_____	_____
26. Gets hurt frequently	26	_____	_____	_____
27. Seems to be having less fun	27	_____	_____	_____
28. Acts younger than children his or her age	28	_____	_____	_____
29. Does not listen to rules	29	_____	_____	_____
30. Does not show feelings	30	_____	_____	_____
31. Does not understand other people's feelings	31	_____	_____	_____
32. Teases others	32	_____	_____	_____
33. Blames others for his or her troubles	33	_____	_____	_____
34. Takes things that do not belong to him or her	34	_____	_____	_____
35. Refuses to share	35	_____	_____	_____

Total score _____

Does your child have any emotional or behavioral problems for which she or he needs help? ( ) N ( ) Y

Are there any services that you would like your child to receive for these problems? ( ) N ( ) Y

If yes, what services?_____

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BRIGHT FUTURES TOOL FOR PROFESSIONALS

Pediatric Symptom Checklist—Youth Report (Y-PSC)

Please mark under the heading that best fits you:

		Never	Sometimes	Often
1. Complain of aches or pains	1	_____	_____	_____
2. Spend more time alone	2	_____	_____	_____
3. Tire easily, little energy	3	_____	_____	_____
4. Fidgety, unable to sit still	4	_____	_____	_____
5. Have trouble with teacher	5	_____	_____	_____
6. Less interested in school	6	_____	_____	_____
7. Act as if driven by motor	7	_____	_____	_____
8. Daydream too much	8	_____	_____	_____
9. Distract easily	9	_____	_____	_____
10. Are afraid of new situations	10	_____	_____	_____
11. Feel sad, unhappy	11	_____	_____	_____
12. Are irritable, angry	12	_____	_____	_____
13. Feel hopeless	13	_____	_____	_____
14. Have trouble concentrating	14	_____	_____	_____
15. Less interested in friends	15	_____	_____	_____
16. Fight with other children	16	_____	_____	_____
17. Absent from school	17	_____	_____	_____
18. School grades dropping	18	_____	_____	_____
19. Down on yourself	19	_____	_____	_____
20. Visit doctor with doctor finding nothing wrong	20	_____	_____	_____
21. Have trouble sleeping	21	_____	_____	_____
22. Worry a lot	22	_____	_____	_____
23. Want to be with parent more than before	23	_____	_____	_____
24. Feel that you are bad	24	_____	_____	_____
25. Take unnecessary risks	25	_____	_____	_____
26. Get hurt frequently	26	_____	_____	_____
27. Seem to be having less fun	27	_____	_____	_____
28. Act younger than children your age	28	_____	_____	_____
29. Do not listen to rules	29	_____	_____	_____
30. Do not show feelings	30	_____	_____	_____
31. Do not understand other people's feelings	31	_____	_____	_____
32. Tease others	32	_____	_____	_____
33. Blame others for your troubles	33	_____	_____	_____
34. Take things that do not belong to you	34	_____	_____	_____
35. Refuse to share	35	_____	_____	_____

Vanderbilt Assessment Scale for ADHD

The Vanderbilt Assessment Scale for attention-deficit/hyperactivity disorder (ADHD) is a diagnosis-specific screening tool designed to aid in the assessment and management of children aged 6 to 12 years who have ADHD. It is reproduced on the next page and is available online at www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales. It is available in long (assessment) and short (treatment monitoring) versions for both parents and teachers. The long versions include an assessment of potential comorbidities.

NICHQ Vanderbilt Assessment Scale: Parent Informant

Today's Date: 08-25-15

Child's Name: _____

Child's Date of Birth: _____

Parent's Name: _____

Parent's Phone Number: _____

Directions: Each rating should be considered in the context of what is appropriate for the age of your child. When completing this form, please think about your child's behaviors in the past 6 months.

Is this evaluation based on a time when the child

○ **was on medication** ○ **was not on medication** ○ **not sure?**

Symptoms	Never	Occasionally	Often	Very Often	
1. Does not pay attention to details or makes careless mistakes with, for example, homework	○	○	○	○	
2. Has difficulty keeping attention to what needs to be done	○	○	○	○	
3. Does not seem to listen when spoken to directly	○	○	○	○	
4. Does not follow through when given directions and fails to finish activities (not due to refusal or failure to understand)	○	○	○	○	
5. Has difficulty organizing tasks and activities	○	○	○	○	
6. Avoids, dislikes, or does not want to start tasks that require ongoing mental effort	○	○	○	○	
7. Loses things necessary for tasks or activities (toys, assignments, pencils, books)	○	○	○	○	
8. Is easily distracted by noises or other stimuli	○	○	○	○	
9. Is forgetful in daily activities	○	○	○	○	For Office Use Only 2 & 3s: 0 /9
10. Fidgets with hands or feet or squirms in seat	○	○	○	○	
11. Leaves seat when remaining seated is expected	○	○	○	○	
12. Runs about or climbs too much when remaining seated is expected	○	○	○	○	
13. Has difficulty playing or beginning quiet play activities	○	○	○	○	
14. Is "on the go" or often acts as if "driven by a motor"	○	○	○	○	
15. Talks too much	○	○	○	○	
16. Blurts out answers before questions have been completed	○	○	○	○	
17. Has difficulty waiting his or her turn	○	○	○	○	
18. Interrupts or intrudes in on others' conversations and/or activities	○	○	○	○	For Office Use Only 2 & 3s: 0 /9

NICHQ Vanderbilt Assessment Scale: Parent Informant

Symptoms (continued)	Never	Occasionally	Often	Very Often	
19. Argues with adults	○	○	○	○	
20. Loses temper	○	○	○	○	
21. Actively defies or refuses to go along with adults' requests or rules	○	○	○	○	
22. Deliberately annoys people	○	○	○	○	
23. Blames others for his or her mistakes or misbehaviors	○	○	○	○	
24. Is touchy or easily annoyed by others	○	○	○	○	
25. Is angry or resentful	○	○	○	○	
26. Is spiteful and wants to get even	○	○	○	○	For Office Use Only 2 & 3s: 0 /8
27. Bullies, threatens, or intimidates others	○	○	○	○	
28. Starts physical fights	○	○	○	○	
29. Lies to get out of trouble or to avoid obligations (ie, "cons" others)	○	○	○	○	
30. Is truant from school (skips school) without permission	○	○	○	○	
31. Is physically cruel to people	○	○	○	○	
32. Has stolen things that have value	○	○	○	○	
33. Deliberately destroys others' property	○	○	○	○	
34. Has used a weapon that can cause serious harm (bat, knife, brick, gun)	○	○	○	○	
35. Is physically cruel to animals	○	○	○	○	
36. Has deliberately set fires to cause damage	○	○	○	○	
37. Has broken into someone else's home, business, or car	○	○	○	○	
38. Has stayed out at night without permission	○	○	○	○	
39. Has run away from home overnight	○	○	○	○	
40. Has forced someone into sexual activity	○	○	○	○	For Office Use Only 2&3s: 0 /14
41. Is fearful, anxious, or worried	○	○	○	○	
42. Is afraid to try new things for fear of making mistakes	○	○	○	○	
43. Feels worthless or inferior	○	○	○	○	
44. Blames self for problems, feels guilty	○	○	○	○	
45. Feels lonely, unwanted, or unloved; complains that "no one loves him or her"	○	○	○	○	
46. Is sad, unhappy, or depressed	○	○	○	○	
47. Is self-conscious or easily embarrassed	○	○	○	○	For Office Use Only 2 & 3s: 0 /7

Performance	Excellent	Above Average	Average	Somewhat of a Problem	Problematic	
48. Reading	○	○	○	○	○	
49. Writing	○	○	○	○	○	For Office Use Only 4s: 0 /3
50. Mathematics	○	○	○	○	○	For Office Use Only 5s: 0 /3
51. Relationship with parents	○	○	○	○	○	
52. Relationship with siblings	○	○	○	○	○	
53. Relationship with peers	○	○	○	○	○	For Office Use Only 4s: 0 /4
54. Participation in organized activities (eg, teams)	○	○	○	○	○	For Office Use Only 5s: 0 /4

Other Conditions

Tic Behaviors: To the best of your knowledge, please indicate if this child displays the following behaviors:

1. **Motor Tics:** Rapid, repetitive movements such as eye blinking, grimacing, nose twitching, head jerks, shoulder shrugs, arm jerks, body jerks, or rapid kicks.

   ☐ No tics present. ☐ Yes, they occur nearly every day but go unnoticed by most people. ☐ Yes, noticeable tics occur nearly every day.

2. **Phonic (Vocal) Tics:** Repetitive noises including but not limited to throat clearing, coughing, whistling, sniffing, snorting, screeching, barking, grunting, or repetition of words or short phrases.

   ☐ No tics present. ☐ Yes, they occur nearly every day but go unnoticed by most people. ☐ Yes, noticeable tics occur nearly every day.

3. If **YES** to 1 or 2, do these tics interfere with the child's activities (like reading, writing, walking, talking, or eating)? ☐ No ☐ Yes

Previous Diagnosis and Treatment: To the best of your knowledge, please answer the following questions:

1.	Has your child been diagnosed with a tic disorder or Tourette syndrome?	☐ No	☐ Yes
2.	Is your child on medication for a tic disorder or Tourette syndrome?	☐ No	☐ Yes
3.	Has your child been diagnosed with depression?	☐ No	☐ Yes
4.	Is your child on medication for depression?	☐ No	☐ Yes
5.	Has your child been diagnosed with an anxiety disorder?	☐ No	☐ Yes
6.	Is your child on medication for an anxiety disorder?	☐ No	☐ Yes
7.	Has your child been diagnosed with a learning or language disorder?	☐ No	☐ Yes

Comments:

NICHQ Vanderbilt Assessment Scale: Parent Informant

For Office Use Only

Total number of questions scored 2 or 3 in questions 1–9: _____

Total number of questions scored 2 or 3 in questions 10–18: _____

Total number of questions scored 2 or 3 in questions 19–26: _____

Total number of questions scored 2 or 3 in questions 27–40: _____

Total number of questions scored 2 or 3 in questions 41–47: _____

Total number of questions scored 4 in questions 48–50: _____

Total number of questions scored 5 in questions 48–50: _____

Total number of questions scored 4 in questions 51–54: _____

Total number of questions scored 5 in questions 51–54: _____

Adapted from the Vanderbilt Rating Scales developed by Mark L. Wolraich, MD.

American Academy of Pediatrics
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QuIIN Quality Improvement Innovation Network
A program of the American Academy of Pediatrics

NICHQ National Initiative for Children's Healthcare Quality

Scoring Instructions for NICHQ Vanderbilt Assessment Scales

Baseline Assessment

The validation studies for the NICHQ Vanderbilt Assessment Scales were for the 6- to 12-year-old age group. However, to the extent that they collect information to establish *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria, they are applicable to other groups, particularly preschoolers, where they have identified that *DSM-5* criteria are still appropriate.

These scales should *not* be used alone to make a diagnosis of ADHD without confirming and elaborating the information with interviews with at least the primary caregivers (usually parents) and patients. You must take into consideration information from multiple sources. Scores of 2 or 3 on a single symptom question reflect *often-occurring* behaviors. Scores of 4 or 5 on performance questions reflect problems in performance.

The initial assessment scales, parent and teacher, have 2 components: symptom assessment and impairment in performance. On both parent and teacher initial scales, the symptom assessment screens for symptoms that meet criteria for inattentive (items 1–9) and hyperactive (items 10–18) attention-deficit/hyperactivity disorder (ADHD).

Scoring for Diagnostic Purposes

To meet *DSM-5* criteria for the diagnosis, one must have at least 6 positive responses to the inattentive 9 or hyperactive 9 core symptoms, or both. A positive response is a 2 or 3 (often, very often) (you could draw a line straight down the page and count the positive answers in each subsegment). There is a place to record the number of positives in each subsegment.

The initial scales have symptom screens for 3 other comorbidities: oppositional-defiant disorder, conduct disorder, and anxiety/depression. (The initial teacher scale also screens for learning disabilities.) These are screened by the number of positive responses in each of the segments. The specific item sets and numbers of positives required for each comorbid symptom screen set are detailed below and on the next page.

The second section of the scale has a set of performance measures, scored 1 to 5, with 4 and 5 being somewhat of a problem/problematic. To meet criteria for ADHD there must be at least 2 items of the performance set in which the child scores a 4, or 1 item of the performance set in which the child scores a 5; ie, there must be impairment, not just symptoms, to meet diagnostic criteria. The sheet has a place to record the number of positives (4s, 5s).

Scoring to Monitor Symptom and Performance Improvement

For the purposes of tracking symptoms and symptom severity, calculate the mean response for each subsegment of the ADHD symptom assessment screen items (inattentive 9 and hyperactive 9). To calculate the mean responses, first total the responses (0s, 1s, 2s, and 3s) from each item within the inattentive subsegment (items 1–9) and divide by the number of items that received a response. For example, if a parent only provided responses to 7 of the first 9 items, the responses would be totaled and divided by 7. Follow the same calculation instructions for the hyperactive subsegment (items 10–18).

Parent Assessment Scale	Teacher Assessment Scale
Predominantly Inattentive subtype ● Must score a 2 or 3 on 6 out of 9 items on questions 1–9. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 48–54.	**Predominantly Inattentive subtype** ● Must score a 2 or 3 on 6 out of 9 items on questions 1–9. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 36–43.
Predominantly Hyperactive/Impulsive subtype ● Must score a 2 or 3 on 6 out of 9 items on questions 10–18. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 48–54.	**Predominantly Hyperactive/Impulsive subtype** ● Must score a 2 or 3 on 6 out of 9 items on questions 10–18. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 36–43.
ADHD Combined Inattention/Hyperactivity ● Requires the criteria on Inattentive AND Hyperactive/Impulsive subtypes	**ADHD Combined Inattention/Hyperactivity** ● Requires the criteria on Inattentive AND Hyperactive/Impulsive subtypes
Oppositional-Defiant Disorder ● Must score a 2 or 3 on 4 out of 8 behaviors on questions 19–26. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 48–54.	**Oppositional-Defiant/Conduct Disorder** ● Must score a 2 or 3 on 3 out of 10 items on questions 19–28. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 36–43.
Conduct Disorder ● Must score a 2 or 3 on 3 out of 14 behaviors on questions 27–40. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 48–54.	

Parent Assessment Scale	Teacher Assessment Scale
Anxiety/Depression ● Must score a 2 or 3 on 3 out of 7 behaviors on questions 41–47. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 48–54.	**Anxiety/Depression** ● Must score a 2 or 3 on 3 out of 7 items on questions 29–35. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 36–43.
	Learning Disabilities ● Must score a 4 on both, or 5 on 1, of questions 36 and 38.

Follow-up Assessment

Scoring for Diagnostic Purposes

The parent and teacher follow-up scales have the first 18 core ADHD symptoms and the comorbid symptoms oppositional-defiant (parent) and oppositional-defiant/conduct (teacher) disorders. The Performance section has the same performance items and impairment assessment as the initial scales; it is followed by a side-effect reporting scale that can be used to assess and monitor the presence of adverse reactions to prescribed medications, if any.

Scoring the follow-up scales involves tracking inattentive (items 1–9) and hyperactive (items 10–18) ADHD, as well as the aforementioned comorbidities, as measures of improvement over time with treatment.

Scoring to Monitor Symptom and Performance Improvement

To determine the score for follow-up, calculate the mean response for each of the ADHD subsegments. Compare the mean response from the follow-up inattentive subsegment (items 1–9) to the mean response from the inattentive subsegment that was calculated at baseline assessment. Conduct the same comparison for the mean responses for the hyperactive subsegment (items 10–18) taken at follow-up and baseline.

Parent Assessment Scale	Teacher Assessment Scale
Predominantly Inattentive subtype ● Must score a 2 or 3 on 6 out of 9 items on questions 1–9. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 27–33.	**Predominantly Inattentive subtype** ● Must score a 2 or 3 on 6 out of 9 items on questions 1–9. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 29–36.
Predominantly Hyperactive/Impulsive subtype ● Must score a 2 or 3 on 6 out of 9 items on questions 10–18. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 27–33.	**Predominantly Hyperactive/Impulsive subtype** ● Must score a 2 or 3 on 6 out of 9 items on questions 10–18. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 29–36.
ADHD Combined Inattention/Hyperactivity ● Requires the criteria on Inattentive AND Hyperactive/Impulsive subtypes	**ADHD Combined Inattention/Hyperactivity** ● Requires the criteria on Inattentive AND Hyperactive/Impulsive subtypes
Oppositional-Defiant Disorder ● Must score a 2 or 3 on 4 out of 8 behaviors on questions 19–26. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 27–33.	**Oppositional-Defiant/Conduct Disorder** ● Must score a 2 or 3 on 3 out of 10 items on questions 19–28. AND ● Score a 4 on at least 2, or 5 on at least 1, of the performance questions 29–36.

Screen for Child Anxiety Related Disorders

The Screen for Child Anxiety Related Disorders (SCARED) is a diagnosis-specific tool designed to aid in the assessment and management of children aged 8 years and older who have anxiety. It is reproduced on the next page and is available at http://pediatricbipolar.pitt.edu/sites/default/files/SCAREDChildVersion_1.19.18.pdf. Parent and teacher versions are available. Subscales include generalized anxiety, social anxiety, separation anxiety, school avoidance, and panic attack symptoms.

Screen for Child Anxiety Related Disorders (SCARED)

CHILD Version—Page 1 of 2 (to be filled out by the CHILD)

Developed by Boris Birmaher, M.D., Suneeta Khetarpal, M.D., Marlane Cully, M.Ed., David Brent, M.D., and Sandra McKenzie, Ph.D., Western Psychiatric Institute and Clinic, University of Pittsburgh *(October, 1995)*. *E-mail:* birmaherb@upmc.edu

See: Birmaher, B., Brent, D. A., Chiappetta, L., Bridge, J., Monga, S., & Baugher, M. (1999). Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(10), 1230–6.

Name: _____ Date: _____

Directions:
Below is a list of sentences that describe how people feel. Read each phrase and decide if it is "Not True or Hardly Ever True" or "Somewhat True or Sometimes True" or "Very True or Often True" for you. Then, for each sentence, fill in one circle that corresponds to the response that seems to describe you *for the last 3 months*.

	0 Not True or Hardly Ever True	1 Somewhat True or Sometimes True	2 Very True or Often True	
1. When I feel frightened, it is hard to breathe	O	O	O	PN
2. I get headaches when I am at school.	O	O	O	SH
3. I don't like to be with people I don't know well.	O	O	O	SC
4. I get scared if I sleep away from home.	O	O	O	SP
5. I worry about other people liking me.	O	O	O	GD
6. When I get frightened, I feel like passing out.	O	O	O	PN
7. I am nervous.	O	O	O	GD
8. I follow my mother or father wherever they go.	O	O	O	SP
9. People tell me that I look nervous.	O	O	O	PN
10. I feel nervous with people I don't know well.	O	O	O	SC
11. I get stomachaches at school.	O	O	O	SH
12. When I get frightened, I feel like I am going crazy.	O	O	O	PN
13. I worry about sleeping alone.	O	O	O	SP
14. I worry about being as good as other kids.	O	O	O	GD
15. When I get frightened, I feel like things are not real.	O	O	O	PN
16. I have nightmares about something bad happening to my parents.	O	O	O	SP
17. I worry about going to school.	O	O	O	SH
18. When I get frightened, my heart beats fast.	O	O	O	PN
19. I get shaky.	O	O	O	PN
20. I have nightmares about something bad happening to me.	O	O	O	SP

Screen for Child Anxiety Related Disorders (SCARED)

CHILD Version—Page 2 of 2 (to be filled out by the CHILD)

	0 Not True or Hardly Ever True	1 Somewhat True or Sometimes True	2 Very True or Often True	
21. I worry about things working out for me.	O	O	O	**GD**
22. When I get frightened, I sweat a lot.	O	O	O	**PN**
23. I am a worrier.	O	O	O	**GD**
24. I get really frightened for no reason at all.	O	O	O	**PN**
25. I am afraid to be alone in the house.	O	O	O	**SP**
26. It is hard for me to talk with people I don't know well.	O	O	O	**SC**
27. When I get frightened, I feel like I am choking.	O	O	O	**PN**
28. People tell me that I worry too much.	O	O	O	**GD**
29. I don't like to be away from my family.	O	O	O	**SP**
30. I am afraid of having anxiety (or panic) attacks.	O	O	O	**PN**
31. I worry that something bad might happen to my parents.	O	O	O	**SP**
32. I feel shy with people I don't know well.	O	O	O	**SC**
33. I worry about what is going to happen in the future.	O	O	O	**GD**
34. When I get frightened, I feel like throwing up.	O	O	O	**PN**
35. I worry about how well I do things.	O	O	O	**GD**
36. I am scared to go to school.	O	O	O	**SH**
37. I worry about things that have already happened.	O	O	O	**GD**
38. When I get frightened, I feel dizzy.	O	O	O	**PN**
39. I feel nervous when I am with other children or adults and I have to do something while they watch me (for example: read aloud, speak, play a game, play a sport).	O	O	O	**SC**
40. I feel nervous when I am going to parties, dances, or any place where there will be people that I don't know well.	O	O	O	**SC**
41. I am shy.	O	O	O	**SC**

SCORING:

A total score of ≥ **25** may indicate the presence of an **Anxiety Disorder**. Scores higher than 30 are more specific. **TOTAL =**

A score of **7** for items 1, 6, 9, 12, 15, 18, 19, 22, 24, 27, 30, 34, 38 may indicate **Panic Disorder** or **Significant Somatic Symptoms**. **PN =**

A score of **9** for items 5, 7, 14, 21, 23, 28, 33, 35, 37 may indicate **Generalized Anxiety Disorder**. **GD =**

A score of **5** for items 4, 8, 13, 16, 20, 25, 29, 31 may indicate **Separation Anxiety SOC**. **SP =**

A score of **8** for items 3, 10, 26, 32, 39, 40, 41 may indicate **Social Anxiety Disorder**. **SC =**

A score of **3** for items 2, 11, 17, 36 may indicate **Significant School Avoidance**. **SH =**

For children ages 8 to 11, it is recommended that the clinician explain all questions, or have the child answer the questionnaire sitting with an adult in case they have any questions.

The SCARED is available at no cost at www.wpic.pitt.edu/research under tools and assessments, or at www.pediatric bipolar.pitt.edu under instruments.

March 27, 2012

Patient Health Questionnaire-9 Modified for Teens

The Patient Health Questionnaire-9 (PHQ-9) Modified for Teens is a diagnosis-specific screening tool designed to assess for symptoms of depression in teenagers. It is reproduced on the next page and is available online at https://www.aacap.org/App_Themes/AACAP/docs/member_resources/toolbox_for_clinical_practice_and_outcomes/symptoms/GLAD-PC_PHQ-9.pdf. It also provides a brief assessment of suicidal ideation.

PHQ-9: Modified for Teens

Name: _____ **Clinician:** _____ **Date:** _____

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an **"X"** in the box beneath the answer that best describes how you have been feeling.

	(0) **Not At All**	*(1)* **Several Days**	*(2)* **More Than Half the Days**	*(3)* **Nearly Every Day**
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				
9. Thoughts that you would be better off dead, or of hurting yourself in some way?				

In the **past year** have you felt depressed or sad most days, even if you felt okay sometimes?
[ ] Yes [ ] No

If you are experiencing any of the problems on this form, how **difficult** have these problems made it for you to do your work, take care of things at home or get along with other people?

[ ] Not difficult at all [ ] Somewhat difficult [ ] Very difficult [ ] Extremely difficult

Has there been a time in the **past month** when you have had serious thoughts about ending your life?
[ ] Yes [ ] No

Have you **EVER**, in your WHOLE LIFE, tried to kill yourself or made a suicide attempt?
[ ] Yes [ ] No

***If you have had thoughts that you would be better off dead or of hurting yourself in some way, please discuss this with your Health Care Clinician, go to a hospital emergency room or call 911.*

Office use only: Severity score: _____

Modified with permission by the GLAD-PC team from the PHQ-9 (Spitzer, Williams, & Kroenke, 1999), Revised PHQ-A (Johnson, 2002), and the CDS (DISC Development Group, 2000)

Used with the permission of the REACH Institute (www.thereachinstitute.org).

Scoring the PHQ-9 modified for Teens

Scoring the PHQ-9 modified for teens is easy but involves thinking about several different aspects of depression.

To use the PHQ-9 as a diagnostic aid for Major Depressive Disorder:

- Questions 1 and/or 2 need to be endorsed as a "2" or "3"
- Need five or more positive symptoms (positive is defined by a "2" or "3" in questions 1-8 and by a "1", "2", or "3" in question 9).
- The functional impairment question (How difficult….) needs to be rated at least as "somewhat difficult."

To use the PHQ-9 to screen for all types of depression or other mental illness:

- All positive answers (positive is defined by a "2" or "3" in questions 1-8 and by a "1", "2", or "3" in question 9) should be followed up by interview.
- A total PHQ-9 score $\geq$ 10 (see below for instructions on how to obtain a total score) has a good sensitivity and specificity for MDD.

To use the PHQ-9 to aid in the diagnosis of dysthymia:

- The dysthymia question (In the past year…) should be endorsed as "yes."

To use the PHQ-9 to screen for suicide risk:

- All positive answers to question 9 as well as the two additional suicide items MUST be followed up by a clinical interview.

To use the PHQ-9 to obtain a total score and assess depressive severity:

- Add up the numbers endorsed for questions 1-9 and obtain a total score.
- See Table below:

Total Score	**Depression Severity**
0-4	No or Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

Other Assessment and Monitoring Tools

Ask Suicide Screening

The Ask Suicide Screening Questions (ASQ) comprise a brief screening tool that can help identify youth at risk for suicide using a set of 4 screening questions that take 20 seconds to administer. Information about the ASQ can be found at https://jamanetwork.com/journals/jamapediatrics/fullarticle/1363508/.

Abnormal Involuntary Movement Scale

The Abnormal Involuntary Movement Scale (AIMS) is designed to systematically assess for the presence of involuntary movements that may be associated with antipsychotic medications. The scale is available at http://imaging.ubmmedica.com/all/editorial/psychiatrictimes/pdfs/clinical-scales-aims-form.pdf. A demonstration of the examination procedure is available at http://imaging.ubmmedica.com/all/editorial/psychiatrictimes/pdfs/clinical-scales-aims-instructions.pdf.

Barnes Akathisia Rating Scale

The Barnes Akathisia Rating Scale is a 4-item tool used to assess the presence and severity of drug-induced akathisia. It is available at http://keltymentalhealth.ca/sites/default/files/BARS.pdf.

Pediatric Sleep Log

The pediatric sleep log is a tool designed to help families track sleep patterns to look for opportunities to improve sleep quality. See more at www.brightfutures.org/mentalhealth/pdf/families/ec/diary.pdf.

Safe Environment for Every Kid Questionnaire

The Safe Environment for Every Kid (SEEK) questionnaire is a brief screening tool designed to identify potential environment needs and safety concerns. It is available at www.uspreventiveservicestaskforce.org/Home/GetFileByID/859.

Screening to Brief Intervention

The Screening to Brief Intervention (S2BI) tool uses frequency-of-use questions to categorize adolescent substance use into different risk categories. It can be found at https://www.drugabuse.gov/ast/s2bi/#/

CRAFFT Screening Tool

The CRAFFT (car, relax, alone, forget, friends, trouble) Screening Tool is designed to identify youths at risk for problems related to substance use. Identifying specific problem behaviors can be useful when planning intervention. It is available at www.ceasar-boston.org/CRAFFT/index.php.

Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ) is a general screening tool for identifying emotional and behavioral concerns in youths aged 2 to 17 years. Parent, teacher, and self-report versions are available online at www.sdqinfo.com. Questions highlight challenges as well as strengths. Versions with and without symptom effect are available. Subscales include emotional problems, conduct problems, hyperactivity, and peer problems.

Tools to Identify Children Exposed to Violence

The "Tools to Identify Children Exposed to Violence" Web page provides a summary of screening tools that can be helpful in identifying children exposed to trauma. It is available at https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/CEV.aspx.

APPENDIX B

Resources for Clinicians

Clinical Practice Guidelines

ADHD

"ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents" can be found at http://pediatrics.aappublications.org/content/128/5/1007

Anxiety

The American Academy of Child and Adolescent Psychiatry Clinical Practice Guideline is in development, and can be found at www.aacap.org when posted.

Depression

The Guidelines for Adolescent Depression in Primary Care (GLAD-PC) can be found at:

- Part I. Practice Preparation, Identification, Assessment, and Initial Management: http://pediatrics.aappublications.org/content/141/3/e20174081
- Part II. Treatment and Ongoing Management: http://pediatrics.aappublications.org/content/141/3/e20174082

Obesity

The policy statement "Stigma Experienced by Children and Adolescents With Obesity" can be found at http://pediatrics.aappublications.org/content/140/6/e20173034 .

The clinical report "The Role of the Pediatrician in Primary Prevention of Obesity" can be found at http://pediatrics.aappublications.org/content/136/1/e275 .

Treatment of Maladaptive Aggression in Youth

Treatment of Maladaptive Aggression in Youth (T-MAY) provides guidelines for management and treatment of maladaptive aggression in the areas of family engagement, assessment and diagnosis, and initial management. It is appropriate for use by primary care clinicians and mental health providers. It was developed by a steering group of national experts and published as a supplement in *Pediatrics*. Part 1 can be accessed at http://pediatrics.aappublications.org/content/129/6/e1562.full?sid=2c6d-87cb-2928-4269-86e2-e4caae4ff805, and Part 2 can be accessed at http://pediatrics.aappublications.org/content/129/6/e1577.full?sid=2c6d87cb-2928-4269-86e2-e4caae4ff805.

Practice Readiness

Mental Health Practice Readiness Inventory

The practice readiness inventory is a questionnaire designed to help primary care practices determine their level of readiness to address mental health concerns. It can be found in *Addressing Mental Health Concerns in Primary Care: A Clinicians Toolkit.* See more at www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Addressing-Mental-Health-Concerns-in-Primary-Care-A-Clinicians-Toolkit.aspx#sthash.ndeXJpGp.dpuf.

Sources of Specialty Services for Children With Mental Health Problems and Their Families

The Sources of Specialty Services for Children With Mental Health Problems and Their Families handout summarizes key mental health referral services for children and adolescents. It can be found in *Addressing Mental Health Concerns in Primary Care: A Clinicians Toolkit.* See more at www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Addressing-Mental-Health-Concerns-in-Primary-Care-A-Clinicians-Toolkit.aspx#sthash.ndeXJpGp.dpuf.

Mental Health Initiatives Web Page

The "Mental Health Initiatives" Web page (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/default.aspx) contains a number of tools and resources for clinicians caring for children with mental health concerns.

Mental Health Competencies for Primary Care

This report from the Task Force on Mental Health can be found at http://pediatrics.aappublications.org/content/125/Supplement_3.toc

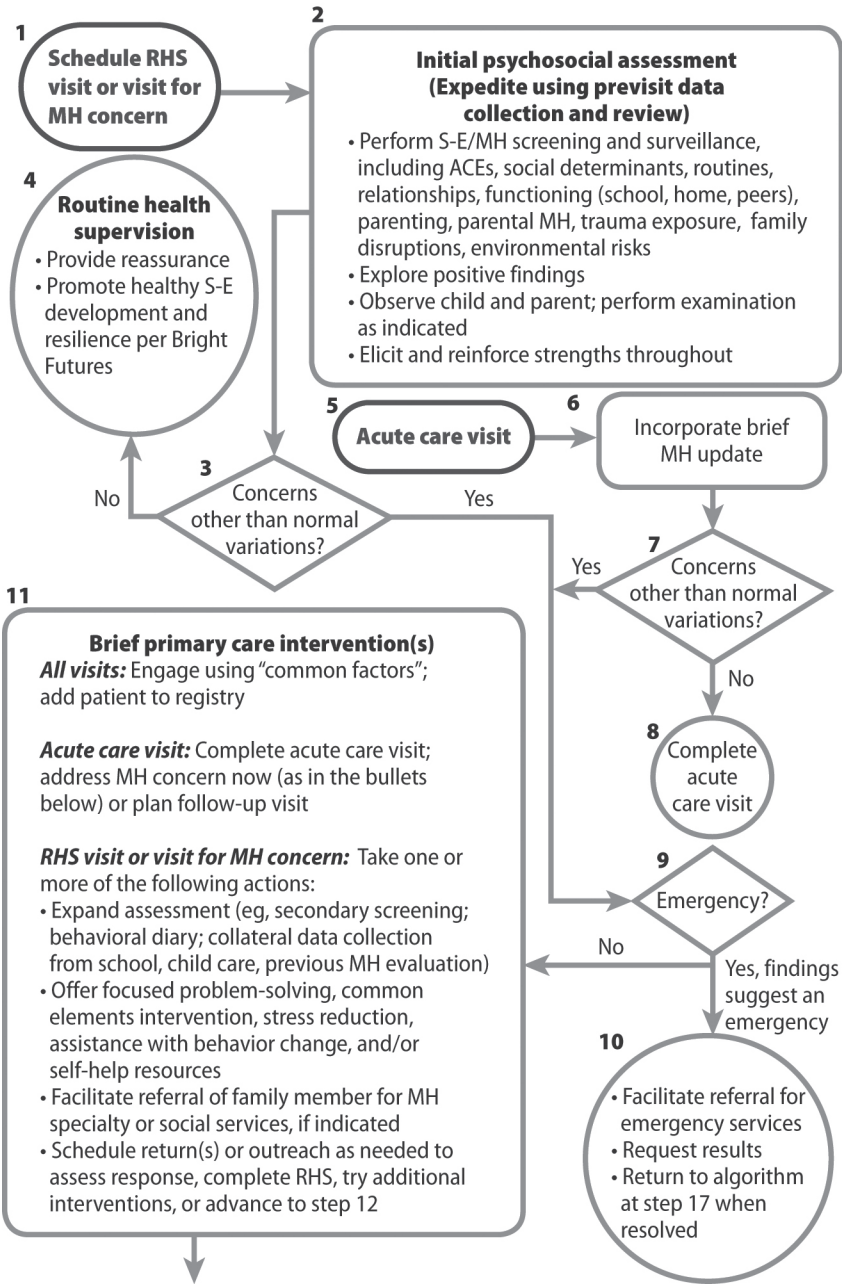
Toolkits

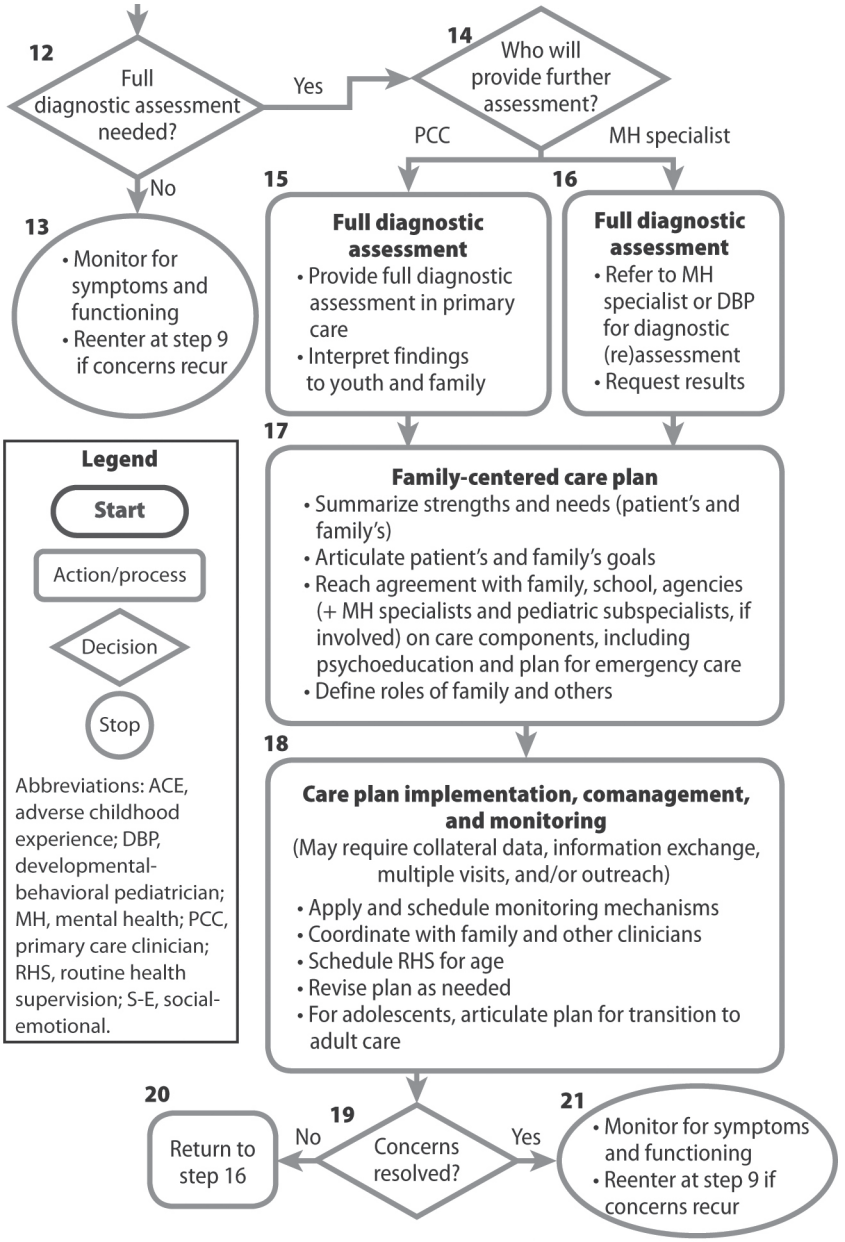
- *Addressing Mental Health Concerns in Primary Care: A Clinicians Toolkit* (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Addressing-Mental-Health-Concerns-in-Primary-Care-A-Clinicians-Toolkit.aspx#sthash.ndeXJpGp.dpuf)
- *Caring for Children with ADHD: A Resource Toolkit for Clinicians* (https://shop.aap.org/caring-for-children-with-adhd-a-resource-toolkit-for-clinicians/)

AAP Mental Health Leadership Work Group's Algorithm

The AAP Mental Health Leadership Work Group's algorithm describing a primary care approach to mental health care highlights the many opportunities pediatric PCCs have to assess the psychosocial well-being of a child and family during routine health supervision and acute care visits, as well as visits scheduled specifically to address mental health problems. The longitudinal relationship that the pediatric PCC often has with a patient and family can facilitate the identification of strengths and assist in the management of mental health concerns.

Each of the algorithm steps—including #2: Initial Psychosocial Assessment; #11: Brief Intervention(s) in Primary Care, #15: Full Diagnostic Assessment in Primary Care; #17: Development of Family-Centered Care Plan; and #18: Care Plan Implementation, Co-management, and Monitoring—contributes to the assessment of a patient and family and the care planning process in particular ways.


1
Schedule RHS visit or visit for MH concern
2
Initial psychosocial assessment (Expedite using previsit data collection and review)
• Perform S-E/MH screening and surveillance, including ACEs, social determinants, routines, relationships, functioning (school, home, peers), parenting, parental MH, trauma exposure, family disruptions, environmental risks
• Explore positive findings
• Observe child and parent; perform examination as indicated
• Elicit and reinforce strengths throughout
4
Routine health supervision
• Provide reassurance
• Promote healthy S-E development and resilience per Bright Futures
5
Acute care visit
6
Incorporate brief MH update
3
Concerns other than normal variations?
No
Yes
7
Concerns other than normal variations?
Yes
No
8
Complete acute care visit
9
Emergency?
No
Yes, findings suggest an emergency
10
• Facilitate referral for emergency services
• Request results
• Return to algorithm at step 17 when resolved
11
Brief primary care intervention(s)
All visits: Engage using "common factors"; add patient to registry
Acute care visit: Complete acute care visit; address MH concern now (as in the bullets below) or plan follow-up visit
RHS visit or visit for MH concern: Take one or more of the following actions:
• Expand assessment (eg, secondary screening; behavioral diary; collateral data collection from school, child care, previous MH evaluation)
• Offer focused problem-solving, common elements intervention, stress reduction, assistance with behavior change, and/or self-help resources
• Facilitate referral of family member for MH specialty or social services, if indicated
• Schedule return(s) or outreach as needed to assess response, complete RHS, try additional interventions, or advance to step 12



Reprinted with permission from Foy JM. *Mental Health Care of Children and Adolescents: A Guide for Primary Care Clinicians*. Itasca, IL: American Academy of Pediatrics; 2018; Appendix 1: Algorithm: A Process for Integrating Mental Health Care Into Pediatric Practice

Neuroscience-Based Nomenclature Application

The Neuroscience-Based Nomenclature application provides useful information about all 108 psychotropic medications that are available in the world, organized by 11 pharmacologic domains and 11 mechanisms of action.

- Apple: https://itunes.apple.com/us/app/nbn-neuroscience-based-nomenclature/id927272449?mt=8
- Android: https://play.google.com/store/apps/details?id=il.co.inmanage.nbnomenclature&hl=en

Patient Counseling Section in US Food and Drug Administration Package Insert

To see an example of the Patient Counseling Information section for fluoxetine, see page 24 of the insert located at www.accessdata.fda.gov/drugsatfda_docs/label/2011/018936s091lbl.pdf.

National Network of Child Psychiatry Access Programs

The National Network of Child Psychiatry Access Programs (NNCPAP) is a collaboration of about 30 US state programs that provide varying levels of child psychiatry collaboration and consultation regarding mental health to pediatric primary care clinicians (www.nncpap.org).

Common Factors Tool (HELP)

Pediatric primary care clinicians, when presented with a child's mental health problem, can often take steps to address parents' distress and children's symptoms, regardless of the specific diagnosis. They can use effective family-centered techniques known as common factors, so-called because they are common factors in a number of evidence-based interventions. These can be represented by the mnemonic HELP: Hope, Empathy, Language, Loyalty, Permission, Partnership, Plan.

A full description of this approach can be found in *Addressing Mental Health Concerns in Primary Care: A Clinicians Toolkit.* See more at www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Addressing-Mental-Health-Concerns-in-Primary-Care-A-Clinicians-Toolkit.aspx#sthash.ndeXJpGp.dpuf.

APPENDIX C

Training Resources for Clinicians

American Academy of Pediatrics

Implementing Mental Health Priorities in Practice Videos

The *Implementing Mental Health Priorities in Practice* videos provide examples of the use of motivational interviewing to approach common mental health concerns in pediatrics (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/introduction.aspx).

Mental Health Leadership Work Group Residency Curriculum, Module 2: Anxiety

This curriculum was developed as a training tool for pediatric continuity clinics to improve residency education on the assessment and management of anxiety in pediatrics (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Module-2-Anxiety.aspx).

Curriculum will be available for ADHD and Low Mood in 2019.

The REACH Institute

The mission of the REACH Institute is to transform children's health services by empowering their care professionals (ie, physicians, therapists, parents, and teachers) to know and use the most effective methods for identifying and assisting children with mental health conditions.

REACH (www.thereachinstitute.org) offers interactive, sustained coaching programs to primary care physicians, behavioral health care professionals, parent advocates, and educators. Specific programs include the Mini-Fellowship in Primary Pediatric Psychopharmacology, Child and Adolescent

Training Institute for Evidence-Based Psychotherapies, and Parent Empowerment Programs designed for parents navigating mental health care systems, juvenile justice, and child welfare.

The Primary Pediatric Psychopharmacology Program is the signature program of REACH. Through it, primary care medical professionals learn 4 essential skills, including how to (1) assess and diagnose children with common mental health problems (eg, depression and anxiety disorders, ADHD); (2) ascertain the presence of more severe conditions that warrant referral to mental health specialists (eg, bipolar disorder, psychosis, or complex comorbid conditions); (3) form a comprehensive treatment plan (including identifying psychotherapy resources); and (4) safely and effectively use psychiatric medications to treat children and adolescents with ADHD, depression, anxiety disorders, and related conditions. The program includes an interactive 16-hour workshop (delivered over 3 days) and 6 months of ongoing case-based consultation with a child psychiatrist and primary care physician selected from the nationally known pediatric psychopharmacology faculty of REACH.

APPENDIX D

Quality Ratings for Psychotherapies and Efficacy Data for Medications

PracticeWise "Evidence-Based Child and Adolescent Psychosocial Interventions"

This report is intended to guide practitioners, educators, youth, and families in developing appropriate plans using psychosocial interventions. It was created using the PracticeWise Evidence-Based Services (PWEBS) database, available at www.practicewise.com. Please check the American Academy of Pediatrics (AAP) mental health Web site (www.aap.org/mentalhealth) for updates.

Please note that this chart represents an independent analysis by PracticeWise and should not be construed as endorsement by the AAP. For an explanation of PracticeWise determination of evidence/level, please visit www.practicewise.com/aap.

Safety and Efficacy Studies Supporting Group 1 Medications (Table D-1)

As a proxy for the magnitude of effect, the rate of responders taking the active drug and placebo is listed. It is important to note that a responder is not the same as a remitter. A patient who remits no longer meets diagnostic criteria and has no or very mild residual symptoms, whereas a responder generally meets a severity criterion of "much better" or "very much better" but may still have mild to moderate symptoms. Thus, a remitter is generally more improved than a responder. The last column notes whether ratings were done by "independent evaluators" (IEs). An IE is a rater who is not involved in data collection other than to conduct blinded symptom severity

ratings at specified times during a study. The use of IEs is thought to reduce bias because the presence or absence of medication adverse effects (which are reported to research clinicians but not to IEs) can help investigators guess the participant's medication status: active or placebo. Finally, all completed National Institute of Health–sponsored studies are included in the tables. However, other unpublished industry-sponsored studies may exist, which are not listed.

Table D-1. Evidence Supporting Short-term Safety and Efficacy of Group 1 Medications in Children and Adolescents

Drug	Indication	Support	Age, y	Rate of Responders, %	IE[a]
Methylphenidate[b]	ADHD	Spencer et al (1996): Review[1]	6–12	A: ~70, P: ~25	NA
		MTA Cooperative Group (1999)[2]	7–9	Not specified	No
		The PATS Team (2006)[3]	3–5	A: 21, P: 13	No
Methylphenidate[c]	ADHD	Greenhill et al (2002)[4]	6–16	A: 64, P: 27	No
		McGough et al (2006): Patch[5]	6–12	A: 71, P: 16	No
		Findling et al (2010): Patch[6]	13–17	A: 66, P: 21	No
Amphetamine[b]	ADHD	Spencer et al (1996): Review[1]	NA	NA	NA
Amphetamine[c]	ADHD	McGough et al (2005)[7]	6–12	Not specified	No
		Domnitei and Madaan (2010)[8]	6–12	A: 70, P: 18	No
Guanfacine[b]	ADHD	Scahill et al (2001)[9]	7–15	A: 53, P: 0	No
		Arnsten et al (2007): Review[10]	NA	NA	NA
Guanfacine[c]	ADHD	Biederman et al (2008)[11]	6–17	A: 50, P: 26	No
		Sallee et al (2009)[12]	6–17	A: 56, P: 30	No
Clonidine[c]	ADHD	Jain et al (2011)[13]	6–17	NA	No
		Kollins et al (2011)[14]	6–17	NA	No
Atomoxetine	ADHD	Michaelson et al (2001)[15]	8–18	Not specified	
Fluoxetine	Anxiety	Birmaher et al (2003)[16]	7–17	A: 61, P: 35	No
	MDD	Emslie et al (1997)[17]	7–17	A: 56, P: 33	No
		Emslie et al (2002)[18]	8–18	A: 65, P: 53	No
		March et al (2004)[19]	12–17	A: 61, P: 35	Yes

continued on next page

Table D-1. Evidence Supporting Short-term Safety and Efficacy of Group 1 Medications in Children and Adolescents (*continued*)

Drug	Indication	Support	Age, y	Rate of Responders, %	IE[a]
Fluoxetine (*continued*)	OCD	Riddle et al (1992)[20]	8–15	A: 33, P: 12	No
		Geller et al (2001)[21]	7–17	A: 49, P: 25	No
		Liebowitz et al (2002)[22]	6–18	A: 57, P: 27	Yes
Sertraline	Anxiety	Walkup et al (2008)[23]	7–17	A: 55, P: 24	Yes
	MDD	Wagner et al (2003)[24]	6–17	A: 36, P: 24	No
	OCD	March et al (1998)[25]	13–17	A: 42, P: 26	No
		The POTS Team (2004)[26]	7–17	A: 21, P: 4	Yes
Escitalopram	MDD	Wagner et al (2006)[27]	6–17	A: 63, P: 52	No
		Emslie et al (2009)[28]	12–17	A: 62, P: 52	No
Fluvoxamine	Anxiety	RUPP Anxiety Group (2001)[29]	6–17	A: 76, P: 29	No
	OCD	Riddle et al (2001)[30]	8–17	A: 42, P: 26	No
Duloxetine	GAD	Strawn et al (2015)[31]	7–17	A: 135, P 137	No

Abbreviations: A, active drug recipients; ADHD, attention-deficit/hyperactivity disorder; GAD, generalized anxiety disorder; IE, independent evaluator; MDD, major depressive disorder; NA, not applicable; OCD, obsessive-compulsive disorder; P, placebo recipients.

[a] Use of IEs to rate symptom severity may help reduce bias because these individuals are blinded to patient adverse effects that could reveal their treatment assignment.

[b] Standard formulation.

[c] Extended-release formulation.

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APPENDIX E

Resources for Caregivers

American Academy of Pediatrics Resources

Books

- *Mental Health, Naturally: The Family Guide to Holistic Care for a Healthy Mind and Body* by Kathi J. Kemper, MD, FAAP
- *ADHD: What Every Parent Needs to Know, 2nd Edition,* edited by Michael I. Reiff, MD, FAAP
- *Autism Spectrum Disorders: What Every Parent Needs to Know* edited by Alan I. Rosenblatt, MD, FAAP, and Paul S. Carbone, MD, FAAP

Patient Education Brochures (http://patiented.solutions.aap.org)

- *Understanding Autism Spectrum Disorders (ASDs)*
- *Your Child's Mental Health*
- *Teen Suicide*

Web Site

HealthyChildren.org: HealthyChildren.org is the only parenting Web site backed by 67,000 pediatricians committed to the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults.

Facts for Families

The American Academy of Child and Adolescent Psychiatry's *Facts for Families* provide concise and up-to-date information on issues that affect children, teenagers, and their families. AACAP provides this important information as a public service. The *Facts for Families* may be duplicated and distributed free of charge as long as the American Academy of Child

and Adolescent Psychiatry is properly credited and no profit is gained from their use. (https://www.aacap.org/aacap/Families_and_Youth/Facts_for_Families/Facts_for_Families_Keyword.aspx)

National Federation of Families for Children's Mental Health

The National Federation of Families for Children's Mental Health is a national family-run organization linking more than 120 chapters and state organizations focused on the issues of children and youth with emotional, behavioral, or mental health needs and their families. The National Federation works to develop and implement policies, legislation, funding mechanisms, and service systems that utilize the strengths of families. Its emphasis on advocacy offers families a voice in the formation of national policy, services, and supports for children with mental health needs and their families.

APPENDIX F

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Complete Criteria of Select Diagnoses

Attention-Deficit/Hyperactivity Disorder

Diagnostic Criteria

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
   b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
   c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
   e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
   g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
   h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
   i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fidgets with or taps hands or feet or squirms in seat.
   b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
   c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
   d. Often unable to play or engage in leisure activities quietly.
   e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
   f. Often talks excessively.
   g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
   h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
   i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

314.01 (F90.2) Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

314.00 (F90.0) Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

314.01 (F90.1) Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

in partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

Disruptive Mood Dysregulation Disorder

Diagnostic Criteria **296.99 (F34.8)**

A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.
B. The temper outbursts are inconsistent with developmental level.
C. The temper outbursts occur, on average, three or more times per week.
D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).
E. Criteria A–D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A–D.
F. Criteria A and D are present in at least two of three settings (i.e., at home, at school, with peers) and are severe in at least one of these.
G. The diagnosis should not be made for the first time before age 6 years or after age 18 years.
H. By history or observation, the age at onset of Criteria A–E is before 10 years.
I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.
Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.
J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).
Note: This diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.
K. The symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition.

Generalized Anxiety Disorder

Diagnostic Criteria **300.02 (F41.1)**

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

   Note: Only one item is required in children.

   1. Restlessness or feeling keyed up or on edge.
   2. Being easily fatigued.
   3. Difficulty concentrating or mind going blank.
   4. Irritability.
   5. Muscle tension.
   6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Major Depressive Disorder

Diagnostic Criteria

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   Note: Do not include symptoms that are clearly attributable to another medical condition.

   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.[1]

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.
Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

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[1] In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in MDE. In grief, self-esteem is generally preserved, whereas in MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in MDE such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

Coding and Recording Procedures

The diagnostic code for major depressive disorder is based on whether this is a single or recurrent episode, current severity, presence of psychotic features, and remission status. Current severity and psychotic features are only indicated if full criteria are currently met for a major depressive episode. Remission specifiers are only indicated if the full criteria are not currently met for a major depressive episode. Codes are as follows:

Severity/course specifier	Single episode	Recurrent episode*
Mild (p. 188)	296.21 (F32.0)	296.31 (F33.0)
Moderate (p. 188)	296.22 (F32.1)	296.32 (F33.1)
Severe (p. 188)	296.23 (F32.2)	296.33 (F33.2)
With psychotic features** (p. 186)	296.24 (F32.3)	296.34 (F33.3)
In partial remission (p. 188)	296.25 (F32.4)	296.35 (F33.41)
In full remission (p. 188)	296.26 (F32.5)	296.36 (F33.42)
Unspecified	296.20 (F32.9)	296.30 (F33.9)

*For an episode to be considered recurrent, there must be an interval of at least 2 consecutive months between separate episodes in which criteria are not met for a major depressive episode. The definitions of specifiers are found on the indicated pages.

**If psychotic features are present, code the "with psychotic features" specifier irrespective of episode severity.

Oppositional Defiant Disorder

Diagnostic Criteria **313.81 (F91.3)**

A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 months as evidenced by at least four symptoms from any of the following categories, and exhibited during interaction with at least one individual who is not a sibling.

Angry/Irritable Mood

1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behavior

4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

Vindictiveness

8. Has been spiteful or vindictive at least twice within the past 6 months.

Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 years, the behavior should occur on most days for a period of at least 6 months unless otherwise noted (Criterion A8). For individuals 5 years or older, the

behavior should occur at least once per week for at least 6 months, unless otherwise noted (Criterion A8). While these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should also be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.

C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

Specify current severity:

Mild: Symptoms are confined to only one setting (e.g., at home, at school, at work, with peers).

Moderate: Some symptoms are present in at least two settings.

Severe: Some symptoms are present in three or more settings.

Separation Anxiety Disorder

Diagnostic Criteria **309.21 (F93.0)**

A. Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached, as evidenced by at least three of the following:

1. Recurrent excessive distress when anticipating or experiencing separation from home or from major attachment figures.
2. Persistent and excessive worry about losing major attachment figures or about possible harm to them, such as illness, injury, disasters, or death.
3. Persistent and excessive worry about experiencing an untoward event (e.g., getting lost, being kidnapped, having an accident, becoming ill) that causes separation from a major attachment figure.
4. Persistent reluctance or refusal to go out, away from home, to school, to work, or elsewhere because of fear of separation.
5. Persistent and excessive fear of or reluctance about being alone or without major attachment figures at home or in other settings.
6. Persistent reluctance or refusal to sleep away from home or to go to sleep without being near a major attachment figure.
7. Repeated nightmares involving the theme of separation.
8. Repeated complaints of physical symptoms (e.g., headaches, stomachaches, nausea, vomiting) when separation from major attachment figures occurs or is anticipated.

B. The fear, anxiety, or avoidance is persistent, lasting at least 4 weeks in children and adolescents and typically 6 months or more in adults.

C. The disturbance causes clinically significant distress or impairment in social, academic, occupational, or other important areas of functioning.

D. The disturbance is not better explained by another mental disorder, such as refusing to leave home because of excessive resistance to change in autism spectrum disorder; delusions or hallucinations concerning separation in psychotic disorders; refusal to go outside without a trusted companion in agoraphobia; worries about ill health or other harm befalling significant others in generalized anxiety disorder; or concerns about having an illness in illness anxiety disorder.

Social Anxiety Disorder (Social Phobia)

Diagnostic Criteria **300.23 (F40.10)**

A. Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).

   Note: In children, the anxiety must occur in peer settings and not just during interactions with adults.

B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).

C. The social situations almost always provoke fear or anxiety.

   Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D. The social situations are avoided or endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The fear, anxiety, or avoidance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.

J. If another medical condition (e.g., Parkinson's disease, obesity, disfigurement from burns or injury) is present, the fear, anxiety, or avoidance is clearly unrelated or is excessive.

Specify if:

Performance only: If the fear is restricted to speaking or performing in public.

Index

Page numbers in *italic* denote a figure, table, or box.

B

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H

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Pediatric Psychopharmacology for Primary Care

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Completely revised and updated, this best-selling resource provides primary care clinicians with practice-tested, condition-specific treatment recommendations for various childhood mental disorders. Obtain clear guidance on dosing, monitoring, and potential adverse reactions of psychotropic medications.

Evidence-based conceptual framework
Ease medication decision-making with a clear, straightforward methodology—based on current research and clinical experience. This simple, systematic approach defines discrete groups of psychotropic medications and spells out group-specific roles and responsibilities in accordance with American Academy of Pediatrics policies.

- Medications for attention-deficit/hyperactivity disorder, anxiety, and depression

  Administration and management information for each drug agent includes
  - Rationale for use
  - Evidence supporting efficacy and safety
  - Initial dosing and subsequent adjustments
  - Measuring therapeutic success
  - When to consult or refer
- Medications typically prescribed by specialists but often monitored in the primary care setting: antipsychotics, mood stabilizers, antidepressants, anxiolytics, and sleep aids

★★★★ **4-Star Review**
"This promises to be a useful book for general practitioners as well as others who would like to learn more about prescribing and monitoring psychotropics for youth with psychiatric diagnoses."
— *Doody's Book Reviews*™ of First Edition

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