Moodiness in ADHD

A Clinician's Guide

W. Burleson Daviss
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Preface

In addition to the key symptoms that characterize patients with attention deficit hyperactive disorder (ADHD) (inattention, hyperactivity, and impulsivity), youth and adults with ADHD frequently have difficulties regulating their mood. Unfortunately, the Diagnostic and Statistical Manual (DSM) has omitted this ubiquitous symptom that has important diagnostic, prognostic, as well as treatment implications. This fact, however, was recently captured in the most recent International Classification of Diseases (ICD) classification of psychiatric disorders.

In this book, Dr. Daviss and colleagues present a comprehensive review of the existing literature regarding the presence of mood dysregulation in patients with ADHD. Given that mood dysregulation is common in several disorders, the authors provide a thorough evaluation of the epidemiology, etiology, phenomenology, differential diagnosis, and tools and strategies for assessment of ADHD and a variety of comorbid disorders. For example, the book includes chapters about ADHD co-occurring with mood disorders, anxiety, disruptive behavior disorders, substance abuse, autism, and medical illness. In addition, the book offers a chapter specifically regarding adults with ADHD and mood lability.

Despite the scarcity of randomized controlled trials for ADHD with comorbid disorders, the chapters also provide helpful suggestions regarding the pharmacological and psychosocial treatments for these conditions.

This book is highly recommended for clinicians as well as researchers treating or studying patients with potential ADHD and mood lability.

Lebanon, NH, USA — W. Burleson Daviss

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Introduction: ADHD, Moodiness, Meteorology, and Elephants

1

W. Burleson Daviss

ADHD is one of the most common mental health disorders, with a prevalence of approximately 8% in children and adolescents and 4–5% in adults in population studies [1]. According to criteria from the Diagnostic and Statistical Manual of Mental Disorders' fifth edition [DSM-5; [2]], patients with ADHD by definition have impairment in multiple functional domains, which can be life-long, especially without treatment [1, 3, 4].

Patients of all ages with ADHD often have other comorbid disorders, both in clinical and epidemiological samples [5–7]. Many such disorders have symptoms of moodiness, variously described as irritability, dysphoria, depression, anxiety, anger, mood dysregulation, affective lability, or explosive aggression. Some diagnoses are limited to children or adolescents, including conduct or oppositional defiant disorders. Depressive disorders can be diagnosed in all ages, but in children or adolescents, irritability as well as depression or anhedonia can be the predominant mood symptom, while irritability in adults is not a mood criterion for depression. Disruptive mood dysregulation disorder is a new mood diagnosis added to DSM-5 limited to patients less than 18, and characterized by persistent irritable or angry moods that are punctuated by recurrent temper outbursts several times a week [2].

Other disorders with moodiness or irritability can only be diagnosed in adults, including borderline, histrionic, and narcissistic personality disorders, as well as antisocial personality disorder (which is considered a continuation of juvenile conduct disorder) [2]. Finally, additional disorders with irritable or moody symptoms can occur in patients of all ages, including bipolar disorders, cyclothymia, drug or alcohol use disorders, autism spectrum disorders, or intermittent explosive disorders [2]. All will be covered in various chapters in the current book.

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While comorbid disorders are relatively common and account for much of the moodiness seen in patients of all ages with ADHD, some experts have argued that moodiness in adult ADHD is a core symptom of the ADHD itself [8, 9]. Others have gone a step further to suggest that the presence of moodiness should be used to define subtypes of ADHD, just as having inattentive or hyperactive/impulsive symptoms do [10, 11]. The section on ADHD in DSM-5, however, describes "low frustration tolerance, irritability, or mood lability" as "associated features" but not diagnostic criteria of ADHD [2, p. 61]. Chapter 11 reviews various explanations of emotional dysregulation in adult ADHD, along with their assessment, and treatment.

Mental health clinicians are taught to use the term "affect" to describe patients' immediate emotional tone, with signs and symptoms conveyed both verbally (with changes in tone, volume, and rapidity) and nonverbally (with changes in facial expressions, motoric activity, and body posture). Such signs of affect can change from seconds to minutes. In contrast, the term "mood" is used to describe more extended emotional states (e.g., anxious, depressed, manic) lasting days to weeks or longer. Such moods color people's views of themselves and their life experiences. The relationship of "affect" to "mood" is considered analogous to that of "weather" to "climate." However, mood and affect are perhaps better described as existing on a continuum. Moods change faster in patients with mental illnesses just as climates change faster with greenhouse gasses. I have deliberately used the informal and nonspecific term "moody" to capture this array of problematic emotional states, both brief and extended.

My first experience working with child and adolescent psychiatric patients was at a busy community mental health clinic, where I often saw patients with comorbid ADHD. My experiences treating such patients were consistent with the literature, which suggests that approximately 3 out of 4 respond to any stimulant tried when dosed correctly [12]. Such work seemed a unique opportunity in psychiatry to "hit a home run with the first pitch." Eventually, as a child and adolescent psychiatry fellow, the ADHD patients I saw in a tertiary mental health clinic at the University of Utah had comorbid presentations at least two-thirds of the time, echoing the comorbidity literature [13]. Such comorbidities included *externalizing disorders* with outbursts of anger, defiance, and aggression. They also included *internalizing disorders* with somatic/vegetative symptoms, excessive worry, poor self-esteem, guilt, and hopelessness, suggesting the social and academic challenges such patients experienced chronically because of their ADHD. An additional challenge was that such patients often had parents with similar symptoms. Dr. Paul Wender and colleagues also at the University of Utah were working with many of these adult patients, diagnosing and treating their ADHD, and challenging the conventional wisdom at the time that ADHD did not extend into adulthood [10]. Adults who continued to have symptoms of ADHD often had co-occurring affective lability, which Wender and colleagues labeled "emotional dysregulation," and argued was an additional symptom of adult ADHD [10, 11]. These adult patients often had a dramatic response regarding ADHD and emotional dysregulation when treated with

stimulants, and a marked improvement in their ability to function as parents, which also improved the lives of their children who were frequently our patients.

My training experiences raised some questions. How could the various causes of moodiness in pediatric or adult ADHD be more effectively diagnosed and treated? Does effective treatment of their ADHD change these patients' risk of developing more severe externalizing and internalizing disorders later? Are there situations in which treating the ADHD worsens patients' moodiness and how can we anticipate those? Conversely, could treating these patients' mood and affective problems lessen the impairment of their ADHD? Are the various diagnoses used to describe mood symptoms in patients with ADHD truly distinct diagnoses, or are these simply examples of us as blind clinicians feeling different parts of the same elephant?

The goals of the current book are to give clinicians the ability to start answering some of the above questions, by providing a clinical framework and pragmatic tools to improve their assessment and treatment of various sources of moodiness in patients with ADHD. Authors of the various chapters were selected based on their clinical and research expertise in their respective topics. The earliest two chapters are devoted to general strategies for assessing ADHD and other comorbidities and ruling out potential organic etiologies for them. Subsequent chapters focus on various "flavors" of diagnoses associated with such moodiness, their epidemiology and public health impact, etiological factors, and strategies for assessment and treatment. Each chapter concludes with a summary of where things stand in that particular area, as well as key un-answered questions. Some chapters review disorders that can occur at any age, others focus on disorders of children, and the last focuses on disorders of adults.

Authors have written their chapters independent of each other, and as a result, there may be some differences about frequencies of various disorders, or about recommendations for assessment and treatment between chapters. Even so, my goal is to present a range of expert perspectives and opinions, some of which may be more relevant or useful than others, depending on the reader's clinical experiences and interests. My hope by providing a review of the main causes of moodiness in individuals with ADHD is to help improve clinicians' understanding, clinical skills and confidence in caring for such patients.

I'd like to acknowledge the contributions of all of the authors of chapters in this book. All have been generous with their time and diligent in writing their respective chapters, reflecting their enthusiasm for their professional work as clinicians and researchers. All have also been exceedingly patient with my sometimes compulsive editorial suggestions. Thanks also to Cheryl Winters-Tetreau and Nadina Persaud with Springer Publishing for their help and patience.

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like to thank my parents, Dave and Claire, my lovely wife Betsy, and my children, David, Madeline, Claire, Jessica and Sanna, for their love and encouragement. All have supported and inspired me, and offered shining examples of how to approach life and work with enthusiasm, grace, determination, and a sense of humor.

Thanks to you as a reader for your interest in this topic and good luck in your work with these challenging but fascinating patients.

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Assessment Strategies for Moody ADHD in Children, Adolescents, and Adults

2

W. Burleson Daviss and Joseph Bond

Introduction

Mood and affect problems and symptoms of inattention, hyperactivity, and impulsivity are common in society, and particularly in mental health and primary care settings. Such problems impair patients' relationships with family and friends, their academic and occupational function, and ultimately the course of their lives. Careful and comprehensive assessment can lay the groundwork for effective treatments that can be life-changing. The list of differential diagnoses is long, and includes mood disorders, anxiety disorders, substance use disorders, personality disorders, and disruptive behavioral disorders, any of which can also have organic or substance-related etiologies. An effective initial interview will consider each of these groups of potential causes for the presenting symptoms, but may require multiple additional steps to gather more information. Sources of such information will include the patient and often other collateral informants, but may also include old medical, mental health, employment and academic evaluations, and sometimes behavioral comments on old report cards. Much of this information can be assimilated prior to the clinician's evaluation.

Often the clinician must integrate incomplete, potentially inaccurate, and sometimes contradictory information from different informants, and carefully weigh such informants' potential accuracy, biases, and motivations. Patients with ADHD, by definition, are inattentive, hyperactive or impulsive, and may give inaccurate answers, whether intentional or not. Patients or family members may underreport the patient's symptoms due to denial, poor insight, skepticism about mental illnesses, discomfort with the patient being "labeled," or simply to defy whichever party requested the evaluation without their blessing. In children or adolescents,

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such discordance may reflect parental conflicts with each other, with the patient, or with the school. Patients with ADHD often tend to overestimate their competence in various areas, a trait known as "positive illusory bias" [1, 2]. On the other hand, patients or family members may overreport the patient's symptoms when anxious or depressed [3], to seek academic or occupational accommodations or a medical excuse, or to obtain medications they hope will be therapeutic for the patient, or that they may divert or misuse. The late US president, Ronald Reagan, when asked about his confidence that his Russian counterparts would comply with a historical treaty intended to reduce both countries' nuclear arsenals, stated simply that he would "trust, but verify." Clinicians should use the same approach with information provided by patients and other informants, especially when their clinical observations and gut feelings raise doubts.

History of Present Illness, Past History, Family History, and Staging the Interview

For patients of all ages, proper psychiatric assessment will often require several stages [4–6]. The first stage will generally include brief introductions with the patient and other informants to review basic identifying information, chief complaints, goals for the evaluation, and further stages. At that time, the clinician can review aspects and limits of confidentiality. The next stages in the case of child or adolescent patients involve interviewing the child/adolescent and parent separately. This gives each party the chance to confidentially discuss their side of the story about the reported problems, as well as other potentially sensitive issues, and for the clinician to observe how reports, behaviors, and attitudes change when the other informant is no longer present. This also gives the clinician the chance to compare each party's answers to similar questions. The time spent with each party will vary, depending on the chief complaints, each party's willingness to participate in a separate interview, and the clinician's opinion about the relative reliability of each party in reporting their clinical concerns [6].

As a general rule, the proportion of time the clinician spends with a child or adolescent patient will generally increase with the patient's age, assuming he or she is cooperative and judged to be a good informant [4–6]. However, even brief interviews with younger children can provide useful observations about their activity level, mood and affect, developmental level, speech and language skills, and ability to handle a brief separation from their parent or other caregiver [4]. Clinicians should adjust their style and language level to the patient's maturity, intelligence and language skills [4, 5]. In young patients, it is particularly important to "break the ice" by adopting a comfortable and reassuring demeanor and asking less probing questions first, perhaps about hobbies, activities, friendships, experiences in school, and relationships with family [4, 5]. Any suggested problems can then be followed up with questions about mood, anxiety, obsessive compulsive, psychotic, and behavioral symptoms, and how those impact such activities. The individual interview also provides the chance to ask about trauma exposure, sexual activity, drug/alcohol use, suicidal ideations and behaviors, and other risky behaviors or

potential safety concerns. Reassuring patients that these are routine questions asked of all patients can make them more forthcoming in disclosing their problems and concerns. Above all, close observation of the patient's mood, affect, and behaviors during the interview is critical. Feelings the patient evokes in the examiner (e.g., sadness, anxiousness, hopelessness, pity, irritation) often provide important clues about patients' underlying mood and thoughts [4, 5].

A similar approach in interviewing adult patients can be equally helpful, assuming they have age-appropriate maturity, communication and cognitive skills. Finding the proper balance between developing an alliance with the patient, and maintaining proper boundaries and a neutral perspective can be especially important but tricky. In adult patients who are the persons of interest, they should be allowed greater say regarding what happens during the diagnostic process and the degree that other informants may participate. The clinician, however, can also set limits when necessary, especially since the diagnosis of ADHD requires such collateral information, and when the patient's thoughts and behaviors represent potential safety concerns.

How patients present themselves in the interview can also be quite informative. Do they seem sincere and trustworthy? Are they appropriately dressed, with good hygiene, or seem disorganized or disheveled? Do they seem distracted, spacey, or forgetful? Do they show signs of hyperactivity such as fidgetiness, or impulsivity such as answering questions prematurely? Do they report cognitive and vegetative symptoms of depression or any signs and symptoms suggestive of mania or psychosis? What kind of feelings do they evoke in you as the clinician through their behaviors and interactions: sympathy, irritation, anxiety, skepticism, fear? Do they have appropriate feelings about their presenting complaints?

Time spent with the parents or other family members, either alone or with the patient, is essential in the case of child and adolescent assessments, and often helpful in the case of adult patients too. Parents and other family members will often be more reliable reporters regarding the patient's ADHD and other externalizing behaviors, and other potentially sensitive issues about the patient's substance use, and social, school, work, family, or legal problems. Parents often will be better able to provide past psychiatric, medical, family, and socio-developmental history as well as relevant stressors or trauma exposure that the patient has no awareness of, or has chosen to withhold [6]. The clinician may use separate time with only the parent of a child patient to share clinical impressions and propose next steps regarding assessment and treatment of the patient. This is often a good time to discuss making sure that the parent's or other family members' mental health needs are also being appropriately addressed. Such time with parents and other family members helps the clinician to anticipate potential problems the patient or parent could have in both accepting and complying with the clinician's recommendations for treatment.

Additional information about the patient's past psychiatric history from the patient or family can also be helpful, including past diagnoses, experiences with prior therapy or pharmacological treatments, suicide attempts or self-injury, hospitalizations and the indications for them. If considering pharmacotherapy, it is important to review any prior medications tried and the patient's response to them. Careful review of past medical history and reports of any current somatic symptoms could suggest a tendency to overreport physical complaints that could be blamed as a

medication side effect, or could suggest a potential medical problem that could interfere with treatment, or at least require a medical workup and medical clearance before starting pharmacotherapy.

Information about the family history, from either the patient or parent, is also useful in understanding the patient's current mental health issues and the environmental context in which they are occurring. Identifying past mental health issues in other family members can help to identify genetic risks for mood, ADHD, substance use, and autism spectrum disorders, as well as for suicidal behaviors. Information about family members' responses to pharmacological treatments can be helpful in anticipating the patient's responses to the same or similar medications. A family member at home with an active substance use problem could increase the patient's risk of environmental adversities and trauma exposure, and is a relative contraindication to prescribing controlled substances like stimulants to the patient.

The Physical and Mental Status Examination

Obtaining vital signs, including blood pressure, pulse, weight, and height, is recommended as a routine part of psychiatric care, especially when considering a trial of a stimulant medication or other ADHD medication. If considering a trial of an atypical neuroleptic, baseline tests, such as an Abnormal Involuntary Movements Exam and measurement of waist circumference, as well as ordering a fasting blood glucose and lipids are recommended [7]. Observations of either motor or vocal tics are important to document and potentially discuss with the patient and family. When considering pharmacological treatment for ADHD, especially with a stimulant, a complete baseline physical exam is recommended, since hypertension, tachycardia, and structural or other heart problems are potential contraindications to such a trial [8, 9].

Structured Interviews and Rating Scales

As summarized in Table 2.1, there are several well-validated structured or semi-structured interviews to help clinicians' reach more accurate diagnoses in patients of all ages. Though such interviews are considered the gold standard for mental health assessment, they are often time-consuming, impractical in clinical settings, and require training to be used validly.

Instead, the current standard of care for patients of all ages is a careful diagnostic interview, supplemented with collateral information from validated rating scales, screening for various diagnoses that could explain patients' presenting complaints, or may require additional attention. Table 2.2 lists multiple different rating scales, along with relevant references. Using additional time during the interview to gather more information about symptoms reported on the questionnaires can be especially helpful. Reports by interview or rating scales about trauma exposure and other recent or ongoing stressors are especially important because they suggest contributing factors that could be targeted and mitigated with psychosocial interventions.

Table 2.1 Structured and semi-structured diagnostic interviews

Measure name	Patient_age informants	Contents	Comments
Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children- Present and Lifetime DSM-5 Version (K-SADS-PL) [17]	6–18 years SR PR	Multiple sections to assess mood disorders, anxiety, disorders, psychotic disorders, trauma-related disorders, eating disorders, substance use, and global assessment of functioning; comprehensive except that it does not contain an autism section	A widely used semi-structured interview for clinician researchers; child and parent interviewed separately, then together to resolve differences in reported sxs. Available at no cost
Diagnostic interview for children and adolescents (DICA) [18]	6–18 years SR PR	Structured interview, which can be used by trained lay-interviewer; multiple sections separately screen patient and parent for various diagnoses based on DSM-criteria for pediatric psychiatric disorders	Available in a computer administered form in which patient reads the questions
Diagnostic Interview Schedule for Children (DISC) [19]	9–17 years SR PR	Structured interview containing multiple sections. Positive screening items open up sections for closer review. Screens for over 30 psychiatric diagnoses in DSM-IV	Used by lay-interviewers with training Computerized version available that reads questions aloud
Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) [20]	6–17 years SR PR	Short battery of questions based on general categories of psychiatric sxs as described in DSM-IV; meant to take less than an hour to interview both child and parent	Parent and child interviewed together for most items, but child/adolescent interviewed alone for items that may be uncomfortable to endorse with parent present
Structured Clinical Interview for DSM-5 (SCID-5) [21]	18+ years SR	Thorough assessment that can take a half hour to 2 h to administer depending on how many screening items are endorsed	This is the most commonly used diagnostic interview and has versions for clinicians (SCID-CV) and for clinical trials (SCID-CT)
Structured Clinical Interview for DSM-5 Personality Disorders (SCID-PD) [22]	18+ years SR	Screening questions based on criteria for all personality disorders described in DSM-5 personality disorders; time required 30″	Adaptation of the SCID used to diagnose personality disorders
Composite International Diagnostic Interview (CIDI) [23]	18+ years SR	Questions regarding 276 sxs related to DSM-IV diagnostic criteria	From the WHO website, but scoring requires special training

DSM Diagnostic and Statistical Manual, *PR* Parent report, *SR* Self Report, *Sxs* symptoms, *TR* Teacher report, *Yrs* years

Table 2.2 Rating Scales and Questionnaires

Measure name	Patient age informants	Contents	Comments
Attention deficit hyperactivity, oppositional defiant and conduct disorders			
Vanderbilt Parent and Teacher Behavioral Scales [24, 25]	11–18 years PR TR	55 questions on parent version and 43 questions on teacher version. Questions assess sxs of ADHD (inattentive and hyperactive clusters), ODD, Conduct Disorder, depression, anxiety, and functional impairment; based on DSM criteria; items considered positive if rated at least "often"	Teacher version combines ODD and Conduct disorder questions into single group; helpful in diagnosis process, treatment-sensitive; no cost
Conners Comprehensive Behavior Rating Scales (CBRS) [26]	8–18 years for CBRS-SR; 6–18 years for CBRS-PR and CBRS-TR	An extensive instrument intended for multiple informant types to provide a full review of behaviors, emotions, and academic/social function	Clinical Index is an auxiliary scale used to help review sxs for specific DSM disorders
Short SNAP-IV [27]	6–18 years PR TR	26-item version of original 90-item SNAP-IV; Questions screen for ADHD and ODD sxs per DSM-IV	Sxs rated "often" or "very often" are counted positive. No cost
Adult ADHD Self-report Scale (ASRS) [28, 29]	18+ SR	18 questions based on DSM-IV criteria for ADHD. Part A Screen: 4 inattentive and 2 hyper/impulsive sxs; Part B has 12 remaining sxs	The 6 Part A items are best discriminators of adult ADHD
Conner's Adult ADHD Rating Scales (CAARS) [30]	18+ years SR	26-item and 66-item forms measuring ADHD and related sxs on 4-point scale. Subscales: *Inattention-Memory, Hyperactive-Restlessness; Impulsivity-Emotional lability* subscale measures sxs of ED [31].	Long form has an Inconsistency Index that measures differing answers to similar questions
The Brown Attention-Deficit Disorder Scale (BADDS) for Adults [32]	18+ years SR or clinician-administered	Developed and normed to assess for poor executive function and ADHD sxs; 40 items rated on a 4-point scale	*Emotional Control* cluster for frustration management and emotional modulation
Behavioral Rating Inventory of Executive Function (BRIEF-A) [33]	18+ years SR Other informant report	75 items of executive function and self-regulation scored on a 3-point scale [33]; gives an overall Global Executive Composite score, a Behavioral Regulation Index (with Emotional Control and 3 other component scales); and a Metacognition Index (of executive function and ADHD). Raw scores can convertible to standard T scores	T-scores of 50 equivalent to population's mean, and T-scores ≥65 are 1.5 standard deviations above it, and suggest the problems are clinically significant [34]

Objective measures of ADHD			
Conners Continuous Performance Test-II [11]	8 years to adult Task-based	A 14″ computerized challenge, in which patients are given a series of letters at varying intervals and told to push the space bar whenever they see any letter other than "X." Measures errors of omission, commission, and declining accuracy over time of test, each suggesting possible ADHD	Provides a score suggesting relative likelihood of ADHD; moderate correlation with parent- and teacher ADHD ratings; treatment-sensitive to ADHD meds [35–38]
Test of Variable Attention (TOVA) [12]	4 years to adult Task-based	22 min computerized assessment for ages 6 and up. Ages 4–5 can take an 11 min test instead	As with CPT-II above, lacks sensitivity and specificity, but is treatment-sensitive
NEBA EEG-Based Test [15]	6–18 years 20–30″	Uses modified EEG to measure electrical activity in the front part of the brain, *specifically the ratio of theta to beta waves*, which has been found to be a biomarker of potential ADHD [16]. Results categorize youths as: (1) is likely to have ADHD, (2) needs additional assessment for ADHD sxs, and (3) needs additional assessment for "other conditions"	Unclear if treatment-sensitive
General measures of symptoms, dysfunction, and change with treatment			
Achenbach System of Empirically Based Assessment (ASEBA) [39]	1.5–5 years for pre-school PR; 6–18 years for School age PR or TR; 11–18 years for Youth SR	4 pages of 100 or more questions about general level of functioning, and questions about problematic behaviors. Behaviors included are: Aggressive, anxious/depressed, attention problems, rule-breaking behavior, somatic complaints, social problems, thought problems, and withdrawn/depressed. All versions take about 30″ to complete	Available in >90 languages with normative data from multiple different societies. The previous version was the Child Behavior Checklist (CBCL) [40]
Strength and Difficulties Questionnaire [41]	2 years to adult SR PR TR	25 items in five categories: Emotional sxs, conduct problems, hyperactivity/inattention, peer relationships, pro-social behaviors	Widely used in clinical settings and studies, especially in Europe; multiple translations available; no cost
Columbia Impairment Scale [42]	9–17 years SR or PR	13 items related to interpersonal relations, occupation, schoolwork, use of leisure time, and affect. Originally meant to done by interview	More recently used as a questionnaire; no cost

(continued)

Table 2.2 (continued)

Measure name	Patient age informants	Contents	Comments
Clinician Global Impressions of Severity Scale (GGI-S) [43]	All ages Clinician-rated estimate of clinical severity relative to other patients with that diagnosis	Widely used in research and clinical practice to assess baseline severity and changes over time. Rater uses all available clinical info including clinical observations. CGI-S ratings from 1 to 7: (1) Normal, not at all ill; (2) Borderline mentally ill; (3) Mildly ill; (4) Moderately ill; (5) Markedly ill; (6) Severely ill; (7) Among the most extremely ill	Suggested by the Texas medications algorithm group to track patients' responses to various treatments, and to guide further treatment decisions. No cost [44]
Clinician Global Impressions of Improvement Scale (GGI-I) [43]	All ages. Clinician-rated estimate of clinical improvement from baseline	Companion measure to CGI-S, used to assess response to treatment. CGI-I ratings from 1 to 7: (1) very much improved; (2) much improved; (3) minimally improved; (4) no change; (5) minimally worse; (6) much worse, and (7) very much worse). Responders often defined in trials by a CGI-I ≤ 2	Persistent CGI-I of 5 or 6 suggests the need to consider a change treatment. No cost [44]
Mood disorders			
Patient Health Questionnaire (PHQ-9) [45]	18+ years SR	None questions about frequency of MDD sxs per DSM-5 criteria. No cost	Useful self-administered screening tool, quick to complete and score
PHQ-9 for Adolescents [46]	13–18 years for SR 6–18 years for PR	13-item measure, with 9 DSM-based sxs of major depression rated on 4-point scale according to frequency	Modified from Adult PHQ-9 to screen for frequency of DSM-5 major depression sxs. No cost
Mood and Feelings Questionnaires (MFQ) [47]	8–18 years SR or PR versions	33 items scale, rating current depressive sxs on a 3-point scale: 0 = "not true," 1 = "sometimes," 2 = "true." Treatment-sensitive; 6–7 year olds can also complete if adult reads the questions [48]	13-item version also available [49]
Children's Depressive Rating Scale, Revised (CDRS-R) [50]	8–18 years SR PR	17-item interview-rated, based on input from both SR and PR. Ratings are on a 5- or 7-item scales. Widely used in research to track changes in the severity of depressive sxs	Score ≥ 40 indicate clinically significant sxs; score <28 used to define depressive remission
Beck Depressive Inventory Version 2 (BDI-2) [51]	13+ years SR	21 items rated on a 3-point scale to assess DSM-IV criteria for depression, created for adult use	Occasionally used in studies with adolescents

Children's Depressive Inventory (CDI) [52]	7–18 years SR	27 items on a 3-point scale. Modeled after BDI, to assess depressive sxs in juveniles	Treatment-sensitive
Center for Epidemiologic Studies Depression Scale (CESD) [53]; CESD-Revised (CESD-R) [54]	18+ years SR	20 items measure the frequency of 9 depressive sxs as defined by DSM-IV. Developed for adults but has been used in adolescent studies; can be administered by phone	No cost
Parent General Behavior Inventory (P-GBI) [55]; Brief P-GBI Mania Scale (GBI-10) [56]	5–17 years PR	The 73-item P-GBI, includes a 28-item Hypomanic/Biphasic and 45-item Depressive subscales. Hypomanic/Biphasic subscale strongly discriminates pediatric bipolarity from ADHD or other psychopathology. Treatment-sensitive [57]	A 10-item brief version of P-GBI (GBI-10) also a valid screen for pediatric mania [56]
Child Mania Rating Scale [58, 59]	9–17 years SR and PR	21-item screen for current sxs of mania based on DSM-IV. 10-item short form also available	Does not assess for lifetime mania. No cost
Young Mania Rating Scale [60] Young Mania Rating Scale-Parent Version [55]	9–17 years Clinician-rated YMRS; Also a PR version	11 questions based on DSM criteria for mania in adults, later modified to be applicable in youths. Newer parent-version enables them to report on potential manic signs/symptoms in juveniles	Often used as an outcome measure in trials of bipolar patients of all ages. No cost
The Mood Disorders Questionnaire (MDQ) adolescent version [61]	11+ years PR SR	Both adolescent SR and PR versions have 13 items related to manic sxs, plus additional items to determine if sxs occurred concurrently, and were impairing; associated with significant impairment	Modified from adult MDQ; only PR version validated for identifying bipolar youth; no cost
Mood Disorders Questionnaire, Adult-version [62]	18+ years SR	13 items of manic sxs, plus additional items assess if reported sxs were concurrent, and significantly impairing	Instead of current sxs, screens for lifetime history of manic sxs No cost
Hamilton Depression Rating Scale (HRDS or HAM-D) [63, 64]	18+ years PR	The original has 17 questions to assess depressive sxs but the most recent revision contains 29 questions	Widely used in adult clinical trials, treatment-sensitive

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Table 2.2 (continued)

Measure name	Patient age informants	Contents	Comments
Anxiety disorders			
Multidimensional Anxiety Scale for Children (MASC) [65]	Child and adolescent SR	39 items classified by four domains of sxs: Physical (tense/restless and somatic/autonomic), social anxiety (humiliation/rejection and public performance fears), harm avoidance (perfectionism and anxious coping), and separation anxiety	Widely used, commercially available under copyright
Screen for Child Anxiety-Related Disorders (SCARED) [66]	8–18 year SR and PR versions	41 items: Generalized Anxiety, Panic Disorder, Separation Anxiety, Social Anxiety, and School Avoidance	Specific scores for sub-categories suggest positive screens; no cost
Zung Self-Rating Anxiety Scale (SAS) [67]	18+ years SR	20-item, with four groups of sxs: Cognitive, autonomic, motor	Widely available
Generalized Anxiety Disorder 7 (GAD7) [68]	Adolescent and adult SR	7 items that screen for generalized anxiety disorder, rated on 4-point scale	Often used in Primary Care (has also been used in adolescents); no cost
Obsessive compulsive disorder			
Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [69]	Child or adolescent Clinician-administered child- or parent-rated interview	Informants first identify OCD sxs from a long list provided by the clinician, then are asked to rate the most sxs based on their severity and levels of interference	A pediatric version modeled after the adult Yale-Brown Obsessive Compulsive Inventory [70]; used in clinical trials and clinical practice [71]
Short Leyton Obsessional Inventory for Children and Adolescents [72]	8–18 years PR SR	11-item, abbreviated version of the 20-item Leyton Obsessional Inventory-Child Version; OCD sxs rated on a 4-point scale. Modified from OCD measure in adults [73]	Brief; separates OCD cases from depressed and community controls; no cost [71]
Obsessive-Compulsive Inventory-Child Version [74]	7–17 years 21-items; a SR or PR screen for OCD	A relatively new, child-version of the Obsessive-Compulsive Inventory (OCI-CV); 6 domains of sxs like original adult measure; scores correlate with clinician-rated OCD severity; treatment-sensitive	Enables brief assessment of pediatric OCD across multiple domains of sxs [75]
Obsessive-Compulsive Inventory-Revised [76]	18+ years SR	18 items rated on a 5-point scale, summed to generate a total score. Contains six subscales: Washing, checking, ordering, obsessing, hoarding, and mental neutralizing; treatment-sensitive [71]	Total scores reported to correlate with clinician-rated measures of OCD severity

Yale-Brown Obsessive Compulsive Scale [70]	Adult Clinician-rated, 10-item scale	10-item scale; Patient first reviews a list of OCD sxs, then rates the severity of impairment related to these sxs, with impairment from obsessions and compulsions rated separately; treatment-sensitive	Used in OCD research and clinical treatment; no cost
Trauma-related disorders			
Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [77];	18+ years SR *11–18* *SR and PR*	30-item interview of recent (weekly and monthly versions) and lifetime sxs, frequency, and impairment related to DSM-5 criteria A-G for PTSD; *New Child/ Adolescent version also available (CAPS-CA-5)* [78]	Currently a gold standard for assessing for PTSD at no cost
Traumatic Events Screening Inventory (TESI) [79]	8+ years for SR Any age for PR	Items ask about lifetime history of 14 types of events and level of distress (e.g. disasters, wrecks, illness, domestic violence, community violence, physical abuse, sexual assault, etc.); measures non-victimization and victimization events	Victimization events linked with depression and suicidal behaviors [79, 80]; no cost
Life Events Checklist for DSM-5 [81]	8+ years SR	16 items regarding occurrence of different potentially traumatic events	
UCLA PTSD Reaction Index for DSM-5 [82]	7–12 years for Child SR 13–18 years for Adolescent SR	Based on DSM-5 criteria; 33 items about traumatic events, and patient's immediate and persistent reactions. 18 items asked by clinician, 15 by patient	Common outcome measure in pediatric PTSD research
Trauma Symptom Checklist for Children/for Young Children [83]	PR for all ages SR for 8–16 years	54 questions in SR and 90 in PR. Child asked to describe frequency of thoughts, feelings, behaviors	
Child PTSD Symptom Scale [84]	8–18 years SR	26 items related to traumatic events, PTSD sxs, impairment; based on DSM-IV criteria	
Young Child PTSD Checklist [85]	1–6 years PR	12 questions about the occurrence of traumatic events and 30 questions about specific sxs	
PTSD Checklist for DSM-5 (PCL-5) [86]	18+ years SR	20-item measure based on diagnostic criteria for PTSD from DSM-5; military and civilians versions	No cost

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Table 2.2 (continued)

Measure name	Patient age informants	Contents	Comments
Autism spectrum disorders			
Modified Checklist for Autism in Toddlers (M-CHAT) revised [87]	16–30 months 20-item parent/caregiver report	Widely used screening to assess for risk for autism spectrum disorders. Often administered and scored as part of a well-child check-up; On-line version too	Allows parent and clinician to estimate autism risk. No cost
Social Responsiveness Scale version 2 (SRS2) [88]	4–18 years PR and TR (both have 65 items)	Dimensional measure of social ability; 5 subscales (Social Awareness, Social Cognition, Social Communication, Social Motivation, Restricted interests/Repetitive Behaviors), consistent with DSM-5 criteria of Autism Spectrum Disorder	Generates raw scores, and T-scores based on normative samples; can assess syndromal and sub-syndromal cases
Gilliam Autism Rating Scale 3rd Edition (GARS-3) [89]	3–22 years PR and TR	56 items, 6 subscales (Restrictive/Repetitive Behaviors, Social Interaction, Social Communication, Emotional Responses, Cognitive Style, Maladaptive Speech; sxs updated based on DSM-5 criteria for autism spectrum disorders	Total and subscale scores suggest probability of an autism spectrum disorder and severity of sxs; Yields raw and T-scores
The Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) [90]	Toddlers-adults 50″ clinician-administered, interview with patient alone	Semi-structured, play based; assesses communication, social interaction, play, and restricted/repetitive behaviors, using specific tasks to elicit certain behaviors; objective; standardized; requires training to use validly	Offers age-specific information for equivocal cases of autism
Substance use disorders			
Child CRAFFT Questionnaire [91]	12–18 years SR	9-question screening tool to assess exposure to, use of, and consequences from drug use. Easy to administer and score with high sensitivity; newest CRAFFT 2.0 version asks about specific substances	Acronym for high risk behaviors: Car, Relax, Alone, Forget, Friends, Trouble. No cost
Alcohol Use Disorder Identification Test—Consumption (AUDIT-C) [92]	Any age	Three questions scored according to frequency of alcohol use. The higher the score, the more likely an alcohol use disorder (AUD) is present	Positive screens: 4+ for men and 3+ for women; no cost

CAGE Questionnaire [93]	Any age SR	Four questions screening for the likelihood of AUD: **C**ut down, **A**nnoyed, **G**uilty, and **E**ye-opener; CAGE alludes to topics of the 4 questions	No cost
Opioid-Related Behaviors in Treatment (ORBIT) Scale [94]	18+ years SR	10 items track recent behaviors related to opioid use (both aberrant use and clinical use)	
Drug Abuse Screening Test (DAST) [95]	Adolescent and adult SR versions	10, 20, or 28-item screens for substance abuse	Moderate to high validity, sensitivity, and specificity; no cost
Short Michigan Alcohol Screening Test (SMAST) [96]	Various SR versions by age	10 to 24 item versions	Shorter versions less specific but still sensitive in detecting alcohol disorders; no cost
Emotional Dysregulation			
The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) [97]	18+ years Clinician-administered scale	Based on the Utah Criteria, which view inattention and hyperactivity, but not impulsivity, as the core sxs of ADHD [97–99]. Assesses multiple sxs within seven symptom domain categories: Difficulties sustaining attention, Disorganization. Hyperactivity/ restlessness, Impulsivity, Temper, Mood lability, and Emotional over-reactivity	Emotion Dysregulation Scale is sum of scores on Emotional overreactivity, Mood lability, and Temper; no cost [100]
Behavior Rating Inventory of Executive Function for Adults (BRIEF-A) [33]	18+ years SR	75 items scored on a 3-point scale; categories include Emotional Control and Metacognition	
Emotional Impulsiveness Scale (EIS) [101]	18+ years SR Other informant	Screens for 7 sxs of emotional dysregulation: (1) impatient; (2) quick to anger; (3) easily frustrated; (4) over-reacts; (5) easily excited; (6) loses temper; (7) touchy/easily annoyed	

CNS central nervous system, *DSM* Diagnostic and Statistical Manual, *EEG* electroencephalogram, *PR* Parent report, *SR* Self Report, *Sxs* symptoms, *TR* Teacher report, *Yrs* years

Neuropsychological, Continuous Performance, and Electroencephalogram (EEG) Tests

Although neuropsychological testing has been suggested to be an important potential component of the workup for ADHD in patients of all ages [10], such testing is often time-consuming and expensive, and not designed specifically to diagnose ADHD at any age according to both the American Academy of Pediatrics [9] and the American Academy of Child and Adolescent Psychiatry [8]. However, neuropsychological testing can be helpful in situations in which an underlying learning disorder or developmental language disorder is suspected, or when accommodations at school or in taking standardized tests are being considered. If possible, this could be done through the school's special education team as it can be quite expensive and insurance may not cover it.

Multiple continuous performance tests have been available for years [11, 12], and are sometimes used in the assessment of potential individuals with ADHD of all ages. A recent literature review of the available options suggested they often have shown problems with retest reliability and in discriminating patients with and without ADHD, due to unacceptably high false positive and false negative tests, especially in the presence of comorbid psychiatric disorders or other brain problems [13]. Continuous performance tests are not a substitute for a good clinical interview. However, they have been treatment-sensitive in pharmacological trials of ADHD medications [14]. Table 2.2 has additional information about these too.

A test involving EEGs (known as NEBA) has recently been validated, and approved by the Food and Drug Administration, as a supplemental test for ADHD in children and adolescents [15]. The NEBA test involves an approximately 25 min EEG in which the patient's ratio of theta to beta waves is determined. This ratio has been demonstrated to be a biomarker of ADHD [16], and may be useful in equivocal cases. See Table 2.2 for more information.

Summary and Next Steps

A careful psychiatric assessment is the cornerstone for diagnosing and effectively treating ADHD and the many disorders of moodiness associated with it. This requires a carefully staged interview of the patient and other key informants about the patient's recent past history of mental health problems. Such interviews vary according to age, cooperativeness, and perceived ability of the patient and other informants to provide useful and accurate information about the reported problems. Rating scales about patients' symptoms and associated impairment can help in screening, and guiding the interview, and may highlight and help to resolve contradictory reports. Once working diagnoses are determined, rating scales can be used subsequently to monitor changes in the patient's symptoms with treatment, and to help guide further adjustments to the treatment. The next chapter will review potential organic causes of moodiness and ADHD symptoms. Later chapters will discuss assessment and treatment strategies for various potential causes of moodiness or mood problems in patients with ADHD.

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Mood Disturbance in ADHD Due to a General Medical Condition

3

John G. Ryder and Jacquelyn M. Silva

The medical evaluation of mood disturbance in patients diagnosed with ADHD, like all great quests, begins with a clear definition of what is being pursued. Taber's cyclopedic medical dictionary defines mood as "a pervasive and sustained emotion that may have a major influence on a person's perception of the world" [1]. The use of the word "sustained" highlights the importance of considering an emotion's duration when defining a particular mood state. Duration is partially determined by the individual's ability to self-regulate emotions, which is a complex learned process. In brief, it is the ability to emotionally respond to the demands of an experience in a manner that is socially normative. Furthermore, the person must demonstrate enough flexibility to willfully permit or deny spontaneous reactions to that experience such that dysfunction does not occur (non-pathological response) [2]. There is a significant association between an inability to do this—emotional dysregulation, and mental disorders for which a disturbance in mood is their primary feature (mood disorders) [3, 4].

In the process of formulating a differential diagnosis, clinicians are often readily alerted to the importance of evaluating for organic causes of new psychiatric presentations, such as depression or anxiety, when they correlate with the onset or exacerbation of a general medical condition. However, sometimes emotional dysregulation is the only harbinger of an insidious mood disorder that may be present or emerging.

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Irritability and emotional lability are two major components of emotional dysregulation and subsequently mood dysregulation to be vigilant for in all patients [5, 6]. Mood and anxiety disorders often coexist with medical conditions, and practically all psychiatric symptoms can be mimicked by a general medical condition. In some patients these disorders can contribute to the medical condition, whereas for others the medical condition is the underlying cause. It is important to be aware that symptoms of depression, irritability, mood lability, and anxiety can be prodromal of medical illness that if not uncovered early, could lead to significant morbidity and mortality.

For instance, in patients with carcinoma of the pancreas, symptoms of depression (affecting 38% to 45% of patients) and anxiety (affecting about 12% of patients) are among the earliest disease manifestations [7]. Endocrine tumors producing adrenaline such as pheochromocytomas are often heralded by panic attacks, anxiety, and irritability [8, 9]. Physical symptoms of hyperthyroidism such as sensitivity to heat, weight loss, restlessness, and sleeping difficulty can mimic an anxiety disorder, and irritability can also be an early disease manifestation [10]. Untreated streptococcal infection may lead to the onset of movements/tics called Sydenham's chorea. In studies of children with Sydenham's chorea, they exhibited obsessive-compulsive symptomatology, increased emotional lability, motoric hyperactivity, irritability, distractibility, and age-regressed behavior [11]. It is well known that irritability, anxiety, depression, dementia, and psychosis are associated with vitamin B12 deficiency [12]. Head injuries can cause post-concussive symptoms that develop within days of the incident and can last anywhere from a couple of days to a few months. These symptoms can mimic depression, anxiety, and attention-deficit disorders [13]. School failure, cognitive loss, hyperactivity, aggression, inattention, distractibility, and delinquent behaviors have all been reported with lead poisoning [14]. There truly is a myriad of general medical conditions associated with, and producing, psychiatric symptoms.

With this in mind, clinicians have an important role in managing the complete care of their patients. Patients with general medical conditions and associated psychiatric symptoms often suffer twice. MEND A MIND is a well-known useful mnemonic for ensuring a broad differential for organic causes of psychiatric presentations and can aid the clinician when evaluating a patient [15]. The mnemonic, which is slightly modified here to consider drugs/intoxication before degenerative causes (given the rarity in children) stands for: **M**etabolic/endocrine, **E**lectrical (seizures) **N**eoplastic, **D**rugs/intoxication, **A**rterial/venous, **M**echanical (trauma), **I**nfectious/inflammation, **N**utrition, **D**egenerative. The following table lists common organic causes of mood disturbance in order of the mnemonic, and provides general (by no means exhaustive) workup approaches to evaluation. The table applies to adults as well as children, but there is an emphasis here on the pediatric population with ADHD. See Table 3.1.

Table 3.1 Organic causes of mood disturbance in children and adults with ADHD

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Metabolic and endocrine	
Abnormal glucose [16, 17]	
• Malaise, lethargy • Polyuria, polydipsia, polyphagia • Weight gain/obesity or weight loss • Acanthosis nigricans	– BMI, blood pressure – Evaluate for orthopedic complications: hyperlordosis, pes planus, genu valgum – Fasting glucose/HgbA1C – Total cholesterol, HDL cholesterol, LDL cholesterol – TSH
Thyroid abnormality [18, 19]	
• Children may appear to be asymptomatic • Family history of thyroid abnormalities	– Physical examination of the thyroid gland – TSH, free T4 if TSH is abnormal – Consider confirmatory TSH – Consider total T3, T4
Calcium abnormality [20, 21]	
• Hypo: tetany, paresthesia, cramping, altered mental status, seizures, laryngospasm, cardiac arrhythmias, neuromuscular irritability with weakness, ECG changes (prolonged QT interval) • Hyper: weakness, irritability, lethargy, seizures, abdominal cramping, lethargy, seizures, vomiting, polyuria, polydipsia, renal calculi, ECG changes (atrial and ventricular ectopy, torsades de pointes)	– Trousseau sign – Total and ionized Ca^{2+}, Mg^{2+}, phosphate – Alkaline phosphatase – Total protein – BUN – Creatinine – 25-OH vitamin D – Parathyroid hormone level – Urine: Ca^{2+}, phosphate, creatinine – ECG
Electrolyte abnormality [22]	
• Emesis, acute/chronic diarrhea • Dry mucus membranes, delayed capillary refill (i.e., >2 seconds) • Tachycardia • Diabetes mellitus	– Screen for infectious illness, food poisoning, and diabetes – Physical exam assessing for dehydration – POCT glucose – Basic metabolic panel
Sleep-related hypoxia [23, 24]	
• Male sex, overweight • Household smoking, history of asthma, respiratory allergy, current respiratory tract infection • Symptoms of sleep-disordered breathing (e.g., habitual snoring or gasping while • Enlarged tonsils and/or adenoids	– Sleep hygiene history – BMI, HEENT and pulmonary physical exam – Consider sleep medicine referral – Consider ENT referral
Addison's disease (chronic primary adrenal insufficiency) [25]	
• Malaise • Anorexia, weight loss • Diarrhea • Joint and back pain • Darkening of the skin	– Rule out by history, labs, and/or other studies: tuberculosis, histoplasmosis, coccidiomycosis, blastomycosis, CMV, MAC – Evaluate for autoimmune disease – Screen for neoplasm (lung, kidney, gut, primary lymphoma)

(continued)

Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Electrical	
Temporal lobe epilepsy/status epilepticus [26–29]	
• Reading difficulty (patient may be less responsive to reading treatments) • Verbal semantic and episodic memory impairment, déjà vu • Abdominal discomfort, sudden intense emotion, abnormal mouth movements, rhythmic muscle contractions	– Neurological physical exam – Check electrolytes – Consider brain imaging – EEG
Neoplastic	
CNS tumors (primary and metastatic) [30–32]	
• Headache, seizures, nausea/vomiting • Behavioral changes (irritability, mood, character, school), sleep disturbance • Neurologic deficits: ataxia, squint, diplopia, papilledema, visual loss, cranial neuropathy, head tilt, hemiparesis • Lethargy, anorexia, weight loss, polyuria, polydipsia, dizziness • Growth failure	– The neurological and systemic dysfunction is related to the site of tumor origin as well as child's age and developmental level – Neurological physical exam – Brain imaging – Referral to neurologist or neuro-oncologist
Leukemia and lymphoma [33]	
• Malaise, fatigue, pallor, anorexia • Fever without identifiable cause • Persistent/recurrent infections • Lymphadenopathy, hepatosplenomegaly • Petechiae, easy bruising • New limp when walking, bone pain (involving joints or generalized) • Neurological symptoms, irritability	– Physical exam with particular attention to integument, lymph nodes, abdomen (assessment of hepatosplenomegaly) – Referral to pediatric cancer center
Drugs and intoxication	
SSRI's [34, 35]	
• FDA Black Box warning: increased risk of suicidal ideations and behavior in patients under the age of 24 • Irritability, hypomania/mania in patients with undiagnosed bipolar disorder • Cognitive slowing, emotional flattening, apathy in some patients • Sexual dysfunction, insomnia, GI upset • Diaphoresis • Bruising, bleeding (rare) • Seizures (rare) • Serotonin Syndrome (increased risk with two or more serotonergic drugs)	– Dose-related side effects – Emotional flattening, apathy, and cognitive slowing from serotonergic effects upon CNS dopamine regulation – Serotonin Syndrome: classic triad of neuromuscular excitation (clonus, myoclonus, hyperreflexia, rigidity), autonomic excitation (hyperthermia, tachycardia), altered mental status (confusion, agitation). Obtain vital signs, labs (CK, Creatinine). Rule out ETOH withdrawal, substance use, non-convulsive seizures, encephalitis

(continued)

Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Alcohol [36, 37]	
• Family dysfunction, FHx of alcoholism, child's stress state, low behavioral self-control, age <20 and irritable, antisocial traits, sensation seeking behavior • Signs of ETOH withdrawal	– Screen for ETOH use including last drink, and change in amount – Vitals signs and physical exam with particular attention to evidence of autonomic hyperarousal – Serum ETOH level
Stimulants: Amphetamine and methylphenidate [38, 39]	
• Hypertension, tachycardia, palpitations, cardiac arrhythmias, tremor • Anorexia, weight loss, GI upset, xerostomia • Agitation, irritability, sleep disturbance • Psychosis • Peak and rebound effects, propensity for habit formation/substance use	– Peripheral side effects from norepinephrine (autonomic) and central side effects from norepinephrine and dopamine (psychosis, motoric effects, sleep disturbance, propensity for habit formation/substance abuse) – Vital signs, cardiovascular exam, ECG – Drug test
Caffeine [40–43]	
• Later bed times • Decreased sleep • Less sleep depth (reduced slow wave activity on sleep EEG) • Consumption of energy drinks may be correlated with increasing ADHD or Conduct Disorder symptoms	– Screen for caffeine consumption – No FDA daily caffeine limit for children (FDA is investigating the safety of caffeine in food products), but discourage caffeine consumption in children (American Academy of Pediatrics recommendations)
Steroids [44–46]	
• Mood swings, irritability, depression, mania, anxiety, psychosis • Children with family psychiatric history, autism spectrum disorder, acquired neurological deficits may be at higher risk	– Screen for anabolic steroid use – Rule out delirium – Consider short-term use of benzodiazepine – Consider low-dose neuroleptic – Consider SSRI
Atomoxetine [47–49]	
• Intellectual disability, developmental disability (Autism Spectrum Disorder) • Agitation, aggression, irritability, anxiety • Fatigue, decreased appetite, xerostomia, nausea, vomiting, dyspepsia • Increased blood pressure and/or heart rate	– Side effects are related to selective norepinephrine reuptake inhibition – Evaluate diet – Vital signs – Taper off
Cannabis [50–52]	
• Paranoia, insomnia, appetite changes • MJ cravings, tremor, perspiration, change in appetite, irritability, restlessness (cannabis withdrawal) • "New" MJ use following cannabis use	– Screen for substance use, specifically ask about cannabis use – 38% of adolescents with cannabis dependence use cannabis to avoid withdrawal symptoms

(continued)

Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Isotretinoin [53–55]	
• Development of depression • Development of suicidal thinking • Fatigue, poor concentration, forgetfulness • Irritability • Sadness, crying spells • Loss of motivation	– Chronological correlation of changes in mood with a course of isotretinoin acne treatment (mood alteration is variable but tends to occur later in treatment) – Discontinuation of the drug may result in rapid resolution of psychiatric symptoms (days to weeks)
Levetiracetam [56, 57]	
• Aggression, hostility, agitation, anxiety • Suicidal thoughts and acts • Sedation • Hematological abnormalities	– Side effects related to action on SV2A and other voltage gated/sensitive channels – Often has to be discontinued due to behavioral problems and sedation
Alpha 2 adrenergic receptor agonist (Clonidine) [58, 59]	
• Hypotension, dizziness, weakness, fatigue, headache, nervousness/agitation • Depression, insomnia • Nausea/vomiting • Has been associated with behavioral irritability	– Side effects related to action on alpha 2 receptors and imidazoline receptors – Adjust dose or taper off medication (careful attention to risk of rebound hypertension risk)
MDMA (ecstasy/molly) [60, 61]	
• Euphoria, energy, closeness to others • Irritability, aggression, impulsivity • Anxiety • Paranoia • Muscle cramps • Hyperthermia	– Screen for MDMA use/environments where it is commonly present (e.g., raves) – Screen for ETOH use – Screen for MJ use – Check electrolytes
Arterial/venous	
Migraines [62]	
• Headaches (often unilateral, throbbing) • Irritability • Decreased appetite • Fatigue • Depressive symptoms • Isolation	– Trigeminovascular projections from the medullary dorsal horn may target midbrain, hypothalamus, amygdala and basal forebrain, producing symptoms – Good history taking to rule out causes such as neoplasms, seizures, substance withdrawal – Neurological examination
Mechanical	
Post-concussion syndrome [63, 64]	
• Headache, fatigue, sleep disturbance • Dizziness • Frustration, irritability, depression • Forgetfulness, poor concentration • Nausea • Double vision	– Most PCS symptoms resolve within the first year – Irritability is one of the longest lasting symptoms among those presenting at about the onset of PCS – Neurological exam – Track cognitive symptoms

(continued)

Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Traumatic brain injury [65]	
• Personality and cognitive changes • Development of ADHD • Aggression, conduct problems, drug abuse • Anxiety, depression	– GCS score, length of post-traumatic amnesia, and duration of loss of consciousness in evaluating TBI severity – Neurological exam – Brain imaging
Infectious/inflammation	
Streptococcal infection [66–69]	
• Evidence of streptococcal infection • Development of OCD and/or Tic disorder • Pediatric onset • Motor hyperactivity • Choreiform movements • Abrupt onset of symptoms • "Sawtooth" clinical course pattern: abrupt onset, followed by quiescence, followed by abrupt exacerbation	– PANDAS is a clinical diagnosis – History (e.g., center criteria) – HEENT physical examination – Rapid antigen test for group A streptococci or throat culture, anti-streptolysin O titers (rise in antistreptococcal antibody within 4–6 weeks of symptom onset), anti-DNase B – Could consider repeat throat cultures during periods of wellness to rule out strep carrier state
Autoimmune epilepsy [70, 71]	
• New onset seizure activity • Mood changes • Psychosis	– Acute or subacute (<12 weeks onset of clinical symptoms) – Absence of evidence for: CNS infection, previous CNS disease, CNS tumor, trauma, toxic exposure, metabolic derangements – Evidence of well-defined clinical syndrome such as limbic encephalitis or NMDAR encephalitis – CSF inflammatory markers and/or evidence of inflammatory histological findings on biopsy – MRI findings (e.g., increased signal in mesial temporal lobe)
Nutrition	
Iron deficiency [72–77]	
• ADHD • Overweight • Restless Leg Syndrome • Poor PO intake • Diet low in meat and alternate foods • Menstruating female • Depends on the degree of deficiency and the rate at which the anemia develops. As the degree of anemia worsens: fatigue, exercise intolerance, tachycardia, cardiac dilatation, poor growth, and systolic murmurs may develop	– Iron is an essential cofactor in the production of dopamine and norepinephrine – Review diet – Consider dietician consult – If applicable, obtain a menstruation history – Iron studies (Ferritin should be included in the overall evaluation of children with ADHD) – Iron replacement with indicated and assessment for response
Copper deficiency [78]	
• Poor PO intake • Diet low in meat and alternate foods	– Copper is an essential cofactor in the production of dopamine and norepinephrine – Copper levels

(continued)

Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Zinc deficiency [78–82]	
• GI malabsorption, diarrhea • Eosinophilic esophagitis • Zinc deficient diet (e.g., diet high in starchy roots and tubers) • Minimal animal source protein • Diet with cereals and legumes high in phytates	– Zinc is an essential cofactor in the production of dopamine and norepinephrine – Review diet – Consider dietician consult – Zinc levels – Dietary changes vs. zinc supplementation
Cyanocobalamin deficiency (vitamin B12) [83]	
• Weakness, fatigue, anorexia • Irritability, personality change • Developmental delay/regression, poor school performance, memory loss • Paresthesias, paralysis, seizures • Vibratory and proprioceptive sense impairment, abnormal movements, ataxia • Anemia, macrocytosis, leukopenia • Glossitis on physical exam • Vomiting/diarrhea • Systolic flow murmur • Icterus	– Review diet – Consider dietician consultation – B12 level – Consider MMA
Magnesium [84]	
• Anxiety, panic attacks, "blocked breathing," "lump in the throat" • Depression • Headache • Insomnia • Dizziness	– Review diet – Consider dietician consult – Check Mg – Check Calcium – BMP (renal function)
Omega-3 fatty acid [85, 86]	
• History of preterm birth, history of decreased birthweight (~10% below average) • Auditory, visual language, reading, and learning difficulties • Serious illness, frequent coughs, colds, or accident in the past year • Polydipsia, polyuria	– Consider omega-3 fatty acid supplementation
Degenerative and neurologic	
Lead [14, 87–90]	
• Lethargy • Decreased activity • Anorexia • Intermittent abdominal pain • Constipation • Vomiting	– Screen for offending source: paint, dust, drinking water, cosmetics, soil, cookware, imported toys, parental occupations – Blood lead level – CBC w/ diff – Iron level – Abdominal radiography if ingestion suspected and bowel decontamination if indicated – Neurodevelopmental monitoring

(continued)

Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Alzheimer's dementia [91, 92]	
• Age greater than 65 years old • Family history of dementia • Memory impairment often the first presentation, declarative episodic memory impairment, semantic memory and immediate recall deficits • Executive function and problem solving impairment • Language and behavioral impairment later in the illness • Down's syndrome	– History, rule out other dementias: frontotemporal dementia, vascular dementia, Parkinson's, Lewy body – Physical examination – Rule out other causes of dementia: frontotemporal dementia, vascular dementia, Parkinson's, Lewy body – MOCA – CBC w/diff, CMP, TSH, B12 level – Brain imaging
Frontotemporal dementia [93, 94]	
• Personality changes • Changes in interpersonal conduct • Disinhibition • Stereotypic behaviors • Emotional dysregulation • Poor insight into symptoms	– History, rule out other dementias: Alzheimer's dementia, vascular dementia, Parkinson's, Lewy body – Physical examination – MOCA – CBC w/diff, CMP, TSH, B12 level – Brain imaging
Vascular dementia [95]	
• Stepwise decline in memory functioning • Cardiovascular history: HTN, heart disease, vascular equivalent (e.g., diabetes)	– History, rule out other dementias: Alzheimer's dementia, frontotemporal dementia, Parkinson's, Lewy body – Physical examination – MOCA – CBC w/diff, CMP, TSH, B12 level – Brain imaging
Mercury [96, 97]	
• Exposure from sources containing mercury such as fish • Another source of mercury exposure is dental amalgam. It has been suggested that dental amalgam does not cause neurobehavioral effects	– Identify exposure source – Mercury level – Assess for other heavy metal exposures
Organophosphates [98]	
• Exposure from sources containing organophosphates (e.g., food, drinking water, residential pesticide use) • Age 6–11	– Urinary metabolites of organophosphate pesticides

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Comorbidity of ADHD with Anxiety Disorders and Obsessive Compulsive Disorder

4

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Prevalence and Morbidity

Child psychiatric disorders have heavily overlapping symptom presentations. It is not atypical for a child to present with multiple symptoms that fall into various diagnostic categories. Comorbidity, however, is defined in epidemiologic samples as an occurrence of co-diagnosis greater than chance. Clinical samples may be useful for looking at mechanisms of comorbidity, but always overstate the amount of comorbidity, because of biases related to the referral of more complex cases to clinics for assessment and treatment. The prevalence of combined ADHD and anxiety is high in clinically referred samples, over 30% [1, 2].

In large epidemiologic samples, both ADHD and anxiety occur at estimated rates of 5–10% each. If truly non-comorbid, one out of 100 or more children would have both. However, these disorders are highly comorbid, with a three times odds ratio for ADHD and anxiety, compared to an 11 times odds ratio for ADHD and conduct disorders, and a five times odds ratio for ADHD and depression [3]. OCD often begins in prepubertal children, and the prevalence of pediatric OCD is about 2–3% [4]. More than 50% of pediatric patients with OCD have been found to have at least one comorbid psychiatric disorder [5], with approximately 30% meeting criteria for

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ADHD [6]. An earlier age of OCD onset predicts increased risk for ADHD. Much more attention has been paid to the comorbidity of externalizing disorders such as conduct disorder with ADHD than to comorbid anxiety or OCD with ADHD.

Etiological Factors

Theoretical Approaches to Comorbidity

As Caron and Rutter have described [7], true comorbid presentations my arise by several different means. *First, separate diagnoses may have shared risk factors*. This is especially true in psychiatric disorders because they are often multifactorial, and causative factors are not specific to only one disorder. Second, separate risk factors for each disorder may themselves tend to co-occur (for instance, parental substance use disorders and traumatic exposure). Third, one disorder could create a risk for the other through a causal chain (e.g., ADHD and its associated chronic school failure triggers long-term anxiety, or creates the need for OCD symptoms as a counter-measure to cope with ADHD's inattentive symptoms). Fourth, the two disorders when they occur together may represent a distinct variety of one of the disorders or a truly separate disorder itself, requiring new treatments or having outcomes that are distinct from either of the two disorders occurring alone [7]. Accordingly, Jensen and colleagues have also discussed ways to examine comorbidity of disorders through their phenomenology and temporal relations between symptoms; other comorbidities; demographic, psychosocial, environmental, and family factors; genetics and temperament; and treatment response and clinical outcome [1].

In reviewing studies on comorbidity, one must keep in mind the potential artifacts related to confounding data and different approaches to the data. Firstly, the bias toward increased comorbidity when using clinical samples has already been mentioned [7]. Secondly, using dimensional rather than categorical measures of symptoms related to the diagnoses in question may be helpful. There are times when both dimensional and categorical approaches may also be useful, though this has generated some controversy [8]. The development of Research Domain Criteria (RDoC) [9] allows the study of diagnosis-crossing concepts such as emotion dysregulation, which may help elucidate biological mechanisms of comorbidity [10].

Next, studies should consider a developmental perspective, looking at the age that symptoms develop, or how comorbidity may change or develop over time [11]. In addition, nonspecific overlapping symptoms may be hallmarks of different diagnoses. For instance, anxious children may have situational inattention, impulsivity, and motor restlessness. Children with ADHD may eventually develop anxieties regarding school performance or peer relationships that may or may not meet full diagnostic status for a syndromal anxiety disorder. Likewise, the obsessions and compulsions of OCD may cause distractions, task avoidance, or restlessness, mirroring the symptoms of ADHD. Also important is to be mindful of contradictory information between informants, which may confound categorization of comorbidity. For example, in the Multimodal Treatment Study of ADHD, findings were different depending on whether analyses used parent- or child-reports of anxiety [12].

A further concern is the problem of severity of diagnosis, which may intensify relationships between separate diagnoses. In some studies, worsening anxiety symptoms lead to more long-standing functional problems with ADHD [13]. There is a high prevalence of ADHD in youth with both OCD and tic disorders, and such children with all three diagnostic categories have more severe symptomatology [14]. However, the presence of ADHD does not seem to alter clinical presentation or OCD or vice versa [15]. Some studies merge multiple anxiety diagnoses into one category or use atypical concepts of ADHD such as "sluggish cognitive tempo" [16]. Finally, it is possible that a third diagnosis explains comorbidity in a particular case, such as anxiety and inattention frequently co-occurring with autism [17], obsessive compulsive symptoms associated with Tourette's syndrome [18], or depression arising from chronic anxiety, as the true comorbid factor [19].

Neurobiology

There is a strong neurobiological basis for ADHD as a diagnosis, such that various biological deficits involving prefrontal systems contribute to various inattentive, hyperactive, and/or impulsive symptoms [20]. First, the dorsolateral prefrontal cortex modulates attention, cognition, and motivation through connections with the thalamus, cerebellum, and circuitry back to the cortex via multiple feedback loops [21]. Second, the orbital and medial prefrontal cortex circuitry connect to the amygdala, nucleus accumbens, and brainstem and modulate attentional processes dependent on reward and emotion. These two types of circuitry have been labeled as "cold" and "hot" processing, with the "cold" processing being more background in nature and the "hot" processing being dependent on emotional reactivity factors [22]. Involved neurochemical systems have included catecholamines, intermediary glutamate and GABA, and more recently, serotonin in the orbitofrontal cortex for attentional processes [23].

The neurobiology of pathological anxiety involves dysregulation in the anterior limbic network, which includes the orbitofrontal, ventrolateral, and ventromedial prefrontal cortices, with connections to the insula, anterior cingulate, and amygdala. Neurochemical systems also overlap with those for attentional processes. Pathological anxiety is thought to be largely related to excessive responsiveness in the amygdala, but other structural and connectivity problems may also play a role [24].

The paradox is that anxiety, associated with behavioral *inhibition* and its related neural systems, often *co-occurs* with ADHD, associated with systems of behavioral *disinhibition*. Both systems share frontal connectivity, as described above, through different but overlapping subcortical networks. The frontal cortex may be a governor for excessive amygdala responsiveness, and the anterior cingulate may modulate dual processes related to both cognitive and emotional systems [25]. The striatum may be an important mediator between what at first appear to be disparate circuits [20]. From a pharmacological perspective, excessive norepinephrine from high doses of stimulants (and possibly in high-anxiety states) may lead to decreasing attentional responses [26].

In order to tie attention processes and anxiety dysfunction, Levy postulates the nucleus accumbens as being central. In her view, poor cortical inputs from impaired frontal reward and punishment circuitry affect nucleus accumbens firing, which further leads to amygdala hyperactivity [27]. McNaughton and Corr offer an alternative, more behavioral, explanation, positing that underactivity of the prefrontal cortex's functions related to behavioral inhibition puts patients with ADHD at greater risk of experiencing situations that involve imminent threats. The experience of such imminent threats, in turn, leads to activation of subcortical anxiety circuits, which lack the inhibitory functions associated with prefrontal cortex [28].

The neurobiology of ADHD and OCD is vastly different. Frontostriatal dysfunction is present in both disorders; however, neuroimaging shows *hypoactivation* with *decreased* functional connectivity in ADHD and *hyperactivation* with *increased* functional connectively in OCD [29]. Specifically, ADHD-specific deficits are seen in the parietal lobes, caudate and posterior cingulate, while there is disorder-specific dysfunction of the dorsolateral prefrontal cortex in OCD [30].

Risk Factors and Associations

ADHD comorbid with anxiety or OCD is a conceptually complex phenotype that is not static, but instead appears to have several possible developmental trajectories. Genetic, psychosocial, familial, perinatal, temperamental, and cognitive correlates (and even the psychopathology itself, i.e. ADHD and OCD or anxiety disorders) may serve as risk factors for development and as moderators of outcome.

The most relevant studies examining the genetic influence on ADHD with comorbid disorders are latent class analysis (LCA) in twin studies and familial association studies. The few LCA studies do not show a differential clustering of internalizing symptoms in either the predominantly inattentive subtype (ADHD-I) or the combined subtype (ADHD-C) of ADHD [2]. Several familial association studies have provided evidence suggesting that ADHD and anxiety disorders are transmitted independently in families [31]. Male probands with ADHD and anxiety were much more likely to have first-degree family members with anxiety than probands with "pure" ADHD [32]. An inability to correlate symptom severity between ADHD and internalizing disorders for affected children and their parents also suggests independent transmission [33]. A familial study of children with ADHD and comorbid anxiety has suggested a strong association of child anxiety with maternal anxiety, but not with paternal anxiety [34]. Having a father with psychiatric illness significantly increases the risk of a child with ADHD having a comorbid internalizing disorder (including anxiety disorders) [35].

Shared genetic risk factors have been found for comorbid ADHD and OCD as part of a clinical triad also including tic disorders [36]. Geller and colleagues have used familial risk analysis to examine children with OCD, ADHD, and both disorders and their first-degree relatives. The studies suggested that comorbid ADHD and OCD could be a distinct familial subtype in which the disorders are genetically

transmitted together [37, 38]. It is important to remember that familial association studies cannot fully separate genetic from environmental sources of family transmission [2].

There is evidence to suggest that the perinatal period may influence the development of ADHD with OCD or anxiety. High levels of antenatal anxiety were predictive of ADHD symptoms and self-reported anxiety in children [39]. ADHD with comorbid anxiety has been associated with hyperemesis and maternal use of stimulant medication while pregnant [40]. OCD has been associated with perinatal complications, such as prolonged labor and edema during pregnancy [41], but there is little information regarding perinatal complications producing ADHD with comorbid OCD. There is a male preponderance seen in both ADHD and pediatric OCD. Even the first few years of a child's life may be clinically predictive. Irritability, temperamental emotionality, and high activity level at age 3 are associated with later onset of comorbid ADHD and internalizing disorders [11].

It is possible that a particular group of vulnerable children develop both ADHD and anxiety symptoms in response to psychosocial and familial stressors. Jensen and colleagues found that children with ADHD and comorbid depression or anxiety have both higher levels of life stress (including parental separation and divorce) and higher levels of maternal psychiatric symptoms [42]. These children also have more school and social difficulties [43], lower self-esteem [44], and are at greater risk for developing suicidality [45]. Conversely, another study found the opposite, that there was no additional social impairment in children with ADHD and anxiety compared to ADHD alone [46]. Families of children with ADHD and anxiety were found to be more insular, more dependent, and to have a more controlling family environment [47].

With respect to response inhibition and impulsivity, anxiety has been found to only partially mitigate impulsivity in ADHD [48]. Behaviorally, ADHD is considered an externalizing disorder, characterized by impulsivity and risk taking, while OCD is an internalizing disorder, characterized by behavioral restraint and harm avoidance. This seemingly puts the disorders on opposite poles of the spectrum, and has been referred to as the impulsive-compulsive continuum of behavior [49]. Accordingly, one would hypothesize that more patients with OCD have ADHD-I than ADHD-C. While there are few studies to prove this hypothesis, one study found the contrary (69% of youth with ADHD and OCD had ADHD-C and 24% had ADHD-I) [50].

The evidence regarding the effect of comorbid anxiety on cognitive performance in children with ADHD has been conflicting. A comparison of children with both ADHD and anxiety to children with either "pure" ADHD or normal controls found no significant difference in information processing between the two ADHD groups [51]. Conversely, some studies show children with ADHD and comorbid anxiety have greater difficulty with tasks of working memory and effortful processing [52], as well as emotional regulation [53]. It has been theorized that anxiety may serve to preempt storage within the working memory system, while paradoxically also improving motivation and performance [52]. The relationship between ADHD, anxiety, and working memory is increasingly complex, and the relationships may vary depending on the ADHD subtype [54]. Finally, studies suggest that children

with sluggish cognitive tempo (SCT) (daydreaming, staring, mental fogginess, apathy, and physical hypo-activity) are more likely to have comorbid anxiety [16].

In both ADHD and OCD there are performance deficiencies in executive function, particularly working memory and response inhibition. Studies have suggested that these deficiencies, although similar, are due to different underlying mechanisms [55]. The obsessions and compulsions of OCD can lead to symptoms resembling ADHD. The executive overload theory of OCD explains this inattention as being caused by exhaustion of the executive system from organizing rigid compulsive rituals and controlling obsessive thoughts [29].

Assessment and Differential Diagnosis

Symptom Presentation and Diagnosis

There is frequently an overlap between ADHD, OCD, and anxiety symptoms, which poses a diagnostic challenge. These disorders can share symptoms of inattention and poor performance at school. Moreover, anxiety can emerge in response to the social and academic deficits caused by ADHD [56]. The hyperactivity of ADHD can include fidgeting, restlessness, and over-activity so that the child appears to be "driven by a motor." Children with anxiety can often appear restless, keyed-up, or on edge, and have concentration problems due to excessive worry. Children with OCD might have externalizing symptoms similar to those seen in ADHD, like trouble sitting in class or paying attention to directions. Unlike children with ADHD, the hyperactivity and inattention would be due to intrusive anxious thoughts [57]. The developmental time course of the disorders can aid in diagnosis. ADHD is usually discovered in early childhood, preceding symptoms of anxiety and OCD [50]. ADHD-like symptoms associated with internal distractions would occur *after* the emergence of OCD as a direct result of the obsessions and compulsions. If ADHD-like symptoms pre-date the OCD symptoms, then true comorbidity is more likely [50]. Children with ADHD and comorbid anxiety or OCD often have cumulative impairment from the combination of these disorders [43].

Diagnostic assessment requires a detailed developmental history and psychiatric interview with guardians and the child. Since much of information in children comes from secondary informants, teachers and other caregivers can also share their observations of the child's behavior. Assessment strategies for diagnosis can include global scales like the Child Behavior Checklist and Behavioral Assessment System for Children (now known as the ASEBA) forms [58]. There are many standardized, disorder-specific scales for anxiety pediatric anxiety disorders such as Multidimensional Anxiety Scale for Children (MASC) [59] and the Screen for Child Anxiety Related Disorders (SCARED) [60]. For assessing OCD, there is a more commonly used measure done by interview, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [61], and a brief questionnaire modified from an adult questionnaire for pediatric ages called the Short Leyton Obsessional Inventory for Children and Adolescents [62]. Finally, to assess ADHD, there are

multiple parent and teacher measures available, including the Vanderbilt [63, 64], the Conners 3 [65], the Iowa Conners [66], or the SNAP-IV [67].

There are no specific labs tests or imaging studies recommended, however, the medical exam should include assessment for hearing and vision problems, thyroid dysfunction, and neurological abnormalities. The clinician should carefully review any psychological testing already completed to rule in or rule out learning disabilities. If the patient is prepubertal in age, with an abrupt onset and episodic course of OCD symptoms or tic-like movements, emotional lability or other psychiatric symptoms (e.g., anxiety, nighttime fears and bedtime rituals, hyperactivity, and oppositionality), and a history suggestive of recent streptococcal throat infection, the clinician might consider additional testing for the so-called Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) syndrome [68]. Please also see Table 3.1 in Chap. 3 for further review of PANDAS.

Treatment

Psychosocial Treatment

To date, there are no evidence-based psychosocial treatments for youth with both ADHD and comorbid OCD or anxiety. Our understanding of treatment has come mainly from the NIMH-funded Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study [69]. This study suggested that children with ADHD and comorbid anxiety might benefit more from behavioral therapy than children with ADHD alone. Behavioral treatment for children with comorbid parent-rated anxiety was as effective as medication management and combined treatment, all of which surpassed community care. Of note, the MTA's behavioral treatment targeted symptoms of ADHD (including aggression, academic productivity, and social skills) and did not specifically address anxiety symptoms [70]. The MTA cooperative group concluded that behavioral treatment should be added for those children with ADHD, strong negative affectivity, and disruptive behaviors. They posited that reducing core ADHD symptoms may lead to improvement of internalizing symptoms such as anxiety. For children with ADHD and comorbid phobic symptoms, however, adding cognitive behavioral therapy (i.e., restructuring and exposure) was recommended [12].

Outside of MTA, only a handful of studies have examined psychosocial treatment response in youth with both ADHD and anxiety disorders, with mixed results. Several studies of CBT-based treatments did not show a difference in treatment response between youth with anxiety and those with comorbid ADHD [71]. However, the Child/Adolescent Anxiety Multimodal Study (CAMS) suggested that comorbid ADHD hinders the effectiveness of CBT for pediatric anxiety [72]. Children with specific phobias and comorbid ADHD also responded less well to brief intensive CBT in comparison to children without ADHD [73]. CBT with exposure and response prevention (ERP) is the first-line treatment for OCD in children. Some have raised concerns that behavioral treatments for ADHD, such as increased

structure and organization, might trigger or worsen checking rituals and other compulsive behaviors of OCD [29]. The exposures in ERP and coding of corrective information from the therapy, as well as the habituation processes key to CBT, may also be less effective in patients with ADHD because of their inattentive, hyperactive, and impulsive symptoms. For these reasons, family CBT-based interventions may be more beneficial than individual CBT in anxious children with high levels of ADHD symptoms [74].

A few other studies have designed unique psychosocial treatment modalities to address co-occurring ADHD and anxiety or obsessive compulsive disorders. A modified cognitive behavioral family-based approach with additional psychoeducation sessions for ADHD resulted in a decrease in anxiety symptoms, but no improvement in ADHD symptoms [75]. More recently, an integrated approach that combined parent training (Barkley's Defiant Child) with a modified family-based CBT approach (Cool Kids Program) has been developed. Improvements in both anxiety and ADHD were noted, though gains were limited for ADHD symptoms [76]. Neuropsychological remediation (i.e., working memory training) may target cognitive difficulties that are common to both ADHD and anxiety [53]. Finally, based on an association between childhood anxiety, ADHD, and sensory over-responsivity (characterized by hypersensitivity to sensory stimuli), occupational therapy can be helpful within a larger treatment plan [77].

Psychopharmacological Treatment

Stimulants are the first-line medication to treat ADHD and selective serotonin reuptake inhibitors (SSRIs) are the preferred treatment for anxiety disorders and OCD [72, 78]. These medications have proven efficacy in randomized controlled trials for their respective disorders, but are not necessarily effective for comorbid conditions. In contrast, atomoxetine offers a single medication that can be used to treat symptoms of both anxiety and ADHD.

Stimulants

Stimulants decrease the core ADHD symptoms of hyperactivity, impulsivity, and inattention. The therapeutic effects are rapid, and stimulants have proven efficacy and safety in randomized controlled trials. Amphetamine and methylphenidate are the stimulants that have received U.S. Food and Drug Administration (FDA) approval for the treatment of youth with ADHD [78].

The studies that have been conducted using stimulants in children with ADHD and comorbid anxiety or OCD have had mixed results. This is likely due to methodological differences or variations in medication titration [12]. Several mainly older studies suggest that stimulant use in children with ADHD and anxiety led to higher dose requirements [79], more side effects, and a poorer response to the drug [80]. Some researchers feel that children with both disorders might make up a distinct population who have a different response to medication than children with ADHD alone [32, 81]. Conversely, more recent studies have found stimulants produce

comparable improvements in children with and without anxiety [81–83] or an even better response to treatment when comorbid anxiety is present [84]. Side effects to stimulants were not significantly greater, and anxiety was not exacerbated in anxious children taking stimulants [12, 83]. In contrast, findings from the few studies regarding the effects of stimulant treatment on OCD have been more consistent. Several case studies suggest that stimulants may exacerbate OCD symptoms or anxiety [85]. Relative to OCD without comorbid ADHD, OCD *with* ADHD is associated with an earlier age of onset of the OCD, more severe and persistent OCD symptoms [86], poorer treatment outcomes [86, 87], and a greater likelihood of relapse of the OCD symptoms after an initially favorable treatment response [4].

Monotherapy with stimulants has not been found to be an effective treatment for anxiety disorders without ADHD, but many studies have shown improvement in anxiety when symptoms of ADHD are treated. This improvement is likely secondary to improvement in ADHD symptoms and associated anxiogenic situations due to the interpersonal and academic problems associated with ADHD. A recent meta-analysis found lower rates of anxiety in children with ADHD given stimulants versus placebo as well as a dosing effect where higher stimulant doses led to lower rates of anxiety [88]. In a study by Abikoff and colleagues, some children with ADHD and comorbid anxiety treated with methylphenidate no longer suffered from anxiety after receiving the stimulant, indicating that impairment in function can improve on stimulant monotherapy for some patients with this comorbid presentation [82].

Nonstimulants

The nonstimulant Atomoxetine, a norepinephrine reuptake inhibitor (NRI), is approved by the FDA to treat ADHD in children and adults. Two randomized controlled trials comparing atomoxetine with placebo for treating pediatric ADHD with comorbid anxiety showed that atomoxetine was efficacious in reducing ADHD symptoms and well tolerated [89, 90]. There was also reduction in anxiety symptoms in clinician- and self-rated scales [90]. Of note atomoxetine takes several weeks to achieve maximum benefit, which is an important clinical consideration [91]. There is no evidence to suggest that atomoxetine is effective in treating OCD.

The evidence base for treatment of children with anxiety has been established for selective serotonin reuptake inhibitors (SSRIs) [72]. The FDA has approved the SSRIs Fluvoxamine, Sertraline, and Fluoxetine for use in children with OCD. In addition, Paroxetine, Citalopram, and Escitalopram have also shown efficacy relative to placebo [92]. There is scant evidence that SSRI monotherapy is useful in treating ADHD symptoms. A small open label pilot study suggested moderate improvement after 6 weeks of fluoxetine in children with ADHD [93], however no further studies are available to support this. A clinical consideration when using SSRIs is the possibility of activation. This is an increase in activity level without a change in mood or manic symptoms, which could be mistaken for worsening ADHD. Symptoms of activation appear early in the course of treatment, or with dose increases. Such symptoms generally dissipate with a decrease in the SSRI's dose or with discontinuation [94]. Another potential concern is the black box warning for all antidepressants regarding the risk of new or worsening suicidal ideations

or behavior [95]. Fortunately, the risk benefit ratios are more favorable for OCD and especially for anxiety disorders relative to MDD in children or adolescents on antidepressants considering the higher base rate of suicidal ideations or behaviors in depressed patients [96], but still suggest the need for clinicians to closely monitor their patients with anxiety disorders or OCD being treated with antidepressants.

Regarding other medication options, Bupropion is an antidepressant with noradrenergic and to a lesser extent dopaminergic properties that has shown modest efficacy in ADHD and has been used off-label for the treatment of ADHD in children [97]. Given the fact that bupropion has no serotoninergic effects, it would not likely be effective for OCD, and the common notion is that it is also not effective for anxiety disorders. However, its mechanism of action is similar to atomoxetine's, which as previously noted has been shown to have some benefit for anxiety. Moreover, one large randomized placebo controlled trial in adults suggested that bupropion's efficacy for anxiety disorders in patients with major depressive disorders was comparable to sertraline's [98]. Tricyclic antidepressants (TCAs) have individually been used to treat ADHD, anxiety, and OCD (most commonly clomipramine) [86]. However, there are no studies evaluating their effectiveness in youth with ADHD and comorbid anxiety or OCD, and their side effects and potentially lethality if taken in overdoses make them rarely used in current clinical practice. The long-acting α2-adrenergic agents guanfacine extended release and clonidine extended release have been FDA approved as monotherapy and adjunctive treatment of ADHD in children 6–17 years old. Guanfacine has been shown to improve traumatic stress related symptoms and PTSD nightmares in children and adolescents [99]. A recent case study described a child with comorbid ADHD and OCD who had a good response to guanfacine for impulsivity and inattention when a previous stimulant trial was poorly tolerated [100].

Combination Pharmacotherapy

Medication combinations are commonly used when patients present with multiple symptoms from comorbid disorders, although the evidence to support this practice is not conclusive. A randomized double-blind study of children with ADHD and anxiety or mood symptoms found similar improvement in patients on atomoxetine alone versus atomoxetine plus fluoxetine. Fluoxetine did not seem to have a direct effect on ADHD symptoms [89]. The combination was well tolerated, but was not superior to atomoxetine monotherapy for anxiety symptoms. If a child was already being treated with fluoxetine, the authors felt that the addition of atomoxetine could be useful. Abikoff and colleagues explored the combination of both methylphenidate and fluvoxamine to treat comorbid anxiety and ADHD. The study suggested a high rate of response in ADHD symptoms to methylphenidate, but no additional benefit for anxiety with the addition of Fluvoxamine versus placebo [82]. When using medication combinations it is important to monitor for possible medication interactions. There are no formal studies examining combination pharmacotherapy for ADHD with comorbid OCD.

General Recommendations

The Texas Medication Algorithm Consensus Panel recommends a trial of stimulant with addition of SSRI if necessary for continued anxiety symptoms in children with ADHD and comorbid anxiety [101]. A combination of medication and psychotherapy is usually indicated [82]. Stimulants have been found to be well tolerated and effective for ADHD in children with comorbid anxiety [70, 82]. Some children may show decreased anxiety when their ADHD symptoms are controlled. Atomoxetine can also be considered, but stimulants have more rapid onset, higher efficacy and usually do not increase symptoms of anxiety. If one disorder is more impairing than the other, it is reasonable to treat the more impairing disorder first [91]. A baseline review of systems is helpful, as children with ADHD and anxiety often have pretreatment physiological symptoms (i.e., headaches and stomachaches) that can be misinterpreted as medication side effects when not properly identified up front [83]. Based on the worsening anxiety on placebo seen in some RCTs, re-challenging a child who has experienced increased anxiety on a stimulant would be reasonable as such anxiety may be unrelated to medication [88]. Children with ADHD and comorbid OCD whose OCD symptoms *worsen* on a stimulant may respond better if their ADHD is instead treated with guanfacine [101].

Concluding Remarks and Critical Next Steps

ADHD that is comorbid with anxiety or OCD seems to have distinct risk factors, but also clear moderators of co-occurrence. Both the ADHD and either the anxiety disorder(s) or OCD must be recognized when they co-occur so that adequate treatment approaches are considered. Combination therapy using psychotherapy and psychopharmacology will in all likelihood produce the most favorable treatment outcomes, but additional clinical studies are needed. Further research should also attend to sequencing and combining treatments, both medication and psychosocial, for these highly prevalent comorbid conditions. Finally, more attention should be given to the longer-term outcomes of these common comorbidities.

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Post-traumatic Stress Disorders and ADHD

5

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Background and Significance

Roughly half of the general population experiences a traumatic event during childhood [1], and such experiences are common reasons for referrals to children's mental health services [2]. Among victims of childhood trauma, approximately 70–80% will experience subsequent negative effects, including PTSD, internalizing disorders (e.g., anxiety, depression, or specific phobias), substance use disorders, eating disorders, or other difficulties [1, 3]. Recent studies of national samples in the USA [4] and the Netherlands [5], respectively, have reported a high lifetime prevalence of trauma exposure (89.7 and 80.7%) and PTSD (8.3 and 7.8%). In both studies, patients with trauma exposure often had multiple types of trauma, and females were more prone to develop PTSD and to have more prolonged episodes of it. Among adolescents, a recent study of one US national sample indicated that 5% had a history of PTSD overall, with a higher prevalence once again in females than in males (8.0% vs. 2.3%) [6].

Approximately 8% of children and adolescents and 4% of adults meet criteria for ADHD in the US, with males outnumbering females 2–4 times, though this ratio decreases with age [7]. Associated symptoms for children experiencing either PTSD or ADHD include inhibitory and self-regulation difficulties, executive functioning deficits, anger and irritability, inattention, reactivity, and hyperarousal. Exposure to trauma may lead to new or increasing hyperactive impulsive symptoms (e.g., restlessness, recklessness, impulsivity, hyperarousal, emotional reactivity) or

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inattentive symptoms (e.g., poor concentration, forgetfulness, distractibility), potentially related to re-experiencing, avoidance, or hyperarousal symptoms of PTSD [2].

Research has highlighted the association between ADHD and trauma exposure or PTSD [8, 9]. Patients with ADHD may have higher levels of trauma exposure in part because of their impulsivity and other behavioral difficulties [2, 10]. Even so, a recent meta-analysis of 22 prior studies including all ages suggested a bidirectional association between ADHD and PTSD, with a 2.9-fold increased risk of PTSD for individuals with ADHD, and a 1.7-fold increased risk of ADHD for individuals with PTSD, relative to healthy controls [11]. The same meta-analysis reported that, among any individuals who have experienced trauma exposure, those with ADHD are 1.6-fold more likely to develop PTSD than those without ADHD, with similar levels of risk between children and adults in this analysis [11]. A separate review of studies regarding abused children diagnosed with PTSD estimated that 14–46% of these children had a secondary diagnosis of ADHD [12]. Comorbidity may be especially pronounced for youth in foster care, with one study reporting that 37% met full criteria for both PTSD and ADHD [13]. Regarding temporal onset, findings are mixed. In the meta-analysis mentioned above, all six of the studies using participants' accounts of temporal onset suggested that the onset of ADHD occurred before the onset of PTSD [11]. In contrast, research in younger children 3–6 years of age, relying on parent reports of temporal onset, have suggested that new internalizing and externalizing disorders including ADHD often emerge instead of comorbid PTSD or along with it after traumatic experiences, suggesting that traumatic stress reactions may account for many of the shared symptoms in this youngest age group [14]. One group has reported that the relationship between trauma exposure and attention problems in youth in war zone was mediated by PTSD rather than by ADHD symptoms [15]. Given the possibility that ADHD symptoms in traumatized individuals may stem from a diagnosis of PTSD, these investigators suggested that clinicians working with potentially traumatized youth should systematically use multiple informants and multiple measures to assess for trauma exposure and PTSD, and consider treating these first before treating the potential ADHD [15].

Etiological Factors

PTSD is one of few disorders with a clear environmental cause: exposure to a psychologically or physically traumatic event. According to recent modifications to diagnostic criteria, evolving from DSM-IVR to DSM-5, a traumatic event no longer must be accompanied by feelings of helplessness or horror, but still must involve exposure to actual or threatened death, serious injury, or sexual violation [16]. The traumatic exposure may now be one or more of the following four types: (1) directly experiencing the traumatic event; (2) witnessing the traumatic event in person; (3) learning of such an event, either accidental or violent, and involving actual or threatened death; or (4) experiencing first-hand, repeated or extreme exposure to the aversive details of such a traumatic event [16].

When functioning normally, the human stress response is adaptive in helping us to survive threatening situations by means of fight, flight, or freeze [17, 18]. Threatening sensory input is processed through the amygdala, which assigns an emotional valence of fear, based in part on past memories registered in the adjacent hippocampus. Once an immediate threat is identified, the amygdala activates two parallel stress-response systems. Stimulation of the hypothalamic-pituitary-adrenal (HPA) axis ultimately leads to the adrenal medulla's release of cortisol, a glucocorticoid hormone that stimulates an increase in blood glucose and suppresses the immune and other bodily functions not essential to the person's immediate response. The amygdala also stimulates the locus coeruleus/norepinephrine-sympathetic (LC/NE) circuits, triggering surges in the release of norepinephrine from the brain and adrenal glands, and epinephrine from the adrenals. These activate the sympathetic nervous system (e.g., racing pulse, increased respirations, vasoconstriction of blood flow to non-essential areas, increased muscle tension, vigilance focused on perceived threats). Several other neurotransmitters and hormones also modulate such responses, including serotonin, dopamine, endogenous opiates, g-aminobutyric acid (GABA), and the glutamatergic systems [17, 18].

PTSD results from the traumatic stressor overwhelming the normal human stress response, in what one PTSD expert describes as "the human stress response gone wrong" [17] (p. 428). Physiological changes associated with PTSD include excessive sympathetic responses in the LC/NE axis as well as dysregulation of the HPA axis, with excessive levels of corticotropin release factor and reduced levels of cortisol [19–21]. Other changes include reduced serotoninergic modulation of the amygdala's fear response, which leads to inappropriately anxious, irritable, aggressive, or depressive responses [20, 22]. The various symptoms of PTSD reflect these physiological, emotional, and behavioral responses [16–18]. PTSD is associated with both functional abnormalities in brain regions responsible for fear conditioning, extinction, and emotional regulation [23], and structural changes in the brain, including atrophy of the medial prefrontal cortex and hippocampus, which compromise memory, attention, and regulation of motoric activity and impulses [20, 24].

In a similar fashion, individuals with ADHD also have neurophysiological and neuroanatomical differences, which are associated with delayed cortical maturation, reduced selective and sustained attention, reduced prefrontal cortical function, and reduced brain volume when compared to healthy controls [24, 25]. All currently available ADHD medications can improve the efficiency of signal transmission in brain regions responsible for attention, vigilance, impulsivity, and motoric response, based on their various effects on catecholamine neurotransmitters [26, 27].

With or without ADHD, many individuals have traumatic experiences, but only a few develop syndromal PTSD. Risk factors for PTSD include preexisting mental health problems, family mental health problems, parental distress at the time of the trauma, minority status, and lower levels of educational attainment and socioeconomic status [28, 29]. Other risk factors include a history of multiple prior traumatic events (especially in childhood), the severity of the index event, and other stressors arising after it occurs [28, 29], while social support is a protective factor [29, 30]. Certain individuals also have genetic or temperamental characteristics (e.g., negative

appraisals, maladaptive coping strategies), which make them more likely to develop PTSD after a traumatic exposure [18, 31, 32].

Shared or compounding environmental factors may play an important role in the overlap between PTSD and ADHD. For example, patients with inattentive, hyperactive, or impulsive symptoms may be more prone to put themselves or be in harm's way due to accidents [15], harsh discipline, maltreatment, or neglect at the hands of frustrated or dysfunctional parents [2, 15]. Trauma exposure and its accompanying physiological dysregulations may worsen preexisting, subclinical attentional or behavioral difficulties [2, 15]. Siblings of individuals with both ADHD and PTSD are more likely to have both conditions, suggesting a familial component to the co-occurrence of these disorders [33].

Assessment and Differential Diagnosis

An essential criterion for a diagnosis of PTSD is having had a traumatic experience prior to developing PTSD symptoms. Ideally, a clinical interview with the patient and caregiver in the case of children or adolescents is used to establish or rule out any history of trauma exposure. As shown in Table 5.1, certain rating scales are available to screen for various lifetime traumatic events based on accounts of the patient and caregiver (e.g., parents, other family). However, many factors complicate the accurate determination of such a trauma history. Amnesia, dissociation, or other avoidance symptoms of PTSD may contribute to an informant's reluctance or inability to report such trauma [29]. Trauma victims of any age and their family members may avoid disclosing events of abuse, maltreatment, or family violence due to issues of shame, and fear of being blamed, disbelieved, or even retaliated against [34]. As such, reports of trauma exposure may vary over time because of the above factors, childhood maturation, the history of such trauma becoming more remote, an increasing feeling of safety, and a therapeutic alliance with the clinician [29, 35]. Clinicians must carefully weigh the credibility, and potential incentives and dis-incentives for various informants when there are discrepant reports of patient trauma, and consider rescreening potential victims of trauma exposure over time if appropriate.

Once a history of trauma exposure has been established, the differentiation of PTSD in patients who have ADHD is complicated by many overlapping symptoms. Table 5.2 lists the various DSM-5 symptoms of PTSD for patients at least 7 years of age, and indicates those which overlap directly with DSM-5 criteria for ADHD, or with related symptoms and disorders often associated with ADHD [16]. Rates of comorbidity in patients with ADHD are quite high (70–90%) [13, 36], and symptoms of other internalizing or externalizing disorders that co-occur with ADHD may overlap even more with potential PTSD, as shown in Table 5.2 [29]. For example, PTSD symptoms, especially the new symptom cluster in DSM-5 regarding negative changes in mood and cognitions, overlap with many symptoms of depression. Moreover, hyperarousal symptoms of PTSD also overlap with depressive or anxiety symptoms (e.g., recklessness/self-destructive behaviors, irritability, insomnia, poor concentration), oppositional defiant, conduct or bipolar disorders (e.g., irritability,

Table 5.1 Trauma, general and ADHD, and PTSD interviews or rating scales

Rating scale	Number of items	Informants	Copyright
Trauma event screeners			
Traumatic Events Screening Inventory [68]	14 events; victimizing and nonvictimizing	Child (interview or rating scale), parent (rating scale)	None
Life Events Checklist for DSM-5[69]	16 potentially traumatic events	Self-report (adults)	None
UCLA PTSD Reaction Index for DSM-5 [70]	33 trauma items (18 clinician-administered, 15 self-reported)	Child	UCLA Intellectual Property
General measures of psychopathology and ADHD			
Child Behavioral Checklist [40]	120 items total, PTSD subscale has 15	Parent, adolescent, teacher	University of Vermont
Strengths and Difficulties Questionnaire [71]	25 items; Emotional, Conduct, Hyperactive, Peer problems subscales	Child, parent, teacher	Copyrighted but freely available
Conners Comprehensive Behavior Rating Scale [72]	Conners Clinical Index 25 items	Parent, teacher, child versions	Multi-Health Systems
Vanderbilt Parent and Teacher Behavioral Scales [73, 74]	55 and 43 items; ADHD, ODD, CD, Anxiety/Depression, Impairment subscales	Parent and teacher versions	None
SNAP-IV [75]	26 items; ADHD and oppositional	Parents and teacher	None
PTSD interviews or symptom scales			
Trauma Symptom Checklist for Children/for Young Children [76]	54 items (older children) 90 item (parents of younger children)	Child and parent versions	Psychological Assessment Resources
Child PTSD Symptom Scale [77]	26 items	Child	None
Young Child PTSD Checklist [78]	12 potentially traumatic events + 30 symptoms	Parent	None
Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [41]	30-item structured interview of recent and lifetime symptoms, frequency, impairment	Child/adolescent and adult versions	None
PTSD Checklist [79]	20 items of post-traumatic stress, updated for DSM-5	Self-report for adults	None

ODD oppositional defiant disorder, *CD* conduct disorder

Table 5.2 Differential diagnosis of PTSD from ADHD and other potential comorbid disorders in DSM-5 [16]

PTSD		ADHD-IT	ADHD-HI	ODD/CD	MDD	Bipolar	GAD
Re-experiencing (≥1)	Recurrent, intrusive recollections of TE	–	–	–	A	–	A
	Recurrent nightmares	–	–	–	–	–	A
	Flashbacks, dissociation	A	A	A	A	A	A
	Psychological distress with TE reminders	–	–	A	A	A	A
	Physiological reactivity with TE reminders	–	A	A	–	–	A
Avoidance numbing (≥1)	Avoids thoughts or feelings related to TE	A	A	A	A	A	A
	Avoids activities or other reminders of TE	A	A	A	A	A	A
	Forgetful about an important detail of TE	A	A	–	A	A	A
Negative thoughts (≥1)	Negative beliefs about self, others or the world	–	A	A	D	A	D
	Blames self/others for TE & effects	A	A	D	D	A	A
	Negative emotional state	A	A	D	D	A	A
	Diminished interests/ participation in activities	A	A	A	D	A	A
	Detachment or estrangement from others	A	A	A	A	A	A
	Unable to experience positive emotions	A	A	A	D	A	A
Hyper-arousal/reactivity (≥2)	Irritability/ angry outbursts	A	A	D	D	D	D
	Recklessness/self-destructiveness	A	D	A	A	D	–
	Hypervigilance	A	–	A	A	A	D
	Exaggerated startle response	–	A	A	A	A	A
	Poor concentration	D	A	–	D	D	D
	Sleep disturbance	A	A	A	D	D	D

TE traumatic event, *IT* Inattentive subtype, *HI* hyperactive impulsive subtype, *ODD* oppositional defiant disorder, *CD* conduct disorder, *MDD* major depressive disorder, *GAD* generalized anxiety disorder, *D* DSM-5 criteria of the other disorder, *A* symptoms often associated with but not DSM-5 criteria of the other disorder

mood lability, aggression, hypervigilance) [2, 37, 38]. Differentiating PTSD from these other disorders requires evidence that the PTSD symptoms have emerged or worsened *after* the traumatic experience, and seem linked to it situationally [38]. In the absence of therapeutic interventions, symptoms of PTSD will tend to worsen with traumatic reminders and reexposures. Given the high level of comorbidity with PTSD, clinicians seeing traumatized patients should be prepared to make other diagnoses in addition to ADHD or PTSD when clinically appropriate [13].

Table 5.1 also summarizes rating scales available for various informants to report symptoms of PTSD and other diagnoses. General measures like the Achenbach System of Empirically Based Assessment (ASEBA) [39], the Vanderbilt Rating Scale, the SNAP rating scale or the Strength and Difficulties Questionnaire allow clinicians to screen for symptoms and impairment related to multiple psychiatric disorders and from various informants' perspectives (e.g., patient, parent, or teacher). On the ASEBA, 15 symptoms approximating various DSM criteria for PTSD have been shown to discriminate youth with and without PTSD [40]. Potential diagnoses should be explored further by a careful clinical interview and mental status exam of the patient.

Also shown in Table 5.2 are some questionnaires and structured or semi-structured interviews designed *specifically* to identify potential PTSD symptoms. For example, the Clinician-Administered PTSD Scale for DSM-5 is a semi-structured interview developed specifically to assess for a diagnosis of PTSD and to track severity of PTSD symptoms over time [41]. Clinicians can use PTSD-specific interviews or scales repeatedly to monitor the patient's response to treatment. Although more time-consuming and not always practical in clinical settings, several other standardized, structured, or semi-structured clinical interviews are available that allow a clinician or trained layperson to systematically assess for the PTSD, ADHD, and the full range of other psychiatric diagnoses [42].

Ford and Connor have published guidelines for differentiating between the primary symptoms of PTSD and ADHD [43]. They suggest a comprehensive assessment for these and other disorders, once again paying careful attention to the sequence of traumas and the onsets of PTSD and ADHD symptoms [43]. Many children are referred for treatment due to behavioral difficulties, and it is often unclear whether behavioral problems (or ADHD) were present before the trauma exposure, or perhaps followed or became worse after it. In such situations, gathering collateral information and observing over time may be required to clarify the child's diagnoses.

Treatment

Psychosocial Treatment

The most important initial intervention in patients who have experienced victimization trauma is to notify the appropriate legal, child- or senior-protective authorities as mandated by state law, and to consult such officials when necessary to establish a

plan for immediate next steps that assure the patient's safety. As summarized in Table 5.3, many evidence-based psychosocial treatments exist for ADHD or other disruptive behaviors, and for PTSD. The most well-studied and efficacious psychosocial treatment for PTSD in children is Trauma-Focused Cognitive Behavioral Therapy (TF-CBT). At least 15 randomized controlled trial (RCT) studies have been conducted with children from ages 3 to 18 years and their parents, and TF-CBT has been found superior to control groups in every circumstance [44]. Review articles have noted that TF-CBT is the only therapy for which there is substantial evidence for use with traumatized children, and trials have consistently shown large effect sizes for PTSD symptoms, and medium effect sizes for depression and parenting skills, but inconsistent effects for child behavior problems [44, 45]. Due to their strong effect sizes for PTSD and low associated risks compared to medications, trauma-focused psychosocial treatment is the first-line treatment for PTSD in patients of all ages [29, 46]. TF-CBT has also been effectively used for patients experiencing acute stress disorder responses in the immediate aftermath of trauma exposure. On the other hand, psychological debriefing in such circumstances is ineffective, often worsens long-term PTSD symptoms, and is no longer recommended [47].

Many parent management training interventions have been developed for disruptive behavior disorders, as also shown in Table 5.3. Parent–Child Interaction Therapy (PCIT) is one such evidence-based treatment, grounded in attachment and social learning theories. PCIT has demonstrated strong efficacy in decreasing children's behavioral difficulties, enhancing the parent–child relationship, and improving parents' confidence in their skills [48]. PCIT has also been recommended for children and families who have experienced trauma [49, 50], and for this reason is a sensible model for children with concurrent PTSD and ADHD diagnoses.

Pharmacological Treatments

There are multiple stimulant and non-stimulant medications now FDA-approved for ADHD in patients at least 3–6 years of age. ADHD medications all have varying effects on dopamine and norepinephrine neurotransmitters in the brain, giving rise to so-called catecholamine hypothesis related to ADHD etiology [26, 27]. As noted earlier, abnormal stress responses in PTSD patients are mediated in large part by catecholamine dysregulation. Three anti-hypertensives that dampen noradrenergic effects, including two alpha 2 agonists, clonidine and guanfacine, and one postsynaptic alpha 1 agonist, prazosin, have in adult trials been shown effective for hyperarousal symptoms, including insomnia, irritability, hypervigilance, and excessive startle response [51]. Extended release versions of clonidine (given twice daily) and guanfacine (given once daily) are now FDA-approved and typically considered second-line treatments for ADHD in children, either alone or in combination with stimulants or atomoxetine, to target ADHD symptoms, irritability and aggression [52, 53]. Given their broad therapeutic effects, these alpha 2 agonists could potentially be used to target both ADHD and PTSD, but further research in such patients is needed. Prazosin is now increasingly used to target symptoms of adult PTSD,

Table 5.3 Evidence-based psychosocial treatments for PTSD/trauma-related and ADHD/disruptive behavioral disorders

Treatment	Ages	Description
A. Trauma-related disorder		
Alternatives for families: cognitive behavioral therapy [80]	5–15	Incorporates cognitive therapy, behavior and learning theories, family therapy, developmental theory, and traumatology
Attachment self-regulation and competency [81]	3–17	Flexible, component-based, for children and adolescents w/complex trauma. Grounded in attachment, trauma, and developmental theories. Three core domains addressed: attachment, self-regulation, developmental competencies
Child and family traumatic stress intervention [82]	7–18	Brief, acute, intended to reduce early PTSD symptoms and long-term trauma disorders, and to assess need for long-term treatment. Focuses on communicating about child's traumatic stress reactions and family's coping skills
Child parent psychotherapy [83]	0–6	Psychodynamic, attachment, trauma, cognitive-behavioral, and social-learning theories. For child and caregiver, targeting effects of trauma on attachment
Eye movement desensitization and reprocessing [84]	13+	Integrative psychotherapy approach. Involves visualizing traumatic event while concentrating on the rapid movements of other visual stimuli
Preschool PTSD treatment [85]	3–6	Uses psychoed, affect modulation, relaxation, and narrative trauma processing. Caregiver learns attunement and understanding of child's trauma responses
Real life heroes [86]	6–17	Safety planning, psycho-education, affect regulation, cognitive restructuring, problem-solving, social support, per creative arts and graded exposure to trauma
Seeking safety [87]	13+	For trauma and substance abuse: (1) safety, (2) integrated treatment, (3) replace lost ideals, (4) cognitive, behavioral, interpersonal, case management, (5) attention to processes
Structured sensory intervention for Traumatized Adolescents and Parents [88]	12–17	For traumatized adolescents on probation for delinquency. Based on structured sensory therapy, sensory-based activities and cognitive-reframing strategies
Trauma affect regulation: guide for education and therapy [89]	13+	Strengths-based. Skills: FREEDOM—focus, recognize triggers, emotion self-check, evaluate thoughts, define goals, options, and make a contribution. Regulate emotional states, manage intrusive memories, promote self-efficacy
Trauma-focused cognitive behavioral therapy [90]	4–17	Psycho-education, parenting support, affect modulation, cognitive coping, trauma narrative, in vivo practice, conjoint session, enhancing future safety

(continued)

Table 5.3 (continued)

Treatment	Ages	Description
Trauma-focused coping [91]	10–18	School-based group intervention. Skills-oriented, peer- and counselor-mediated, cognitive behavioral approach. Gradual exposure to trauma
Traumatic incident reduction [92, 93]	13+	Brief, memory-based; targets PTSD, depression, low self-efficacy and anxiety. Integrates dissociated cognitive and emotional aspects of traumatic memory
B. ADHD and other disruptive behavior disorders		
Brief strategic family therapy [94]	6–17	Designed to: treat adolescent behavior problems; improve prosocial behaviors; improve family functioning, including parental leadership and management, positive parenting, parental involvement
Cognitive problem-solving skills training [95]	7–13	Goal is to decrease child's inappropriate or disruptive behaviors, child is the focus, taught to develop new perspectives and solutions, teaches problem-solving and challenges dysfunctional thoughts
Helping the non-compliant child [96]	3–8	Family-based, for children w/ODD to improve parent–child interaction. Parents teach children acceptable behavior through positive attention and improved parenting management skills
Incredible years [97]	0–12	Focuses on building social and emotional skills, for both parents and children in various settings. Delivered 2–3 times per week in a group
Multidimensional treatment Foster Care/Treatment Foster Care Oregon (TFCO) [98]	3–17	Alternate treatment for youth in residential facilities, given therapeutic environment in foster home, improves ability to live in the home institution, prepares caregivers for youth's return home
Multi-systemic therapy [99]	12–1	Family and community based, changes systems impacting chronic, violent juvenile offenders, assumes that systems play role in the child's behavior, and should be the focus
Parent–child interactional therapy [100]	0–8	For young children with emotional and behavioral disorders. Improves quality of parent–child relationship and changes interaction w/ live coaching in dyadic treatment
Parent management training [101]	3–16	Teaches parent's discipline techniques and age-appropriate supervision. Embraces positive parenting, decreases negative parenting, consistent, mild punishment, predictable, immediate parental response
Parent management training-Oregon [102]	2–18	For children and teens with serious conduct problems. Core parenting skills: (1) encouragement, (2) limit setting, (3) monitoring and supervision, (4) family problem-solving (5) positive parenting
Parenting with love and limits [103]	10–18	Applied skill group and family therapy, for children and adolescents w/ severe emotional, behavioral, co-occurring problems. Teaches families consistent limit setting and to reclaim loving relationship
Triple P-Positive Parenting Program [104]	0–16	Draws on social learning, cognitive behavioral, developmental theories, and risk factors research. Increases knowledge, skills, confidence of parents

including nightmares and flashbacks, fragmented sleep, and other symptoms of hyperarousal [54, 55]. Given the autonomic effects of each of these three antihypertensives, prescribers must regularly monitor for sedation, bradycardia, and hypotension, and avoid combinations of these medications if possible. Such antihypertensives should also be avoided in potentially noncompliant patients, because missed doses can lead to rebound hypertension and tachycardia.

Given serotonin's role in modulating anxiety, obsessive-compulsive, depressive, and stress-related symptoms, investigators have increasingly studied the efficacy of the selective serotoninergic reuptake inhibitors (SSRIs) and selective serotoninergic noradrenergic reuptake inhibitors (SNRI) for adult patients with PTSD. Two SSRIs, paroxetine and sertraline, are FDA-approved for treating adult PTSD. Venlafaxine, which is an SNRI with both serotoninergic and catecholaminergic effects, has been shown effective for adult PTSD [56] and for pediatric and adult ADHD [57, 58]. According to the VA/DoD Clinical Practice Guideline for PTSD, Effexor, along with paroxetine, sertraline, and fluoxetine are considered first-line treatments for PTSD in adults [46].

After a meta-analysis of multiple randomized controlled trials demonstrated an increased risk of suicidal thoughts or behaviors in these age groups [59], the FDA issued a black box warning regarding the use of all antidepressants in children, adolescents, and young adults. Even so, the level of efficacy and the risk of suicidal thoughts or behaviors have been shown to be more favorable for young patients who receive antidepressants for anxiety disorders instead of depressive disorders [59]. Although not FDA-approved for pediatric PTSD, antidepressants are sometimes used to treat PTSD in this age group [29]. A single, randomized control trial of sertraline in children with PTSD suggested that it was not efficacious relative to placebo [60]. However, because sertraline, along with fluoxetine and escitalopram are FDA-approved for other pediatric indications and have good evidence for their safety in this age group, any of these SSRIs is a reasonable pharmacologic option for pediatric PTSD. Paroxetine and venlafaxine are typically avoided in children or adolescents because of their greater risks of withdrawal symptoms if abruptly discontinued and suicidal thoughts or behaviors [59].

Stimulant medications, both the methylphenidates and the amphetamines, are first-line pharmacological treatments for patients with ADHD at least 6 years of age, with response rates of about 70% [61]. Stimulants are generally well tolerated, with potential adverse effects including insomnia, weight loss and growth suppression, rebound irritability, and mild increases in blood pressure and pulse. There have been no studies we are aware of examining the potential moderating effects of comorbid PTSD in patients with ADHD treated with stimulants. However, the VA/DoD guideline for adult PTSD urges caution when prescribing stimulants to patients with PTSD having symptoms of anger or insomnia because of the hypothetical risk of worsening such symptoms with stimulant treatment [46].

The norepinephrine reuptake inhibitor, atomoxetine, has been shown efficacious in one RCT for ADHD and comorbid anxiety disorders [62], though this study did not specifically report the responses of patients with PTSD. Another noradrenergic medication, bupropion, has demonstrated efficacy in one RCT of children with

ADHD [63], and effectiveness for both ADHD and depression in an open label trial of adolescents with both disorders [64]. In this open label study, both the ADHD and depressive symptoms of patients with comorbid anxiety disorders (including 4 with PTSD) responded as well to bupropion as other youth without anxiety disorders [64], but PTSD response was not specifically measured. The FDA's black box warning about increased risk of suicidal thoughts or behaviors also pertains to atomoxetine and bupropion, so close monitoring in young patients on these medications is also recommended.

No pharmacotherapies have demonstrated efficacy for patients with ADHD and PTSD together. However, comorbid ADHD has not reduced the effectiveness of antidepressants for treating various anxiety disorders [65], nor has comorbid anxiety reduced the effectiveness of stimulant pharmacotherapy for ADHD [66, 67]. The concomitant use of an SSRI antidepressant for the PTSD and a stimulant for the ADHD seems reasonable when not contraindicated by other factors. Clinicians should also be vigilant for other comorbid diagnoses that may impact treatment decisions. When a patient has a history of a bipolar or psychotic disorder, or an active substance use disorder, prescribers generally should treat such conditions first [7, 29, 55]. If there is some family history of bipolarity or psychosis, prescribers should be vigilant for the potential emergence of such disorders in patients with ADHD and PTSD prescribed certain ADHD medications (e.g., stimulants, atomoxetine) or antidepressants [7, 29, 55].

When considering pharmacotherapy for ADHD and PTSD, we recommend the approach suggested by the Texas Children's Medication Algorithm Project (CMAP) group for treating ADHD and other comorbid anxiety disorders [61]. The CMAP group suggested first targeting either the ADHD or anxiety, depending on which disorder was most severe and impairing. They also suggested a "start low and go slow" approach, making only one medication change at a time to simplify the interpretation of positive or negative effects. Because ADHD and PTSD symptoms may respond independently, the clinician should monitor each disorder separately with specific rating scales and carefully observe for new side effects, and new or worsening clinical symptoms.

If PTSD is the bigger concern and has not responded adequately to an initial trial of trauma-focused therapy, or if ADHD is treated first but PTSD symptoms persist, the prescriber could use an antidepressant approved for other indications in children (e.g., sertraline, fluoxetine, or escitalopram). If ADHD is the bigger concern, we'd recommend monotherapy with a stimulant or atomoxetine (which may be potentially helpful for comorbid anxiety). Stimulants work relatively quickly when prescribed at proper doses, and intolerable side effects wear off quickly after the medication is stopped. Improving ADHD may improve a child's ability to concentrate and benefit from therapy. Of note, patients with ADHD and other anxiety disorders have been shown to respond well to stimulant monotherapy [67]. Additional options include alpha agonists, given their FDA approval for ADHD and their potential benefits for certain PTSD symptoms. When patients have unexpected or new symptoms, or worsening symptoms with selected treatments, prescribers should reconsider their working diagnoses and treatment strategies.

Combination Treatments

Once again, the most empirically supported treatment for PTSD is TF-CBT, and this treatment should generally be considered the first-line treatment for PTSD. There is currently very little literature to guide the relative effectiveness of adding medication to such psychosocial treatment. In general, concomitant pharmacotherapy for these conditions should be considered when symptoms of either the PTSD or ADHD are pronounced and impairing, or put patients at greater risk of re-traumatization or other safety concerns. Informing patients and caregivers of the potential risks, benefits, and alternatives to the proposed pharmacological treatment, and helping them to make informed decisions is essential. Numerous psychoeducational materials and decision aids are now available on-line at sites sponsored by the American Academy of Child and Adolescent Psychiatry, National Center of PTSD, Children and Adults with Attention-Deficit/Hyperactivity Disorder, Ottawa Decision Aids, and the Option Grid Collaborative. A reasonable approach is to first target the more severe condition (ADHD, PTSD, or another comorbidity), monitor how it and the other condition(s) respond to treatment, and then modify or add treatments based on such responses, making one change at a time.

Future Directions

Irritability and mood dysregulation are potential symptoms of trauma exposure and PTSD in patients who also have ADHD. There is strong evidence for the efficacy of trauma-focused cognitive behavioral therapy and modest evidence for certain pharmacological treatments to target the emotional dysregulation, hyperarousal, and negative cognitions associated with trauma exposure and PTSD. On the other hand, there is strong evidence for the efficacy of pharmacological treatments and to a lesser extent psychotherapy treatments to target symptoms of ADHD and externalizing comorbidities. There has been limited if any research to inform treatment approaches, psychosocial or pharmacological, for patients with both ADHD and PTSD-related moodiness combined, though together these comorbid conditions can be quite impairing. In short, there is a clear need for additional research to develop and demonstrate efficacious and safe pharmacological and psychosocial treatments for patients with PTSD alone or co-occurring with ADHD.

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Disruptive Mood Dysregulation, and Other Disruptive or Aggressive Disorders in ADHD

6

Joseph C. Blader

Background, Phenomenology, and Prevalence

Approximately 30–45% of children with attention-deficit/hyperactivity disorder (ADHD) experience significant impairments because they are prone to anger, rageful outbursts, irritability, or other manifestations of excessive, negative emotionality [1–4]. These incidents most often occur after provocations or irritations that age-mates without ADHD would usually handle with composure. Related descriptors of the clinical picture include brittle frustration tolerance, irritability, abrupt and extreme changes in mood, and drastic and exaggerated behavioral reactions. For a number of these youngsters, the resulting behavior often escalates to interpersonal or self-directed aggression. Massive upsets of this sort are deeply disturbing to others, and high vulnerability to them is not conducive to a satisfying self-image or an enjoyable childhood. Bearing in mind that ADHD alone has adverse risks for quality of life, these additional features of disturbed emotion regulation further increase the likelihood of serious impairments as well as family strain, social marginalization, and numerous long-term disadvantages. Since ADHD is the most prevalent and chronic psychiatric disorder among children receiving mental health care, the high rate of these mood-related difficulties results in a large patient population of young people with symptoms of poor impulse control and high negative emotional reactivity.

Overblown anger and hostile behavior in the face of easily triggered irritations are prominent symptoms of oppositional defiant disorder (ODD). They are also quite common among those with conduct disorder (CD). Similarly, chronic rageful outbursts are the hallmark of disruptive mood dysregulation disorder (DMDD), introduced in DSM-5 within the mood disorder group. Despite their frequency, fundamental questions remain unresolved that concern the disturbances in emotional processes these behaviors seem to reflect. Do these troubling clinical problems

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reflect a distinct disturbance of mood or are they better regarded as a component or complication of more severe ADHD? In any event, why should problems that clearly involve emotional functioning be so prevalent among those ADHD? What are the implications for treatment?

To veteran practitioners and investigators, this line of questioning reflects years of controversies that still linger. Newcomers who soon learn that these difficulties characterize a large proportion of their patients may be surprised that these issues have not been settled yet, and that their mentors and teachers propose diverse diagnoses and treatment strategies for what seem like the same kinds of problems. This chapter's objectives are to review the psychopathology and other influences that contribute to such highly negative and excessive emotional reactivity in ADHD patients, to offer a framework for assessment, and to summarize current treatment approaches and possible directions for future research and improved clinical care.

Associations of Aggressive Behavior, Negative Affect, and ADHD

In youth, the association between ADHD, negative affect, and harmful behavior is well documented, and a literature concerning adults with these problems is also emerging [1–12]. The emotion-related constructs in this research vary, and studies purport to examine emotional lability, emotional regulation/dysregulation, emotional reactivity, emotional impulsivity, and irritability, among other related terms. In principle, one can meaningfully distinguish each of these concepts and define it as a separate process. Practically speaking, however, the content of various measures' items overlap considerably, and emphasize quickness to anger, hostile behavior, angry outbursts, low frustration tolerance, and other indicators of "hot" affect.

Most studies in this area have evaluated aspects of emotional processes (e.g., prevalence, correlates, neuroimaging, and longitudinal stability) *related to the level of* ADHD symptoms (cases vs. controls, high vs. lower severity, etc.) in population- or clinic-based samples. From a clinical standpoint, though, volatility and touchiness frequently motivate coming for care, in which case the inverse of the question is informative: *given that* one has these disturbing emotion-related problems, what is the diagnostic context in which they develop? This approach shows that ADHD is ubiquitous in clinical and epidemiological samples of children and adolescents characterized as high in emotional lability/dysregulation and aggression [13–16]. We discuss the implications for treatment later in this chapter.

History and Conceptual Issues

The susceptibility of people with impulse control deficits, attentional problems, and hyperactivity to showing drastic displays of anger and hostile behavior was recognized long before ADHD became formalized as a medical diagnosis [5]. In the late 1700s, Melchior Weikard in Germany and Alexander Crichton in England described attentional problems that resemble today's conception of ADHD. In their few

references to emotion, they appeared to view affective disturbances as potential drivers of the attentional ones. Weikard referred to overactivity as "excessive mercuriality," and under-excitability as "*inactive floppiness"* [17, p. 628 (italics added)]. Crichton observed that "some men … are disposed to certain emotions or passions, rather than to others…for instance to the violent emotions of anger…. Such men have their attention most readily engaged by every object or thought which excites these emotions" [18, pp. 262–3]. He thus hinted at a major research focus of modern times, biases in cognition related to uncontrolled affective states (a so-called "bottom-up" etiology).

Influenced by the American philosopher, William James, and his own clinical observations of 43 children with intellectual as case studies, the British pediatrician, Dr. George Still, published three lectures in 1902, widely believed to be the earliest extensive medical discussions of behavioral disorders in children. The aim of Dr. Still's presentations was to place problematic behaviors of children into what would be described today as a developmental psychopathology framework. The emphasis of these talks was on symptoms much like today's disruptive disorders and DMDD, which were thought to arise from impaired development of inhibitory control, and diminished capacity for emotional regulation. He described a "predominance of passionateness" as the most common sign of "morbid diminution or defect of moral control…," which he viewed being based on a lack of inhibitory control [19, p. 1009]. He went on to suggest that "outbursts of rage in some of the cases where there is no evidence of cerebral lesion may be due to a similar exaggeration of excitability with consequent insufficiency of inhibitory volition" [20, p. 1165]. Dr. Still suggested that intense and volatile affective reactions are common drivers of severe conduct problems. These deficits are not exclusively the result of global developmental impairments nor of other obvious neuropathological causes. Toward the end of this work, he drew a connection between conduct problems, affective volatility, and attentional problems, saying "a notable feature in many of these cases … is a quite abnormal incapacity for sustained attention" [20, p. 1166]. In contrast to others' suggestion that strong emotions subvert cognition, Dr. Still pointed to the reverse process, in which weakened cognitive control contributes to problematic behavior by impeding emotion regulation.

Taken together, passages of these various early ADHD luminaries anticipate what we now view as the interplay between "bottom-up" and "top-down" neural processes in generating emotional states. On one hand, susceptibility to intense and rapid experiences of strong emotions that compromise judgment, inhibitory control, and the capacity to direct one's behavior to more adaptive ends might suggest poor "bottom-up" control. On the other hand, when one shows impaired self-control across a range of cognitive and behavioral functions (e.g., inattention, hyperactivity, impulsivity), the incapacity to willfully regulate emotional expression might suggest poor "top-down" control.

Emotion-related problems of any sort are not among the formal diagnostic criteria for ADHD, but some have been mentioned as associated features of ADHD since DSM-III. Based on the frequent co-occurrence of affect problems and ADHD, and on models of ADHD that emphasize a pervasive inadequacy of self-regulatory

functions, some experts consider emotional under-control an integral manifestation of ADHD, at least regarding its hyperactive/impulsive components [21–23]. At the same time, not all children with ADHD are irritable, prone to anger, or have massive overreactions to minor irritations. Furthermore, these problems are not specific to ADHD, and become relatively more associated with mood disorders with age [24, 25]. Although having ADHD increases the risk for periodic, extreme bursts of emotional expression that are poorly controlled, it seems parsimonious to think that such moodiness is explainable only as a form of emotional impulsivity to go along with the behavioral impulsivity and "cognitive impulsivity" (or distractibility) of ADHD. Nevertheless, emotion-related problems were essentially defined out of ADHD from DSM-II onward. Barkley [5] attributes this to several factors operating in the 1970s and 1980s, including a growing interest in behavioral phenomena that researchers of ADHD could quantify in experimental paradigms. DSM-III also introduced ODD, in which four of eight symptom criteria involved hostile affect, despite its classification among the disruptive behavior rather than among the affective disorders. The comorbidity between ADHD and ODD is among the strongest in psychiatry, rivaling that between depression and anxiety in adults in clinical populations [26, 27].

One consequence is that, over time, ADHD has increasingly been viewed as a more circumscribed problem involving attention problems and restlessness. ODD likewise evoked the image of bratty insubordination, a mere "behavior problem," and became regarded as not quite a real psychiatric illness. Even so, these patients kept coming—behaving in harmful ways to themselves and to others, suspended from schools, seen in emergency rooms, and admitted to inpatient care. In this context, concerns arose that ADHD and ODD underemphasized the affective disturbances that dominated the clinical picture, and the common refrain in the 1990s was that such patients had "more than just ADHD." For some years thereafter, it became common to diagnose this presentation as a form of bipolar disorder (BD), which introduced its own new set of difficulties, including a vast inflation of BD's incidence among youth in the US [28, 29]. Although BD has been defined by demarcated episodes of mania and major depression, very few preadolescents with the BD diagnosis have shown this pattern of episodic symptomatology. DMDD more recently is now intended to provide a new rubric for periodic enraged outbursts that occur consistently over time, along with a prevailing mood state or irritability or anger in between such outbursts.

Currently, emotion regulation has developed into a significant focus of research interest [30]. Neuroimaging and psychophysiological approaches now have a range of available tools for measurement and analysis, and paradigms for eliciting neural processes having greater precision to study underlying mechanisms. It may soon become possible to parse such aberrant emotional processes and maladaptive behavior into specific emotion generating (bottom-up) and emotion modulating (top-down) components [31, 32]. Alternatively, such a distinction may be an oversimplification, in part because bidirectional influences are common in neural networks and behavioral processes. Suppose that difficulty modulating even mild angry arousal leads quickly to hostile screaming and threatening. The behavior itself may amplify the

negative emotion, and understandably harsh reactions from others may further inflame the emotional upset, making it even harder to rein in. Then again, sensory gating abnormalities seen in a variety of disorders including ADHD may intensify bothersome stimuli so that they become more highly noxious.

In the meantime, current diagnostic approaches remain anchored in a taxonomy of mood disorders which emphasize pervasive disturbances in emotional tone and behavior, not the brief flashes of affective dyscontrol or blowups that are quickly followed by a return to a more normal baseline. These later "mood problems" are what characterize the majority of children with ADHD and severe behavioral disturbances [33, 34]. In short, a diagnosis of ADHD with ODD/CD can represent a wide range of variations in severity, and does not always convey the magnitude of these youngsters volatility. On the other hand, mood disorder diagnoses including DMDD reflect sustained abnormalities in affect that seem only seldom present. This large patient group has been appropriately characterized as "diagnostically homeless" [35]. The significance for practitioners is that making such diagnoses for these youngsters does little to direct their core responsibilities of evaluation, psychoeducation, treatment planning, and clinical management. Rather, the clinician most often has to weigh the relative contributions of (a) emotional impulse control deficits, (b) mood-related problems having "a life of their own," and (c) the environmental and social factors that may also be contributing to these problems. The following sections on assessment and treatment elaborate on this approach.

Assessment

Typical presenting complaints from families include poor frustration tolerance, excessive irritability, inexplicable anger, and belligerent often unpredictable reactions to minor provocations. The clinician's task is to determine which among many potential psychiatric, developmental, medical, and environmental factors is contributing to such behaviors and may require clinical attention in a given patient. This section suggests tactics for assessment of such behaviors and their contributing factors, but is limited to the common clinical scenario where ADHD is in the differential diagnosis. Experts have published excellent, evidence-based clinical recommendations and best practices regarding the evaluation and treatment of ADHD [36, 37]. Some offer guidance regarding specific comorbidities and complications, including aggression and mood disorders, or impulsive aggression [38, 39]. As such, we will not review in great detail the fundamentals of ADHD and its treatment here.

Is ADHD Really a Part of the Clinical Picture?

There are several reasons to determine early on whether ADHD is present, *regardless* of other disorders. First, even in the typical situation in which comorbid conditions are quite serious (e.g., disruptive behavior, mood, or anxiety disorders), high impulsivity increases their severity, and may have hindered prior efforts to manage

these symptoms [e.g. 40–42]. Second, the effect sizes for current ADHD pharmacotherapies are large, and such treatments when done systematically can lead to substantial reductions in affective volatility, aggression, and even mood symptoms. Accordingly, expert consensus algorithms suggest prioritizing ADHD treatment [43]. Third, these trials can be done quickly—it usually takes only a week or so to determine the efficacy and tolerability of a stimulant regimen and adjustments to the medication and dosage can be done promptly. Fourth, improved attention and diminished hyperactivity increase the likelihood that psychosocial treatments will gain traction. Fifth, stimulant pharmacotherapy has a reasonable chance of affecting not only core ADHD symptoms but also co-occurring impairments related to negative emotionality and explosiveness. In contrast, monotherapies that target mood-related disturbances (antidepressants, antipsychotics, mood stabilizers, etc.) are seldom effective treatments for ADHD symptoms.

Some common expressions to identify ADHD symptoms could also apply to people who lose their tempers often (e.g., "acts without thinking," "gets distracted," "impulsive," "impatient," "over-sensitive"). It is important to ask informants not only about times when the patient is upset, but also about the full breadth of ADHD symptoms and whether their onset and course is consistent with an ADHD diagnosis. It is helpful to compare rating scales from teachers and parents. However, clinicians should be vigilant for the so-called "horns effect" bias (a reversal of the "halo effect"), in which parents or teachers so annoyed or distraught by these behaviors in the child may overreport the child's true symptoms [44, 45].

Is a Mood Disorder Present?

While irritability is a common feature of major depressive, bipolar, and other mood disorders, a diagnostic criterion of these other conditions requires that the patient must have such abnormal moods *most* of the time. In contrast, many youth who become easily upset are otherwise euthymic without an event that unsettles them. However, if their negative reactions and outbursts are frequent or drastic enough, others may regard them as having an "irritable mood." Time spent during assessment to make this distinction is worthwhile. Examples of helpful questions to ask may include: "What is his mood like when things are going his way?" "When good things happen, how much does she seem to enjoy herself, or is she grouchy even at those times?" "If no one is doing anything to get on your nerves, do you still feel really down or aggravated? Do you keep thinking about things that annoy you even if there's nobody bugging you at the moment? Does that get in the way of having fun?" "Can you usually figure out what sets her off, or does she sometimes seem to become upset from out of nowhere?" "When he's starting to have a 'meltdown' and you give into what he wants, does that change his mood, or does he still seem pretty mad?" "Does she put herself down or say that no one likes her at other times?" [i.e., not acutely agitated after some provocation]. Weepiness, anhedonia, and sadness are less common in such emotional storms, and may be more suggestive of depression [34].

Many youth with ADHD experience school frustrations and interpersonal conflict, followed by demoralization and statements that they "don't care" about school, other people, and so forth. Seeing patients at a single time point can make it hard to distinguish such feelings rooted in frustration and futility from the more severe mood symptoms of anhedonia, loss of interest, and hopelessness.

Sleep problems in children with ADHD and disruptive behaviors are common, but most often involve problems settling into bed, anxieties about being alone, and sleep hygiene factors (inappropriate bedtimes, lack of calming routine, etc.); "true" insomnia or inability to fall and remain asleep even when fatigued is less common. Among US adolescents, sleep difficulties are so widespread that they are probably less pathognomonic of specific disorders [46]. However, impaired sleep often correlates with depression severity in patients with mood disorders [47].

Identifying a primary mood disorder, with or without comorbid ADHD or a disruptive disorder, has management implications. Psychoeducation and encouragement of behavioral activation toward positive experiences are certainly indicated. Diminished *capacity* for enjoyment and dampened goal-orientation may undermine behavioral interventions that use rewards to increase adaptive behavior, or cognitive approaches to motivate behavior change by aligning it with personal goals. The impact on the patient's family must also be addressed, especially when the patient's affect seldom brightens and is repeatedly punctuated by outbursts of anger.

What Are the Influences of Other Contributing or Complicating Factors?

Other Disorders

As addressed in other chapters of this book, numerous psychiatric, developmental, and medical disorders affecting children can lead to severe agitation or irritability that resembles the behavioral disturbances of ODD, CD, or DMDD. Often, history and assessment indicate these other conditions are comorbid with ADHD and disruptive disorders, and sometimes the more egregious emotional outbursts may stem from these other "underlying" disorders whose treatment must take first priority. We'll now mention a few that are not always obvious.

Anxiety Disorders. The comorbidity ("trimorbidity") between ADHD, disruptive disorders and anxiety disorders is high [27]. When faced with uncomfortable situations such as separating from caregivers, having to confront the object of a phobia or worry, or a stressful social situation, impulsive children with limited distress tolerance are more likely to use physical means of avoiding, escaping, or protesting. Some impulsive youngsters with obsessive-compulsive disorder can become quite distraught and hostile when blocked from completing a behavior driven by a compulsion. Agitated behavior can be a complication of a primary anxiety disorder when the explosions are limited to such situations, rather than being the general overreactivity to many types of frustration typical of disruptive and mood disorders. Of course, anxiety as a source of distress and impairment requires attention, whatever its etiological significance

for emotional explosiveness. It is important to recognize situations in which anxiety is primary, both to avoid over-diagnosing other problems as potential causes of child's volatility, and for effective management.

Specific Learning and Related Developmental Disorders. Learning disorders cause children to have enormous frustration such that the classroom environment can become highly aversive, and struggles over homework lead to greater conflicts at home. These problems are also highly prevalent among those with ADHD. Frequently, learning disorders are first identified only after years of slow academic skills development. For children who are inattentive, overactive, and disruptive, it is tempting and partly understandable to attribute underachievement to unruliness that interferes with learning. Unfortunately, it can be difficult to evaluate these learning disorders among children with severe ADHD. Their inattentiveness and restlessness can hinder their global performance on the tests used to tease out specific neuropsychological functions signalling learning disabilities. One approach is to defer the investment in formal assessment until ADHD symptoms subside with treatment. At that point, when emotional outbursts seem to coincide mainly with academic demands, support services and modifications to the educational program may be especially helpful.

Adverse Effects of Pharmacotherapy

Although literature is limited, some clinical trial data and clinical experience suggest that stimulant medications may at times adversely affect emotion, causing new or worsening irritability or dysphoria. These in turn lead to increased aggressive outbursts and disruptive behavior symptoms. Such "affective toxicity" is often a dose-dependent phenomenon, and the relative risks of amphetamine-based or methylphenidate-based stimulants are unclear. Many other medications can also have adverse impact on a child's mood and affect affective experiences. Clinicians who have known their patient for some time are in the best position to detect such treatment-emergent changes. Unfortunately, child and adolescent specialists often assume care of patients already on some regimen prescribed by the primary care physician, another specialist, or even an inpatient provider. In history-taking, it is useful to sort out if emotional symptoms might have been affected by a medication of dose change. In the case of stimulants, or of alpha-2 agonists at minimal doses, brief discontinuations, say over a weekend or holiday, can help rule in or rule out iatrogenic effects. Clinicians will need more time to reach a conclusion for drugs having longer half-lives or needing more gradual tapering (e.g., higher alpha-2 agonist doses).

Social and Familial Factors

Almost by definition, children with disruptive disorders compounded by negative emotional reactivity are prone to antagonistic interpersonal relationships, especially with family members. Such patterns may originate from parental psychopathology, child factors that elicit unhelpful parental reactions, or other factors. Whatever their origins, such hostile behaviors between the child and parent often generate retaliation or resentment in the other party, and that leads to a cycle that sustains the child's behavioral and emotional difficulties.

There are ample data to support that impulsive, easily frustrated, and aggressive children pose definite stresses and hardships for their families [48–51]. At the same time, children who experience antagonistic environments in which people influence one another's behavior through harsh and negative behaviors often adopt this way of interacting themselves through several processes: (1) learning from adult examples, (2) intermittent rewards that occur when coercive behavior is successful, and (3) high-frequency anger that arises from others' provocative behavior. Therefore, family strife and caregiver stress are common, and these difficulties are likely to exacerbate children's emotional negativity.

Child behavior management practices that are overly permissive can also promote disruptive behavior symptoms and emotion-regulatory problems. Such permissiveness can stem from parental disengagement, or from ambivalence about setting age-appropriate limits that would upset the child. Such patterns increase the chance that a child's misbehaviors will be reinforced, and deprive the child of opportunities to develop frustration tolerance typically gained through experiencing emotional upsets and having to cope with them.

In some situations, a clinician may perceive caregivers' impatience and discipline practices as especially unsuitable for an impulsive child, which leads the clinician to blame the child's behavioral problems and emotional outbursts on family factors. A fair number of children show behavioral disturbances more severely at home than in school or other settings [52, 53], which sometimes is taken to support a causal role for the family environment in these problems. There has traditionally been some tension about how to apportion the root causes of severe conduct problems between innate and experiential factors. On one hand, there has also been a reluctance to diagnose psychopathology in children whose behavior reflects shortcomings or disadvantages in their interpersonal milieu. On the other hand, it seems unwarranted if not cruel to implicitly blame family members for a child's impulsiveness and negative emotional reactivity that may stem as much from neurodevelopmental predispositions. Parental reactions to a child's behavior may appear overly harsh, indulgent, inconsistent, or counterproductive, but may also be potential consequences rather than causes of the child's difficult behavior. In contrast to such absolute positions, evidence has mounted over the years to support an interactive model that emphasizes the synergism for both types of influence. While problematic caregiver–child interactions are often a critical source of the apparent intractability of such behavioral problems in children, clinicians may eventually be forced to consider more aggressive, complex pharmacotherapy for such harmful behaviors in children.

Intervention Approaches

Issues in Treatment Selection: Diagnostically or Trans-diagnostically Based and Prioritizing Targets

Currently, there is some debate in psychiatric neuroscience whether the phenomena of impulsivity, affective dysregulation, emotional overreactivity, and aggression we have addressed in this chapter are "transdiagnostic" processes that go awry in a similar way regardless of the specific clinical psychopathology, or are distinct for the various

disorders that give rise to them. For instance, impulsivity might reflect impaired cognitive control that has the same neural substrate regardless of whether, using clinical taxonomy, the individual seems to have ADHD, bipolar disorder, or an autism-spectrum disorder. The hope is that we could identify a common mechanism that produces a problem like impulsivity and devise treatments that alter or compensate for that process. For the moment, however, clinical psychiatric practice continues to take the approach that identifying specific psychopathology that "underlies" these concerns offers the best leverage in treatment.

From this specific-psychopathology standpoint, children with ADHD, high emotional lability, or explosiveness by definition have numerous different impairments, and prioritizing them becomes an important issue. To the extent that there are specific interventions that address ADHD symptom, mood instability, and disruptive behaviors, is there a preferred sequence? One point of view is that for very labile individuals, mood stabilization is a prerequisite for improvements in attention, impulse control, and other concerns [e.g., 54]. Alternatively, some algorithms suggest giving priority to treatments that address ADHD symptoms and disruptive behaviors. The few studies that have examined sequences of treatments in this patient group indicate that, at least in the absence of a primary major mood disorder, targeting symptoms of ADHD and disruptive behaviors first is a reasonable starting point for most patients that balances efficacy, safety, and simplicity [55, 56].

Pharmacotherapy

Recent trials evaluating treatment approaches for preadolescents with ADHD and significant aggressive behavior indicate that the most robust impact on both the core symptoms of ADHD *and* aggressive behavior comes from first-line stimulant treatments for ADHD, accompanied by caregiver guidance on behavioral management strategies [55, 56]. Two studies included extensive efforts to titrate stimulant monotherapy in order to optimize response during an open-lead-in, after which children having persistent aggression could be randomized to controlled, blinded trials with adjunctive treatments (divalproex sodium, risperidone, or placebo) [55, 57]. These trials recruited only children who had had prior stimulant treatment with insufficient reductions in aggression—the lead-ins were intended to confirm that aggressive behavior was indeed refractory to stimulant monotherapy prior to the controlled trials of add-on medication. Despite this criterion (and other indices suggestive of their severity such as history of ED visits or hospitalization, special education services for behavioral reasons, etc.), well over half of such patients experienced *remission* of aggressive behavior during the lead-in phase. Another trial for children with aggressive behavior also had a 3-week stimulant monotherapy titration phase, after which children were randomly allocated to adjunctive risperidone or placebo for a six-week trial. The add-on placebo group who continued stimulant monotherapy showed further improvements that nearly matched those reported for the add-on risperidone group. In these studies, irritability, dysphoria, and emotional lability also improved with stimulant monotherapy [34].

These findings largely support the approach to pharmacotherapy that several expert-consensus algorithms have recommended, using first-line stimulant treatment when ADHD is present accompanied by close monitoring and prompt adjustments to optimize efficacy and tolerability [39, 58]. Even so, treatments involving combinations of medications remain widespread, despite the lack of an evidence base to support such combinations, especially for adolescents. In high-acuity clinical situations, a dilemma often arises for clinicians and families regarding when to persist with a single agent or another that may have a less favorable risk/benefit ratio but may stabilize things more quickly. Time to response becomes even more critical in settings where high service demands and a dearth of providers lead to long intervals between follow-up visits.

Among those who do not gain sufficient benefit from stimulant monotherapy, the effect size for risperidone is appreciable [56, 57]. Two other second-generation antipsychotics, aripiprazole and quetiapine, are also widely used in this context, but lack data from controlled trials. Adverse cardio-metabolic effects of SGAs are evident both acutely (e.g., during the initial weeks of treatment) and progressively following long-term use, and concern about the proliferation of these medications for youth without nonpsychotic illness has intensified [59]. Current guidelines for youth treated with SGAs for behavioral dyscontrol recommend time-limited trials, with tapering attempted within 6 months or so [60]. One controlled discontinuation trial [61] found a lower risk for recurrence of disruptive behaviors with continuation of risperidone monotherapy vs. placebo substitution (29% vs. 47%), as well as all-cause discontinuation (42% vs. 62%). It is not known whether careful adjustment of first-line ADHD treatments would have diminished relapse rates, but a trial that were to examine this issue would have strong clinical relevance.

Alternatives to SGAs widely used for impulsive aggression include antimanic/mood stabilizer treatments (antiepileptic drugs [AEDs] and lithium) and noradrenergic α_2 receptor agonists (guanfacine and clonidine-based products FDA-approved to treat ADHD). Evaluations of these treatments remain sparse. Among children with inadequate reductions in aggressive behavior following stimulant monotherapy, adding divalproex sodium culminated in improved aggression and mood-related symptoms compared to adding placebo [55]. Oxcarbazepine has come into common clinical use, but has no supportive data. Most alpha-2 agonist trials to date have reported on disruptive behavior as a secondary outcome in trials of youngsters with ADHD, and have not studied cohorts selected for high baseline aggression or mood problems [62]. Trials that have evaluated clonidine in combination with stimulants have shown modest benefits over monotherapy [63, 64]. These compounds have short elimination half-lives and the development of long-acting preparations of clonidine and guanfacine with FDA-approval has contributed to wider use. Given their more favorable risk/benefit profiles, formal studies of these two medications' usefulness for disruptive behaviors cause by negative affect are sorely needed.

Increased interest in mood dysregulation, irritability, and mood lability as transdiagnostic concepts may heighten interest in antidepressant (AD) treatments for this patient group. Clinicians may also perceive that the inclusion of DMDD within the depressive disorders implicitly endorses AD use. However, empirical support for

AD treatment of major depressive disorders among youth is modest, especially among SSRI antidepressants apart from fluoxetine for adolescents [65, 66]. Effect sizes for treatment of anxiety disorders are larger and more consistent, especially when combined with therapy that emphasizes exposure and the development of coping and skills to facilitate and dampen the associated worry [67, 68]. In the context of children's negative emotionality and explosiveness coupled with impulsivity, subsequent research may eventually identify specific symptoms, patient subgroups, or co-therapy regimens for which AD treatments prove useful, but this remains speculative.

Psychotherapy and Psychosocial Interventions

The most established psychosocial treatments for disruptive behavior symptoms emphasize the interaction between caregivers and youth so that they promote prosocial behaviors and reduce problematic ones. The contents and formats of specific approaches vary somewhat, especially to the extent that are tailored to a particular age range. Nevertheless, they tend to share some basic principles and goals. First among these common elements is to ensure that the parent–child interactions are for the most part positive and mutually enjoyable. Acrimonious interactions undermine the success of any behavior management strategy, and, moreover, worsen the quality of life for all involved. Second, clear, consistent, and reasonable behavioral expectations and consequences should be communicated calmly, and prosocial behavior and efforts to handle upsets constructively should be recognized and thoroughly praised and rewarded. Third, various approaches to managing problematic behaviors are provided, often in a hierarchy of ignoring mild negative attention-seeking behaviors, warnings, response cost (i.e., lost points or privileges), time out, etc. Such consequences should be proportionate to the misbehavior and things like loss of a privilege should last only the minimum time needed in order for the child to then "re-earn" them through more positive behavior. The latter point is significant for many caregivers who have come to rely on excessive punishments, often as heat-of-the-moment overreactions to their own anger.

There has been some concern that, for impulsive children with brittle frustration tolerance, behavioral strategies based on delivering consequences for the child's behavior may in some instances be counterproductive or end up being overly punitive. If one lacks an adequate capacity to inhibit expressions of rapid-onset rage and to reason out and implement alternative responses, the prospect of further punishment may have little behavior-modifying impact. This would be especially true in high-intensity situations, and may further embitter the patient. Some approaches focus instead on "antecedent control," or altering expectations of the environment to reduce the likelihood of situations that will provoke the child's outbursts, while helping the child to develop better skills to manage such frustrations when they arise [69–73].

Another group of treatment approaches seek to scaffold the youth's development of more adaptive responses to irritations through direct instruction and rehearsal of skills thought to underlie emotion regulation. Such skills include self-monitoring

for early warning signs of heightened arousal and anger; reappraising challenging situations to avoid thinking of each one is a matter of life-or-death importance; acceptance of setbacks and frustrations as normal and not catastrophic; relaxation; and alternative, more composed behaviors that help the child to achieve his or her objectives with others. Often enough, highly impulsive youth with behavior disturbances may know what they are *supposed* to do, can role-play these behaviors, and can even give good advice to others on managing provocations. Yet, problems arise because suppressing drastic emotional reactions and utilizing alternatives in the heat of the moment requires Herculean self-restraint. Nevertheless, explicit identification and practice of substitutive coping behaviors insures that these skills are in the child's repertoire, provides prosocial models for handling upsets, and offers an opportunity for the parents and others to acknowledge and praise the child for a job well done, even if only in artificial, role-play or problem-solving settings.

Future Directions

It seems likely that the development of a comprehensive neurobehavioral of negative emotional reactivity in the context of ADHD will need to address some recurrent issues that this chapter touched on. Are there some manifestations of ADHD that include "emotional impulsivity" as a basic phenotype? Or do some youth showing highly irritable and aggressive behavior necessarily have a distinct disturbance in affective processing? Current clinical concepts of mood disorders focus on sustained sadness, irritability, and anhedonia, but these ideas do not seem quite adequate for the phenomenon of acute rages that revert to a euthymic baseline. Methodological approaches and theories in affective neuroscience that address "affective chronometry," however, may offer useful ways to consider these sorts of problems from a developmental psychopathology [74, 75].

Several treatments have the potential to yield profound improvements across areas of impairment. Among them, first-line treatments for ADHD can be highly beneficial when measurement-based treatment is provided that systematically optimizes the child's regimen and basic guidance in behavioral support strategies, though unfortunately such a standard of care remains uncommon in community settings [76, 77]. Overall, the impact of treatment on long-term outcomes remains unclear, partly because of difficulties disentangling quality and adherence of ongoing interventions from the natural course of the disorders.

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Depressive Disorders and ADHD

7

W. Burleson Daviss

Prevalence and Morbidity

Major and minor depressive disorders are relatively common in the pediatric age-group, with a one-year prevalence of about 2% in children and 8% by adolescence [1]. In children, the female-to-male ratio of depressive disorders is approximately 1:1 [1], but from adolescence onward, increases to 2:1 [1, 2]. Epidemiological studies in the United States have reported the prevalence of ADHD to be as high as 11% in children and adolescents, lessening to 4.7% in adults [3]. Epidemiological studies have estimated that the risk of having at least one episode of MDD before adulthood to be as high as 50% in individuals with ADHD, approximately 5.5 times more than in individuals without ADHD [4]. Conversely, the prevalence of ADHD in the National Comorbidity Study among adults with *current* depressive disorders was 22.6% in those with dysthymic disorders, and 9.4% in those with MDD [3].

Major and minor depressive disorders are both associated with significant long-term impairment, morbidity, and mortality [1, 5]. Likewise, individuals with ADHD have significantly greater problems than those without it regarding academic and occupational attainment, unplanned pregnancies, divorce, motor vehicle accidents and accidental deaths [6–8], along with a threefold higher risk of completed suicide [9]. Individuals with comorbid depression and ADHD have greater levels of impairment than those with either disorder alone [10–13], and a more severe course of depression. For instance, adolescents with Dep/ADHD have a higher risk of depressive recurrences relative to others with depression alone [13]. Young adult females with both MDD and ADHD have earlier ages of depressive onset, longer durations of depressive episodes, and higher rates of psychiatric hospitalizations and

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suicidality than females with only MDD [10]. The comorbidity of Dep/ADHD is thus a sizeable public health problem in all ages.

Risk and Etiological Factors

The estimated heritability of ADHD based on twin studies is 76% [14], while that of MDD is lower at 31–42% [15]. Individual risk factors for pediatric depressive disorders include female sex, and having other psychiatric disorders such as anxiety, oppositional, and conduct disorders [1, 4, 16]. ADHD and MDD share familial risk factors, and while both run in the same families, the predominant determinants of which ADHD patients go on to develop comorbid depressive disorders are more environmental than genetic [17]. Environmental risk factors for pediatric depressive disorders include exposure to traumatic life events, adverse family environments, family conflicts, and poor parental or peer relationships [1, 16]. Any lifetime history of comorbid depression among adolescents with ADHD has been associated with family conflict, negative life events, and trauma [12]. In children with ADHD, adverse family environments, poor parenting behaviors, and poor peer relationships are independent predictors of depressive symptoms [18]. Finally, interpersonal deficits have been shown to predict MDD *persistence* among youths with ADHD and MDD at outset [19].

Because the onset of depressive disorders typically is several years after that of ADHD, another potential environmental risk factor for developing Dep/ADHD could be pharmacotherapy for the ADHD. Stimulant medications, the most widely used treatment for ADHD, can occasionally cause dysphoric or labile moods [20, 21]. Moreover, two animal studies of young rodents have hinted that early stimulant exposure could increase the risk of developing comorbid depression in young humans [22, 23]. However, studies of humans with ADHD have more recently suggested that earlier ADHD pharmacotherapy [24] or any history of stimulant treatment [25] may reduce the risk of developing later MDD. Moreover, a recent population study has reported that patients with ADHD are more likely to attempt or complete suicide during periods when they are not taking their stimulant medication [26].

Assessment and Differential Diagnosis

Case 1. Henry: This is a 13-year-old male in the 8th grade. He was diagnosed with ADHD combined subtype and oppositional defiant disorder in the 3rd grade, and was treated with a stimulant at a low dose without benefit, as his parents doubted the diagnosis and Henry's need for treatment. He has long struggled academically, but has lately had persistent irritability, sleep problems, anergia, poor appetite, and made comments about wanting to be dead when reprimanded. He says that his mom always exaggerates his symptoms, and should instead worry about his dad who "hits her when he's drunk." In the interview, Henry is sullen, dysphoric, and

minimizes current symptoms. Teachers and mom indicate he's increasingly become more isolated from family and peers. His total score on the PHQ-9 depressive scale is 9 (minimally depressed), while his mom's rating of his symptoms on the parent-version is 19 (severely depressed). Mom's and teachers' Vanderbilt Scales report multiple inattentive, hyperactive, oppositional, and anxiety/depressive symptoms, along with a recent decline in his grades, effort, attitude, and peer relationships. Henry's mom takes and SSRI for depression, and has previously worked at a day care center. Henry's dad had behavioral problems as a child, dropped out of high school, and now works as a machinist. He refused to complete the parent Vanderbilt but wrote at the top of it: "ADHD does not exist! I don't want my son on mild-altering drugs!" A maternal grandfather was an adult with "bipolar" and eventually suicided.

As Henry's case illustrates, proper assessment of pediatric depression with ADHD involves gathering a wide array of potentially contradictory information from multiple informants, including the child/adolescent, parent(s), and teachers [27–29]. Parents and youths may provide discrepant information about the patient's depressive symptoms [30]. The clinician should resolve such discrepancies when possible, but when not, must then weigh the credibility of each informant on a case-by-case basis. Parents, in general, are better informants than children of the temporal course of depressive symptoms [31], and, along with teachers, are also better informants of ADHD symptoms, irritability, and externalizing disorder symptoms [29]. However, parents and teachers may confuse depressive symptoms in the child with symptoms of other comorbidities such as oppositional defiant or anxiety disorders [32, 33]. Parents with their own mental health problems may likewise overreport their child's symptoms [27, 30, 34]. Youths, in general, are better informants of their depressive cognitions, suicidal ideations, and vegetative symptoms as they get older [30]. However, youths with ADHD may underestimate their depressive symptoms and overestimate their social and academic function relative to parents, teachers, and peers [33, 35].

Rating scales have been well reviewed [36–38], and offer a useful and efficient way to gather information from multiple informants in order to screen for symptoms of ADHD, depression, and other potential comorbidities. Table 7.1 summarizes common measures of pediatric depression. Chapter 2 reviews general strategies for interviewing patients of different ages and their parents, and how to integrate data from various informants' interviews, rating scales, and other information in order to make a more accurate diagnosis. While rating scales are only as accurate as the informants completing them, and are no substitute for a thorough diagnostic interview, they can guide the clinician to consider certain diagnoses more carefully during the interview, and help to show discrepancies in informants' reports that can potentially be further investigated during the interview. Several depressive rating scales, including the Patient Health Questionnaire (PHQ-9) [39] and Mood and Feelings Questionnaires [40], are available both in child- and parent-versions, or in abbreviated forms, which make them good for repeated administrations over time. Parent- and teacher-rating scales such as the Vanderbilt, Iowa Conners, or SNAP allow the clinician to screen for and monitor symptoms of ADHD and other

Table 7.1 Rating scales for diagnosing comorbid depressive disorders

Measure	Informant(s)	Ages	Notes	Public domain?
Mood and Feelings Questionnaire (MFQ) [40, 94]	PR, SR	8–18	33-item and 13-item short scale with items specific to children/adolescents, items scored on 3 point scale (True, Sometimes, Not true)	Yes
Patient Health Questionnaire (PHQ-9) [95]	SR	18+	9 DSM-5 symptoms of MDD rated on 4-point scale per frequency	Yes
PHQ-9 for Adolescents [39]	SR PR	13–18 6–18	Modified from adult PHQ9 as an adolescent self-report, or parent-report. Includes all 9 DSM-5 symptom criteria for MDD, and items regarding impairment, suicidal intent, and lifetime suicide attempts	Yes
Children's Depressive Rating Scale, Revised (CDRS-R) [96]	PR, SR	8–18	Child and parent interview with 17-items rated on 5- or 7-point scales, widely used in clinical trials to assess changes in severity; scores ≥40 are clinically significant, while scores ≤28 suggest depressive remission	Yes
Beck Depressive Inventory (BDI) [97]	SR	13+	Adult rating scale with 21 items rated on 3-point scale, used in some adolescent studies, though some items may not be appropriate	No
Children's Depressive Inventory (CDI) [98]	SR	7–18	Adapted from BDI, has 27 items rated on 3-point scale, using language appropriate for children	No

SR self-report, *PR* parent-report

disorders [37]. Serial use of such scales allows clinicians to systematically track changes in mood and behavioral symptoms with treatment, and to improve clinical outcomes in their patients with Dep/ADHD [41].

As Henry's case illustrates, the clinician must also be mindful that symptoms of depression may overlap with those of ADHD, and with other common disorders, including internalizing disorders (e.g., anxiety) and externalizing disorders (oppositional defiant or conduct) [32, 42]. ADHD medications also commonly cause side effects similar to depression, including its vegetative symptoms (e.g., changes in sleep, appetite, energy, and activity levels) and its affective symptoms (moodiness, irritability, depression) [20, 21, 32]. Table 7.2 illustrates examples of such symptom overlaps. The depressive symptoms most useful for discriminating MDD in young patients with ADHD are anhedonia, social withdrawal, depressive cognitions, suicidal thoughts, and psychomotor retardation [32, 43]. A thorough initial review of the history and time course of such emotional and physical complaints, and close monitoring of such symptoms over time will often clarify whether any reported

Table 7.2 Overlap of ADHD, depressive, and bipolar manic symptoms

Symptom	ADHD	Depression	Bipolar mania
Poor concentration/ distractibility	D	D	D
Hyperactivity/psychomotor agitation	D	D	D
Impulsivity	D		D
Persistently depressed mood		D	
Mood swings	A, M	A, M	D, M
Irritability	A, M	D, M	D, M
Boredom	A	D	
Loss of interests or pleasure (anhedonia)		D	
Hypersomnia	M	D, M	A, M
Insomnia	A, M	D, M	D, M
Decreased need for sleep			D
Decreased appetite	M	D, M	
Talkativeness	D		D
Low energy/psychomotor retardation	M	D, M	M
Low self-esteem	A	A	
Worthlessness/Excessive Guilt		D	
Hopelessness		D	
Suicidal thoughts or behaviors		D	
Overestimation of abilities	A		A
Grandiosity			D
Psychotic symptoms		A	A
Psychosocial impairment	D	D	D

M medication side effect, *D* diagnostic criterion, *A* associated symptom

mood symptoms represent a true depressive disorder, medication side effects, or other psychopathology [27, 28]. Chapter 3 offers a thorough review of other organic causes for such symptoms.

Another critical goal when assessing patients with potential symptoms of Dep/ADHD is to carefully screen for any history of manic or hypomanic symptoms. Classic symptoms of mania at any age include marked elation or irritability, grandiose or racing thoughts, increased goal-directed activity, reckless pursuit of pleasurable behaviors, talkativeness, and decreased need for sleep [44]. As with depressive symptoms, manic symptoms are easily confused with symptoms of ADHD and of other comorbidities (e.g., distractibility, talkativeness, impulsivity, irritable and oppositional behaviors) or even with the common side effects of ADHD and other medications. Additional warning signs of ensuing bipolarity in children or adolescents include psychotic symptoms, age-inappropriate levels of sexual interest, *early* onset of any mood symptoms, inappropriately intense and prolonged emotional outbursts, pharmacologically induced mania/hypomania, and a family history of bipolar disorder [29, 45, 46]. Because of the potential risk of triggering mania by using an antidepressant or ADHD medication in an ADHD patient with undetected bipolar disorder, clinicians should be vigilant for such signs and symptoms when starting or increasing doses of these medications in their patients with Dep/ADHD.

An alternate path that can eventually lead a diagnosis of Dep/ADHD may begin with complaints of depressive symptoms, but a careful review of past psychiatric and educational history also suggests long-standing ADHD [24, 28, 47]. The DSM-IV field trials found that ADHD youths with the inattentive subtype often had symptoms emerge beyond 7 years, yet were quite symptomatic and impaired when they were formally diagnosed years later [48]. This clinical observation largely motivated the more liberal diagnostic criteria for ADHD in DSM-5 relative to DSM-IV, requiring that "some" (rather than all) of the ADHD symptoms be evident before 12 years (rather than 7 years) of age [44]. If any such criteria are uncertain, however, additional history from parents, significant others, old school reports, and even employment records may clarify the presence and course of such symptoms, and ultimately the diagnosis [47, 49]. A diagnosis of Dep/ADHD should also be considered if ADHD symptoms of unclear duration persist after the patient gets effective treatment of the depressive disorder [28]. In summary, clinicians must make "best estimate" diagnoses based on all of the information available at the time of the interview, but also be prepared to modify their diagnoses as new clinical data emerge in working with such patients [28, 47, 49].

Treatment

Pharmacotherapy

Two groups of stimulant medications, the amphetamines and methylphenidates, have long been considered first-line treatments for uncomplicated ADHD, with response rates of 70–80%, and larger effect sizes than non-stimulant medications or psychosocial treatments [20, 29, 50, 51]. The amphetamines include mixed amphetamine salts (Addreall®), dextroamphetamine (Dexedrine®), and lisdexamfetamine (Vyvanse®), while the methylphenidates include methylphenidates (Ritalin®, Metadate®, Concerta®, Quillivante®) and dexmethylphenidates (Focalin®). Each group also has short-, medium-, and extended-release formulations [20]. Randomized controlled trials (RCTs) involving children with ADHD and comorbid anxiety or depressive symptoms have yielded contradictory findings about whether such internalizing symptoms reduce the ADHD's response to a stimulant [52, 53]. No study to date has compared the relative efficacy of stimulant pharmacotherapy in ADHD subjects with and without comorbid depressive disorders. Several non-stimulant medications are also now approved by the Food and Drug Administration (FDA) for ADHD, including atomoxetine (Strattera®), and extended-release formulations of the alpha agonists guanfacine (Intuniv®) and clonidine (Kapvay®).

Antidepressants with catecholaminergic effects (e.g., bupropion, desipramine, imipramine) have also proven efficacious as off-label treatments for ADHD in children and adults [29, 50, 54, 55], and there is growing evidence for the selective serotoninergic reuptake inhibitors (SSRIs), especially fluoxetine, regarding their efficacy in treating pediatric MDD [27, 56–58]. Two SSRIs, fluoxetine (in children and adolescents) and escitalopram (in adolescents) are now FDA-approved for

pediatric MDD. Because initial meta-analyses of antidepressant RCTs in younger patients suggested an increased risk of suicidal thoughts and behaviors relative to placebo, the FDA issued black box warnings to the labels of all antidepressants regarding their potential to increase the risk of suicidality in children, adolescents, and young adults [59, 60]. A subsequent, more comprehensive meta-analysis of 15 antidepressant trials for pediatric MDD, both published and unpublished, noted that subjects on active medications had an 11% greater risk of responding than those on placebo (e.g., 10 MDD subjects would need to be treated to see one additional subject respond). On the other hand, those on active medication were just 0.9% more likely to have suicidal ideations/behaviors, a difference that was not statistically significant (e.g., 111 MDD subjects would need to be treated to see one additional subject adversely affected) [61]. In the years after the FDA's black box warning, rates of prescriptions to young people fell sharply while deaths by suicide in this age group rose for the first time in years [62].

Birmaher and colleagues revised the practice parameters for pediatric depression of the American Academy of Child and Adolescent Psychiatry (AACAP), recommending that antidepressant trials should generally be reserved for patients with depressive disorders of greater severity, longer durations, melancholia, psychotic symptoms, or suicidal ideations or behaviors [27]. The stated aim of such treatment should be having the patient achieve full depressive remission [27]. They advised that patients receiving an antidepressant should be closely monitored for suicidal thoughts and other associated side effects as reported by the FDA's black box warning (e.g., akathisia, irritability, agitation, sleep disruption, and induction of mania or a mixed state), especially in patients early in treatment or at higher risk (those having a prior history of suicidality, impulsivity, or substance abuse, or a family history of suicide or bipolar disorders) [27]. Once patients have experienced remission, they should continue their antidepressant for at least 6–12 months, and even longer if they have experienced multiple, severe, or extended depressive episodes [27]. Generally, the withdrawal of effective treatments in patients with Dep/ADHD should occur outside of the school year to lessen the morbidity of potential relapses of depressive or ADHD symptoms [28].

Only a few studies have examined the effects of pharmacological treatments *specifically* in patients with both depressive disorders and ADHD, as summarized in Table 7.3. Many of these studies have been limited by small sample sizes and open label treatments. Two studies have provided preliminary evidence for the effectiveness of combining a stimulant and an SSRI for treating Dep/ADHD [63, 64], which allows the prescriber to adjust the dose of either medication based patients' specific depressive and ADHD responses, respectively. Disadvantages of such medication combinations are the increased risk of treatment noncompliance, drug–drug interactions, and other side effects. Two other studies have examined the effectiveness of using a single medication to target both disorders. Bupropion, an FDA-approved antidepressant for adults, with demonstrated efficacy in both pediatric and adult ADHD [54, 55], was also effective and well tolerated in 24 adolescents with ADHD and MDD or dysthymic disorders [65]. A second, open label study examined the antidepressant effects over 12 weeks of methylphenidate in 47 children and

Table 7.3 Pharmacological trials specifically of youths with ADHD and depression

Reference	*N*	Subjects	Design	Key findings
[63]	32	Youths with ADHD refractory to MPH; 25 had DD, of which 6 also had MDD	12 week prospective study, with fluoxetine added and gradually titrated while MPH maintained	Adding fluoxetine helpful for both ADHD and depression in all Ss, and well-tolerated
[64]	11	Adolescents and adults with MDD and ADHD whose depression had responded to SSRI monotherapy	SSRI maintained with MPH or Dex added	Combination of SSRI and stimulant was well tolerated and effective for residual ADHD
[65]	24	Adolescents with ADHD and MDD or DD	2-week placebo run-in, followed by flexible dosing of bupropion SR for 8 weeks	Overall response rates of 88% for depression and 63% for ADHD; medication generally well-tolerated
[66]	47	Youth with ADHD and subsyndromal depressive disorders: depressed/irritable or anhedonic moods × 2 weeks, with 1–3 other symptoms of MDD, and no history of suicidal thoughts or behaviors	12 week, open label treatment with methylphenidate, monitoring ADHD and depressive responses	Improvements in ADHD and depressive symptoms were highly significant ($p < 0.0001$). Depressive response correlated directly with ADHD response, and inversely with initial depressive severity.
[69]	142	Adolescents with ADHD & MDD	9-week, placebo-controlled RCT of ATX	Ss on ATX had greater improvement in ADHD ($p < 0.001$) but not depressive sxs, due to high depressive responses to PBO

ADHD attention-deficit/hyperactivity disorder, *AE* adverse event, *ATX* atomoxetine *Dex* dextroamphetamine, *DD* dsythymic disorder, *MDD* major depressive disorder, *MPH* methylphenidate, *RCT* randomized controlled trial, *SR* sustained release, *PBO* placebo, *Ss* subjects, *SSRI* fluoxetine or sertraline, *Sxs* symptoms

adolescents with ADHD and *subsyndromal* depressive disorders (SSD) [66], finding that methylphenidate was associated with significant reductions in both ADHD *and* depressive symptoms. Of note, the symptom criteria for SSD in this study, as summarized in Table 7.3, were fairly substantial, with the mean baseline CDRS-R score of 41 (CDRS-R scores ≥40 are a typical inclusion criterion for clinical trials of pediatric MDD [67, 68]). The study's conclusion was that methylphenidate is a reasonable first-line pharmacotherapy for young patients with Dep/ADHD and milder depressive symptoms [66]. Another study summarized is the only RCT published to date for Dep/ADHD [69]. This study examined the efficacy of atomoxetine in youth with both ADHD and MDD. Atomoxetine was superior to placebo for the ADHD but not for the MDD, because of the high level of depressive responses to placebo. High placebo response rates have long plagued antidepressant trials of

Table 7.4 Summary of the Texas Children's medication algorithm for ADHD and MDD

A. Impairment from ADHD worse than from MDD [74, 99]*:*
Step 1: Start stimulant monotherapy per ADHD algorithm
Step 2: How do ADHD and depression respond?
• If ADHD but not depression responds, add SSRI to target depression
• If ADHD and the depression stay the same, switch to new stimulant class (i.e., amphetamine to methylphenidate OR methylphenidate to amphetamine)
• If ADHD and/or depression worsen, switch to SSRI via MDD algorithm [57, 73]
B. Impairment from MDD worse than from ADHD [57]*, or suicidal ideations/behaviors* [72]:
Step 1: Start SSRI monotherapy per MDD algorithm [57]
Step 2: How do depression and ADHD respond?
• If depression but not ADHD responds, add stimulant to target ADHD
• If depression stays the same or worsens, switch to new SSRI
Step 3: How do depression and ADHD respond?
• If depression but not ADHD responds, add stimulant to target ADHD
• If depression stays the same or worsens, try a non-SSRI antidepressant (e.g., bupropion, mirtazapine)

pediatric MDD, relative to antidepressant trials of adult MDD, or stimulant trials of pediatric ADHD [70]. Of note, atomoxetine carries a similar FDA black box warning as the antidepressants, based on cases of emerging suicidal ideations in RCTs of atomoxetine for pediatric ADHD [71]. However, no subjects with ADHD in the current RCT had emerging suicidality, despite their increased risk of suicidality in having comorbid MDD [69].

Based on a review of the medical literature, and group consensus, a panel of clinical and research experts developed pharmacotherapy algorithms for ADHD, MDD, and the two disorders in combination, as part of the Texas Children's Medication Algorithm Project (CMAP) [72, 73]. The same group then revised these algorithms a few years later, based on more recent published studies [57, 74]. Table 7.4 summarizes the most recent pharmacotherapy algorithms for patients with both MDD and ADHD. A key recommendation of the CMAP group was to identify and treat the bigger, more impairing problem first. If the depressive disorder is considered the bigger problem, then the prescriber should start with an SSRI antidepressant first, followed by another SSRI if necessary, then a non-SSRI such as bupropion or mirtazapine if still necessary. If ADHD is the bigger problem, the prescriber should first start with a stimulant trial (a methylphenidate or an amphetamine), then another stimulant trial (switching from a methylphenidate to an amphetamine or vice versa), then if necessary to atomoxetine, then to a fourth-line ADHD treatment such as bupropion or a tricyclic antidepressant. The algorithm for Dep/ADHD offers additional treatment steps that vary according to how each of the two disorders responds to each successive treatment. Regardless of the treatment and stage, the prescriber should closely observe how both the ADHD and depression respond to that treatment. In situations where a medication for ADHD seems to worsen the depressive symptoms, the clinician should then switch to the depression

algorithm and use an antidepressant instead. Two additional cases now illustrate how clinicians could use the CMAP algorithms to guide their pharmacological choices depending on the patient's specific clinical history.

Case 2. Collin: This is an 18-year-old male, self-referred due to concerns about possible ADHD and depression related to poor school performance and conflicts with his parents. His PHQ-9 total is 18 (severe range) with multiple cognitive and vegetative symptoms of depression reported, along with daily suicidal ideations and vague plans but no true intent. On the ADHD Self-Report measure, he reports 4 clinically significant ADHD symptoms in Part A (reflecting a positive screen), and an additional 4 ADHD symptoms in Part B, all but one of which are inattentive. He has had no previous trials of medication or therapy. However, when he recently tried his boarding school room-mate's methylphenidate, he said "it helped me get through my exams". He denies other history of illicit substance or alcohol use, and his past psychiatric and medical history are unremarkable.

Comments on Case 2: Collin clearly has MDD, and may also have ADHD, depending on whether collateral information from parents and teachers suggests long-standing, impairing ADHD symptoms that preceded the depressive symptoms. Because he reports suicidal ideations, we'd generally consider his depressive disorder to be the "bigger problem," regardless of whether the collateral information suggested ADHD, and despite his request for a stimulant. Collin was offered only antidepressant treatment, and he agreed to try escitalopram rather than fluoxetine, based on a family member's history of a positive response to it. If significant ADHD symptoms persisted according to parent and teacher ratings, information from these collateral informants supported an added diagnosis of ADHD, and he had no contra-indications (e.g., a substance use disorder, or a history of a structural hear problem), then the prescriber could later add either a methylphenidate or amphetamine stimulant to target the ADHD [72, 73].

Case 3. Amanda: This is a 14-year-old girl referred by parents for moodiness, poor grades, and defiant behaviors. Her pediatrician evaluated her previously when she was in the 4th grade, due to parent and teacher concerns about ADHD and oppositional behaviors, but parents declined the pediatrician's offer to do a stimulant trial because "it could change her personality" or make her "drug dependent." Parents and teachers continue to endorse many inattentive, hyperactive/impulsive and oppositional defiant symptoms. Her self-reported PHQ-9 total is 14 ("moderate" severity). She endorses depressed/irritable moods, anhedonia, insomnia, anergia, poor concentration, feelings of worthlessness, poor relationships with her parents and peers, and hopelessness about going to college. There is no history of suicidal ideations/behaviors, trauma exposure, drug or alcohol problems, or symptoms of anxiety, mania, or psychosis.

Comments on Case 3: Amanda's ADHD symptoms have clearly been chronic and severe enough to lead her pediatrician to offer a stimulant trial several years ago. The depressive symptoms seem relatively mild compared to the ADHD and oppositional symptoms, and could potentially be the result of long-standing social and

academic impairment related to ADHD. A stimulant trial would be the most likely to address the immediate and seemingly bigger problems related to the ADHD and oppositional symptoms at home and school. Moreover, if she experienced emotional side effects such as worsening moods, these could be quickly resolved by stopping the stimulant. Her pediatrician initiated a trial of OROS Methylphenidate, and referred her to receive individual and family therapy. The parents were also encouraged to request in writing that Amanda receive a formal evaluation by her school for potential educational accommodations.

CMAP offered additional useful suggestions related to providing pharmacological care to patients with Dep/ADHD. First, the prescriber should educate the patient and parents about potential benefits and risks of potential treatments, including worsening moods, suicidality, and iatrogenic mania, and the need for close monitoring both initially and over time [72, 74]. Second, the prescriber should try to make one medication change at a time, in order to simplify the interpretation of treatment responses. Third, the CMAP panel suggested systematic monitoring of parent and patient reports of depressive symptoms, and parent and teacher reports of ADHD and disruptive behavioral disorder symptoms using specific rating scales over time. Based on such data and clinical observations, the prescriber should document changes in the patient's ADHD and depressive symptoms over time, using separate ratings on the Clinician's Global Impressions of Improvement (CGI-I) scale for each problem [75]. The CGI-I is a commonly used clinician-rated measure to assess patients' response to treatments in clinical trials (with scales ranging from 1 to 7, as follows: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse, and 7 = very much worse) [75]. Such CGI-I ratings should be done based on all available information. The goal of treatment in CMAP is to achieve separate CGI-I ratings of at least "much improved" for both the ADHD and the depressive disorders. If the patient developed new symptoms inconsistent with the primary diagnoses, unexpected responses or clinical deterioration with such treatment, CMAP would then urge the prescriber to reassess and consider modifying the patient's working diagnoses and treatment [57, 72–74]. A study of the CMAP algorithms for ADHD and depressive disorders found that they could be implemented in a community mental health setting, and were often useful in guiding effective pharmacological treatment of patients with Dep/ADHD. However, patients receiving such algorithmically guided treatments still need close follow-up, and may need to go beyond the first stages of the ADHD or depressive disorder algorithms to achieve a positive response for both disorders [76].

Psychotherapy and Other Psychosocial Interventions

What if patients like Collin and Amanda or their parents are unwilling to consider a medication trial, or have milder levels of depressive or ADHD symptoms? Psychosocial interventions are widely considered less effective than pharmacotherapy for children with ADHD [77], and there have been no studies of such treatments specifically in patients with Dep/ADHD. Even so, there are now several psychosocial treatments with well-established efficacy for ADHD, including behavioral

parent training, behavioral classroom management, behavioral peer interventions, and organizational training [78]. A recent review of treatments for adolescent ADHD suggests that these psychosocial treatments can improve not only parent- and teacher-reported symptoms of ADHD, but also functional outcomes like homework completion and organizational skills [79]. They also can improve comorbid psychopathology related to oppositional defiant or conduct disorders [80]. Likewise, studies of both individual and group CBT in adults with ADHD have shown promising results [79, 81].

For patients whose predominant problem is a depressive disorder, there are also other manualized psychotherapies with demonstrated efficacy for pediatric and adult depressive disorders. Cognitive behavioral therapy (CBT) has well-established efficacy for child and adolescent depressive disorders [82], and improves problem-solving and coping skills, social and communication skills, emotional regulation, and negative thoughts [82]. Studies suggest that combining an antidepressant with CBT increases the likelihood of depressive remission relative to antidepressant treatment alone [68, 83].

Interpersonal therapy (IPT) also has well-established efficacy for the treatment of adolescent depression [82]. IPT helps individuals to adapt to changes in their relationships, and to transition more effectively in their personal roles [84]. Interpersonal therapy has proven more effective than wait-list control groups getting no therapy, and equally or more effective than CBT [84, 85], but has not been directly compared to antidepressant treatments to date. The growing literature in support of CBT and IPT has led the American Academy of Child and Adolescent Psychiatry and the American Psychiatric Association to recommend that either of these therapies should be tried first in patients with mild depressive disorders, or be used in combination with an antidepressant in patients with moderate to severe depression [86].

Combination Treatment

Patients with both ADHD and depression will often benefit most from the combination of pharmacotherapy and therapy, in part because therapy can target environmental factors contributing to the depressive episode or to persistent ADHD symptoms and impairment. Regular therapy also allows for closer monitoring of ADHD and depressive symptoms, and for emerging or worsening suicidal ideations and behaviors that are possible on either antidepressant or ADHD medications. Like the CMAP group, our group generally defines depressive disorders with suicidal ideations or behaviors as being moderate to severe, which would indicate the need for both therapy and an antidepressant from the start.

The Multimodal Treatment of ADHD (MTA) study provides *indirect evidence* for the potential benefit of combining behavioral treatment with intensive ADHD pharmacotherapy when treating ADHD patients with internalizing and externalizing comorbidities [87]. Subjects in MTA were children with ADHD randomized for 14 months to three active groups (including expert behavioral therapy, expert ADHD

pharmacotherapy, or a combination of both expert treatments), or to a control group who received treatment-as-usual in the community. Key components of the expert behavioral therapy groups were parent-oriented skills training in behavioral therapy, and the therapist's advocacy at school for appropriate educational accommodations and other services [88]. Post hoc analyses suggested that *the combination of expert behavioral therapy and expert pharmacotherapy* was superior to either expert treatment by itself in the ADHD children with both comorbid anxiety and other externalizing disorders. Because patients with Dep/ADHD have similar challenges psychiatrically, academically, and socially [10–13, 28], combining pharmacotherapy with such psychosocial interventions could also be especially helpful for them.

On the other hand, the Treatment for Adolescents with Depression Study (TADS) provides more *direct evidence* for the potential clinical advantages of concomitant CBT for comorbid depression [67]. The TADS study first compared four different treatment groups of adolescents with MDD over a 12-week period of randomization: (1) fluoxetine + CBT, (2) fluoxetine-only, (3) placebo + CBT, and (4) placebo-only. TADS suggested that depressive responses at 12 weeks in either of the two groups on fluoxetine were superior to those of the other two groups. On the other hand, post hoc analyses suggested that subjects with more chronic and severe MDD, more comorbidities, and more baseline impairment, responded significantly better at week 12 in the two groups getting CBT (groups 1 and 3) relative to the groups not getting CBT (groups 2 and 4) [89]. From week 12 on, the groups who had received active treatment (groups 1–3) continued it for another 20 weeks in a double-blind fashion [90]. By week 32, response rates had reached 86% for subjects getting fluoxetine + CBT, 81% for those getting fluoxetine-only, and 81% for those getting CBT-only. This suggests that depressive responses in CBT-only group eventually caught up with the other groups getting fluoxetine. Of note, suicidal behaviors were higher in the fluoxetine-only group (14.7%), relative to combined treatment group (8.4%) or the CBT-only group (6.3%), suggesting that CBT had a protective effect against suicidal behaviors [90].

A second trial for adolescents with MDD refractory to a prior SSRI, the so-called Treatment of Refractory Depression in Adolescents (TORDIA) study, provides similar evidence for the benefits of concomitant CBT [68]. Using a 2 by 2 design, TORDIA compared responses among subjects with MDD that had been refractory to one SSRI. All subjects were randomized to be switched to either another SSRI or to venlafaxine. They were also randomized to either receive CBT or not. TORDIA's findings indicated that adding CBT to either antidepressant treatment strategy offered significant advantages for multiple depressive and functional outcomes [68].

Both TADS and TORDIA enrolled some subjects with MDD who also had comorbid ADHD, which allowed for post hoc analyses regarding the effects of comorbid ADHD on depressive responses [68, 91]. The TORDIA study reported that comorbid ADHD had *no effect* on depressive responses to either antidepressant treatment, or to CBT [68], while the first 12 weeks of the TADS study curiously suggested that subjects with comorbid ADHD had *better* depressive responses than those without it in each of the three active treatment arms (fluoxetine-only,

fluoxetine + CBT, or placebo + CBT) [91]. Both TADS and TORDIA permitted patients with comorbid ADHD to continue previously initiated stimulant treatments, so any negative effects of having comorbid ADHD on depressive responses may have been muted [92, 93]. In short, comorbid cases of Dep/ADHD may do best on a combination of empirically supported therapies and pharmacotherapies that target both conditions.

Conclusions and Future Directions

In summary, depressive disorders commonly occur in youths with ADHD, are quite impairing, and are challenging to diagnose and treat. Increasing evidence suggests that comorbid depression in youths with ADHD results from a chronic history of functional deficits along with a mix of environmental and genetic factors. Despite the scarcity of well-designed treatment studies for youths with ADHD and comorbid depression, there is some preliminary evidence for the use of pharmacological treatments such as stimulants, SSRIs, bupropion, and atomoxetine to target either or both disorders. There is also some suggestion for the benefit of concomitant psychosocial interventions, including behavioral therapies such as CBT or IPT, to target the child's functional deficits, contributing environmental factors, depressive symptoms, and risk of suicidal behaviors, especially in more severe and highly comorbid cases. Whatever treatments are initiated, these patients will often need closer follow-up and monitoring because of their higher risk of suicide and other safety concerns. They may also need a diagnostic reassessment when reasonable treatments have resulted in inadequate, adverse, or unexpected outcomes. Future research in patients with Dep/ADHD is clearly needed to improve our knowledge of the etiologies and phenomenology of these co-occurring disorders, along with our ability to identify, treat, and prevent them.

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Pediatric Bipolar Disorders and ADHD

8

Rasim S. Diler

Background and Significance

Introduction

Bipolar disorder (BD) is a familial illness characterized by episodes of abnormally elevated mood that are above and beyond the child's developmental stage [1, 2]. It is now widely accepted that Bipolar Disorder (BD) occurs in children and adolescents and the controversy has shifted from a debate about *whether* it can be diagnosed in youth, now to *how* it can be diagnosed, differentiated from more common psychiatric disorders in childhood such as attention deficit hyperactivity disorder (ADHD), and *how* it can be treated and prevented [3].

BD in youth is increasingly recognized as a significant public health problem that is often associated with impaired family and peer relationships, poor academic performance, high rates of chronic mood symptoms and mixed presentations, psychosis, disruptive behavior disorders, anxiety disorders, substance use disorders, medical problems (e.g., obesity, thyroid problems, diabetes), hospitalizations, and suicide attempts and completions [3]. Early identification of BD in youth is essential for not only stabilizing their mood but also for enabling them to follow a normative developmental path and prevent an unrecoverable loss in their psychosocial development and education [4]. Moreover, youth with BD can have greater utilization of medical services and higher behavioral health costs relative to youth with unipolar depression or non-mood disorders. Youth with *undiagnosed* BD may have even more behavioral health costs than those with *diagnosed* BD [3]. This chapter reviews the epidemiology, clinical aspects, differential diagnosis, natural course, and treatment of pediatric BD with ADHD.

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Epidemiology

Recent studies have shown dramatic increases in recognition and rates of BD in youth over the past 20 years and some authors have questioned the possibility of overdiagnosing children with BD in the US, whereas many others have brought up the possibility of long neglecting the presence of this condition in childhood [5]. The prevalence BD spectrum in adults is around 5% (BD I is around 1%), and the majority had the onset of their mood symptoms before age 20 years [6]. Those with ADHD usually have an early onset BD.

In clinical populations of youth in the US, the prevalence of BD has been reported between 0.6 and 15% depending on the setting, the referral source, and the methodology to ascertain BD [7]. Based on findings from two separate samples of juveniles with ADHD, Wozniak, Biederman, and colleagues have reported 20–21% had comorbid bipolar disorders [8, 9]. Other investigators have been skeptical about so many patients with ADHD meeting true diagnostic criteria for bipolar disorders. The skeptics have argued that: (1) the chronic irritability of these children was inconsistent with the episodic nature of mania described in DSM criteria; (2) the investigators did not consider the overlap of ADHD and manic symptoms (e.g., talkativeness, distractibility and hyperactivity); and (3) there was also an unusually high rate of bipolar disorders among subjects in the control groups of these samples. Instead, Klein and colleagues have argued that the children with ADHD described by the MGH group as having bipolar disorders most likely had severe conduct disorders or intermittent explosive disorders instead [10].

A recent meta-analysis about epidemiology of BD in youth around the world reported that the overall rate of BD was 1.8% (95% CI, 1.1–3.0%), enrolling 16,222 youth between the ages of 7 and 21 years during a period from 1985 to 2007 [11]. This meta-analysis suggested that there was no significant difference in the mean rates of BD-I in youth between the US and the non-US studies, but the US studies had a wider range of rates, especially when a broader definition of BD was used. In addition, the prevalence of BD-I in youth is similar to the current prevalence estimates of BD in adults, and while BD it is being diagnosed more commonly in clinical settings, the prevalence of BD in youth in the community is not increasing [11]. The same meta-analysis concluded that BD can begin in childhood, but the prevalence is much higher during the adolescence [11]. A large epidemiological study in the US reported slightly higher rates of BD-I and BD-II in female than in male adolescents (3.3% vs. 2.6%, respectively) with increasing rates of BD with older ages [12]. Studies in clinical populations have reported that the rates of bipolar spectrum disorders in youth are equally common in males and females [1, 13]. The rates of BD-II and adolescent-onset BD are more common in females [2].

Etiological Factors

Twin and adoption studies have demonstrated that the heritability of BD is quite high at 80%, indicating that 80% of the condition is determined by genetic rather than environmental factors [14–16]. However, several genes and epigenetic factors

seem relevant to the manifestation of this illness, and identification of the genes associated with BD has not been conclusive. Other factors such as variation in ascertainment, phenotype definition, control selection, and limited power have led to inconsistent results.

Studies evaluating the risk for BD in offspring of parents with BD and in first-degree relatives of youth with BD have provided further evidence that BD runs in families [2, 16, 17]. It is suggested that offspring of parents with BD have up to 25-fold greater rates of BD when compared to offspring of control parents [2, 18, 19]. Importantly, a large prospective, high-risk BD study has suggested that offspring with mood lability, depression/anxiety, and in particular having subsyndromal manic symptoms and parents who had early-onset BD were at 50% risk to develop BD [20]. However, children of parents with BD are also at risk to develop depression, anxiety, ADHD, and behavioral problems [2, 21]. It is suggested that ADHD was associated with a significantly higher risk for switches from unipolar to bipolar disorder (28% vs. 6%, over 7 years) [22]; however, a review of high-risk studies suggested that the clinical diagnosis of childhood ADHD is not a reliable predictor of the development of BD in offspring studies [23]. Similarly, in Pittsburgh Bipolar Offspring Study, the rates of ADHD were not statistically different (38.9% vs. 19.8%) between bipolar offspring who did or did not develop BD during follow-up [2]. However, symptoms of inattention (in addition to depression and anxiety) may be part of a mixed clinical presentation during the early stages of evolving BD in high-risk offspring [23]. The same analysis reported preliminary evidence that childhood ADHD may form part of a neurodevelopmental phenotype in offspring at risk for developing a subtype of bipolar disorder unresponsive to lithium stabilization [23].

Research and clinical experience also suggest that trauma or stressful life events can trigger an episode of BD, though many BD episodes occur without an obvious or identifiable cause. In brief, the etiology is multifactorial, with complex interactions of biological vulnerabilities and environmental influences. The few studies that have evaluated the effects of psychosocial factors on the onset and maintenance of pediatric BD have found that low socioeconomic status (SES), exposure to negative events, and high "expressed-emotion" (EE) in the family are associated with poor prognosis [2, 24–27].

Assessment and Differential Diagnosis

Bipolar Symptoms and Subtypes

It is very important to have a common language and to use similar terms appropriately between professionals (and with patients and families) when describing, reporting, and monitoring mood changes in youth. According to the DSM-IV, there were four subtypes of BD: Bipolar I, Bipolar II, Cyclothymia and Other Specified/Unspecified Bipolar and Related Disorders (BD-Not Otherwise Specified; NOS) and their diagnostic criteria were the same between adults and children, with the exception of cyclothymia [28]. Of note, subtypes of BD in youth may not be stable over time. In a 4-year follow-up study, 25% of youth with BD-II converted to

bipolar I and 45% of those with BD-NOS converted to BD-I or II [29]. Similar to the offspring studies [2, 23], it is important to note that the rates of ADHD in converters vs. non-converters were not significantly different (61.9% vs. 63.6%, respectively), nor were rates of stimulant use (33.33% vs. 28.6%) or family history of ADHD (42.9% vs. 40.3%), respectively [29].

To date, almost all studies in pediatric BD have employed the Diagnostic and Statistical Manual (DSM)-IV criteria [30]. However, there are important differences to keep in mind regarding the diagnostic criteria of BD in DSM-5 [31]. Key changes regarding criteria for bipolar and related disorders in DSM-5 relative to DSM-IV include: (1) requiring "increased energy or goal-directed activity" as a main symptom criteria for a manic episode (in addition to "elated mood or irritability"); (2) replacing mixed episodes with the new specifier of "mixed features (presence of three or more depressive symptoms during the course of a manic episode); and (3) introducing the new specifier of "anxiety features (presence of anxiety symptoms specifically during the course of an manic episode)" [31].

There are also now several important differences in the diagnostic criteria of DSM-5 relative to the latest International Classification System (ICD-10) [32]. In order to make the bipolar affective disorder diagnosis, in DSM-5 only a single manic episode is required [31], while in ICD-10, at least two mood episodes are required, one of which is manic or mixed (e.g., a mixture or rapid alteration of manic and depressive symptoms), while the other could be a depressive, hypomanic, manic, or mixed [32]. In both DSM-5 and ICD-10, duration criteria for hypomanic and a manic episodes are 4 and 7 days, respectively. Having a history of a hypomanic episode plus at least one major depressive episode is classified as a "bipolar II disorder" in DSM-5, and as an "other bipolar affective disorder" in ICD 10. Finally, the DSM-5 criteria require the presence of functional impairment with these altered moods, while ICD-10 criteria require that mood and activity levels must be "significantly disturbed."

Figure 8.1 shows various presentations of either BD-I or BD-2 based on their combination of manic, hypomanic, and major depressive episodes. BD-I requires presence or history of a manic episode with or without major depressive episode. For BD-I diagnosis, both symptom criteria (three or four symptoms in addition to elation or irritability, respectively) and duration criteria should be met, in addition to the "significant functional impairment or psychosis" during mania. For the duration criteria, a manic episode should last at least seven consecutive days or lead to an inpatient admission anytime during the episode. Mixed presentations of mania in DSM-5 require three or more depressive symptoms during a manic episode, while mixed episodes in DSM-IV required meeting symptom criteria of both mania and major depression during the same mood episode (simultaneously or in rapid sequence).

BD-II is characterized by at least one major depressive episode (for at least 2 weeks with functional impairment) and at least one hypomanic episode (lasting at least four consecutive days). Hypomania is described as the milder form of a manic episode during which the patient has a "distinct change" from the baseline functioning (sometimes patients may appreciate these changes in functioning, for example being able to work on more projects), but should "not have marked functional impairment" during the course of the hypomanic episode.

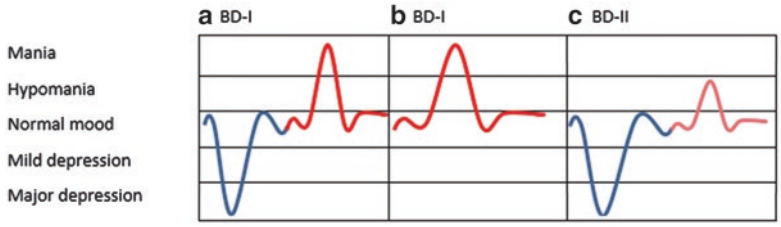


Fig. 8.1 This figure illustrates the minimum combinations of mood episodes required over time for patients with the two main types of bipolar disorders. Figure (**a**) depicts one potential presentation of a patient with bipolar I (BD-I), who has had an early major depressive episode followed by a manic episode. Figure (**b**) depicts another potential presentation of BD-I, in a patient who has had a single episode of mania but no other mood episodes. Figure (**c**) depicts a potential presentation of a bipolar II disorder (BD-II), with at least one major depressive episode, followed by an episode of hypomania with insufficient duration and symptom severity to meet criteria for full manic episode, which would make it convert to a BD-I diagnosis

Cyclothymia is characterized by numerous periods of hypomania alternating with numerous periods of depressive mood or loss of interest or pleasure, which do not meet full criteria for a BD or a major depressive episode. The abnormal mood swings must be present for at least 1 year in youth or for 2 years in adults for the diagnosis.

Other specified BD (a.k.a. BD-NOS) is used when there are features of hypomanic or mixed episodes that do not meet the diagnostic criteria for any of the more specific BD subtypes. Because BD-NOS criteria is vague in DSM, researchers have developed clearer definitions to identify a BD-NOS diagnosis, such as having had at least one episode of hypomanic symptoms for 2 days, or at least four episodes of hypomania lasting 4 h each but being one symptom shy of meeting full symptom criteria [13, 15].

Clinical Presentations and Assessment of Bipolar Disorder

There is consensus in the field that children and adolescents may fulfill the strict DSM criteria for BD-I and II. The American Academy of Child and Adolescent Psychiatry (AACAP) has released the practice parameters for BD and recommended that clinicians should adhere to the DSM, including the duration criteria (requirement of an episodic change in mood lasting at least 4 days for hypomania and 7 days for mania) [33]. Typically, youth are given a BD NOS diagnosis, when they do not meet the duration criteria for a diagnosis of BD-I or BD-II [29].

The assessment of symptoms of mania, hypomania, and depression requires careful probing and in most cases, longitudinal assessment. In addition to the specific manic/hypomanic and depressive symptoms, it is important to ascertain the frequency, intensity, number, and duration (FIND) of the depressive and manic/hypomanic episodes [1, 3]. *Most experts agree that these mood symptoms should exist as a collection of concurrent symptoms and behaviors* (i.e., *"cluster together"), occur episodically, and reflect a change in the child's baseline characteristics. For example, preexisting hyperactivity and inattentiveness should not be counted towards mood symptoms unless there is significant worsening of these symptoms during the mood episode.*

It is also imperative to obtain information from caregivers, teachers, and other providers in order to accurately assess symptoms and potential change in functioning. Children's chronological age, intellectual capabilities, and environmental factors are important when assessing their levels of functional impairment or improvement.

The most widely used interviews in BD studies are the Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children-Present and Lifetime version (K-SADS-PL) (available for free at http://www.wpic.pitt.edu/research under tools and assessments) and the Washington University KSADS (WASH-U-KSADS) [1, 2]. However, these are mainly used for research purposes, require training of the interviewer, and are lengthy and time-consuming. Thus, symptom checklists for BD are also useful, such as Parent General Behavior Inventory (GBI-10; [34]) and the parent Child Mania Rating Scale (CMRS-10; [35]). Dimensional scales such as Child Behavior Checklist (CBCL) [36] and some of its subscales such as dysregulation profile (attention, aggression, and anxiety/depression) and externalizing problems can help identify significant psychopathology in those with ADHD and/or at risk for BD [37], but they are not specific for BD [38].

As expected, because of varying methodologies and conceptualizations of pediatric BD, there is also significant variability in the prevalence of individual manic symptoms among the studies. Similar to the meta-analysis published in 2005 [39], a recent meta-analysis (average age: 11.5 years old, 64% male, mainly Caucasian, 2226 youth in 20 published studies) reported that the most common symptoms across BD subtypes include increased energy, irritability and mood lability, distractibility, and goal directed activity (all approximately 75%) [40]. Grandiosity and hypersexuality were the most specific symptoms, but they were less common (57% and 32%, respectively). There are key issues about making an accurate BD diagnosis in youth, such as the requirement of clearly identified mood episodes (e.g., episodicity), the importance of cardinal symptoms and irritability, subthreshold presentations, bipolar depression, and preschool presentations.

Episodicity

Despite suggestions by some investigators that episodicity is not needed to diagnose pediatric BD, most other investigators and clinicians, as well as the AACAP guidelines [33], recommend that episodicity be required to diagnose BD diagnosis in youth. In fact, it is suggested to first focus on determining the presence of mood episodes based on the DSM manic/hypomanic symptoms, and then to determine how much these DSM manic/hypomanic symptoms occur during an identifiable time frame.

Cardinal Symptoms

Few investigators, aiming to be more specific and avoid misdiagnosing BD in youth, have suggested that elated mood and grandiosity must be present together to diagnose pediatric BD [41]. However, this is not required in DSM and some youth may

have BD without elation and grandiosity. There is considerable heterogeneity among studies in the rates of these symptoms reflecting differences in samples (e.g., origin and age) and methodologies. It is important to consider difficulties in identifying elation and grandiosity, especially in younger children.

Irritability

Irritability is a very common symptom present in BD youth [39] and the absence of any episodes with irritability decreases the likelihood of a BD diagnosis. *On the other hand*, *irritability rarely occurs in manic youth without elation*. Irritability is also part of the other disorders such as Oppositional Defiant, Major Depressive, Generalized Anxiety, and Post-Traumatic Stress Disorders, and is also frequently present in youth with other psychiatric diagnoses such as ADHD and Autism Spectrum Disorders. Thus, *irritability has low specificity for BD, and is analogous to how having fever/pain suggests only suggests that "something is wrong"* [39]. DSM criteria for a manic episode explicitly allows for the presence of irritable mood alone to satisfy the main criterion. However, they require an additional manic symptom to meet the manic episode criteria (e.g., four or more manic symptoms should accompany irritability during the same time frame (clustering) for the mood episode). It is suggested that the severity and duration of irritability (the "super-angry/grouchy/cranky-type" of irritability, but not the "mad/cranky" or oppositional defiant disorder-type irritability) [42] are important clinical factors when assessing BD subjects. Furthermore, in order to be counted as a symptom of manic episode, irritability needs to be episodic even if the child has preexisting irritability (e.g., worsening of irritability during the manic episode when other comorbid disorders exist such as anxiety disorders, ADHD, or ODD) [43].

In contrast to episodic irritability, chronic irritability has recently been conceptualized as the core feature of a new diagnosis category that is included in the DSM-5 (a.k.a. disruptive mood dysregulation disorder (DMDD)). DMDD has previously been referred to as temper dysregulation disorder with dysphoria (TDDD) and severe mood dysregulation (SMD). Chronic irritability has also been associated with attention deficit hyperactivity disorder, oppositional defiant disorder, and major depressive disorder rather than with BD, whereas episodic irritability has been associated with BD and anxiety [44].

Depression

Most youth seen in psychiatric clinics experience their first episode of BD as depression (Birmaher et al. 2007) [2]. Similar to adults, depressive episodes are reported to be the most common manifestation of BD in children and adolescents based on both frequency and duration [15]. The presence of psychosis, family history of BD, and pharmacologically induced mania/hypomania may indicate susceptibility to develop

BD [45–47]. Early identification and treatment of BD depression is of vital importance, because it is associated with increased risk for psychosocial impairment and suicide as compared to unipolar depression [48].

Preschool Presentations

Validity of manic symptoms such as grandiosity and elation have been questioned in preschool children (aged from 3 to 7 year old) given the emotional and cognitive developmental stage of the younger children. Few available studies have suggested that preschool children may have BD diagnosis [49]. Irritability is more common, and grandiosity and elation are also suggested as helpful in preschool children when differentiating BD from other disorders such as major depressive disorder and disruptive behavior disorder (DBD) [49].

Bipolarity and Comorbidities

The presence of the comorbid disorders affects the child's and adolescent's response to treatment and prognosis, indicating the need to identify and treat them effectively. Comorbid disorders, particularly disruptive behavior disorders (DBD; 30–70%), ADHD, (50–80%), and anxiety disorders (30–70%) are very common [1, 3]. Beginning in adolescence, the rate of comorbid substance abuse steadily increases [50, 51]. The prevalence of these disorders will depend on the methods used to diagnose them, the source of the sample studied (e.g., more common in clinical versus community), and the age range of its members, with more ADHD and Oppositional Defiant Disorder (ODD) in children, and more conduct and substance use disorders in adolescents.

Bipolar Disorders and ADHD

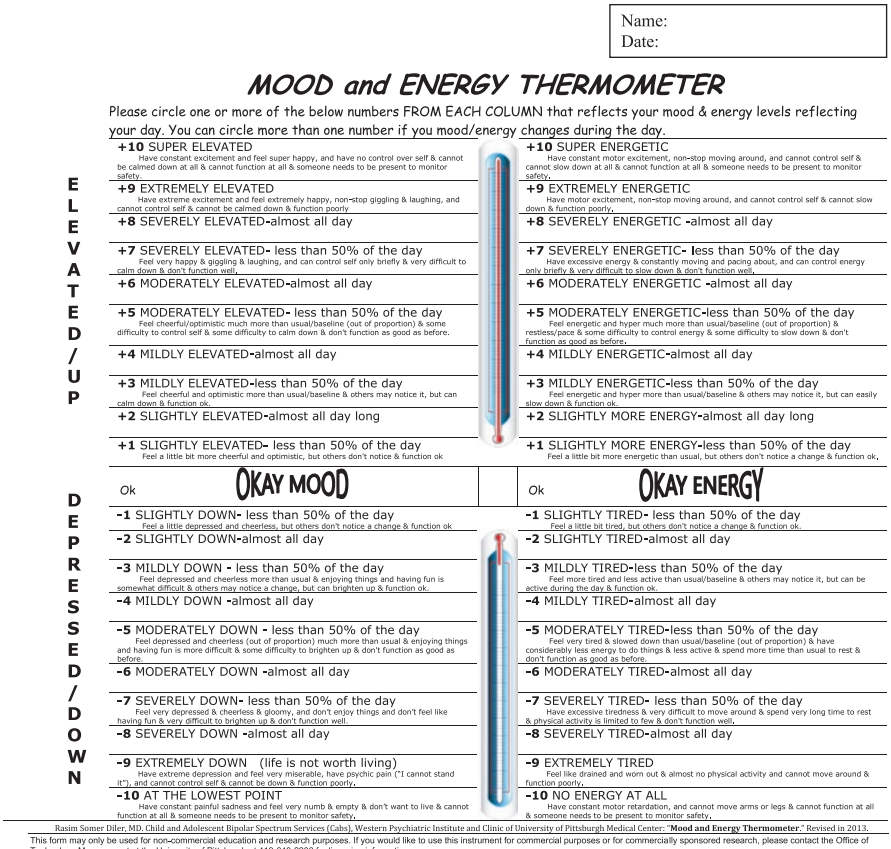
Clinicians must be cautious about attributing symptoms to mania or hypomania unless they show a clear temporal association with the abnormally elevated, expansive and/or irritable mood (plus increased activity/energy levels). *Clinicians should also carefully observe in a child with possible BD whether the symptoms of the comorbid disorder disappear or persist while the suspected child with BD is euthymic, and whether the symptoms associated with BD worsen during the mood episode.* Biederman and colleagues have argued that comorbidity between ADHD and BD cannot be dismissed due to the shared features of the two disorders (e.g., distractibility, motor hyperactivity, and talkativeness) [52]. These investigators have shown that even after removing overlapping diagnostic criteria, children with each condition can still be distinguished. Geller and colleagues have reported that several manic symptoms such as elated mood, grandiosity, hypersexuality, decreased need for sleep, racing thoughts (but not hyperenergetic and distractibility) are substantially and significantly more frequent

among youth with BD relative to youth with ADHD [53]. The following features, when present, were *suggested* to help distinguish the diagnosis of BD in a child with ADHD: (a) the ADHD symptoms appear later in life (e.g., after age 12 years old), (b) the symptoms of ADHD appear abruptly in an otherwise healthy child, (c) the ADHD symptoms previously responded to stimulants but now do not, (d) the ADHD symptoms come and go and tend to occur with mood changes, (e) periods of exaggerated elation, grandiosity, depression, no need for sleep, or inappropriate sexual behaviors, (f) recurrent, severe mood swings, temper outbursts, or rages, (g) hallucinations and/or delusions, (h) a strong family history of BD, particularly if the child is not responding to appropriate ADHD treatments [54].

Longitudinal Course and Differential Diagnosis

The differential diagnosis may require longitudinal rather than a cross-sectional assessment. Mood time-lines or diaries and using school years, birthdays, and holidays as anchors are very helpful in the assessment and monitoring mood symptoms and episodes. The mood time lines (mood monitoring) instruments should be user/child-friendly and can be modified (regarding the child's age, culture, and interests) to increase compliance. In addition to mood, energy levels can be monitored simultaneously for diagnostic clarification. *From this perspective, Dr. Diler has developed a novel self-report mood rating (the "Mood and Energy Thermometer, MET©") for daily assessment and monitoring of mood state in bipolar track adolescents (as shown in* Fig. 8.2*)* [55]. This scale aims to provide a practical way of monitoring complex mood cycles and daily schedule. Given the confusion about several 1 to 10 scales (e.g., a 10 could mean extreme depression or extreme mania or no depression), a common language between the youth, care givers, and providers is necessary. Moreover, many children report their energy levels more accurately than their mood and therefore, energy levels are incorporated in the mood rating. The Mood and Energy Thermometer (MET©) rates mania and increased energy on a 1 to 10 scale and rates depression and tiredness on −1 to −10 scale, and aims to form a common language between patients, families, and clinicians (please see MET© at the end of the chapter). The inclusion of energy level measurements is consistent with the DSM-5, because energy level is now considered as a main symptom criterion for mania. Bipolar or depressed patients are encouraged to rate their mood and energy levels every day on this scale to make them better able to identify and record their mood symptoms, which has significant clinical value for not only treatment but also to detect and prevent a future episode early.

It is important to be aware of various potential trajectories of mood and ADHD symptoms over time. For example, though youth with ADHD may show different trajectories, their hyperactivity and impulsivity may lessen as they age into adolescence and adulthood [56]. Recent studies have shown that BD is mainly characterized by recovery and recurrences, and that ongoing fluctuations in mood symptoms, especially subsyndromal depressive and mixed symptoms, are common [15, 26]. In a sample of youth with BD followed over a 9-year period, a recent study used


Name:
Date:

MOOD and ENERGY THERMOMETER

Please circle one or more of the below numbers FROM EACH COLUMN that reflects your mood & energy levels reflecting your day. You can circle more than one number if you mood/energy changes during the day.

ELEVATED/UP

+10 SUPER ELEVATED
Have constant excitement and feel super happy, and have no control over self & cannot be calmed down at all & cannot function at all & someone needs to be present to monitor safety.

+9 EXTREMELY ELEVATED
Have extreme excitement and feel extremely happy, non-stop giggling & laughing, and cannot control self & cannot be calmed down & function poorly

+8 SEVERELY ELEVATED-almost all day

+7 SEVERELY ELEVATED- less than 50% of the day
Feel very happy & giggling & laughing, and can control self only briefly & very difficult to calm down & don't function well.

+6 MODERATELY ELEVATED-almost all day

+5 MODERATELY ELEVATED- less than 50% of the day
Feel cheerful/optimistic much more than usual/baseline (out of proportion) & some difficulty to control self & some difficulty to calm down & don't function as good as before.

+4 MILDLY ELEVATED-almost all day

+3 MILDLY ELEVATED-less than 50% of the day
Feel cheerful and optimistic more than usual/baseline & others may notice it, but can calm down & function ok.

+2 SLIGHTLY ELEVATED-almost all day long

+1 SLIGHTLY ELEVATED- less than 50% of the day
Feel a little bit more cheerful and optimistic, but others don't notice & function ok

+10 SUPER ENERGETIC
Have constant motor excitement, non-stop moving around, and cannot control self & cannot slow down at all & cannot function at all & someone needs to be present to monitor safety.

+9 EXTREMELY ENERGETIC
Have motor excitement, non-stop moving around, and cannot control self & cannot slow down & function poorly.

+8 SEVERELY ENERGETIC -almost all day

+7 SEVERELY ENERGETIC- less than 50% of the day
Have excessive energy & constantly moving and pacing about, and can control energy only briefly & very difficult to slow down & don't function well.

+6 MODERATELY ENERGETIC -almost all day

+5 MODERATELY ENERGETIC-less than 50% of the day
Feel energetic and hyper much more than usual/baseline (out of proportion) & restless/pace & some difficulty to control energy & some difficulty to slow down & don't function as good as before.

+4 MILDLY ENERGETIC-almost all day

+3 MILDLY ENERGETIC-less than 50% of the day
Feel energetic and hyper more than usual/baseline & others may notice it, but can easily slow down & function ok.

+2 SLIGHTLY MORE ENERGY-almost all day long

+1 SLIGHTLY MORE ENERGY-less than 50% of the day
Feel a little bit more energetic than usual, but others don't notice a change & function ok.

Ok OKAY MOOD

Ok OKAY ENERGY

DEPRESSED/DOWN

-1 SLIGHTLY DOWN- less than 50% of the day
Feel a little depressed and cheerless, but others don't notice a change & function ok

-2 SLIGHTLY DOWN-almost all day

-3 MILDLY DOWN - less than 50% of the day
Feel depressed and cheerless more than usual & enjoying things and having fun is somewhat difficult & others may notice a change, but can brighten up & function ok.

-4 MILDLY DOWN -almost all day

-5 MODERATELY DOWN - less than 50% of the day
Feel depressed and cheerless (out of proportion) much more than usual & enjoying things and having fun is more difficult & some difficulty to brighten up & don't function as good as before.

-6 MODERATELY DOWN -almost all day

-7 SEVERELY DOWN- less than 50% of the day
Feel very depressed & cheerless & gloomy, and don't enjoy things and don't feel like having fun & very difficult to brighten up & don't function well.

-8 SEVERELY DOWN -almost all day

-9 EXTREMELY DOWN (life is not worth living)
Have extreme depression and feel very miserable, have psychic pain ("I cannot stand it"), and cannot control self & cannot be down & function poorly.

-10 AT THE LOWEST POINT
Have constant painful sadness and feel very numb & empty & don't want to live & cannot function at all & someone needs to be present to monitor safety.

-1 SLIGHTLY TIRED- less than 50% of the day
Feel a little bit tired, but others don't notice a change & function ok.

-2 SLIGHTLY TIRED-almost all day

-3 MILDLY TIRED-less than 50% of the day
Feel more tired and less active than usual/baseline & others may notice it, but can be active during the day & function ok.

-4 MILDLY TIRED-almost all day

-5 MODERATELY TIRED-less than 50% of the day
Feel very tired & slowed down than usual/baseline (out of proportion) & have considerably less energy to do things & less active & spend more time than usual to rest & don't function as good as before.

-6 MODERATELY TIRED-almost all day

-7 SEVERELY TIRED- less than 50% of the day
Have excessive tiredness & very difficult to move around & spend very long time to rest & physical activity is limited to few & don't function well.

-8 SEVERELY TIRED-almost all day

-9 EXTREMELY TIRED
Feel like drained and worn out & almost no physical activity and cannot move around & function poorly.

-10 NO ENERGY AT ALL
Have constant motor retardation, and cannot move arms or legs & cannot function at all & someone needs to be present to monitor safety.

Rasim Somer Diler, MD. Child and Adolescent Bipolar Spectrum Services (Cabs), Western Psychiatric Institute and Clinic of University of Pittsburgh Medical Center: "**Mood and Energy Thermometer.**" Revised in 2013.

Fig. 8.2 This figure shows the Mood and Energy Thermometer, which allows patients with potential bipolar disorders to quantify how their levels of mood and energy vary over time

latent growth class analyses to identify the proportions of the overall sample falling into one of four different mood trajectories: (1) 24.0% had a "predominantly euthymic" course; (2) 34.6% had a "moderately euthymic" course, (3) 19.1% had an "ill with improving" course, and (4) 22.3% had a "predominantly ill" course [57]. While a majority of all youth with BD in this study (59%) had at least a somewhat favorable course (groups 1 and 2), each less favorable trajectory group had a higher rate of ADHD (42.1% in "predominantly euthymic" group, 59.1% in "moderately euthymic" group, 64.3% in "ill with improving" group, and 72% in "predominantly ill" group) [57]. However, whether subjects managed to achieve a euthymic mood of ≥18 months during the study, was *not* associated with having ADHD. While many children and adolescents with BD may also have ADHD, most longitudinal studies have not reported an association between ADHD or

stimulant treatment with conversions to mania [23, 29]. In another study, which involved the longitudinal assessment 707 children for manic symptoms, 421 had ADHD alone, 45 had manic-symptoms alone, 117 had both ADHD and manic symptoms, and 124 had neither [58]. Comorbidity (16.5%) was slightly *less* than expected by chance (17.5%), suggesting ADHD was not a risk factor for manic symptoms [58]. The investigators speculated that the increased rates of bipolarity noted in other studies of ADHD samples are likely due to excessive rates of these disorders in child outpatient settings, not because ADHD is a true risk factor for BD [58]. Once again, the co-occurrence of ADHD and BD was associated with significantly worse global functioning, symptom severity, and comorbidities relative than in either condition alone [58]. However, the rates of ADHD were not significantly different between the four different trajectories of manic symptoms during the 24-month follow-up [59].

Treatment

Psychoeducation and support start with the assessment phase and are always indicated at any phases of treatment. Family members and the patient should be educated about the causes, symptoms, course, and different treatments of BD and the risks associated with treatment options [1]. Sleep hygiene and routine are also very important, especially because sleep deprivation leading to worsening of mood symptoms. Ensuring a stable circadian rhythm has a positive effect on physiology and daily functioning. In addition to supportive psychotherapy, specific psychosocial treatment packages for youth with BD target acute affective symptoms and prevention, or delay of recurrences, improvement of adherence to treatment, and management of comorbid conditions. A central feature of all psychosocial treatment models [such as Child and Family Focused Cognitive Behavior Therapy (CFF-CBT) [61], Multi-family Psychoeducation Groups (MFPG) and Individual Family Psychoeducation (IFP) [61], Family Focused Therapy (FFT) specifically for adolescents with BD (FFT-A) [62], Interpersonal and Social Rhythm Therapy (IPSRT) [63], and Dialectical Behavior Therapy (DBT) [64] for pediatric BD] is that they include psychoeducation, problem-solving, and coping skills. Parents are closely engaged in their child's therapy and are referred for treatment themselves if they too have clinically significant symptoms.

Current studies suggest that the most efficacious and fastest way to yield response for acute manic/mixed episodes is with the atypical antipsychotics such as aripiprazole [65], asenapine [66], olanzapine [67], risperidone [68], quetiapine [69], and ziprasidone [70]. Response rates to the atypical antipsychotics in studies of acute manic and mixed episodes among children and adolescents are comparable to those among adults, but youth are more sensitive to these medications' metabolic side effects [71, 72]. The antiepileptic mood stabilizers and lithium can also be helpful, but seem less efficacious in younger patients than in adults. However, most of the studies in children or adolescents have lasted only 8 weeks, possibly an inadequate time to observe a full response to these medications [1].

BD comorbid with ADHD presents unique treatment considerations. The AACAP treatment guidelines advise that symptoms of BD should be stabilized first, and if impairing symptoms of ADHD persist, they may be judiciously treated, with stimulants as first-line [73]. Several studies have suggested that comorbid ADHD may reduce the responsivity of acute mania to pharmacotherapy [74–77], especially in patients who are adolescents or have BD-I [76]. Although longitudinal, naturalistic studies did not find an association between stimulant treatment and emergence of BD [2, 29], there have been concerns about the risk of treatment-emergent mania or mood destabilization with stimulant treatment [78]. For example, 2.5–10% of BD youth treated with stimulants or atomoxetine (adjunctive to mood-stabilizing medication) experience psychiatric adverse events (i.e., hypo/mania and/or suicidality), and discontinuation of stimulants is often associated with an improvement in such events [79–82].

Tricyclic antidepressants have been reported to help improve comorbid ADHD symptoms, but also significantly increase the risk for manic symptoms [83]. In an open-label trial of valproate in 40 youth with BD and ADHD, only 7.5% had a positive response for their ADHD, while 80% had a positive response for their bipolar disorder. In the same study, using a 2-week crossover design with mixed amphetamine salts (MAS; 5 mg twice daily) or placebo, ADHD symptom reduction was significantly greater for MAS compared to placebo [81]. Similarly, a subsequent 4-week, randomized control trial of adjunctive methylphenidate vs. placebo reported significant improvement with methylphenidate [80]. In a randomized trial of adjunctive methylphenidate or placebo added to aripiprazole, ADHD symptoms showed no significant between-group differences, but self-reported depressive symptoms improved more with methylphenidate [79]. An open-treatment study of atomoxetine suggested that it may be effective for comorbid BD and ADHD [82].

Conclusions and Future Directions

Much evidence now shows that youth may manifest classical symptoms of BD; however, many youth do not fulfill the current DSM BD-I or II criteria for such diagnoses, primarily because they lack the required duration of symptoms. Moreover, many youth referred for evaluation for BD have severe mood lability, irritability, inattentiveness, hyperactivity, verbal and/or physical aggression that need careful baseline assessment, and longitudinal follow-up to ascertain whether these symptoms are indeed manifestations of BD (e.g., clustering of manic symptoms, change from baseline and functional impairment). Early recognition and acute and maintenance treatment of BD in children and adolescents is of vital importance to ameliorate ongoing syndromal and subsyndromal symptomatology and to reduce or prevent the serious psychosocial morbidity and risk for suicide. There are growing numbers of imaging [84–86] and neurocognitive [87–90] studies attempting to identify core features of BD that can distinguish it from other disorders including ADHD; however, larger longitudinal studies are needed in BD and ADHD youth for this expanding knowledge about neurobiology/cognition to be implemented into clinical practice for each patient.

The extant pharmacological studies suggest that the atypical antipsychotics are helpful for the acute treatment of manic/mixed symptoms, and stimulants can be added for ADHD *after* mood stabilization. However, studies of longer duration, including maintenance trials to reduce the risk of relapses and recurrences, as well as to examine the effects of development, family environment and psychopathology, and side effects are urgently needed in BD and ADHD youth. Future studies evaluating possible preventative strategies for ADHD and depressed youth at high risk for BD are indicated. In addition, studies to evaluate protective factors (e.g., cognitive development, social and coping skills, environmental factors) are warranted. Genetic and other biological studies, including pharmacogenetic studies that correlate the effects of treatment and biochemical changes on the brain, are also needed to improve precision in matching potentially helpful treatments with the most suitable patients.

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Autism Spectrum and Other Developmental Disorders and ADHD

9

Jennifer L. McLaren, Jonathan D. Lichtenstein, Sarah Y. Bessen, and Fern Baldwin

Prevalence and Morbidity

Symptoms of ADHD (inattention, impulsivity, and hyperactivity) are present in 37–85% of children with ASD [1–3]. The co-occurrence of ASD and ADHD increases with age [4]. Children with ASD more commonly experience the inattentive symptoms of ADHD than the hyperactive or impulsive symptoms, and male children with high functioning ASD are four times more likely to have comorbid ADHD than those without ASD [5]. Historically, ADHD could not be co-diagnosed in a child with ASD. However, this changed in 2013 with the release of DSM-5, which reflected what was being seen in clinical practice: children with ASD also commonly met criteria for ADHD.

For children with ASD, their functional impairment becomes more pronounced when ADHD is present. Children with this comorbidity experience greater impairment in adaptive skills and poorer quality of life [6]. Children with ASD and ADHD struggle with negative mood, mood lability, self-control, and cognitive shifting [4].

It is important for clinicians to evaluate all children being seen for symptoms consistent with ADHD to also screen for symptoms of ASD. It is not uncommon for children with social impairments to be initially diagnosed with ADHD, and the comorbid symptoms of ASD are overlooked. Later some of these children diagnosed with ADHD are then diagnosed with ASD and ADHD. Their diagnosis of ASD is typically delayed by approximately 3 years [7], thus delaying the most appropriate therapeutic interventions and modalities to treat their disorders.

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Etiological Factors

Despite ASD and ADHD being different disorders, they share some etiological factors such as environmental factors, genetic factors, and neural pathways. Several studies suggest a higher level of toxic metal burden in children with either ASD or ADHD compared to typically developing children, and have found a direct correlation between levels of metal burden and severity of symptoms [8–13]. Mercury and lead have been found to be the important causative factors in both ASD and ADHD, respectively. Children can be exposed to mercury prenatally and during development through the consumption of fish. Lead-based paint is the most common source of lead exposure for children.

Multiple studies have noted that there are shared genetic factors of ASD and ADHD [14–16]. Genetic risk factors define individuals for which environmental exposures are most problematic, and gene variants related to oxidation and methylation are risk factors for both ASD and ADHD [13–20]. Current standard of care is to offer children diagnosed with ASD genetic testing such as a DNA probe for Fragile X and a chromosomal microarray.

Studies have also suggested a parallel between brain pathology in ASD and ADHD. Several studies have shown hypoperfusion in ASD and ADHD in the prefrontal cortex [17–20]. In a 2011 review of studies examining the brains of people with both ASD and ADHD, Rommelse and colleagues reported that the frontostriatal system was involved in both disorders, in addition to a smaller corpus callosum and cerebellum volumes [21]. Individuals with these disorders have also demonstrated abnormal neuronal connectivity that contributes to deficits in integration of information and decreases the speed of neuronal communication [22].

Assessment

As already mentioned, ASD and ADHD have a lot in common. They share significant overlap in symptoms, as well as similar types of impairment. Their underlying neurobiological etiology for problematic behaviors may even be shared [23] . Therefore, when the referral question is about a potential diagnosis of ASD or ADHD, the clinician should use a multistep approach for determining the presence, absence, or co-occurrence of these disorders.

A good place to begin in this process is to use rating scales to screen for various symptoms and types of impairment. In ADHD, there are specific scales that are more narrowly focused on symptom presence (e.g., the Vanderbilt rating scale) [24], as well as broad-band rating scales, which survey for a range of psychopathologies (e.g., the Child Behavior Checklist and the Behavior Assessment System for Children) [25]. While both types of questionnaires possess adequate reliability and validity for evidence-based assessment in ADHD [26], the symptom scales are specifically designed for determining whether or not the child has enough symptoms to meet criteria as defined by diagnostic manuals (DSM-IV and DSM-5). Some of these narrow band scales also provide information on disorders that are highly

comorbid with ADHD, such as oppositional defiant disorder (ODD) or conduct disorder (CD) (e.g., Disruptive Behavior Disorders rating scales, DBD) [27]. Broad-band questionnaires are norm-referenced instruments, which allow the clinician to compare a child's ratings to a group of peers similar in age and of the same gender. Furthermore, by offering information about other types of symptoms and areas of dysfunction (emotional disturbance, somatic complaints), broad-band scales provide a broader perspective for the clinician about patients' problems relative to their true peer group.

ASD rating scales have experienced greater difficulty gaining acceptance as established elements of evidence-based assessment, possibly due to the relative lack of scientific investigation dedicated to them. From the work already done, many of the available tools either under- or over-classify individuals with ASD [28]. Furthermore, many of these specific instruments (e.g., Social Responsiveness Scale, Gilliam Scales) [29, 30] have not shown consistent agreement with structured interviews or play-based assessments [31]. Furthermore, while they might help with differentiating children with ASD from typically developing kids, their classification accuracy is greatly reduced for differentiating ASD from the many other diagnoses with social impairment [32]. However, certain broad-band scales have shown promise for discriminating children and adolescents with ASD from those with other disorders having adaptive impairments [33], and can be useful for the school-aged population.

It is particularly important that rating scales be collected from multiple environmental settings, most commonly home and school. For one, ADHD diagnostic criteria require that symptoms be present across multiple settings, and ASD is also a pervasive disorder. The skill deficits must be seen across multiple environments (ADHD) or in all settings (ASD). The perspectives of teachers' can be valuable due to their experience with same-age children. Thus their expectations of what is or is not normal will often be more accurate than parents'. Also, they have many opportunities to observe a child interacting with peers. Furthermore, the clinician must be aware of bias in parent reporting. Research has demonstrated that parental depression can bias parental ratings toward over-reporting their child's psychopathology [34]. Perhaps more so for ASD than ADHD, parental reporting may also be biased by parents' desire for their child to receive additional services from a school or community-service provider. Thus, for multiple reasons, it is crucial that clinicians rely on reports of behavior from different settings and informants.

Use of these ratings scales is an important component of the assessment. However, for both ASD and ADHD, the central focus of assessment should be on the child's impairment. Symptom counts are not hard to amass, but they fall short of explaining or helping a clinician understand the child's impairment. Even broad-band questionnaires may not provide the wealth of information needed to fully understand the child's areas of impairment, which are critical for informing treatment. Careful clinical interviewing is the best tool at the clinician's disposal for determining potential explanations for the child's impairment. Standardized structured interviews for both disorders are the most evidence-based methods in this regard. However, instruments such as the Kiddie Schedule for Affective Disorders

and Schizophrenia (K-SADS) and the Autism Diagnostic Interview, Revised (ADI-R) are time-consuming and require significant training to be administered reliably. Our experiences have taught us that the same goals are achievable without standardized interviews if clinicians have an adequate conceptualization of these disorders and are systematic and meticulous in their questioning.

Clinicians must do a detailed history to create a narrative of the child's development, behavior, family history and relationships, and current functioning. Specific questions can help to color children's developmental story, such as how they responded to emotional reactions in others, when they engaged their parents in their play, if they showed things to their parents to gain their attention, and if their conversations were about being friendly (rather than to obtain something specific). Garnering a sense of the child's nonverbal behavior and communication can also be useful. While social impairments are also very common in ADHD [35], executive dysfunction is generally considered the underlying cause [1] rather than the communication deficit more typical of ASD. Thus, establishing the presence/absence of eye contact, reciprocal smiles, the ability to vary facial expressions to context, and the use gestures to communicate can be helpful to distinguish long-standing traits of autism from the social problems of ADHD.

Another area of overlap that can lead the clinician astray is a parent's report of highly restricted or fixated interests. For example, some parents may find a child's desire to play video games abnormal in focus or intensity. However, many children enjoy video games. This behavior only reaches the level of a restricted interest when the topic of the game may be highly inappropriate for their developmental or intellectual level, or when all opportunities for conversation relate back to that game. If a child chooses not to discuss his or her game during most interactions, this does not amount to a restricted interest. Furthermore, there is a common misunderstanding that a child who can play video games for hours must not have ADHD. This is incorrect, as children with ADHD are able to utilize selective attention, especially for tasks that engage so many senses and sensory systems. This type of knowledge can be helpful psychoeducation for parents regarding their child's strengths and weaknesses.

In certain cases, even after all rating scales have been scored and examined, and the developmental interview has been completed, the question of whether the child has ASD may still remain. Observation of the child's behavior within his or her regular environments (school, home) can be particularly helpful in identifying impairing behaviors, their antecedents, along with the environmental consequences. Such observations allow the clinician to see the child in comparison to real-life peers, but such assessments may not be covered by insurance. In more challenging diagnostic scenarios, the clinician can also use the child's visit to the office to gather clinical observations that may also be helpful. The Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) is a semi-structured, standardized assessment of communication, social interaction, play, and restricted/repetitive behaviors [36]. The ADOS-2 recreates a social environment, in which tasks occur that elicit and/or require particular behaviors on the part of the child in order to allow for a fluent and comfortable interaction. Similar to the structured interviews mentioned earlier,

reliable administration of the ADOS-2 requires training and practice. However, the play-based element of this task offers something unique to the clinical assessment, which can often provide objective, very useful information to help determine the diagnosis in complicated presentations or when reporters are unreliable and/or discrepant.

Despite the promise that patterns of cognitive functioning could provide help with differential diagnosis, neuropsychological assessment is not particularly helpful in differentiating ADHD from ASD. There is no distinctively specific cognitive profile for ASD, and neuropsychological tests lack both sensitivity and specificity in diagnosing ADHD [37, 38]. Both diagnostic groups tend to demonstrate patterns of executive dysfunction, which may serve as a neurocognitive underpinning in their functional impairments. While the field has attempted to develop tests directed at capturing concepts thought to be unique to ASD (such as theory of mind and deficits in recognition of affect), results have not yielded diagnostic utility [39]. Parent and teacher rating scales of the child's adaptive functioning (independent execution of daily living skills) should be another part of the assessment process. Children with ASD and normal intellectual functioning will often present with adaptive deficits [40], whereas this is not typically the case in pure ADHD.

Treatment

Psychosocial Treatments

Psychosocial Interventions for ADHD

There has been no consistent body of evidence to suggest that individual therapy with a child provides benefit for ADHD [41]. Alternative treatment fads such as changes in diet, neurofeedback, and computerized cognitive training have never generalized nor had a lasting impact upon participants [42]. Aerobic physical activity interventions are an area of budding research that shows great promise in reducing ADHD symptoms and impairment [43, 44]. For children with ADHD, the two treatments with the strongest evidence-base are psychostimulant medications and behavioral interventions [41, 45].

In the MTA Group multimodal intervention study, psychostimulant intervention was the most effective treatment of ADHD symptomology. It was proven to be more effective than behavioral intervention alone, and the addition of the behavioral intervention to medication management did not add significant benefit beyond medication alone, at least in ADHD children without a comorbid diagnosis [46]. While these findings were observed over a 14-month period, longer term effectiveness has not been demonstrated [41]. Not surprisingly, for youth with ADHD and any comorbid anxiety disorder, combined treatment of medication and behavioral management yielded the best response [46].

Behavioral treatment for youth with ADHD typically involves parents as the recipients of intervention. In what is sometimes referred to as parent training, these adults are taught how to deconstruct tasks into component parts and provide routine

reinforcement for positive behaviors and negative consequences for undesirable behaviors. The theory is that over time these responses and rules will result in improved self-regulation on the part of the child. Parent training may not only have a positive effect on the child's behavior, but research suggests that it may also reduce parental stress and improve their confidence as parents [47]. Similarly, direct contingency management programs can be enacted in the school setting to improve the child's behavior.

Psychosocial Interventions for ASD

While pharmaceuticals can certainly be of benefit for individuals with ASD, psychosocial and behavioral interventions are the most efficacious treatments in this population. Because intellectual and adaptive functioning in ASD is so wide-ranging, various interventions must span a wide gamut regarding their levels of support. Applied Behavior Analysis (ABA) uses discrete trials for learning and teaching to mastery before moving on to additional concepts, and is most effective for improving functional skills, but not communication abilities. ABA appears to have the strongest effects when delivered intensively and in early intervention programs [48]. Particular programs founded in behavioral management, such as VB-MAPP [49], utilize ABA techniques in aiding individuals to build their language and communication capacity. Assistive technology and the use of other alternative communication methods (e.g., Picture Exchange Communication System) have been found to enhance communicative competence in children with ASD, but further research is needed to determine whether they enhance functional outcomes.

Social skills enhancement are often a key need across the functioning spectrum in ASD. Interventions in this area are often delivered in the school setting, and there is some evidence to suggest that they improve social competence for children with ASD [50]. Social Stories is one such intervention, but the empirical evidence is variable and limited. However, there is preliminary evidence to support that it is a promising intervention for social skills [48]. Another social skills intervention is Marcia Garcia Winner's Social Thinking. This program attempts to alter the individual's social behaviors by changing their thinking. Thus, it differs fundamentally from behavioral treatments, as the mechanism for behavior change is a shift in social cognition, rather than using consequences, reinforcements, and manipulations to the environment to change behavior. There is currently not enough research available examining the Social Thinking curriculum to consider it an evidence-based or empirically supported intervention for ASD [51].

Psychopharmacological Treatment

Overall, children with ASD are more vulnerable to the side effects of psychotropic medications compared to their typically developing peers. This is concerning as communication impairments in children with ASD make it difficult at times to detect the side effects. Thus, when starting a medication, clinicians should carefully

assess symptoms and determine an appropriate target for psychotropic intervention. Medications should be started at low doses and slowly titrated over time based on tolerability and effectiveness. Further, clinicians should make one medication change at a time. In determining positive benefit and side effects, the clinician should rely on both observed behavioral changes and verbal reports, because the child's communication deficits may limit accurate self-reports. It is important for parents to fully understand the side effect profile of the medications so they can relay any observed difficulties. It is also important that parents have realistic expectations of what of medications' potential effects on target symptoms; they may be able to reduce some but not all of the symptoms their child is experiencing.

Table 9.1 provides a summary of the randomized clinical trials of pharmacological treatment studies for children with ASD and ADHD. The following section will further review the medication treatment of ADHD in children with ASD.

Methylphenidate has been studied in children with ASD in a large, double-blind, placebo-controlled, crossover trial [52]. The study found children with ASD experienced a significant decrease in hyperactivity with methylphenidate. However, the response rate for children with ASD treated with methylphenidate was 49% in this study, lower than the usual response rate of 70–80% for children with ADHD treated with the same medication [53]. Also, children with ASD are more likely than typically developing children to experience an increase in irritability secondary to treatment with methylphenidate. Overall, children with ASD typically do better on low to moderate dosing of stimulants and at higher doses are more likely to experience side effects. Since stimulants have a fairly benign side effect profile and with positive benefit noted fairly quickly, they are typically considered a first-line medication for children with ASD and comorbid ADHD.

Regarding the alpha agonists, there have been two small placebo-controlled trials of clonidine in children with ASD which noted improvement in hyperactivity, irritability, and oppositionality [54, 55]. However, clinicians in one of the studies noted no benefit in clonidine over placebo. In a small placebo-controlled trial of guanfacine, children with developmental disabilities that were primarily ASD showed improvement in hyperactivity [56]. In an eight-week, five-site double-blind placebo-controlled fixed-flexible dose study in children with ASD, extended release guanfacine improved hyperactivity and impulsivity at both home and school [57]. Furthermore, parents noted a decrease in inattention and oppositionality and improvements in social skills. Extended release guanfacine was well tolerated in children with ASD with side effect rates being comparable to those seen for typically developing children.

There have been three randomized placebo-controlled trials of atomoxetine in children with ASD and symptoms of ADHD. The largest study suggested that, relative to placebo, atomoxetine was efficacious for the ADHD and behavioral noncompliance. Because this study also compared groups receiving and not receiving a psychosocial treatment, it will be discussed further in the next section [58]. The other two studies of atomoxetine in children with ASD, including a large RCT [59], and a smaller study using a crossover design, reported significant improvements in ADHD symptoms [59, 60]. Relative to children on placebo, those assigned to

Table 9.1 Randomized controlled pharmacological trials in individuals with autism spectrum disorders

Reference	Drug (dose)	Study design	Sample (ages)	Results	Adverse events
Gordon et al. [63]	Clomipramine for 5 weeks (152 ± 56 mg/day) placebo for 5 weeks	2-week, single-blind, placebo washout 10-week, double-blind crossover	*N* = 7 (7–15 y.o.)	Clomipramine > placebo for hyperactivity	1 subject developed prolonged QT interval another subject experienced severe tachycardia
Gordon et al. [62]	Clomipramine for 5 weeks (152 + 56 mg/day) Desipramine for 5 weeks (127 ± 52 mg/day)	2-week, single-blind, placebo washout 10-week, double-blind crossover	*N* = 12 (6–18 y.o.)	Clomipramine and desipramine were both > placebo for hyperactivity, clomipramine was superior to both placebo and desipramine regarding ASD symptoms	1 subject experienced a grand mal seizure on clomipramine. 8 subjects had an increase in irritability, temper outbursts and aggression on desipramine
King et al. [61]	Amantadine hydrochloride (2.5 mg/kg/day for 1 week then 5 mg/kg/day for 2 week vs. placebo for 4 weeks	1-week, single-blind, placebo run-in, 4-week, double-blind, placebo-controlled, parallel groups	*N* = 39 (5–15 y.o.)	Amantadine > placebo for hyperactivity	4 subjects had insomnia and 2 had somnolence
RUPP Autism Network [66]	Risperidone (1.8 ± 0.7 mg/day) for 8 weeks vs. placebo for 8 weeks	8-week double-blind placebo-controlled, parallel groups	*N* = 101 (5–17 y.o.)	Risperidone > placebo for hyperactivity	Subjects on risperidone were more likely to experience weight gain, increased appetite, drooling, fatigue, dizziness, and drowsiness

Reference	Drug (dose)	Study design	Sample (ages)	Results	Adverse events
Shea et al. [67]	Risperidone (1.2 mg/day) for 8 weeks vs. placebo for 8 weeks	8-week double-blind placebo-controlled, parallel groups	*N* = 79 (5–12 y.o.)	Risperidone > placebo for hyperactivity	Subjects on risperidone were more likely to experience weight gain, increased pulse and increased systolic blood pressure
RUPP Autism Network 2005 [52]	Methylphenidate (0.125 mg/kg/day low, 0.25 mg/kg/day medium, and 0.5 mg/kg/day high doses) for 1 week and placebo for 1 week	4-week double-blind placebo-controlled, crossover	*N* = 66 (5–14 y.o.)	Methylphenidate > placebo for hyperactivity	Subjects on methylphenidate were more likely to experience irritability, lower appetite, difficulty falling asleep, and emotional outbursts
Arnold et al. [60]	Atomoxetine (44.2 ± 21.9 mg/day) for 6 weeks vs. placebo for 6 weeks with a 1 week washout	13-week double-blind placebo-controlled crossover	*N* = 16 (5–15 y.o.)	Atomoxetine > placebo for hyperactivity	Subjects on atomoxetine were more likely to experience upset stomach, nausea, vomiting, tiredness/fatigue, and racing heart
Marcus et al. [68]	Aripiprazole (5, 10 or 15 mg/day) vs. placebo for 8 weeks	8-week double-blind placebo-controlled, parallel groups	*N* = 218 (6–17 y.o.)	Aripiprazole > placebo for hyperactivity	Subjects on aripiprazole were more likely to experience sedation, weight gain and EPS
Owen et al. [69]	Aripiprazole (8.5 mg/day) vs. placebo for 8 weeks	8-week double-blind placebo-controlled, parallel groups	*N* = 98 (6–17 y.o.)	Aripiprazole > placebo for hyperactivity	Subjects on aripiprazole more likely to experience weight gain, fatigue and somnolence

(continued)

Table 9.1 (continued)

Reference	Drug (dose)	Study design	Sample (ages)	Results	Adverse events
Harfterkamp et al. [59]	Atomoxetine (1.2 mg/kg/day) vs. placebo for 8 weeks	8-week double-blind placebo-controlled parallel groups	*N* = 97 (6–17 years)	Atomoxetine > placebo for ADHD symptoms	Subjects reported upset stomach, nausea, reduced appetite, fatigue, early morning awakening
Scahill et al. [57]	Guanfacine extended release (range 1–4 mg/day) vs placebo for 8 weeks	8-week five-site double-blind placebo-controlled fixed-flexible dose	*N* = 62 (5–14 y.o.)	Guanfacine extended release > placebo reducing hyperactivity, impulsiveness, and distractibility	Subjects were more likely to experience drowsiness, fatigue, decreased appetite
Handen et al. [58]	Atomoxetine (increased by 0.3 mg/kg/day per week with range 0.3 mg/kg/day −1.8 mg/kg/day) for six weeks and maintained for 4 additional weeks vs placebo	3-site 10 week double-blind 2 × 2 factorial design with atomoxetine and parent training	*N* = 128 (5–14 y.o.)	Atomoxetine, atomoxetine with parent training and placebo with parent training > placebo for ADHD symptoms. Atomoxetine (alone and combined with parent training) > placebo for noncompliance	Subjects on atomoxetine were more likely to experience decreased appetite and abdominal pain (significant) (also nonsignificantly greater concerns with sleep onset. Atomoxetine appeared to have better side effects profile than psychostimulants in ASD subjects

atomoxetine in these trials more often had side effects such as irritability, insomnia, fatigue, abdominal pain, or nausea, suggesting the potential need for lower starting doses and more gradual dose titrations of atomoxetine in ASD patients [59, 60]. One group's study suggested that atomoxetine with such dosing modifications was better tolerated than stimulants in such children [58].

Other potential pharmacotherapies have been studied with regard to the treatment of ASD and ADHD. First, a placebo-controlled study of amantadine in 39 children with ASD showed statistically significant improvement in clinician rated symptoms of hyperactivity and improvement in parent rated hyperactivity. However, the parent rated symptoms did not reach statistical significance [61]. Second, in two small placebo-controlled studies of clomipramine there was a statistically significant reduction in hyperactivity [62, 63], and clomipramine was well tolerated. However, open label studies of clomipramine have suggested more significant side effects in children such as constipation, increased aggression, irritability, and urinary retention that required catheterization [64, 65]. Finally, risperidone and aripiprazole have US Food and Drug Administration (FDA) indications for irritability associated with ASD, and have had large effect sizes for this indication [66–69]. Risperidone and aripiprazole have also been shown to significantly reduce symptoms of hyperactivity in children with ASD. However, second generation antipsychotics have significant side effects such as weight gain, diabetes mellitus Type II, hyperlipidemia, and tardive dyskinesia. Given their less favorable side effect profiles, these medications should be used only when trials of other medications have failed, or when a child with ASD has significant irritability (temper tantrums, self-injury, and aggression).

Combination Treatment

The largest study of any medication with or without a psychosocial treatment involved atomoxetine [58]. This was a 10-week, 3-site, double-blind trial involving a 2 × 2 factorial design. A total of 128 subjects 5–14 years old with both ADHD and ASD were randomized to either atomoxetine or placebo, and to either get or not get parent training. Such parent training consisted of weekly, individual sessions covering topics such as prevention of behavioral problems, reinforcement, time outs, and planned ignoring, along with educational materials, role playing, weekly homework assignments, and regular monitoring of problematic behaviors. Parents noted a decrease in ADHD symptoms in all three active treatment groups (e.g., atomoxetine alone, atomoxetine with parent training, placebo with parent training) relative to the group only on placebo. The two groups assigned to atomoxetine (alone or with parent training) had better responses regarding noncompliant behaviors than the two groups on placebo (with or without parent training). Parent training did not enhance ADHD response in subjects also assigned to atomoxetine, but was superior to placebo, suggesting it may be a reasonable alternative for patients with ASD or their families who are unwilling to use medication [58].

Future Directions

In the area of assessment, gold standard work requires the use of tools that are time-consuming to administer and require significant training to become reliable. Enhanced tools that save time, while not sacrificing classification accuracy are needed. In general, while clinicians have many ratings scales with good reliability, validity, sensitivity, and specificity at their disposal for ADHD, this is not the case in ASD. Further study of rating scales that can correctly classify ASD would fill a current void in the literature and be of great benefit to clinicians. In terms of treatment, more randomized clinical trials of psychopharmacologic and combination treatment studies of children with ASD and ADHD are needed to inform care. Finally, other evidence-based, empirically supported social skills interventions for ASD are critically needed.

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Moodiness in Patients with ADHD and Substance Use Disorders

10

Oscar G. Bukstein and Aaron Roberto

ADHD, SUD, and Moodiness: Prevalence, Morbidity, and Comorbidity

Research has established that ADHD is relatively common in individuals with SUDs, in both clinical and community populations. In a report on data from 4930 adolescents and 1956 adults admitted for substance abuse treatment in multisite studies, Chan and colleagues [1] found that approximately half of the adolescents under 15 and about a third of adults met diagnostic criteria for ADHD. The National Comorbidity Survey-Replication found that 15.2% of individuals with adult ADHD met DSM-IV criteria for a SUD, compared with 5.6% without ADHD, suggesting that having ADHD as an adult more than doubles the risk of having a SUD [2]. Conversely, a meta-analysis estimated the prevalence of ADHD in individuals with SUDs to be 19–27%, depending on the preferred substance [3]. In another study of treatment-seeking adults with SUDs, the prevalence of adult ADHD was even higher at 46% [4, 5].

As reported by the National Institute of Drug Abuse, multiple types of abused substances are associated with mood symptoms, which may include irritability, anger, aggression, agitation, depression, anxiety, or even psychosis, and can vary depending on whether the person is experiencing intoxication or withdrawal [6]. Comorbid ADHD and SUD in childhood are also associated with increases in other psychiatric disorders, including externalizing conduct and oppositional defiant disorders, and internalizing depressive and anxiety disorders [7]. Having comorbid ADHD as a child is associated with earlier substance use, abuse, and dependency, and more severe substance use and functional impairment [8], as well as a poorer response to

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SUD treatment [9]. Two meta-analyses of longitudinal studies regarding the course of SUD and ADHD have reported that subjects with childhood ADHD are more likely to develop SUDs in late adolescence or early adulthood [10, 11]. Patients with ADHD that persists into adulthood are more likely to develop SUDs than those with nonpersistent or no history of ADHD [12–14]. After first use of various substances in early adolescence, individuals with ADHD are more likely than those without ADHD to develop full alcohol, tobacco, and cannabis use disorders by adulthood [15]. Similarly, ADHD is a risk factor in young adult males for continuing, problematic use of alcohol, tobacco, and cannabis further into adulthood [16].

Similar to the increased risk of substance use disorders in adolescents and adults with ADHD, studies have noted an increased risk for major depressive disorder (MDD) and bipolar disorder (BPD) in those with ADHD as well as an increase in MDD and BPD in individuals with SUDs [17, 18]. Not surprisingly, depressive and anxiety disorders are also commonly associated with both ADHD and SUD [19, 20].

Etiological Factors

The relationship between ADHD, mood disorders, and SUDs is encapsulated in the notion of neurobehavioral disinhibition. Neurobehavioral disinhibition is a cluster of emotional tendencies, behavioral symptoms, and problems in cognitive function, related to inadequate neurological development of self-regulation [21, 22]. Tarter and colleagues have considered neurobehavioral disinhibition a latent trait, based on composite scores of behavioral dysregulation and executive dysfunction, associated with deficits in executive functioning, behavioral control, and emotional modulation and regulation [21]. Prominent deficits in behavioral control and executive functioning are noted in ADHD, and prominent mood disturbances are reflected by the presence of poor emotion modulation or affect/mood dysregulation.

Neurobehavioral disinhibition is also an important factor in the development of SUDs. Behavioral dysregulation is noted clinically in the form of irritability, tantrums, aggression, and other impulsive behaviors and can be considered part of a larger construct of dysregulation that includes both behavioral and mood symptoms. Irritability, tantrums and aggression can be symptoms of either intoxication or withdrawal from various drugs of abuse or alcohol [6]. Behavioral and mood dysregulation appear to be prominent risk factors for earlier use of substances, a quicker progression to developing full SUDs in adolescents, and the persistence of SUDs into adulthood [21].

Assessment and Differential Diagnosis of Mood Issues in ADHD and SUD

Screening for SUDs and alcohol use disorders in patients with ADHD is important because they are common, have negative effects on the ADHD and other comorbid disorders, and worsen treatment responses and long-term prognosis. Table 10.1 lists

Table 10.1 Useful drug and alcohol screening tools

Screening tool	Self-administered	Clinician-administered
Alcohol Use Disorders Identification Test-(AUDIT)—C and full [23]	X	X
NIDA Drug Use Screening Tool and Quick Screen [24]	X	X
Opioid Risk Tool [25]	X	
Drug Abuse Screening Tool (DAST) [26]	X	
NIDA-Modified ASSIST (APA) Pre- and general screen [27]	X	

some commonly used questionnaires that screen for SUDs for both adolescent and adult age groups [23–27]. If drug or alcohol disorders are suggested, a more comprehensive evaluation is needed regarding the course of other psychiatric disorders in relationship to the SUD, severity, family history, and treatment response. Among patients with SUDs, additional screening for ADHD, mood, anxiety, and other psychiatric disorders is also critical, given the frequent co-occurrence of such disorders with SUDs.

When the clinician strongly suspects a SUD but the patient denies one, urine drug screens may be helpful, because they are fast, noninvasive, easily collected, and offer a longer window of detection than blood samples do [28]. It is important when using such drug screens to be aware of the drugs they screen (e.g., the standard Federal Workplace urine test screens only for marijuana, cocaine, opiates, phencyclidine, and methamphetamines). It is also important to keep in mind how long after a person's use can various drugs be detected, and what are the potential sources of false positive screens. Such information is available on-line [29]. Clinicians must also be mindful of the dramatic and illicit steps patients may sometimes take to avoid having a positive drug screen [28]. Urine drug screens can be used over time to check whether patients are continuing to abstain from drug use during treatment, and favorable results can be rewarded using contingency management to reinforce staying "clean" [30].

In the vast majority of cases, both conduct disorder and ADHD occur before SUD. Review of past records (psychological/psychiatric evaluations and/or report cards/school records) as well as information from other informants (parents and teachers) is usually needed, because adolescents and adults with ADHD may have poor insight into its associated symptoms and impairment. Youth should be seen separately for a confidential interview. The attitude of the clinician should be flexible, empathic, and nonjudgmental in order to engage the patient in the assessment process and to encourage a more valid estimate from the patient of substance use and abuse. However, caution should be taken in interviewing patients with SUDs, who may falsely report their symptoms and history of ADHD, and insist on getting treatment with a more abusable, short-acting stimulant. Accurate self-reports may be particularly hard to come by when patients have a strong incentive to avoid reporting deviant behaviors (e.g., in a forensic setting), or to respond in a more

socially desirable way (e.g., in a clinical setting). Such behaviors highlight the need for multiple responsible adults to weigh in on the patient's history of ADHD symptoms if possible. The clinician can request additional collateral evidence of ADHD symptoms and impairment, including old report cards with teacher comments, and reports of childhood symptoms from parents or other relatives. *The clinician's key task is to determine whether there is sufficient evidence to support the DSM-5 criteria for ADHD, including symptoms sufficient in number and impairment to be evident before the age of 12, and that preceded the onset of the SUD behaviors*. Chapter 11 covers specific rating scales and additional strategies for properly evaluating childhood onsets of ADHD symptoms in adults.

Many factors lead to an underdiagnosis of ADHD. Clinicians may not ask about ADHD (having limited knowledge or insight about how it is manifested through the life-span). Adolescent or adult patients may be unable to accurately recall childhood ADHD symptoms. Patients and clinicians may incorrectly assume that having other psychiatric disorders (e.g., hypomania, depression) precludes a diagnosis of ADHD. Clinicians less experienced in assessing ADHD may have trouble remembering the 18 DSM-5 symptoms, and how to screen for them most accurately in adults. They also may not recognize that hyperactive and impulsive symptoms of ADHD often lessen with age, and that inattentive symptoms may become less obvious or better compensated for in adolescents or adults with ADHD. It is especially critical to keep in mind the frequent comorbidity of ADHD and SUDs, even in community samples. A final challenge in co-diagnosing these two disorders is that they share many overlapping symptoms. For optimal assessment, the clinician should collect a detailed substance use history, and be particularly vigilant when certain risk factors are present, beyond the patient's age as an adolescent or young adult, including having a comorbid conduct disorder or antisocial personality disorder, or having a family history of substance use. Finally, the clinician must decide whether the observed symptoms and impairment are related to the ADHD, a SUD, another comorbid disorder, or even withdrawal symptoms from tobacco or other substances.

Treating Mood Problems in Patients with SUD, Other Comorbidities, and ADHD

For patients with multiple disorders and several potential treatment options, the clinician must decide which interventions to use, for which target problems, and in what order. For example, in the case of comorbid ADHD and SUD, what disorder should be treated first? If a mood disorder is present, where do interventions fit in relative to SUD and ADHD? Despite increasing efforts to provide concurrent treatment of SUD-psychiatric comorbidity, a specific sequence of the treatment modalities is almost always necessary. *The general rule is to first treat the disorder that will have the most immediate effect on outcome(s). For ADHD-SUD comorbidity, this will almost always be the SUDs, and control of substance use should be an immediate goal*. However, when severe mood disorders are also present (e.g., with suicidality, psychosis, mania), these will also need immediate treatment.

Once the clinician has achieved some stabilization in substance use and any comorbid mood disorder, he or she can then shift attention to diagnosing and treating the ADHD. However, it can be difficult to make a diagnosis of ADHD and to monitor changes in ADHD symptoms when residual symptoms of drug and alcohol use disorders or mood disorders remain. *Another general rule is to avoid starting ADHD treatment, until any changes related to ADHD treatment can be accurately discerned.* As we consider interventions for ADHD and other comorbidities, we must consider how untreated ADHD may impact the ability of patients with SUDs and/or mood disorders to respond to the specific treatments targeting those disorders. Whether treated ADHD leads to better treatment outcomes for the SUDs or mood disorders remains an unanswered empirical question.

Psychosocial Treatments for SUD and Comorbid Disorders

As medications alone are seldom sufficient to treat SUD in a patient with comorbid ADHD and SUD, the clinician must generally use one or more evidence-based psychosocial interventions. Some of these include *cognitive behavioral therapy (CBT)*, *motivational interviewing*, *contingency management*, *family therapy*, *12-step approaches*, or even *combination approaches* using two or more of the above. Interventions for SUDs, irrespective of comorbidity, provide a good platform for the treatment of adolescents and adults with coexisting SUD and ADHD. Evidence-based treatments (EBTs) for SUDs can be categorized by several target domains, making their selection by clinicians dependent upon the patient's specific situation, such as living with family or alone, the presence of high vs. low motivation, and the presence of specific skills for dealing with urges to use, and to avoid or to deal with various cues that have prompted their substance use. EBTs *for adolescents* include motivational interviewing [24, 31, 32], family-based interventions [33–38], cognitive-behavioral therapy (CBT) [35, 36], and contingency management [30, 39]. *EBTs for adults* include CBT [40, 41], contingency management [30], 12-step programs [42], and combination interventions [43].

Brief interventions for SUDs typically consist of one to four sessions [44, 45]. They can be stand-alone interventions or be delivered before starting other EBTs such as CBT or family approaches. Brief interventions for SUDs usually include a motivational component, which may emphasize increasing patients' motivation to abstain or lessen their substance use, or participate in a more intensive level of treatment [31, 32].

A knowledge of motivational interviewing and its constituent principles and techniques is critical for administering brief interventions. Motivational interviewing and motivational enhancement therapy attempt to increase the individual's intrinsic motivation to change substance use behaviors [31, 32]. Contingency management interventions and/or motivational incentives involve giving patients tangible rewards to reinforce positive behaviors such as abstinence or attendance at treatment sessions [39]. Voucher-based reinforcement augments other community-based treatments by offering patients a voucher for every drug-free urine sample and/or for attendance at treatment sessions [30]. These vouchers can then be

exchanged for food items, movie passes, and other goods and services that are consistent with a drug-free lifestyle.

The best known skill-based intervention for SUDs is CBT [40, 41, 46]. Patients getting CBT are assisted in identifying and correcting problematic behaviors through the application of various skills. These skills can be used to stop substance abuse, to address other co-occurring problems such as mood and anxiety disorders, and to develop effective coping strategies. Specific techniques include exploring the positive and negative consequences of continued drug use, self-monitoring to recognize cues and cravings early, identifying situations that may increase the risk for use, and developing strategies to cope with cravings and to avoid high-risk situations.

Family-based interventions include several EBTs for adolescents, such as Brief Strategic Family Therapy [47], Family Support Network [48], Functional Family Therapy [49], Multi-Dimensional Family Therapy [37], and Multi-Systemic Therapy (MST) [38]. The focus of such family-based interventions is to improve parent-adolescent communication and parent management skills, such as negotiating rules and consequences.

Some treatment strategies combine multiple EBT modalities. For example, motivational interviewing techniques may increase the patient's motivation to seek treatment in a CBT-oriented group that also uses contingency management to reinforce group attendance and abstinence. Multi-systemic therapy combines a variety of individual interventions within the context of intensive family-based therapy. Similarly, the Matrix Model, developed for the treatment of stimulant use disorder, includes elements of motivational interviewing, relapse prevention, family and group therapies, drug education, and self-help participation.

While peer support groups such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) do not have the evidence base of the interventions above [50], AA and NA are widely used and endorsed by patients, general clinicians, and experts in treatment and research related to SUDs [51]. AA and NA are similar 12-step programs in which individuals wanting to recover from alcohol or drug use problems can participate, at no cost to themselves, in a support group with others having the same problems. While such groups are not led by trained clinicians, they offer patients with SUDs the opportunity to interact with others who have similar substance-related challenges and who are also working to get better. Key therapeutic aspects of AA and NA are the ability to share their experiences in a confidential, nonjudgmental way, and to benefit from both receiving and giving peer support as often as multiple times a week [51]. A 12-step Facilitation Therapy has been developed to help clinicians more effectively motivate their patients with such problems to participate in AA, NA, or other support groups [52].

Medication Treatment for ADHD in Patients with SUDs

Both adolescents and adults with ADHD report improvements with ADHD medication treatment, using either stimulants or non-stimulants [53, 54]. Two questions have impeded the adoption of medication for SUD-ADHD comorbidity. First, do

any medications work for patients with this comorbidity? Second, are such medications (including stimulants) safe to use in such patients in terms of risks for adverse events, illicit use, and diversion?

The literature on medication treatment for ADHD + SUD is mixed. For the most part, controlled clinical trials suggest limited, if any, effects on either substance use or ADHD variables when using stimulants or atomoxetine [55–58]. More recently, in a 12-week multisite randomized controlled trial (RCT) in briefly abstinent alcoholic adults, atomoxetine reduced ADHD, alcohol craving scores, and heavy drinking, but not rates of relapse [59]. In a 13-week, 3-arm RCT (placebo vs. mixed amphetamine salts extended-release at 60 mg or 80 mg) in subjects with ADHD and cocaine use disorders, Levin and associates [60] reported differences between placebo and active medication in the percentage of participants achieving at least a 30% reduction in ADHD symptom severity during the medication maintenance phase (weeks 2–13). They also noted differences in the number of cocaine-negative weeks (both by self-report, and by clean weekly urine screens). The percentage of participants achieving abstinence for the last 3 weeks was also superior in the active medication group.

Riggs and colleagues [61] conducted a 16-week, multisite RCT of 300 adolescents with mixed SUD and ADHD receiving CBT for SUD, and either osmotic release oral system-methylphenidate (OROS MPH) or placebo. They reported significant improvements in symptoms for both treatment arms based on the primary outcome measures of self-reported ADHD symptoms and substance use, but no group differences regarding improvement in ADHD or SUD. However, in a secondary outcome, they noted a greater improvement in parent reports of ADHD symptoms in the group on OROS-MPH.

What about the risk with stimulants of potential diversion? Pharmacotherapy studies have reported side effects similar to studies of non-substance abusing patients with ADHD and no discernible misuse or abuse, suggesting relatively low abuse liability [55]. Even so, concerns about misuse, abuse, and potential diversion of stimulants are realistic. Stimulants are controlled substances that increase dopamine in the brain's reward centers that are also involved in the development of addictive behaviors [62]. As such, stimulants are sometimes used recreationally and abused [63].

Recreational use and performance enhancement are both potential motivations for such nonmedical misuse. As a result of nonmedical misuse, diversion may be an issue. For example, in college students, stimulants appear to be the most commonly diverted medication. Among students with stimulant prescriptions, 62% report having shared or sold their medication at least once [64]. Studies report that as many as 43% of college students have misused stimulant medication in their lifetime [65], and 22% of high school students report misuse of their controlled medications [66]. A number of these studies have asked students how they obtained stimulant medications for misuse. Peers are overwhelmingly the most common source for obtaining stimulants. For example, DeSantis et al. [67] found that 91% of the undergraduates interviewed obtained stimulant medications from friends or significant others. Students with stimulant prescriptions have high rate of misuse themselves [68], but

they are also the most common source from which other students obtain stimulant medication to misuse [69].

A question related to concerns about substance abuse in individuals with ADHD is whether stimulants prescribed to target ADHD in children and adolescents promote or protect against the eventual development of SUDs [70]? Results of more recent meta-analyses have suggested that treatment of ADHD with stimulants did not influence substance use outcomes in either direction [71]. While very little of the existent literature supports a negative effect of stimulants (i.e., increasing substance use of SUDs in later adolescence or adulthood), some studies do support a positive effect (i.e., a decrease level of substance use of SUDs during or following stimulant treatment) [55]. Hence, the fear of eventual SUDs should not deter clinicians from using stimulants to treat their patients with ADHD when indicated.

In selecting an appropriate agent for patients with comorbid ADHD and SUD, there are a number of considerations. If stimulants are being considered, the physician should consider several questions. Is the patient reliable, and can family members or close non-substance-abusing friends be involved in the treatment plan? If not, then non-stimulant options should be strongly considered. Next, have the patient/family been adequately informed of potential risks involved in using stimulants? Finally, the history and motivations of the patient's substance use are also a critical consideration. While past use with an established period of abstinence and/or ongoing SUD treatment prompts less concern, more recent problems with a history of stimulant or amphetamine abuse may preclude stimulant treatment. For youth who have "misused" stimulants, the physician should obviously consider their stated reasons for use ("to get work done" versus to "to get high").

A staged approach to pharmacotherapy in adolescent or adult patients with ADHD and SUD, based largely on an assessment of the risk or severity of SUDs, maybe useful in making clinical decisions about pharmacotherapy [36]. *Low-risk patients* would include those with no history of an actual SUD but have some risk status due to some level of substance use (alcohol, marijuana), and/or a family history of SUD. For low-risk patients, the physician may use stimulants as first line agents and augment this with brief office interventions focusing on prevention skills and resources, discussion of the risks and boundaries of substance use, and warnings regarding diversion. Families should be involved whenever possible. The physician should monitor both the response of ADHD symptoms to the medications but also patterns of substance use or abuse. *Moderate-risk patients* are those with an active alcohol or marijuana use disorder, but no other SUD (e.g., opiates, cocaine, or other drugs). For these patients, depending on the specific circumstances, the physician may use either stimulants or non-stimulants as first line agents, but should augment pharmacotherapy with the same psychosocial approaches as the low-risk patient, and also consider specific outpatient SUD interventions such as counseling, self-help groups, and family therapy, as indicated. Toxicology (e.g., urine drug screens) should be considered to verify continued abstinence from drugs of abuse. *High-risk patients* are those with current or prior cocaine, stimulant, opiate, or prescription SUD. For high-risk patients, the physician should choose non-stimulant options such as atomoxetine or bupropion as first line agents, using stimulants only

Table 10.2. Prescribing precautions in patients with ADHD and substance use disorders

• Use non-stimulant medications if possible
• Limit and keep track of pills
• Obtain urine toxicology screens regularly
• Frequent patient visits
• Use of long-acting preparations (vs. short-acting)
• Emphasis to take medications regularly and not on a PRN basis
• Discussion with patient about safe storage and to avoid advertising their potentially abusable medications to peers

under careful supervision and monitoring. Levels of psychosocial treatment may vary across residential, intensive outpatient and outpatient settings and may include the psychosocial modalities mentioned above. The physician may delay ADHD pharmacotherapy until the SUD is in full or at least partial remission for weeks to months. For high-risk patients, careful monitoring and toxicology is especially imperative. When stimulants are indicated, long-acting stimulants are preferred for all risk groups to decrease the risk of abuse or diversion. Such formulations lack the rapid absorption and rapid elimination characteristic of substances likely to be abused [70, 72–74]. Most research shows that the shorter-acting preparations of these medications are misused more frequently than the extended-release stimulants [55, 75].

Particularly with patients having SUDs, there a number of safety issues requiring physician oversight and monitoring. These issues include the need for careful screening of the patient's cardiovascular risk, the medication's overdose potential, the potential use of prescribed medications with other stimulants, and interactions with other non-stimulant drugs. Psychoeducation is critical to help make sure patients are aware of contraindications and precautions related to such prescribed medications.

The physician or other clinician can monitor for red flags that indicate a high suspicion for diversion or misuse, including evidence of continued substance abuse or dependence, medication-related emergencies, demands for short- or immediate-release stimulant compounds, repeated discordant pill counts, lost prescriptions, continuously escalating doses, infrequent prescription use, cardiovascular symptoms (e.g., palpitations, syncope, shortness of breath), and/or symptoms of psychosis or mania. To manage or prevent problems related to diversion or misuse, the physician should carefully monitor compliance and apply necessary psychoeducation whenever possible when prescribing medications with abuse potential (see Table 10.2).

Case One: John

John is a 16.5-year-old male who presents for a regular checkup at his primary care physician's office. John's doctor had recently begun to administer a screening program for common psychiatric disorders seen in adolescents. A Patient

Health Questionnaire (PHQ-9) score shows a score of 21, which is in the severe range for depression, though no suicidal ideations or behaviors are endorsed. John also endorses a score of 4 on the CRAFFT screen for substance use problems. When looking at John's medical record, his PCP finds that John was diagnosed and treated for ADHD when he was in grade school but stopped successful stimulant treatment in middle school when he began to rebel and refuse medication. His mother reports his academic progress began to deteriorate, and he began to "hang around" a deviant peer group. Mother suspects that John is smoking marijuana. He is failing most classes in school and was recently arrested on charges of having drug paraphernalia at school. Discussion with a behavioral health therapist working out of the PCP's office and using a motivational interviewing style suggests that John feels "stuck and "numb." He smokes marijuana almost daily but does not drink alcohol or use other substances. He reports depressed mood about 80% of the time, with low energy, periods and periods of hopelessness and erratic sleep with periods of hypersomnia alternating with difficulty falling and staying asleep. He does smoke cigarettes—about 5–10 per day.

More than a few times in the past, he has recognized that he "heading in the wrong direction" but low energy, his impulsive behavior and difficulty staying on task have prevented him from succeeding in turning around. The results of a comprehensive psychiatric assessment reveal DSM-5 diagnoses of Major Depressive Disorder; ADHD, predominately inattentive type; and Cannabis use Disorder, severe. The PCP's office refers John to a community SUD outpatient program, which starts out a bit rocky due to John's impulsivity and inattention. The physician feels that the depression, though quite symptomatic on the PHQ-9, seems overreported relative to the John's interview, and he denies suicidal ideations or behaviors. The physician focuses on the ADHD-related impairment. Following an unsuccessful trial of atomoxetine, the physician starts John on a long-acting methylphenidate preparation, which, once titrated to an effective dose, is well tolerated. Six weeks after the visit described above, John reports that he is doing better in school and at the SUD treatment program.

Comments: In this case, John's physician has the advantage of a paper trail with a well-documented history of ADHD diagnosed and treated as a child. Alternatively, he could request parents to be additional informants about the patient's symptoms and behavior and fill out a standardized ADHD rating scale. In addition, the presence of a depressive disorder justifies the physician's regular screening of risk factors for depression and SUDs, since they often overlap. The patient's main concern is his depression, and the regular follow up for that provides an opportunity for the clinician to improve John's motivation for treatment of not only the depression but also the SUDs that may be contributing to it. The physician plays it safe by first trying a non-stimulant medication, but eventually uses a long-acting stimulant to achieve improvement in psychosocial functioning. The improvement in functioning appears to have positive results on John's mood, such that use of an antidepressant becomes unnecessary.

Conclusion and Next Steps

SUDs are a common comorbidity of both adolescent and adult ADHD. Clinicians should routinely screen for SUDs in their patients with ADHD and moodiness, and conversely screen for ADHD and other mood disorders in their patients with SUDs, then treat or refer as appropriate. Optimal treatment for SUDs and ADHD requires a multi-modal approach, including evidence-based psychotherapies for both disorders, and possible medication management for the ADHD. Generally, initiating psychosocial treatments of the SUDs is a top priority, as well as treating severe comorbid mood disorders, before treating the ADHD. A review of the substance use history, particularly regarding abuse, misuse, and/or diversion of stimulants, is needed to assess the overall risk level of prescribing a stimulant for such a patient's ADHD. In patients at greater risk of misusing a prescribed stimulant, the clinician can treat the ADHD with a long-acting stimulant and close monitoring, or with a non-stimulant. Future research is needed regarding how ADHD and other comorbid disorders impact the course and treatment of individuals with SUDs, and vice versa. Psychosocial and pharmacological treatments having empirical support for ADHD *or* SUDs that occur separately need further study regarding their efficacy for patients with ADHD *and* SUDs. Other lingering questions are whether such treatments are efficacious for the more complex presentations (of mood disorders, ADHD, and SUDs), or can prevent such complex presentations from occurring.

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Moody Adults with ADHD

11

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Background, Prevalence, and Morbidity

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neuropsychiatric disorder characterized by symptoms of inattention, hyperactivity, and impulsivity [1, 2]. ADHD is prevalent in 6–8% of school-age children [3] with persistence rates as high as 75% into adolescence [4] and 50–60% into adulthood [5, 6], such that approximately 4–5% of the American adults have ADHD [5, 7]. Adult ADHD is typically accompanied by impaired executive function (e.g., difficulties with planning, organization, time management, task completion, and remembering), as well as restlessness, talkativeness, impatience, and impulsivity. These symptoms are distressing and cause clinically significant impairment across multiple domains of function, including difficulties with employment, social interactions, and education,

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along with financial and legal difficulties [8–11]. At the US population level, workplace effects of ADHD are estimated at 120 million in lost workdays and $19.5 billion in lost human capital per year [5].

ADHD has been recognized for over a century [12], while co-occurring emotional dysregulation (ED) has only been recognized for the last 3–4 decades. Symptoms of ED include rapidly shifting affective disturbances, impulsivity, mood lability, and emotional over-reactivity [13, 14]. In adult ADHD, such symptoms have also been called mood dysregulation, emotional impairment, deficits of emotional control, or deficient emotional self-regulation. In the current chapter, ED will be used rather than these other terms to avoid confusion.

Studies of adults have suggested ADHD often occurs with ED symptoms. For example, past research has demonstrated that mood instability, irritability, volatility, and low frustration tolerance are common in adult ADHD, and that 53–86% of adults with ADHD have clinically significant levels of ED [10, 13, 15–19]. ED adds to the impairment observed in adults with ADHD alone. Reimherr and colleagues [17] have shown that adults with ADHD and ED have more severe ADHD symptoms and impairment than those with ADHD alone, but their groups' samples have consisted of patients participating in clinical trials that excluded other comorbidities. Barkley and Fischer [10], in a naturalistic observational study of patients from childhood to adulthood, found that comorbid ED was associated with increased impairment, independent of the ADHD symptoms.

Adults with ADHD also frequently have other comorbid mood, anxiety, and personality disorders [20–22]. For example, among adults with ADHD, 10% also have Antisocial Personality Disorder, 35% Major Depressive Disorder, 15% Bipolar Disorder, 40% Anxiety Disorder, and 50% Substance Abuse Disorders [23–25]. Having ADHD as an adult raises the risk of drug or alcohol abuse disorders by 50–100% [21]. Conversely, rates of comorbid ADHD are also high among adults with other disorders, including Major Depression (9%), Dysthymia (23%), Bipolar Disorder (21%), Generalized Anxiety (12%), and drug dependence disorders (25%) [5].

The frequency of other comorbidities in adults with ADHD and the overlap of their symptoms with ED raise questions about whether such associations of ED and ADHD persist independent of other comorbid disorders. Studies that have examined these questions have had conflicting results. Some have reported that the association of ADHD and ED remains significant after controlling for the effects of other comorbidity [15, 26, 27]. In contrast, one study *in children* found that ED symptoms correlated primarily with other psychiatric comorbidities [28], while a study of adults in a community sample found that individuals were equally likely to have ED regardless of whether they had ADHD [29].

Models of the Adult ADHD-ED Relationship

Based on previously mentioned and other studies, three main theoretical models have emerged about the association of ED and ADHD in adults. Table 11.1 summarizes these theoretical models along with evidence that supports them.

Table 11.1 Models of emotional dysregulation and ADHD and their empirical support

First author [Reference]	Sample	Methods and results	Interpretations
A. Support for emotional dysregulation as a subtype of ADHD			
Wender [14]	Studied adult patients in a university-based ADHD clinic and clinical trial setting. Ss mostly white	Published Utah criteria for diagnosing ADHD, based both on clinical observations and EFA findings that sxs of ED occur in adults with ADHD even without anhedonic or vegetative sxs	In Utah criteria, there are three distinct groups of Sxs in adult ADHD: Inattention, hyperactivity/impulsivity (H/I) and emotionality. Others have questioned the generalizability of this group's observations to other more diverse samples
Reimherr et al. [19]	126 adults with ADHD in trials of ATX (72% had ED)	Ss with ED (per Utah criteria) had more H/I sxs and clinician-rated impairment (per CGI-S) than those without ED	In adults with ADHD, having ED associated with greater H/I sxs and impairment. Ss mostly white. Excluded Ss with other comorbidities
Corbisiero et al. [15]	393 adult cases with ADHD (some with other comorbidities) and 121 adult controls with no psychiatric disorders	ED levels assessed with ED subscale of WRAADDS. Adding ED sxs to core H/I and IA sxs of ADHD significantly improved ($p < 0.001$) a model's prediction of ADHD. ED predicted ADHD severity independent of psychiatric disorders	Independent of the core sxs of ADHD, ED is a significant indicator of ADHD. Sxs of H/I, IA, and other comorbidities independently predicted ED, though less than ADHD sxs did. ED sxs should be a part of the dx of ADHD, like H/I and IA sxs are
Marchant et al. [30]	762 Ss from 5 clinical trials with ADHD per DSM–IV-TR. 120 controls had no lifetime, personal or family history of ADHD	3 ED and 4 ADHD sx groups of the WRAADDS correctly categorized 120 ADHD from 120 non-ADHD Ss. EFA of 762 ADHD Ss had a 2-factor solution: (1) emotionality, and (2) attention/disorganization. WRAADDS's hyperactivity and impulsivity sxs loaded onto each of two factors	Each of the 7 WRAADDS scales symptom groups (including three related to ED) distinguishes adults with and without ADHD. ED is a distinct symptom group in patients with ADHD, and should be considered an additional subtype of adult ADHD
B. Support for emotional dysregulation as a core symptom of ADHD			
Barkley and Fischer [10]	Studied 135 youth with ADHD and 75 healthy controls till mid-20s	Ss with persistent ADHD as adults had more ED sxs than Ss with nonpersistent ADHD or healthy controls. ED sxs contributed to impairment in 7 of 10 major life activities	ED is a key component of adult ADHD that contributes uniquely to impairments in multiple life areas (e.g., legal, educational, occupational, financial)

(continued)

Table 11.1 (continued)

First author [Reference]	Sample	Methods and results	Interpretations
Barkley [6]	Examined the frequency and severity of ED in three groups: 146 ADHD Ss; 97 clinical controls; and 109 other Ss as community controls	Used self- and others' ratings to measure ED sxs across the three groups. First examined the association of ED with ADHD, and dysfunction (e.g., marital, parental, educational, occupational, legal). Then examined the association of ED with the severity of disruptive behavioral sxs in the children of the study's Ss	ED and its severity are clearly associated with adult ADHD and its impairment, independent of ADHD severity. In offspring of the study Ss, ED is even more associated with sxs of disruptive behavior. ED is a core part of adult ADHD, along with sxs of IA and H/I, and is potentially familial
C. Support for emotional dysregulation as frequent co-traveler with ADHD			
APA [31]	N/A	N/A	APA views ED and its sxs as being associated with but not a core part of ADHD
Surman et al. [26]	Ss from a family study: 206 Ss with and 123 without ADHD Ss. Non-ADHD Ss may have other mental health disorders	ED measured with 8 items from Barkley's current behavior scale. Structured interviews diagnosed any histories of other disorders (e.g., mood, anxiety, drug or alcohol use, antisocial). Regression models identified correlates of ED severity (including ADHD sxs and lifetime comorbidity counts)	ED severity was greater in adults with ADHD than without ADHD. ED co-occurring with ADHD was a significant correlate of impairment and reduced quality of life. Counts of lifetime comorbid disorders were a more significant correlate of ED severity than ADHD sxs were
Adler et al. [29]	108 Ss from the NCS-R study, 161 participants from managed care, and 191 clinically referred Ss	ED loaded 50% of the time on ADHD-CT cases and 50% of the time on non-ADHD cases. ED often co-occurred in adults with ADHD, perhaps due to effects of other psychiatric dxs and not the ADHD itself. EFA yielded 4 factors: Executive function, inattention, hyperactivity- impulsivity, and ED	ED is co-traveler with adult ADHD but not a core symptom of it. Sxs of other comorbidities may contribute to adult ED more than sxs of the ADHD do. ED is a weak fourth factor in adult patients with ADHD. Of note, most other EFA studies of adult ADHD have not found that ED is a distinct factor

Abbreviations: *ADHD* attention deficit hyperactivity disorder, *APA* American Psychiatric Association, *CFA* confirmatory factor analysis, *CD* pediatric conduct disorder, *CGI-S* Clinical Global Impressions Severity scale, *CT* combined subtype, *Dxs* diagnoses, *ED* emotional dysregulation, *EFA* exploratory factor analysis, *H/I* hyperactive/impulsive subtype, *IA* inattentive subtype, *NCS-R* National Comorbidity Replication Study, *ODD* pediatric oppositional conduct disorder, *RCT* randomized, placebo-controlled trial, *Ss* subjects, *Sxs* Symptoms, *WRAADDS* Wender-Reimherr Adult Attention Deficit Disorder Scale

The first model, supported by several studies from Wender and colleagues at the University of Utah [14, 17, 30], highlights the importance of ED symptoms, and argues for their inclusion in the diagnostic criteria for ADHD specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [31, 32]. Wender observed early in his clinical research that patients seen in his groups' ADHD research clinic had a variety of symptoms of ED (e.g., affective lability and reactive dysphoria), even without having other comorbid mood disorders. Along with a childhood history consistent with ADHD, his group proposed seven characteristic symptoms of adult ADHD, including four of typical ADHD (attention difficulties; disorganization; hyperactivity; impulsivity) and three of ED (temper; affective lability; emotional over-reactivity). According to the "Utah Criteria," a diagnosis of adult ADHD requires a childhood history consistent with ADHD, along with adult symptoms of hyperactivity and poor concentration, and at least two additional symptoms from among the following: (1) affective lability, (2) hot temper, (3) stress intolerance, (4) impulsivity, and (5) disorganization with inability to complete tasks [14]. These characteristics were incorporated into the Wender Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), one of several rating scales used to diagnose adult ADHD and ED symptoms [14]. The Utah group reported that each of these seven symptom groups discriminated adults diagnosed with ADHD based on criteria in the text-revised, 4th edition of DSM (DSM-IV-TR) [31]. A factor analysis of the WRAADDS in the same sample yielded a two-factor solution, with a subscale of attentional items (inattention and disorganization) loading onto the first factor, a subscale of three emotionality items (temper, affective liability, emotional over-reactivity) loading onto the second factor, and remaining scales of hyperactivity/restless and impulsivity loading onto each of the above factors. Accordingly, this first model suggests that *ED symptoms along with more classic symptoms of ADHD should be used to diagnose adult ADHD, and to classify subtypes of it.* The findings that support this group's model of ADHD are potentially limited by the fact that their study samples were fairly ethnically and racially homogeneous, recruited from a tertiary medical center, and often drawn from clinical trials excluding other comorbidities. However, Corbisiero and colleagues recently reported similar findings in a European sample using similar methods to diagnose adult ADHD [15]. In their study, adding ED symptoms to a predictive model significantly improved the identification of ADHD, even with inattentive and hyperactive/impulsive symptoms already included.

Others have argued in favor of a second model, in which *ED is a core feature of adult ADHD, but not be a distinct subtype* [6, 19, 33]. These researchers point to studies showing that aspects of ED (e.g., mood instability, emotional impulsiveness) occur in a majority of adult ADHD cases, and load more highly in patients with hyperactive/impulsive and combined ADHD than in patients with inattentive ADHD [10, 13]. Using this approach, Barkley and Murphy [13] have explained that emotional self-control comprises a two-stage process: (1) inhibition of strong emotional reactions to events, and (2) self-regulation actions, such as self-soothing and moderation of the initial emotional reaction. Inability to employ these components of emotional regulation leads to impulsive emotional behavior and deficient emotional control. These

deficits are highly related to the more recent DSM conceptualizations of adult ADHD [31, 32] entailing hyperactive-impulsive and/or inattentive symptoms, and also to Barkley's [6] understanding of ED and deficient self-regulation as core features of ADHD. Having hyperactive/impulsive symptoms (i.e., lacking behavioral inhibition), adults with ADHD have stronger emotional reactions to events. Having inattention (i.e., lacking executive function), they are unable to recognize and ultimately regulate their emotional states, which leads to socially inappropriate, dysfunctional emotional responses. Accordingly, ED symptomology is both highly related to and a potential result of one's ADHD symptoms, but not its own subtype of ADHD. Potential arguments against this second model are that only half of adults with ADHD have ED in clinical samples, and even less in community samples.

A third model, which echoes the diagnostic criteria of the most recent versions of DSM-IV-TR [31] or DSM-5 [32] for ADHD, is that ED is neither a subtype nor a core feature of adult ADHD; instead *ED simply a "co-travelling" symptom with ADHD* [29]. Kessler and colleagues [34] did a factor analysis in a large, nationally representative sample, which combined 131 subjects with ADHD from the National Comorbidity Survey Replication (NCS-R) database with 214 respondents from a large managed healthcare plan. Their analysis extracted three factors, related to ADHD but not to ED, casting doubt that ED is a "core feature" of ADHD. A more recent factor analysis conducted by Adler and colleagues [29] is also summarized in Table 11.1. Their sample of 536 subjects combined the two samples in Kessler's study, with an additional 191 clinically referred individuals to the New York University Langone Medical Center's Adult ADHD Program [29]. Adler and colleague's analysis, which included a factor simulation, once again raised doubt that ED was a core feature of adult ADHD. Instead they identified four factors: (1) executive dysfunction/inattention (including the DSM-5 inattentive symptoms [31]), (2) hyperactivity, (3) impulsivity, and (4) ED. Curiously, Adler and colleagues' study shared 345 of the same subjects, yet had results that contrasted with findings of Kessler and colleagues [34]. Moreover, when they examined subjects scoring highly on ED symptoms, less than 1% met criteria for adult ADHD. Lastly, the 4-factor model of adult ADHD has only been reported in one other study, involving a sample of German adults with ADHD [35]. As a result, Adler's group has been hesitant to consider ED as truly independent from other ADHD symptoms. Instead, they see ED as a likely co-traveler with adult ADHD [29].

Etiological Factors

Studies have also shown a neuropsychological relationship between ADHD and ED. The amygdala and the prefrontal cortex (PFC) are highly involved in behavioral, emotional, and impulse control [36–39]. For example, a study by Schulz and colleagues using functional magnet resonance imaging (fMRI) suggested that the dorsolateral prefrontal cortex (DLPFC) is potentially responsible for the dysfunction of emotional control in ADHD [40]. Additional fMRI studies have shown that adults with ADHD have increased activity in the right amygdala and smaller

amygdala volumes relative to healthy controls [41–43]. Together these findings suggest that ADHD may be related to deficits in emotional processing and impulse control, and that higher amygdala activity may explain the link between adult ADHD and ED [42].

Some recent studies have examined the genetic relationships between ADHD and ED. ADHD is a highly heritable psychiatric disorder [44, 45], and studies have suggested a strong genetic influence in the determination of ADHD [46, 47]. Parents and siblings of children with ADHD have a two- to eightfold increased risk of having ADHD, compared to parents and siblings of children without ADHD, and relatives of adults with ADHD also have an increased risk of having the disorder [48]. Finding DNA variants for ADHD heritability, however, has been challenging. Perry and Faraone [49] note that, although studies have implicated certain genes as being related to ADHD, some studies' findings have not reached significant thresholds, and others have been contradictory. In short, the genetic influences on ADHD have not been adequately identified yet.

Another genetic study by Robison and colleagues noted specific genetic variants were associated with adult ADHD, and suggested that understanding the genetics underlying ED may help to identify the genetic components of adult ADHD [18]. They studied genes linked with either ADHD or ED (e.g., the MAOA gene, which has been linked to aggressive behaviors [50]), by examining specific allele frequencies for adults who had ADHD with and without ED. Of eight genes studied, only the 5-HT1B gene was significantly associated with ED [18]. Another study of a large sample of young males with combined-type ADHD showed that effects of maternal expressed emotion on these males' conduct problems were moderated by variants of dopamine (DAT1) and serotonergic (5HTT) genes, suggesting that such individuals' genetic make-up may alter their sensitivity to the effects of their family environment [51].

Other conditions with ED symptoms also frequently co-occur with ADHD, such as borderline personality disorder (BoPD). Available data suggest that ADHD and BoPD share underlying genetic and environmental etiologies [52], and that ADHD could be a developmental precursor to BoPD [53]. While there is also clearly a biological relationship between ED and ADHD, the exact nature of this relationship and the relative importance of environmental factors is uncertain. Future research regarding the genetic, neurological, and environmental factors related to ADHD, ED, and other disorders with moodiness could eventually inform better strategies for their assessment and treatment.

Assessment

Key steps in the evaluation process are the clinician's face-to-face interview with the patient, reviewing current and past history, and observing for signs of ADHD, ED, and other disorders during the patient's mental status exam. The clinician must be careful to establish that the patient's ADHD symptoms have been chronic, and began early enough to meet the age of onset criteria of DSM 5 (i.e., most symptoms were present and causing impairment by the age of 12) [32]. Often it is helpful to

gather additional information, with the patient's cooperation, from other family members, significant others, bosses or peers at work, or even old report cards to surmise the patient's attention and behavior as a child [54–56]. Informants will often give varying accounts of the patient's history and symptoms, and in such cases, the clinician must weigh each informant's perceived reliability, biases, and motivations, then make an informed "best guess." Adults with ADHD or ED may be less accurate reporters because of their inattention, restlessness, impulsivity, or affective lability. They may *underreport* symptoms (due to poor insight, or to avoid treatment or being "labeled") or they may *overreport* symptoms when anxious, attention-seeking, or wanting a prescription for inappropriate purposes [54, 55]. It is also important to rule out other potentially more serious disorders (e.g., a depressive, bipolar, alcohol use or substance use disorder, or medical problems) because pharmacotherapy for the ADHD could destabilize or delay treatment of these [55–57]. Symptoms of underlying ADHD are easily missed when a patient presents with any of these more acutely serious disorders [55–58]. The clinician should generally postpone a formal diagnosis of ADHD until clarifying that the ADHD symptoms truly preceded the other disorder, and have remained after the other disorder is addressed. At that point, diagnosing and treating the ADHD can often be appropriate and life-changing [54, 55].

In a recent review article, Asherson and colleagues have reported that ADHD o*ccurs in about 20%* of adults with borderline personality disorders (BoPD) or bipolar disorders. These other disorders have overlapping symptoms with ADHD and ED, but also distinct characteristics [58]. Both BoPD and ADHD are chronic, with persistent traits and impairment. Shared symptoms of BoPD and ADHD may include impulsive behaviors and ED, while symptoms that distinguish BoPD from ADHD include suicidal and self-harming behaviors, stress-related dissociation, marked distress related to abandonment, and persistent feelings of "emptiness." In contrast, bipolar mood episodes are episodic and interspersed with periods of more normal moods, though the symptoms of untreated ADHD or ED may be persistent without treatment. Correct diagnosis of comorbid BoPD or bipolar disorders with ADHD is critical because these require distinct treatment approaches [58]. For BoPD, first-line treatment is typically intensive dialectical behavioral therapy, coupled with pharmacological treatment of ADHD, ED, or other comorbidities. Bipolar disorders, however, are typically treated before the ADHD with mood stabilizers or atypical antipsychotics, because medications for the ADHD may worsen mood and psychotic symptoms of a patient with untreated bipolar disorder [58].

Rating scales can be especially useful in gathering information from collateral informants and comparing their reports [59]. Some scales are designed to assess and diagnose adult ADHD by DSM criteria, but have additional items that capture ED, while other scales focus primarily on ED symptoms in adult ADHD rather than the DSM criteria for ADHD. Additional scales measure ED as its own entity, or as a component of executive dysfunction. The clinician must use the interview to review such information and to clarify the nature and course of any symptoms identified in order to reach an accurate diagnosis [54–56, 59].

Scales That Assess ADHD Symptoms and Expand to Include ED

Often adults with ADHD present initially with chief complaints related to mood, anxiety, or personality disorder symptoms, but on closer assessment also have underlying ADHD. Expert clinicians and researchers have stressed the need to routinely screen for ADHD in adult patients [54, 55]. There are interviews and several well-validated rating scales that screen for current ADHD in adults. The Adult Clinician ADHD Diagnostic Scale version 1.2 (ACDS) [34] is a clinician-administered, semi-structured diagnostic interview used in prior clinical trials to diagnose ADHD [61–63]. The ACDS uses a retrospective assessment of childhood ADHD symptoms with age-specific prompts, then assesses DSM symptoms of ADHD over the past year. Each item is rated on symptom severity scale ranging from 1 (none) to 4 (severe). This measure also contains prompts for 14 non-DSM symptoms, measuring deficits in higher-level executive function and emotional control also relevant to adult ADHD.

The Adult ADHD Self-Report Scales (ASRS) [25] are 18-item symptom checklists useful in screening for ADHD in adults. Both scales were developed by the World Health Organization (WHO) workgroup on adult ADHD, and consist of symptom domains found in the DSM-IV, but modified to reflect their presentation in the adult population, along with a context for each symptom. Symptoms are scored according to frequency, ranging from 0 (none) to 4 (very often). The 6-item screener (extracted from the 18 symptoms) consists of the best screening items (four inattentive and two hyperactive/impulsive), selected based on their ability to discriminate patients with and without ADHD based on systematic diagnostic interviews in the NCS-R [25]. A third ASRS scale, the Expanded ASRS v1.1 symptom checklist, consists of the original 18 DSM symptoms of ADHD and an additional 14 ADHD-related symptoms of executive function and emotional control previously validated with the ACDS v1.2 [34].

The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) is a clinician-administered scale that is not based on DSM criteria but instead on the Utah Criteria, where only inattention and hyperactivity, and not impulsivity, are the core symptoms of ADHD [14, 30, 60]. The WRAADDS assesses multiple symptoms within each of seven symptom domain categories: difficulties sustaining attention, disorganization, hyperactivity/restlessness, and impulsivity, as well as temper, mood lability, and emotional over-reactivity. Likert scales are used to rate each symptom from 0 (not present) to 2 (clearly present), and then to rate each of the seven domain categories with anchors that include 0 (none) to 4 (very much), based on the severity of symptoms and their impairment. Researchers have combined scores of temper, mood lability, and emotional over-reactivity categories to create a related Emotion Dysregulation Scale [61].

The Conner's Adult ADHD Rating Scales (CAARS) [62] are validated self-report questionnaires, and include a 66-item long form, and a 26-item short form, with their items rated on a 4-point Likert-type scale, from 0 (not at all, never) to 3 (very much, very frequently). Both versions have subscales measuring standard *inattention/memory* and *hyperactivity/restlessness* symptoms, as well as an *impulsivity/emotional*

lability subscale that measures symptoms consistent with ED [63]. The long form of the CAARS also contains an Inconsistency Index, that assesses the degree respondent's answers vary across items of similar content.

The Brown Attention-Deficit Disorder Scale (BADDS) for Adults is a self-report or clinician-administered measure developed and normed to assess executive function impairments common in adults with ADHD [64]. The 40 items of this scale are each rated on a 4-point Likert scale from 0 (never) to 3 (almost daily). Along with four clusters assessing symptoms of executive function or ADHD, BADDS has another cluster labeled *Emotional Control*, with symptoms assessing frustration management and emotional modulation.

Scales of Executive Function Deficit That Include ED

The BRIEF-A scale is a 75-item, self-report or informant-report measure that assesses adult executive function and self-regulation. Each item is scored on a 3-point Likert scale from 1 (behavior is never observed) to 3(behavior is often observed) [65]. Along with an overall summary score which is labeled Global Executive Composite, the BRIEF-A contains a Behavioral Regulation Index (with 4 component scales including one of Emotional Control), and a Metacognition Index (with 5 component scales measuring executive function and DSM symptoms of ADHD). Raw scores are transformed to T-scores, allowing comparison to a standardized population. A T-score of 50 is equivalent to the population mean, while a T-score $\geq$65 is 1.5 standard deviations over it, suggesting clinical significance [66].

From the Barkley Deficits in Executive Functioning scale, Barkley has used 7 items related to adult ED to create an Emotional Impulsiveness Scale (EIS) [13]. The EIS is completed by the patient or another informant and has the following items: (1) impatient; (2) quick to anger; (3) easily frustrated; (4) overreacts; (5) easily excited; (6) loses temper; and (7) touchy/annoyed. Its conceptualization of ADHD largely differs from that of the DSM criteria. The EIS has good psychometric properties, good external validity, and strong correlations with measures of functional impairment in adult ADHD [13]. Surman and colleagues have developed and validated a slightly different questionnaire, using items from the Barkley Current Behavior Scale that include six items shared with the EIS [26].

Scales of Mood, Anxiety, Substance Use, and Personality Disorders

As mentioned already, mood, anxiety, substance use, and personality disorders often co-occur with adult ADHD and share many symptoms with ADHD and ED. As a result they can be challenging to differentiate. Along with a careful history, there are multiple, self-report measures of adult depression that have been validated in samples with ADHD, including the PHQ-9 [67] and Beck Depressive Inventory [68]. Other questionnaires screen for a lifetime history of manic

symptoms, such as the Mood Disorders Questionnaire [69] and the short questionnaire version of the Composite International Diagnostic Interview used in the WHO study [70]. Several self-report or clinician-administered measures, such as the CAGE, MAST, AUDIT, or DAST-10 are useful in screening for alcohol or drug problems [71–73].

In summary, while the DSM has not accepted ED as a main symptom of adult ADHD, numerous rating scales and interviews are now available to screen adults for ED, ADHD, and other comorbid disorders from the perspective of various informants. These help to guide and supplement the clinical interview, and may also be used over time to monitor patients' response to treatment.

Treatment

Psychotherapy

Effective psychotherapies for adult ADHD have often included modules targeting mood dysregulation, thus reiterating the importance of ED in adult ADHD (see Solanto [74] for a thorough review). Bramham and colleagues [75], in their group cognitive behavioral therapy (CBT) for adult ADHD, include modules addressing ED and poor interpersonal relationship skills. Other modified CBT treatments have modules for ED, including Meta-Cognitive Therapy (MCT) for adults with ADHD, which foster executive self-management skills [76, 77]. Virta and colleagues [78] developed a "Content of the Cognitive–Behaviorally Oriented Group Rehabilitation Program" using a neuropsychological perspective. Their program of CBT and skills training has an entire session on emotion regulation [79].

While CBT has been the most widely studied, aspects of other therapies may also be effective for ADHD and ED. For example, the behavioral skills learned in dialectic behavioral therapy (DBT) may be useful, given their focus on emotion regulation. Two-thirds of ADHD patients in one study reported that emotion regulation was the most helpful part of DBT for them [80]. Other studies have suggested the benefits of DBT in adults with both ADHD and ED [81, 82]. Other useful components are the breathing and relaxation methods of mindfulness-based meditation, which help patients to understand, accept, and regulate their emotional experiences [83]. A trial of mindfulness meditation has shown effectiveness for both ED and ADHD symptoms [84].

Pharmacotherapy

The literature has supported a variety of available pharmacological treatments for adult ADHD, but focused less on treating the ED often associated with it. The main groups of pharmacological treatments for adult ADHD are stimulants, including methylphenidates (MPH) or amphetamines (AMPH), and non-stimulants, such as atomoxetine or antidepressants with noradrenergic effects like bupropion. Table 11.2

Table 11.2. Clinical trials for adults with ADHD

Authors	Study type	Subjects	Outcome measures	Primary findings (effect sizes)	Limitations
Stimulants					
Reimherr et al. [16]	Crossover RCT of OROS MPH and PBO, each arm lasting 4 weeks	47 adult Ss with ADHD by DSM-IV and Utah Criteria; 78% had ED	ADHD-RS total, WRAADDS total and WRAADS ED scores	• OROS MPH efficacious vs. PBO in decreasing sxs of ADHD and ED • Effect sizes: ADHD-RS (0.69); WRAADDS total (0.83) and ED scores (0.70)	• A relatively small, and homogeneous sample
Marchant et al. [87]	A 6-month, OLC of OROS MPH, after Ss completed RCT by Reimherr et al. [16]	34 adults with ADHD per DSM-IV and Utah criteria	WRAADDS for ED, CAARS for ADHD	• Improvements in ADHD and ED sxs were highly correlated • Significant improvements on OROS MPH for both ADHD (1.09) and ED (0.99)	• Only 18 finished study • Open-label
Rosler et al. [61]	Multicenter, 24-week RCT of MPH-ER's effects on emotional sxs in adult ADHD	363 adults with ADHD	ED sxs per WRAADDS EDS and CAARS ELS subscales; total ADHD sxs per CAARS subscale	• Ss on MPH-ER had significantly lower ED sxs on the EDS (0.37–0.42) and ELS (0.30–0.35); and ADHD sxs on CAARS (0.39) • Sxs of anxiety, depression, anger, and hostility did not improve on MPH-ER	• Used a relatively low dose of MPH-ER • Low completion rate
Marchant et al. [88]	RCT crossover trial of MPH transdermal system (MTS), flexibly dosed	90 adults with ADHD (77% had ED and/or ODD sxs)	WRAADDS for ED, CAARS for ADHD	• MTS efficacious for ADHD sxs (1.09), and ED sxs (0.99)	• Excluded Ss with MDD or anxiety disorders

Wender et al. [89]	2-week, crossover RCT of MPH, then a 1-year OLC for MPH responders	116 adults with ADHD	WRAADDS total and subscale scores (including EC)	• During RCT, significant improvements from baseline in total and all 7 subscale scores of WRAADDS relative to PBO	• Excluded most comorbid Axis I disorders
Retz et al. [90]	Multicenter RCT of MPH-ER	162	WRAADDS, CAARS	• MPH-ER superior to PBO for ADHD (0.59) and emotional lability (0.31) sxs, but not hot temper, and emotional reactivity	• Excluded MDD and anxiety disorders
Adler et al. [91]	RCT of LDX dimesylate vs. PBO	161 adults with severe executive dysfunction, ADHD and mild ED, randomized to LDS or PBO	BRIEF-A: All 3 indices and subscales and EC; relatively lower baseline EC scores (mean T-scores of 62.2 or for Ss on LDX and 65.1 for Ss on PBO)	• Baseline severity for EC less than for other BRIEF subscales • LDX superior to PBO per changes in BRIEF total and BRIEF subscale scores • Treatment effect on EC subscale (0.34) less than on other BRIEF subscales (0.44–0.84) and indices (0.55–0.83).	• Many comorbid disorders were excluded • At entry, Ss had severe executive dysfunction • Baseline "floor effects" for EC changes?
Adler et al. [92]	Crossover clinical trial of LDX and MAS-IR in a fixed order (LDX then MAS)	24 adults with ADHD	BRIEF-A total score and EC score; Clinician's global impressions of improvement scale	• LDX and MAS-IR effective in reducing ADHD sxs • LDX was significantly better than MAS in improving many of the BRIEF components, including EC	• Small study in a fixed sequence • LDX given single-blind, then MAS-IR given open label

(continued)

Table 11.2. (continued)

		Non-stimulants			
Reimherr et al. [60]	Post hoc analysis of two multicenter RCTs of ATX, examining ED response [94]	529, which included 170 (32%) with ED per 3 sxs WRAADDS	WRAADDS, CAARS, HAM-A, HAM-D	• ATX efficacious for sxs of ED (0.66), IA (0.61) and HI (0.42), but not for subthreshold anxiety or depressive sxs • Having ED was associated with reduced response to PBO and a higher response to atomoxetine	• Relatively low percent with ED • Other DSM-IV diagnoses (e.g., depression, anxiety) were excluded
Marchant et al. [94]	Long-term OLC of ATX in adult ADHD	384 (113 with ED)	WRAADDS, CAARS	• 3 year OLC of ATX (OLC for 2 RCTs of ATX studies) • Improvements were parallel and significant in WRAADDS and CAARS • Baseline ED predicted greater reductions in ED, inattention, hyperactivity, and impulsivity	• Open label • Only 18% completed the full 145 weeks
Brown et al. [95]	Effect of ATX on EF and on emotion	501 adults with ADHD	BADDS	• ATX significantly improved BADDS total and all five cluster scores (including modulating emotions) relative to PBO • Emotion had lowest initial scores, and improved the least	• Based only on self-report • Floor effect for changes in emotion cluster?

Adler et al. [96, 97]	12-week open label trial, followed by a 37-week RCT maintenance phase, where Ss for last 12 weeks assigned to stop or stay on ATX. Study docs and Ss blind to when RCT began	524 adults with ADHD	EC and other subscale and index scores on BRIEF-A	• In initial 12-week open-label, significant improvements in all BRIEF indices, including EC • In last 25 weeks, there was continued improvement relative to baseline in BRIEF indices for Ss on PBO or ATX • Improvement in EC less than in other BRIEF-A indices • Improvement in EF prior to RCT, correlated with rising EF and ADHD sxs on PBO	• PBO group potentially affected by lingering positive effects of ATX or by negative effects coming off it
Adler et al. [98]	A 12-week RCT of ATX examining effects on EF	445 young adults with ADHD	BRIEF-A	• Relative changes in major BRIEF-A indices (GEC, BRI, and MI) but not in EC favored ATX group (vs. on PBO)	• Low baseline EC scores may have led to floor effect for EC
Asherson et al. [99]	The effects of ATX on EC, with an integrated analysis of multicenter RCTs	829 adults with ADHD from one of three RCTs of ATX	BRIEF-A subscales	• In overall sample, ATX superior to PBO for ADHD sxs (0.42–0.46) and EC sxs (0.19) • When analysis was limited to Ss with greater baseline ED (EC > 20), treatment effect of ATX improved (0.32)	• Exploratory pooled analysis of three studies • Statistically vs. clinically significant effects?

(continued)

Table 11.2. (continued)

Wender and Reimherr [100]	Bupropion in adult ADHD	19 adults with ADHD per Utah criteria	Targeted attention-deficit disorder Sxs scale	• Bupropion effective in treating ADHD, as well as in decreasing all seven items on the targeted attention disorder symptom scale (including "hot temper" and "affective lability")	• Open trial • Did not specify magnitude of effect on mood dysregulation
Hedges et al. [101]	An open trial of venlafaxine; the mean dose of Venlafaxine was 96 mg/day	18 adults with ADHD by Utah Criteria	Utah Criteria (WRAADDS)	• 7 Ss had intolerable side effects • Venlafaxine effective in 8 of the 11 remaining Ss for attention, mood, temper, and over-reactivity • No report of comorbidities	• Venlafaxine poorly tolerated, despite low dose • Small sample
CBT and medication combination trials					
Rostain et al. [102]	Open label study of the combination of CBT and amphetamine	43 adults with ADHD	BADDS, BAI, BDI-II, BHS, HAM-D, HAM-A	• The combination of AMPH and CBT improved ADHD sxs from baseline on BADDS affect subscale (0.47), and on tBADDS total score and other subscale scores (0.70–1.06) • Significant improvements in self-reported depressive, anxiety and hopelessness sxs	• No comparator group • Treatments were all combined

summarizes key pharmacological trials of ADHD and co-occurring ED, and lists effect sizes when available. Such effect sizes can be roughly categorized using criteria recommended by Cohen as small (0.20), medium (0.50), or large (0.80) [85]. Stimulants, the most widely used pharmacotherapy for adults with ADHD, have typically shown higher response rates and effect sizes than non-stimulants, and most pharmacological effect sizes have been larger for ADHD than for ED symptoms [86]. Often, the changes in ADHD and ED symptoms are highly inter-correlated.

Stimulants

Several studies have examined the effects of MPH stimulants on symptoms of ED. In 47 participants with ADHD (78% also having ED), Reimherr and colleagues [16] did a placebo-controlled, crossover trial of osmotic-release oral system (OROS) MPH, finding that OROS MPH was efficacious for ADHD symptoms (moderate to large effect sizes), and for ED symptoms (moderate to large effect sizes). A follow-up continuation study led by Marchant and colleagues in the same group reported similar improvements in inattentive, hyperactive-impulsive, and ED symptoms [87]. In a larger, randomized, placebo-controlled trial (RCT) (n = 363), Rösler and colleagues found extended-release MPH was efficacious for ED and ADHD (at mild to moderate effect sizes) but not for anxiety, depression, or anger [61].

In another RCT of 90 adults with ADHD (67% with significant ED), Marchant and colleagues [88] found that MPH transdermal system (MTS) was superior to placebo for both ADHD and ED symptoms (at large effect sizes for both). Combining data from two previously mentioned MPH trials [16, 88], Reimherr and colleagues [17] reported that participants with significant ED were more likely to be women, have the combined subtype of ADHD, and have more symptoms of ADHD throughout life. In their analysis, ADHD response was independent of whether subjects had ED. In a 2-week placebo-controlled crossover RCT, Wender and colleagues [89] noted significant improvements for patients on MPH regarding WRAADDS total and subscale scores (including Emotional Control). In a RCT of MPH extended-release, Retz and colleagues [90] showed that effects relative to placebo on ADHD symptoms were moderate or more, on affective lability were mild to moderate, and on hot temper and emotional reactivity were nonsignificant.

In contrast to multiple trials of MPH, only two trials to date have reported the effects of the AMPH stimulants on symptoms of ED. First, Adler and colleagues [91] completed a RCT of lisdexamfetamine (LDX) targeting ADHD symptoms, executive function and self-regulation based on the BRIEF-A scale. Improvements in all BRIEF-A indices and subscales were significantly greater on LDX than placebo, with effect sizes that were small for the Emotional Control subscale, and medium to large for other subscales and indices. Of note, baseline scores for Emotional Control were low relative to other scores on the BRIEF-A, likely creating a "floor effect," limiting the ability to show superior benefits of active drug on this subscale. A second study by Adler and colleagues [92] compared the effectiveness of LDX and mixed-AMPH salts (MAS), showing that LDX relative to MAS

was significantly more effective for ED on most BRIEF-A scores (including for Emotional Control), and also on clinician's global impressions of improvement. Both formulations of AMPH had beneficial effects on ADHD symptoms.

Non-stimulants

Atomoxetine (ATX) and antidepressants with noradrenergic effects have also been found efficacious in reducing ADHD symptoms and ED symptoms. Using data from two previous placebo-controlled RCTs of ATX, Michelson and colleagues [93] did an analysis of 536 adult patients with ADHD, of which 32 met criteria for ED (here defined by three symptoms from the WRAADDS: temper, affective lability, and emotional reactivity). The analysis showed that ATX was efficacious for adult ADHD [93]. Reimherr and colleagues used data from the same combined sample to examine ATX's efficacy for ED in 529 subjects [60]. The treatment effect for WRAADDS ED symptoms was significant, similar to that for ADHD symptoms on the CAARS. The presence of ED was associated with a *better* treatment response regarding ADHD symptoms. Baseline depressive or anxiety symptoms did not predict ED responses.

In a three-year open label follow-up to these two studies, Marchant and colleagues [94] reported greater improvements in total WRAADDS, inattentive and hyperactive-impulsive scores for subjects with ED. Improvements in ED scores correlated with improvements in inattentive and hyperactive/impulsive symptoms on the CAARS. In another trial, Brown and colleagues [95] noted that, while improvements in all BADDS clusters were significant on ATX, they were larger for executive function and ADHD symptoms than for Emotion symptoms. Of note, relatively low baseline Emotion scores once again may have led to a "floor effect."

Adler and colleagues conducted a study of ATX with several stages [96]. The first stage was 12 weeks of open-label treatment. Responders to that phase then entered a 37-week double-blind RCT maintenance phase, in which they and the investigators were blind not both to assigned treatments but also to the timing of randomized treatment. Initially during the maintenance phase, all continued ATX for another 12 weeks, and those whose responses persisted on the ATX (524 total), were then assigned 1:1 to remain on ATX or switch to placebo for another 25 weeks. ATX was associated with significant improvements in the BRIEF's Emotional Control subscale throughout the maintenance phase, though improvements in other BRIEF subscales were more pronounced. Additional analyses suggested that patients having worse Executive Function at enrollment, or greater improvements of Executive Function while on ATX, were more prone to have worsening Executive Function, ED and ADHD symptoms after stopping the ATX. Improvements in Executive Function were associated with improvements in ADHD symptoms [97]. While the initial improvements from baseline in these variables diminished over time in subjects switched to placebo, ratings in Executive Function and ADHD symptoms were still significantly better than

baseline in the final, 6-month placebo phase [97]. In another RCT of ATX, this involving 445 adults with ADHD assigned to ATX or placebo for 12 weeks, Adler and colleagues reported significant improvements in the BRIEF-A's overall Global Executive Composite, and in its index scores of Metacognition and Behavioral Regulation, though not in its Emotional Control subscale of Behavioral Regulation [98].

In contrast to the studies above, Asherson and colleagues [99], after pooling three placebo-controlled studies of ATX in adult ADHD to have a sample size of 829 adults, reported that ATX was superior to placebo for Emotional Control symptoms on the BRIEF-A and for ADHD symptoms. Once again, however, the effect size of ATX on Emotional Control, while statistically significant with the large sample size, was small, and substantially lower than the effect size on ADHD symptoms. In an additional post hoc analysis, after investigators included only subjects with more severe Emotional Control symptoms, the treatment effect size on Emotional Control grew somewhat (now a small to moderate effect). Improvements in Emotion Control correlated with those of ADHD symptoms, but also with those of Quality of Life scores.

Antidepressants like bupropion and venlafaxine have also been used to treat ADHD and emotional symptoms. In an open-label trial of bupropion in 19 adults with ADHD diagnosed based on Utah Criteria, Wender and Reimherr [100] reported bupropion was effective for both ADHD and mood symptoms (specifically affective lability and hot temper). Another open-label study by Hedges and colleagues [101] examined the effectiveness of venlafaxine, a serotonin norepinephrine reuptake-inhibitor, in a sample of 18 adults diagnosed with ADHD (based on the WRAADDS scale and the Utah Criteria). Venlafaxine was effective in decreasing both emotional and cognitive symptoms, with the greatest improvement seen in attention, temper, mood, and over-reactivity symptoms. While the authors speculated that these changes may reflect effective treatment of comorbid conditions, they stressed that such mood symptoms are common even in patients with non-comorbid ADHD [101]. In summary, open label and placebo-controlled trials have now examined the effects of stimulant and non-stimulant treatments on adult ADHD and ED, and have shown significant reductions of ED paralleling those of ADHD and executive function, though effects on ED are typically smaller.

Combining Psychotherapy and Pharmacotherapy

While there have been a number of studies examining the effects on ADHD alone of combining pharmacotherapy with psychotherapy [99], only a few have examined the effects of combined treatments *on ED* (Table 11.2). Rostain and Ramsay [102] reported that the combination of AMPH and CBT significantly improved the BADDS total score and cluster scores, and to a lesser extent the Affect subscale score and measures of depression, anxiety, and hopelessness. In contrast, other studies have found no effect of ATX or MPH on these variables [64, 65].

Conclusions and Future Directions

Substantial evidence now suggests that ADHD, which starts in childhood, often continues into adulthood, and in adults is associated with substantial academic, ocupational, and interpersonal impairment. Adults with ADHD often have other co-occurring disorders with ED and and other mood problems that can add substantially to their overall impairment. Accurate diagnosis of ADHD and ED is thus critical, but complicated by symptoms shared with other mood, anxiety, substance use, and personality disorders. Such overlapping symptoms and their shared genetic and environmental bases are not well defined or understood. Key remaining research questions include how early treatment of ADHD impacts the development of ED and other comorbidities in adulthood. Growing evidence suggests that adults with ADHD and ED often respond to similar pharmacological and psychosocial treatments as youth, but the relative place of pharmacotherapy and psychosocial treatments like CBT or DBT is another open question. Clearly, targeting only ADHD symptoms in such patients may leave symptoms of ED *incompletely treated*, or even worse, *completely untreated*.

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