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

W.B. Daviss, M.D. (✉)
Department of Psychiatry, Dartmouth Hitchcock Medical Center,
Dartmouth Geisel School of Medicine, Lebanon, NH, USA
e-mail: william.b.daviss@dartmouth.edu

W.B. Daviss (ed.), *Moodiness in ADHD*, https://doi.org/10.1007/978-3-319-64251-2_7

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.

References

1. Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J, Dahl RE, et al. Childhood and adolescent depression: a review of the past 10 years. Part I. J Am Acad Child Adolesc Psychiatry. 1996;35(11):1427–39.
2. Kessler RC, McGonagle KA, Nelson CB, Hughes M, Swartz M, Blazer DG. Sex and depression in the National Comorbidity Survey. II: Cohort effects. J Affect Disord. 1994;30(1):15–26.
3. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatr. 2006;163:716.
4. Angold A, Costello EJ, Erkanli A. Comorbidity. J Child Psychol Psychiatry. 1999;40(1):57–87.
5. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013;34:119–38.
6. Barkley RA. Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment. 2nd ed. New York: Guilford Press; 1998. 628 p.
7. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. J Clin Psychiatry. 2006;67(04):524–40.

8. Klein RG, Mannuzza S, Olazagasti MA, Roizen E, Hutchison JA, Lashua EC, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch Gen Psychiatry. 2012;69(12):1295–303.
9. James A, Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: a review of possible associations. Acta Psychiatr Scand. 2004;110(6):408–15.
10. Biederman J, Ball SW, Monuteaux MC, Mick E, Spencer TJ, McCreary M, et al. New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. J Am Acad Child Adolesc Psychiatry. 2008;47(4):426–34.
11. Blackman GL, Ostrander R, Herman KC. Children with ADHD and depression: a multisource, multimethod assessment of clinical, social, and academic functioning. J Atten Disord. 2005;8(4):195–207.
12. Daviss WB, Weinman DR, Diler RS, Birmaher B, editors. Risk factors for comorbid depression in adolescents with ADHD. Poster, 53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry; 2006; San Diego, CA.
13. Rohde P, Clarke GN, Lewinsohn PM, Seeley JR, Kaufman NK. Impact of comorbidity on a cognitive-behavioral group treatment for adolescent depression. J Am Acad Child Adolesc Psychiatry. 2001;40(7):795–802.
14. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005;57(11):1313–23.
15. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157(10):1552–62.
16. Zalsman G, Brent DA, Weersing VR. Depressive disorders in childhood and adolescence: an overview: epidemiology, clinical manifestation and risk factors. Child Adolesc Psychiatr Clin N Am. 2006;15(4):827–41.
17. Faraone SV, Biederman J. Do attention deficit hyperactivity disorder and major depression share familial risk factors? J Nerv Ment Dis. 1997;185(9):533–41.
18. Drabick DA, Gadow KD, Sprafkin J. Co-occurrence of conduct disorder and depression in a clinic-based sample of boys with ADHD. J Child Psychol Psychiatry. 2006;47(8):766–74.
19. Biederman J, Mick E, Faraone SV. Depression in attention deficit hyperactivity disorder (ADHD) children: "true" depression or demoralization? J Affect Disord. 1998;47(1-3):113–22.
20. Wilens TE, Spencer TJ. The stimulants revisited. Child Adolesc Psychiatr Clin N Am. 2000;9(3):573–603, viii.
21. Pliszka SR. Pharmacologic treatment of attention-deficit/hyperactivity disorder: efficacy, safety and mechanisms of action. Neuropsychol Rev. 2007;17(1):61–72.
22. Bolanos CA, Barrot M, Berton O, Wallace-Black D, Nestler EJ. Methylphenidate treatment during pre- and periadolescence alters behavioral responses to emotional stimuli at adulthood. Biol Psychiatry. 2003;54(12):1317–29.
23. Carlezon WA Jr, Mague SD, Andersen SL. Enduring behavioral effects of early exposure to methylphenidate in rats. Biol Psychiatry. 2003;54(12):1330–7.
24. Daviss WB, Birmaher B, Diler RS, Mintz J. Does pharmacotherapy for attention-deficit/hyperactivity disorder predict risk of later major depression? J Child Adolesc Psychopharmacol. 2008;18(3):257–64.
25. Biederman J, Monuteaux MC, Spencer T, Wilens TE, Faraone SV. Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. Pediatrics. 2009;124(1):71–8.
26. Chen Q, Sjölander A, Runeson B, D'Onofrio BM, Lichtenstein P, Larsson H. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. BMJ. 2014;348:g3769.
27. Birmaher B, Brent D, Bernet W, Bukstein O, Walter H, Benson RS, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(11):1503–26.
28. Daviss WB. A review of co-morbid depression in pediatric ADHD: etiology, phenomenology, and treatment. J Child Adolesc Psychopharmacol. 2008;18(6):565–71.

29. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(7):894–921.
30. Jensen PS, Rubio-Stipec M, Canino G, Bird HR, Dulcan MK, Schwab-Stone ME, et al. Parent and child contributions to diagnosis of mental disorder: are both informants always necessary? J Am Acad Child Adolesc Psychiatry. 1999;38(12):1569–79.
31. Kovacs M. A developmental perspective on the methods and measures in the assessment of depressive disorders: the clinical interview. In: Rutter M, Izard CE, Read PB, editors. Depression in young people: Developmental and clinical perspectives. New York City: Guilford; 1986. p. 435–65.
32. Diler RS, Daviss WB, Lopez A, Axelson D, Iyengar S, Birmaher B. Differentiating major depressive disorder in youths with attention deficit hyperactivity disorder. J Affect Disord. 2007;102(1–3):125–30.
33. Daviss WB, Birmaher B, Melhem NA, Axelson DA, Michaels SM, Brent DA. Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. J Child Psychol Psychiatry. 2006;47(9):927–34.
34. Shea K, Daviss WB, editors. Caregiver depressive symptoms predict discrepancies between caregiver, teacher, and youth ratings of psychopathology in adolescents with ADHD. Poster, 60th annual meeting of the American Academy of Child and Adolescent Psychiatry; 2013; Orlando, FL.
35. Hoza B, Pelham WE, Milich R, Pillow D, McBride K. The self-perceptions and attributions of attention deficit hyperactivity disordered and nonreferred boys. J Abnorm Child Psychol. 1993;21(3):271–86.
36. Pelham WE Jr, Fabiano GA, Massetti GM. Evidence-based assessment of attention deficit hyperactivity disorder in children and adolescents. J Clin Child Adolesc Psychol. 2005;34(3):449–76.
37. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: scales assessing attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2003;42(9):1015–37.
38. Myers K, Winters NC. Ten-year review of rating scales. II: scales for internalizing disorders. J Am Acad Child Adolesc Psychiatry. 2002;41(6):634–59.
39. Johnson JG, Harris ES, Spitzer RL, Williams JB. The Patient Health Questionnaire for adolescents: validation of an instrument for the assessment of mental disorders among adolescent primary care patients. J Adolesc Health. 2002;30(3):196–204.
40. Costello EJ, Angold A. Scales to assess child and adolescent depression: checklists, screens, and nets. J Am Acad Child Adolesc Psychiatry. 1988;27(6):726–37.
41. Jensen PS, Hinshaw SP, Swanson JM, Greenhill LL, Conners CK, Arnold LE, et al. Findings from the NIMH Multimodal Treatment Study of ADHD (MTA): implications and applications for primary care providers. J Dev Behav Pediatr. 2001;22(1):60–73.
42. Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT. Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. Am J Psychiatry. 1995;152(12):1793–9.
43. Daviss WB, Nery FG, Olvera RL, Diler RS, Mezzomo KM, Soares JC, editors. Exploratory factor analysis of the CDRS-R in youths with ADHD poster. 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; 2007; Boston, MA.
44. American Psychological Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: APA; 2013.
45. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch Gen Psychiatry. 1982;39(5):549–55.
46. Geller B, Fox LW, Clark KA. Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. J Am Acad Child Adolesc Psychiatry. 1994;33(4):461–8.
47. Goodman DW, Thase ME. Recognizing ADHD in adults with comorbid mood disorders: implications for identification and management. Postgrad Med. 2009;121(5):20–30.

48. Applegate B, Lahey BB, Hart EL, Biederman J, Hynd GW, Barkley RA, et al. Validity of the age-of-onset criterion for ADHD: a report from the DSM-IV field trials. J Am Acad Child Adolesc Psychiatry. 1997;36(9):1211–21.
49. Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am. 2004;27(2):187–201.
50. Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. J Am Acad Child Adolesc Psychiatry. 1996;35(4):409–32.
51. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56(12):1073–86.
52. Gadow KD, Nolan EE, Sverd J, Sprafkin J, Schwartz J. Anxiety and depression symptoms and response to methylphenidate in children with attention-deficit hyperactivity disorder and tic disorder. J Clin Psychopharmacol. 2002;22(3):267–74.
53. DuPaul GJ, Barkley RA, McMurray MB. Response of children with ADHD to methylphenidate: interaction with internalizing symptoms. J Am Acad Child Adolesc Psychiatry. 1994;33(6):894–903.
54. Conners CK, Casat CD, Gualtieri CT, Weller E, Reader M, Reiss A, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry. 1996;35(10):1314–21.
55. Wilens TE, Spencer TJ, Biederman J, Girard K, Doyle R, Prince J, et al. A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. Am J Psychiatry. 2001;158(2):282–8.
56. Cheung AH, Emslie GJ, Mayes TL. The use of antidepressants to treat depression in children and adolescents. Can Med Assoc J. 2006;174(2):193–200.
57. Hughes CW, Emslie GJ, Crismon ML, Posner K, Birmaher B, Ryan N, et al. Texas Children's Medication Algorithm Project: update from Texas consensus conference panel on medication treatment of childhood major depressive disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(6):667–86.
58. Kratochvil CJ, Vitiello B, Walkup J, Emslie G, Waslick BD, Weller EB, et al. Selective serotonin reuptake inhibitors in pediatric depression: is the balance between benefits and risks favorable? J Child Adolesc Psychopharmacol. 2006;16(1–2):11–24.
59. Leslie LK, Newman TB, Chesney PJ, Perrin JM. The Food and Drug Administration's deliberations on antidepressant use in pediatric patients. Pediatrics. 2005;116(1):195–204.
60. Friedman RA, Leon AC. Expanding the black box—depression, antidepressants, and the risk of suicide. N Engl J Med. 2007;356(23):2343–6.
61. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007;297(15):1683–96.
62. Friedman RA. Antidepressants' black-box warning—10 years later. N Engl J Med. 2014;371(18):1666–8.
63. Gammon GD, Brown TE. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. J Child Adolesc Psychopharmacol. 1993;3(1):1–10.
64. Findling RL. Open-label treatment of comorbid depression and attentional disorders with coadministration of serotonin reuptake inhibitors and psychostimulants in children, adolescents, and adults: a case series. J Child Adolesc Psychopharmacol. 1996;6(3):165–75.
65. Daviss WB, Bentivoglio P, Racusin R, Brown KM, Bostic JQ, Wiley L. Bupropion sustained release in adolescents with comorbid attention-deficit/hyperactivity disorder and depression. J Am Acad Child Adolesc Psychiatry. 2001;40(3):307–14.
66. Golubchik P, Kodesh A, Weizman A. Attention-deficit/hyperactivity disorder and comorbid subsyndromal depression: what is the impact of methylphenidate on mood? Clin Neuropharmacol. 2013;36(5):141–5.

67. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. JAMA. 2004;292(7):807–20.
68. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA. 2008;299(8):901–13.
69. Bangs ME, Emslie GJ, Spencer TJ, Ramsey JL, Carlson C, Bartky EJ, et al. Efficacy and safety of atomoxetine in adolescents with attention-deficit/hyperactivity disorder and major depression. J Child Adolesc Psychopharmacol. 2007;17(4):407–19.
70. Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. Pediatr Res. 2013;74(1):96–102.
71. Lilly. Prescribing Information for Strattera® (Atomoxetine). Indianapolis: Lilly USA, LLC; 2015. http://pi.lilly.com/us/strattera-pi.pdf
72. Pliszka SR, Greenhill LL, Crismon ML, Sedillo A, Carlson C, Conners CK, et al. The Texas Children's Medication Algorithm Project: report of the Texas consensus conference panel on medication treatment of childhood attention-deficit/hyperactivity disorder. Part I. J Am Acad Child Adolesc Psychiatry. 2000;39(7):908–19.
73. Hughes CW, Emslie GJ, Crismon ML, Wagner KD, Birmaher B, Geller B, et al. The Texas Children's Medication Algorithm Project: report of the Texas consensus conference panel on medication treatment of childhood major depressive disorder. J Am Acad Child Adolesc Psychiatry. 1999;38(11):1442–54.
74. Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, et al. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45(6):642–57.
75. Guy W. ECDEU assessment manual for psychopharmacology, revised. Rockville: U.S. Department of Health, Education and Welfare; 1976.
76. Kratochvil CJ, Newcorn JH, Arnold LE, Duesenberg D, Emslie GJ, Quintana H, et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. J Am Acad Child Adolesc Psychiatry. 2005;44(9):915–24.
77. Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry. 2013;170(3):275–89.
78. Evans SW, Owens JS, Bunford N. Evidence-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder. J Clin Child Adolesc Psychol. 2014;43(4):527–51.
79. Solanto MV, Marks DJ, Wasserstein J, Mitchell K, Abikoff H, Alvir JMJ, et al. Efficacy of meta-cognitive therapy (MCT) for adult ADHD. Am J Psychiatry. 2010;167(8):958–68.
80. Chan E, Fogler JM, Hammerness PG. Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. JAMA. 2016;315(18):1997–2008.
81. Antshel KM, Hargrave TM, Simonescu M, Kaul P, Hendricks K, Faraone SV. Advances in understanding and treating ADHD. BMC Med. 2011;9(1):1–12.
82. David-Ferdon C, Kaslow NJ. Evidence-based psychosocial treatments for child and adolescent depression. J Clin Child Psychol. 2008;37(1):62–104.
83. Kennard B, Silva S, Vitiello B, Curry J, Kratochvil C, Simons A, et al. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry. 2006;45(12):1404–11.
84. Klomek AB, Mufson L. Interpersonal psychotherapy for depressed adolescents. Child Adolesc Psychiatr Clin N Am. 2006;15(4):959–75.
85. Rossello J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. J Consult Clin Psychol. 1999;67(5):734–45.

86. American Psychiatric Association, American Academy of Child and Adolescent Psychiatry. The use of medication in treating childhood and adolescent depression: information for patients and families 2010. http://www.parentsmedguide.org/parentsmedguide.pdf.
87. MTA Cooperative Group. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: the Multimodal Treatment Study of children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56(12):1088–96.
88. Wells KC, Pelham WE, Kotkin RA, Hoza B, Abikoff HB, Abramowitz A, et al. Psychosocial treatment strategies in the MTA study: rationale, methods, and critical issues in design and implementation. J Abnorm Child Psychol. 2000;28(6):483–505.
89. Curry J, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil C, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry. 2006;45(12):1427–39.
90. March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007;64(10):1132–43.
91. Kratochvil CJ, May DE, Silva SG, Madaan V, Puumala SE, Curry JF, et al. Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. J Child Adolesc Psychopharmacol. 2009;19(5):519–27.
92. Birmaher B, McCafferty JP, Bellew KM, Beebe KL, editors. Comorbid ADHD and disruptive behavior disorders as predictors of response in adolescents treated for major depression. Annual Meeting of the American Psychiatric Association; 2000 May; Chicago, IL.
93. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry. 2001;40(7):762–72.
94. Angold A, Costello EJ, Messer SC, Pickles A. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. Int J Methods Psychiatr Res. 1995;5(4):237–49.
95. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.
96. Poznanski EO, Cook SC, Carroll BJ. A depression rating scale for children. Pediatrics. 1979;64(4):442–50.
97. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
98. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull. 1985;21(4):995–8.
99. Pliszka SR, Greenhill LL, Crismon ML, Sedillo A, Carlson C, Conners CK, et al. The Texas Children's Medication Algorithm Project: report of the Texas consensus conference panel on medication treatment of childhood attention-deficit/hyperactivity disorder. Part II: tactics. J Am Acad Child Adolesc Psychiatry. 2000;39(7):920–7.