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REVIEW ARTICLE

The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder

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BACKGROUND: Patients with bipolar disorder (BD) and major depressive disorder (MDD) experience adult attention-deficit/hyperactivity disorder (ADHD) at rates substantially greater than the general population. Nonetheless, ADHD frequently goes untreated in this population.

METHODS: We reviewed the literature regarding the management of adult ADHD in patients with mood disorders. Because a limited number of studies have been conducted in adults, our treatment recommendations also are partly informed by research in children and adolescents with BD+ADHD or MDD+ADHD, adults with ADHD, and our clinical experience.

RESULTS: In individuals with mood disorders, ADHD is best diagnosed when typical symptoms persist during periods of sustained euthymia. Individuals with BD+ADHD, particularly those with bipolar I disorder (BD I), are at risk for mood destabilization with many ADHD treatments, and should be prescribed mood-stabilizing medications before initiating ADHD therapies. Bupropion is a reasonable first-line treatment for BD+ADHD, while mixed amphetamine salts and methylphenidate also may be considered in patients determined to be at low risk for manic switch. Modafinil and cognitive-behavioral therapy (CBT) are second-line choices. In patients with MDD+ADHD and moderate to severe depression, MDD should be the treatment priority, whereas in mildly depressed or euthymic patients the order may be reversed. First-line treatments for MDD+ADHD include bupropion, an antidepressant plus a long-acting stimulant, or an antidepressant plus CBT. Desipramine, nortriptyline, and venlafaxine are second-line options.

CONCLUSIONS: Clinicians should be vigilant in screening for comorbid ADHD in mood disorder patients. ADHD symptoms can respond to appropriately chosen treatments.

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INTRODUCTION

Adult attention-deficit/hyperactivity disorder (ADHD) is one of the most common and disabling, yet also one of the most covert comorbidities in persons with mood disorders. ADHD adds substantially to the burden of illness and disability caused by bipolar disorder (BD) and major depressive disorder (MDD), but there is emerging evidence that it can be effectively treated. The objective of this article is to provide a practical guide for the diagnosis and management of adult patients with mood disorders and ADHD. We begin with an overview of the common presentations of adult ADHD, and then examine its prevalence, impact, and diagnosis in persons with BD and MDD. We conclude with a review of relevant treatment studies and our recommendations for management. For clarity, the terms BD+ADHD and MDD+ADHD will refer to patients with both disorders, while BD, MDD, and ADHD denote noncomorbid patients.

Adult ADHD

Epidemiology. ADHD is one of the most common neuropsychiatric disorders of childhood, affecting an estimated 4% to 10% of North American children.[1,2] A recent meta-analysis of prospective studies reported that 65% of persons with pediatric ADHD remained symptomatic into early adulthood, with 15% meeting full diagnostic criteria and the remainder displaying clinically impairing subthreshold symptoms.[3] Population-based studies have reported that the prevalence of ADHD in persons age 18 to 44 is 3.4% to 4.4%.[4,5]

Presentation. As people mature, some attenuation of ADHD severity is common. Nonetheless, 78% to 90% of adults with the disorder continue to experience inattentiveness, and 38% to 44% remain affected by hyperactivity-impulsivity.[6-9] Hyperactivity in adults may manifest as difficulty relaxing, overworking, and participation in high-stimulus activities such as extreme sports. Impulsivity may be apparent in abruptly quitting work or school, excessive purchases, sexual indiscretions, substance use, and aggression. Inattentive symptoms include distractibility (missing details, losing one's train of thought), inadequate organizational skills (poor time management, inability to prioritize), mismanagement of finances (failure to pay bills or taxes), and family problems ("not listening" to a spouse, poor parenting because of difficulty maintaining routines).[10-14] A substantial number of patients also have executive dysfunction, which adds considerably to the morbidity associated with ADHD.[15-17]

Disability. Because cognitive and executive functions play increasingly important roles as people mature and take on independent family and occupational responsibilities, ADHD continues to cause impairment into adulthood, symptom attenuation notwithstanding. Adults with ADHD are less likely to be successful in postsecondary education, more likely to be unemployed, have greater rates of divorce, and are more likely to be involved in traffic accidents and criminal activity than adults without ADHD.[4,5,9,18-21] Those who are employed often have reduced productivity, increased absenteeism, and more frequent workplace accidents.[19,22] The total direct and indirect costs attributable to adult ADHD in the United States in 2000 were estimated at $24.4 billion.[23]

Adult ADHD in persons with mood disorders

Epidemiology. Persons with mood disorders experience adult ADHD more frequently than the general population. In clinical studies examining comorbidity (**TABLE 1**), the mean rates of ADHD were 12.8% for BD and 7.8% for MDD, weighted by sample size and excluding the Kessler study, which reported a population estimate.[4,24-31] Thus, if the population prevalence of adult ADHD is approximately 4%, patients with BD have a 3-fold increased prevalence, and patients with MDD a 2-fold increased prevalence. In the National Comorbidity Survey Replication, ADHD was the fifth most common comorbidity among individuals with BD, after alcohol abuse, specific phobia, social phobia, and oppositional defiant disorder.[32]

Comorbidity and illness course. Patients with BD+ADHD and MDD+ADHD experience ADHD symptoms and accompanying impairment even during periods of euthymia, increasing their burden of illness and reducing their likelihood of achieving optimal functioning between mood episodes.[31] In addition, they experience more severe mood illnesses than patients without ADHD (**TABLE 2**),[24-31,33-37] with an earlier age at onset of mood symptoms,[25,27,29-31] more frequent mood episodes, particularly depressive episodes,[25-27,29-31] and more suicide attempts.[25,29] In pediatric samples, BD+ADHD is associated with lower response rates to lithium and divalproex.[33-36] BD+ADHD and MDD+ADHD are

TABLE 1
Rates of comorbid adult ADHD in patients with BD and MDD

Study	Diagnostic instrument for ADHD	Sample	Sample size	Diagnosis	Age	Reported rate of adult ADHD
Bipolar disorder						
McIntyre et al, 2010[30]	Mini International Neuropsychiatric Interview–Plus	Consecutive patients enrolled in a naturalistic study in Canada and the United States	N = 176	BD I, BD II	≥18	17.6%
Bernardi et al, 2010[31]	Clinical interview using DSM-IV criteria + Wender Utah Rating Scale	Consecutive euthymic outpatients from Italy	N = 100	BD I, BD II	18 to 30	10.0%
Rydén et al, 2009[29]	Adult ADHD Self-Report Scale, Brown ADD Scale	Euthymic outpatients from Sweden	N = 159	BD I, BD II, BD NOS	≥18	16.4%
Sentissi et al, 2008[28]	Adult ADHD Self-Report Scale	Euthymic outpatients from France	N = 73	BD I, BD II	≤60	30.1%
Tamam et al, 2008[27]	Clinical interview using DSM-IV criteria + Current Symptoms Scale	Consecutive euthymic outpatients from Turkey	N = 159	BD I, BD II, BD NOS	18 to 65	16.3%
Kessler et al, 2006[4]	Adult ADHD Clinical Diagnostic Scale v. 1.2	Representative community survey in the United States	N = 3199 (4.4% of total sample had BD)	BD I, BD II, BD NOS	18 to 44	21.2%
Tamam et al, 2006[26]	Clinical interview using DSM-IV criteria	Consecutive euthymic outpatients from Turkey	N = 44	BDI	19 to 58	15.9%
Nierenberg et al, 2005[25]	Mini International Neuropsychiatric Interview	Consecutive US patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder	N = 919	BD I, BD II, BD NOS	≥15	9.5%
Major depressive disorder						
McIntyre et al, 2010[30]	Mini International Neuropsychiatric Interview–Plus	Consecutive patients enrolled in a naturalistic study in Canada and the United States	N = 203	MDD	≥18	5.4%
Kessler et al, 2006[4]	Adult ADHD Clinical Diagnostic Scale v. 1.2	Representative community survey in the United States	N = 3199 (16.2% of total sample had MDD)	MDD	18 to 44	9.4%
Alpert et al, 1996[24]	14-item self-rating ADHD questionnaire; companion module for ADHD from the childhood version of the Schedule for Affective Disorders and Schizophrenia	Consecutive depressed patients enrolled in a depression research program in the United States	N = 116	MDD	18 to 65	12.1%

ADD: attention-deficit disorder; ADHD: attention-deficit/hyperactivity disorder; BD: bipolar disorder; MDD: major depressive disorder; NOS: not otherwise specified.

strongly associated with the presence of additional comorbidities, including anxiety disorders, substance use disorders, and antisocial personality disorder,[25,27,29,30] and with reduced social functioning, employment rates, work productivity, and overall quality of life.[28,30] At a public health level, mood disorder patients with ADHD have substantially higher medical costs than patients with a mood disorder alone.[38,39]

Case detection. Adult ADHD often goes unrecognized and untreated in patients with mood disorders, as evidenced by the fact that only 9% of BD+ADHD patients who enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder were properly diagnosed and received pharmacotherapy for ADHD.[40] This underscores the numerous difficulties inherent in diagnosing ADHD in adults with BD and MDD, which include:

1. Its chronic, non-episodic course means that many affected individuals do not recognize it as an illness and may minimize the presence and functional impact of their symptoms.[41,42]

2. Patients frequently develop coping strategies (eg, list-making) or make accommodations (eg, choosing high-stimulus occupations such as stockbroker or salesperson) that mitigate functional impairment from ADHD.

3. Patients are unlikely to manifest observable signs and symptoms in a structured, salient situation such as a psychiatric assessment.[11]

4. Because hyperactive symptoms diminish with age, ADHD is not obvious to collateral informants such as family members and friends.[6-9]

5. Patients generally have poor recall for childhood symptoms,[43,44] and it often is difficult to obtain collateral history needed to establish childhood symptom onset (eg, report cards are unavailable; parents are elderly or deceased). In any case, the requirement for early childhood onset is controversial,[45] and ADHD not otherwise specified (NOS) without this criterion has been shown to be equally responsive to treatment.[46]

6. In contrast to ADHD, mania and depression are episodic and cause acute distress and impairment, and are more likely to lead people to seek medical care. Even among clinicians, there may be a misperception that ADHD is a childhood disorder and a lack of perceived need to screen for it after mood episodes have resolved.[11]

7. There is a substantial overlap between mood and ADHD symptoms, which can make them difficult to differentiate.[47] Similarities between hypomania/mania and ADHD include hyperactivity, impulsivity, and distractibility, whereas similarities between depression and ADHD include difficulty concentrating and psychomotor agitation.

8. It is challenging to distinguish ADHD from residual interepisode mood symptoms. For instance, BD frequently is associated with trait impulsivity and impaired ability to sustain attention,[48-52] and euthymic MDD is also associated with deficits in sustained attention.[53,54]

Relationship between ADHD and mood disorders

Three theories have been proposed to explain the frequent co-occurrence of mood disorders and ADHD[55,56]:

1. The apparent comorbidity is in fact artifactual, and patients with mood disorders are misdiagnosed with ADHD when clinicians misattribute mood symptoms to ADHD.

2. There are subtypes of BD and MDD characterized by an early-onset ADHD-like prodrome, with symptoms also persisting between mood episodes.

3. There is true comorbidity between mood disorders and ADHD, likely due to a shared neurobiologic diathesis.

The misattribution theory seems unlikely because studies of children and adolescents with ADHD and mood disorders found that most patients continued to meet criteria for both, even when overlapping symptoms were discounted.[57,58] Even more compelling, particularly in patients with BD+ADHD, ADHD symptoms generally do not respond to mood-stabilizing medications, persist when mood episodes have resolved, and improve with the administration of ADHD treatments.[59-62] Thus, it is our view that most patients diagnosed with both disorders have an ADHD-type syndrome, which may be either a component of their mood disorder or a separate illness, which requires ADHD-specific therapies.

Neurobiology of mood disorders with comorbid ADHD

Mood disorders and ADHD frequently coexist in the same family,[63-73] and in families with both disorders, the tendency for comorbidity also is inherited—ie, ADHD and mood disorders cosegregate. Thus, BD+ADHD is transmitted at a greater rate than expected, given the frequency of each disorder,[65,66] and a smaller, though nonsignificant, tendency for cosegregation has also been observed for MDD+ADHD.[64]

Structural and functional neuroimaging studies reveal both shared and unique neurobiologic features

TABLE 2
Sociodemographic and clinical correlates of comorbid adult ADHD in studies of patients with BD and MDD

Finding	Studies supporting finding	Studies not supporting finding
Bipolar disorder		
Earlier age of onset	McIntyre et al, 2010[30] Bernardi et al, 2010[31] Rydén et al, 2009[29] Tamam et al, 2008[27] Nierenberg et al, 2005[25]	Tamam et al, 2006[26] Sentissi et al, 2008[27]
More depressive episodes	Bernardi et al, 2010[31] Rydén et al, 2009[29] Tamam et al, 2008[27] Tamam et al, 2006[26] Nierenberg et al, 2005[25]	McIntyre et al, 2010[30]
More hypomanic/manic episodes	Rydén et al, 2009[29] Tamam et al, 2008[27] McIntyre et al, 2010[30]	Bernardi et al, 2010[31] Tamam et al, 2006[26]
More suicide attempts	Rydén et al, 2009[29] Nierenberg et al, 2005[25]	Tamam et al, 2008[27]
More frequent anxiety disorder comorbidity	McIntyre et al, 2010[30] Tamam et al, 2008[27] Nierenberg et al, 2005[25]	
More frequent substance abuse comorbidity	McIntyre et al, 2010[30] Tamam et al, 2008[27] Nierenberg et al, 2005[25]	Sentissi et al, 2008[28] Bernardi et al, 2010[31]
More frequent antisocial personality disorder comorbidity or history of violence	McIntyre et al, 2010[30] Rydén et al, 2009[29] Nierenberg et al, 2005[25]	
Poor response to mood stabilizers[a]	Masi et al, 2010[36] (c/a) Masi et al, 2004[35] (c/a) State et al, 2004[34] (c/a) Strober 1998[33] (c/a)	Kafantaris et al, 2003[37] (c/a)
Poor psychosocial functioning	McIntyre et al, 2010[30] Sentissi et al, 2008[28] Nierenberg et al, 2005[25]	
Major depressive disorder		
Earlier age of onset	McIntyre et al, 2010[30]	Alpert et al, 1996[24]
More depressive episodes		Alpert et al, 1996[24]
Greater anxiety disorder comorbidity	McIntyre et al, 2010[30]	Alpert et al, 1996[24]
Greater substance abuse comorbidity	McIntyre et al, 2010[30]	Alpert et al, 1996[24]
Greater antisocial personality disorder comorbidity or history of violence	McIntyre et al, 2010[30]	

[a]"c/a" denotes studies that were carried out in child and adolescent samples.

ADHD: attention-deficit/hyperactivity disorder; BD: bipolar disorder; MDD: major depressive disorder.

between mood disorders and ADHD. Areas of overlap primarily involve reduced volumes and altered activity of frontal lobe structures that regulate attention, behavior selection, and emotion, such as the anterior cingulate cortex,[74-82] the ventrolateral prefrontal cortex,[76,83,84] the dorsolateral prefrontal cortex,[78-80] and the orbitofrontal cortex.[80,85] Distinguishing features include amygdala volume, which typically is larger in adult ADHD than MDD,[86] and basal ganglia and corpus callosum volumes, which are more consistently reduced in ADHD than BD,

TABLE 3
Strength of evidence for the treatment of ADHD in adults with BD+ADHD

Level of evidence[a]	Treatment	Source of data/sample(s)[b]
1	Methylphenidate	BD+ADHD(P)[60,112]
2	Mixed amphetamine salts	BD+ADHD(P)[59]
3	Bupropion Atomoxetine	BD+ADHD(A),[101] ADHD(A)[122-125] BD+ADHD(P)[62]
4	CBT Modafinil Venlafaxine Desipramine Nortriptyline Lisdexamfetamine	ADHD(A)[145-156] ADHD(A)[109,110] ADHD(A)[133-136] ADHD(A)[128] ADHD(A)[137] ADHD(A)[164,166]

Data from clinical trials in adult or pediatric BD+ADHD samples were designated as having first-, second-, or third-line evidence as above. Regardless of study design or sample size, medications that were assessed only in noncomorbid adult ADHD patients were assigned level 4 status.

[a]Level 1 = ≥2 placebo-controlled trials or meta-analysis; 2 = 1 RCT with placebo arm or active comparator; 3 = prospective open-label trial with n ≥ 10.

[b]BD+ADHD(A) = based on studies in adult samples with BD+ADHD; BD+ADHD(P) = based on studies in pediatric samples with BD+ADHD; ADHD(A) = based on studies in adults with ADHD only.

ADHD: attention-deficit/hyperactivity disorder; BD: bipolar disorder; CBT: cognitive-behavioral therapy.

at least in children.[80,87-89] Interestingly, the small number of studies that have directly compared adult mood disorder patients with and without ADHD have generally distinguished BD+ADHD and MDD+ADHD from BD and MDD by the fact that comorbid patients had brain changes characteristic of both illnesses.[90,91]

Studies of neurotransmitters offer additional evidence of shared and unique features between ADHD and mood disorders because abnormalities in dopamine and norepinephrine signaling are implicated in the pathophysiology of both illnesses,[92-97] whereas cerebrospinal fluid serotonin metabolites are lower in adults with BD+ADHD than pure BD.[98] Taken together, then, neurobiologic studies suggest that BD+ADHD and MDD+ADHD are subtypes of BD and MDD that are heritable, likely arise from overlapping pathophysiologies, and yet are distinguishable from BD and MDD on a number of neurobiologic measures.

Treatment studies in patients with mood disorders and comorbid ADHD

Despite the frequent co-occurrence of mood disorders and ADHD, few clinical trials have assessed the efficacy of treatments in patients with both conditions. Fewer still have been conducted in adults. We will review the literature broadly to capture information relevant to managing patients with BD+ADHD and MDD+ADHD, including clinical practice guidelines for the management of adult ADHD, clinical trials in adult and pediatric BD+ADHD and MDD+ADHD samples, and studies examining the efficacy of mood stabilizers and antidepressants in ADHD and the efficacy of stimulants and other ADHD medications in mood disorders.

Clinical practice guidelines for the management of adult ADHD

First-line pharmacotherapeutic options for adult ADHD recommended by the Canadian ADHD Resource Alliance (CADDRA)[14] and the British Association for Psychopharmacology[99] include long-acting preparations of mixed amphetamine salts (MAS), methylphenidate, and atomoxetine. Second-line or adjunctive choices include short-acting stimulants or atomoxetine, antidepressants such as venlafaxine or bupropion, and modafinil. Although no head-to-head trials have assessed the relative efficacy of different medication classes, a meta-analysis of 19 placebo-controlled trials found a larger effect size for stimulants than for atomoxetine, antidepressants, or modafinil.[100] It also confirmed previous reports that the effect sizes for adults for all treatment classes were similar to those in children and adolescents. The guidelines do not offer specific recommendations regarding the selection or sequencing of treatments in adults with BD+ADHD or MDD+ADHD.

Treatment studies in BD+ADHD, ADHD, and BD

Treatment studies in BD+ADHD. The only study that has assessed any treatment in adults with BD+ADHD was a 6-week open-label trial of bupropion in 36 euthymic patients predominantly diagnosed with BD II (89%, BD II; 11%, BD I).[101] Other than bupropion, most patients (89%) were medication-free. ADHD symptoms improved by a mean of 55% during treatment, and hypomanic and depressive symptoms, which were mild at baseline, also improved. One patient experienced treatment-emergent hypomania.

In contrast to the limited data in adults, a number of medications have been examined in pediatric BD+ADHD samples. Three placebo-controlled randomized controlled trials (RCTs) examined the efficacy of adjunctive

stimulants for ADHD symptoms in this population. In 1 crossover study, 30 patients with persistent ADHD after mood stabilization with divalproex received double-blind treatment with MAS or placebo for 2 weeks each.[59] The response rates were 90% for MAS and 10% for placebo, with no worsening of manic symptoms. Efficacy was maintained for an additional 12 weeks in 23 patients who continued open-label divalproex + MAS, although 1 patient had a manic episode that resolved after discontinuing MAS. In 2 placebo-controlled crossover studies of methylphenidate in euthymic patients, 1 study (N = 16) reported that methylphenidate was significantly better than placebo for ADHD when given in combination with lithium and/or divalproex, although the study was limited by assessing efficacy during the "best treatment week" rather than at endpoint.[60] The second study (N = 16) reported no difference in efficacy between methylphenidate and placebo as adjuncts to aripiprazole.[102] One treatment-emergent mixed episode occurred in the methylphenidate arm in the aripiprazole study. In addition, a single small (N = 12) 8-week open-label study suggested benefit for atomoxetine as an adjunct to mood stabilizers and/or antipsychotics for treating ADHD, although 17% of patients experienced a worsening of their mood symptoms.[62]

Second-generation antipsychotics (SGAs) also have been examined in pediatric BD+ADHD. One small open-label study (N = 10) suggested that aripiprazole was effective in treating both mood and ADHD symptoms in acutely manic patients,[103] but a larger placebo-controlled trial (N = 43) by the same research group confirmed only its antimanic benefit.[61] Open-label data (N = 31) similarly suggest that risperidone leads to improvement in mania but minimal change in ADHD symptoms.[104]

Mood stabilizers have been assessed only in open-label studies. Divalproex was effective in treating mania in 40 children/adolescents with BD+ADHD but had essentially no effect on ADHD symptoms.[59] A study of combination treatment with lithium and divalproex in manic (n = 78) or depressed (n = 8) youths reported that mood symptoms responded to treatment in 42% diagnosed with BD+ADHD, compared with 57% with BD alone.[105] In an 18-month extension of that trial, patients with and without comorbid ADHD did not differ in relapse rates into mania or depression during monotherapy with lithium or divalproex, and there was no difference in efficacy between the 2 medications.[106]

Mood stabilizers in ADHD. We are aware of only 1 small 18-week double-blind crossover study (N = 23) that compared lithium and methylphenidate in adult ADHD. Both medications were associated with comparable but relatively low response rates of 37% and 48%, respectively.[107]

TABLE 4
Strength of evidence for the treatment of ADHD in adults with MDD+ADHD[a]

Level of evidence[a]	Treatment	Source of data/sample(s)[b]
1	None	—
2	Atomoxetine	MDD+ADHD(P)[117,118]
3	Bupropion	MDD+ADHD(P),[119] ADHD(A)[122-125]
	SSRIs	MDD+ADHD(P) (negative),[120] (positive),[121] ADHD(A) (negative)[132]
	SSRIs + stimulants	MDD+ADHD(A),[116] MDD+ADHD(P),[120] ADHD(A)[132]
4	CBT	ADHD(A)[145-156]
	Modafinil	ADHD(A)[109,110]
	Venlafaxine	MDD+ADHD(A),[115] ADHD(A)[133-136]
	Desipramine	ADHD(A)[128]
	Nortriptyline	ADHD(A)[137]
	Lisdexamfetamine	ADHD(A)[164,165]

Data from clinical trials in adult or pediatric MDD+ADHD samples were designated as having first-, second-, or third-line evidence as above. Regardless of study design or sample size, medications that were assessed only in noncomorbid adult ADHD patients were assigned level 4 status.

[a]Level 1 = ≥ 2 placebo-controlled trials or meta-analysis; 2 = 1 RCT with placebo arm or active comparator; 3 = prospective open-label trial with n ≥ 10; 4 = anecdotal data or expert opinion.

[b]MDD+ADHD(A) = based on studies in adult samples with MDD+ADHD; MDD+ADHD(P) = based on studies in pediatric samples with MDD+ADHD; ADHD(A) = based on studies in adults with ADHD only.

ADHD: attention-deficit/hyperactivity disorder; CBT: cognitive-behavioral therapy; MDD: major depressive disorder; SSRIs: selective serotonin reuptake inhibitors.

Modafinil and stimulants in BD. One RCT compared modafinil with placebo in the treatment of bipolar depression.[108] It reported a significantly greater improvement in depressive symptoms with modafinil (n = 41) than placebo (n = 44) over 6 weeks. Switch rates into mania and hypomania were low and similar between medication and placebo. Placebo-controlled studies also have demonstrated short-term efficacy for modafinil in adult ADHD.[109,110] Finally, open-label and retrospective data support the use of stimulant medications in BD depression without ADHD.[111,112]

In conclusion, no RCTs have evaluated any treatment in adults with BD+ADHD. One small open-label study suggested that bupropion was effective in treating ADHD

symptoms in this population, but it must be interpreted in light of its design, its small sample size, and the fact that it enrolled predominantly BD II patients. In RCTs in pediatric samples, stimulants as adjuncts to mood stabilizers were effective in treating ADHD symptoms, although 1 small study suggested that they were not effective in patients treated with the SGA aripiprazole. Furthermore, the efficacy of stimulants must be balanced against the possibility of stimulant-induced mania, although the frequency of this problem during long-term treatment in clinical settings is unclear.[113,114] Finally, mood stabilizers and SGAs were effective in treating mania in pediatric patients with BD+ADHD but had little effect on ADHD symptoms.

Treatment studies in MDD, ADHD, and MDD+ADHD

Treatment studies in MDD+ADHD. No RCTs have evaluated medications for adults with MDD+ADHD. One retrospective study (N = 17) reported that 80% of patients treated with venlafaxine demonstrated improvement in depressive and ADHD symptoms, compared with 88% treated with a stimulant-antidepressant combination and only 33% treated with stimulant monotherapy.[115] A second small (N = 11) open-label trial found that coadministered selective serotonin reuptake inhibitors (SSRIs) and stimulants also improved both depressive and ADHD symptoms.[116]

In children and adolescents with MDD+ADHD, 2 clinical trials of atomoxetine showed benefit in treating ADHD but limited impact on depressive symptoms. The first was an RCT in which atomoxetine monotherapy (n = 72) demonstrated a significant benefit over placebo (n = 70) in reducing ADHD symptoms, but not depressive symptoms.[117] The second was an open-label add-on study, in which children and adolescents with ADHD and comorbid depression or anxiety (62% of whom met full criteria for MDD or dysthymia) were treated with fluoxetine (n = 127) or placebo (n = 46) for 8 weeks, with the subsequent addition of adjunctive atomoxetine for 5 weeks.[118] By study endpoint, similar proportions had a response in ADHD symptoms (66% for atomoxetine + fluoxetine and 58% for atomoxetine + placebo), but a significantly greater proportion who received atomoxetine + fluoxetine responded for depression (98% vs 80%).

Data for antidepressants in pediatric MDD+ADHD are limited to open-label studies. These suggested that bupropion (N = 24) and fluoxetine/methylphenidate combination treatment (N = 32) were both effective in treating depressive and ADHD symptoms.[119,120] The efficacy of fluoxetine monotherapy for ADHD, however, was unclear, with only 1 of 2 studies suggesting improvement.[120,121]

Antidepressants in ADHD. A number of antidepressants have been evaluated in RCTs in adult ADHD. The best evidence is for bupropion, which has been evaluated in 4 double-blind RCTs. Three of the 4 studies showed significant superiority of bupropion over placebo,[122-124] and the fourth showed large differences in response that did not reach significance, likely because of the small sample size (N = 59).[125] There are similar efficacy data for bupropion from controlled trials in children/adolescents with ADHD.[126,127]

With respect to other antidepressants, desipramine also showed benefit for ADHD in a small placebo-controlled RCT (N = 41) in adults[128] and in several studies in children/adolescents.[129-131] One RCT (N = 98) comparing the SSRI paroxetine, dextroamphetamine, the combination, and placebo in adult patients with ADHD reported that ADHD symptoms improved significantly with dextroamphetamine alone, whereas paroxetine alone was no better than placebo, and the combination of paroxetine and dextroamphetamine was no better than dextroamphetamine alone.[132]

Other antidepressants have been studied only in retrospective or open-label studies in adults with ADHD, with preliminary evidence available for venlafaxine[133-136] and nortriptyline.[137] In children/adolescents, RCTs have demonstrated efficacy for reboxetine,[138-142] although it has not been studied in adult ADHD, whereas open-label studies show benefit for nortriptyline.[143,144]

Cognitive-behavioral therapy (CBT) in ADHD. RCTs also have shown efficacy for CBT in adult ADHD.[145-147] All of the studies examined structured, short-term interventions that included psychoeducation, skills training, and cognitive therapy. One study in 86 medication-treated adults found that 12 weeks of CBT significantly improved residual ADHD symptoms compared with a relaxation therapy control group.[147] Importantly, improvements were maintained throughout a 9-month posttreatment follow-up period. In a second study (N = 88), group meta-cognitive therapy, a psychotherapeutic technique that addresses people's dysfunctional appraisals of their cognition, resulted in significantly greater reduction in ADHD symptoms than supportive group therapy.[146] No significant changes were observed overall in measures of depression, likely because symptoms were mild in

most patients, but the subset of patients with concurrent depression showed improvement with both treatments. Open-label studies also have yielded positive results for CBT in adult ADHD.[148-156]

In summary, no RCTs have evaluated any treatments in adults with MDD+ADHD. Retrospective and open-label studies in adult patients have shown benefit for venlafaxine monotherapy, and venlafaxine or SSRIs coadministered with stimulants, in improving both ADHD and depressive symptoms. In contrast, the preponderance of data suggests that SSRI monotherapy is effective in treating depression but has limited benefit for ADHD symptoms. In adults with ADHD, a somewhat larger evidence base demonstrates that antidepressants with noradrenergic and/or dopaminergic activity, particularly bupropion, improve ADHD symptoms, and also suggests a role for CBT. In children and adolescents with MDD+ADHD, open-label studies of bupropion show benefit for depressive and ADHD symptoms, while RCTs of atomoxetine demonstrate efficacy for ADHD symptoms but limited results for depressive symptoms.

TABLE 5
Treatment recommendations for the management of ADHD in adults with BD+ADHD[a]

Lines of treatment	Treatment recommendation
First line	Bupropion
Second line	Mixed amphetamine salts,[b,c] methylphenidate,[b,c] modafinil, CBT
Third line	Atomoxetine, venlafaxine, nortriptyline, desipramine, lisdexamfetamine

[a]In individuals with BD I, ADHD pharmacotherapy should be prescribed in conjunction with optimal doses of mood stabilizers and/or SGAs, due to the risk of mood destabilization. The potential for mood destabilization in BD II is less clear. Although many patients with BD II will need ongoing treatment for mood symptoms, ADHD may sometimes be the first treatment priority, and monotherapy with antidepressants may be considered in carefully selected patients.
[b]Stimulants may sometimes be considered first-line treatments in carefully selected patients thought to be at low risk of manic switch.
[c]Stimulants may be less effective when coprescribed with dopamine-modifying agents such as SGAs.

ADHD: attention-deficit/hyperactivity disorder; BD: bipolar disorder; CBT: cognitive-behavioral therapy; SGA: second-generation antipsychotics.

Recommendations for diagnosing and managing adults with mood disorders and comorbid ADHD

Diagnosing ADHD in patients with mood disorders. Clinicians should routinely assess patients with BD and MDD for comorbid ADHD. The assessment should include:

1. A screening instrument such as the patient-rated Adult ADHD Self-Report Scale (ASRS) 6-item screen[157] or the clinician-rated ADHD Rating Scale.[158] These instruments can help identify patients at risk but do not confirm diagnoses.

2. A thorough psychiatric history to assess current and past mood and ADHD symptoms, and their relationship over time, as well as their onset, severity, pervasiveness, and functional impact, and to screen for additional comorbidities. Collateral history from a spouse, friend, or other informant enhances the reliability of this information.

3. Rating scales can be a useful adjunct to clinical assessment for fully exploring and quantifying all symptom domains, and for monitoring treatment response. There are a number of validated rating scales to choose from,[159,160] including the full version of the ASRS,[157] the Conners' Adult ADHD Rating Scales,[161] and the Weiss Symptom Record,[162] which also may be helpful in assessing for additional comorbid conditions.

4. A developmental history, supplemented by collateral information when available, to determine whether symptoms were present during childhood to a degree sufficient to impair functioning. The Wender Utah Rating Scale[163] is a validated tool for retrospectively assessing childhood ADHD symptoms.

It is crucial to distinguish ADHD from syndromal and subsyndromal mood symptoms, and clinicians should consider the diagnosis of adult ADHD in patients with typical symptoms, which are present for ≥6 months during euthymia and are significant enough to result in distress or functional impairment. However, in patients with ongoing mood symptoms, a convincing history of ADHD during euthymia supplemented by collateral information also can suffice. Confidence in the diagnosis is increased in patients with a definite history of childhood symptoms, although this is not absolutely required to make the diagnosis.

Treating patients with mood disorders and comorbid ADHD. Patients with BD or MDD and comorbid ADHD should be managed according to the general principles for treating adult ADHD outlined in the CADDRA clinical practice guidelines. These include 1) psychoeducation regarding ADHD, its functional impact, and treatment; 2) recommendations regarding behavioral interventions, such as personal organizers and modify-

TABLE 6
Treatment recommendations for the management of ADHD in adults with MDD+ADHD

Lines of treatment	Treatment recommendation
First line	Bupropion, antidepressant + long-acting stimulant, antidepressant + CBT
Second line	Desipramine, nortriptyline, venlafaxine
Third line	Antidepressant + short-acting stimulant, antidepressant + atomoxetine, antidepressant + lisdexamfetamine

ADHD: attention-deficit/hyperactivity disorder; CBT: cognitive-behavioral therapy; MDD: major depressive disorder.

ing educational, work, and other responsibilities; and 3) implementing and monitoring a specific treatment plan, which may involve medications, psychotherapy, or both.[14]

With respect to selecting specific treatments, it is clear that there is a paucity of data on the management of adults with mood disorders and comorbid ADHD. In particular, given the chronic course of ADHD, the lack of long-term studies is striking. Thus, our treatment recommendations also are informed by studies carried out in children and adolescents with BD+ADHD and MDD+ADHD and in adults with ADHD, and by our clinical experience. We have designated treatments as having level 1, 2, 3, or 4 evidence (**TABLE 3**[59,60,62,101,109,110,112,122-125,128,133-137,164,165] and **TABLE 4**[109,110,115-125,128,132-137,115-152,164,165]; see footnotes for an explanation of the levels of evidence). We have chosen first-, second-, and third-line treatments for BD+ADHD and MDD+ADHD based on the totality of efficacy and safety data and our clinical experience (**TABLE 5** and **TABLE 6**). The rationales for our choices are outlined below. It is important to note that although the available evidence suggests that adult response to treatments is similar to that of children and adolescents,[100] we cannot be certain that patients with BD+ADHD or MDD+ADHD respond similarly to those with ADHD alone. Readers should apply our recommendations with the appropriate caution, incorporating them with their clinical judgment and taking into account each patient's clinical presentation.

Bearing in mind the current state of the evidence base, our first—and strongest—recommendation is a call to the field to conduct well-designed RCTs to assess medications and other treatments in adults with BD+ADHD and MDD+ADHD.

Treatment recommendations for BD+ADHD **(TABLE 5).** Some ADHD therapies, including stimulants and antidepressants, may increase the risk of mood destabilization in patients with BD I.[114,166] ADHD should therefore be treated only in euthymic patients who are stabilized with optimal doses of mood stabilizers and/or SGAs. The potential for mood destabilization in BD II is less clear, although many patients will need ongoing treatment with mood stabilizers for mood symptoms.

For treating mania, data from pediatric samples support the use of standard mood stabilizers and SGAs such as lithium, divalproex, and aripiprazole in patients with BD+ADHD. However, there are no data regarding other antimanic therapies or for the treatment of BD depression. In the absence of compelling evidence for the superiority of any particular medications in BD+ADHD samples, we recommend that patients be treated according to CANMAT guidelines for mania and bipolar depression.[167]

For comorbid ADHD, we recommend bupropion as an adjunct to mood stabilizers as a first-line treatment, based on open-label data in adults with BD+ADHD, established efficacy in adult ADHD, and a lower likelihood of inducing mania compared with other antidepressants during treatment periods of up to 1 year.[166]

For patients who do not respond to bupropion, or are unable to tolerate it, MAS or methylphenidate as adjuncts to mood stabilizers can be recommended as second-line options, based on placebo-controlled data from studies of children and adolescents with BD+ADHD and established efficacy in adult ADHD. In fact, in light of evidence that stimulants may be more effective than antidepressants in adult ADHD, there may be situations where these medications are chosen as first-line treatments, particularly when the risk of manic switch is thought to be low. One small-sample RCT suggested a lack of efficacy for stimulants when given as adjuncts to the SGA aripiprazole, raising the possibility that dopamine-modifying agents such as SGAs may reduce the efficacy of dopamine-enhancing agents such as stimulants. Clinicians may thus consider tapering and discontinuing SGAs and substituting a mood stabilizer, if clinically warranted, when ADHD does not respond to stimulants.

Modafinil also may be recommended as a second-line treatment based on efficacy data in adult ADHD and short-term efficacy and safety in BD depression. Clinicians should be aware that there are no long-term RCT data for stimulants or modafinil in patients with BD, and their potential to destabilize mood during long-term

treatment is unclear. Thus, patients should be monitored carefully for hypomania/mania or mood cycling, and stimulants should be withdrawn if these are thought to be due to stimulant treatment.

CBT has shown evidence for efficacy in adult ADHD and is unlikely to pose a risk for mood destabilization, and also may be recommended as a second-line option. There is very limited evidence for atomoxetine, which may be considered only as a third-line treatment for patients who do not respond well to other therapies. Serotonergic-noradrenergic antidepressants such as venlafaxine, desipramine, and nortriptyline are associated with relatively high rates of treatment-emergent mania in patients with BD,[166,168,169] and should be prescribed only as third-line agents after other treatment options have failed. Finally, we note that some clinicians prefer lisdexamfetamine as a stimulant, based on data in adult ADHD and possible reduced abuse potential compared with other stimulants.[166,167] However, due to a lack of data in BD+ADHD, we include it here as a third-line option.

Treatment recommendations for MDD+ADHD **(TABLE 6).** Unlike patients with BD, individuals with MDD are not at risk for mood destabilization during ADHD treatment. However, some evidence suggests that ADHD treatments may be less effective in patients with active depression and may lead to an exacerbation of dysphoria, poor sleep, and decreased appetite.[132] Thus, in patients with moderate to severe depression, MDD should be the treatment priority. In mildly depressed or euthymic patients with significant ADHD symptoms, the order may be reversed. The following recommendations address common treatment scenarios.

ACUTE MAJOR DEPRESSIVE EPISODE + ESTABLISHED DIAGNOSIS OF ADHD. Initiating treatment with an antidepressant that has proven efficacy in depression and empirical support in adult ADHD may eliminate the need for multiple medications. As a first-line recommendation, we suggest beginning treatment with bupropion, because it is a first-line treatment for MDD and has demonstrated efficacy in uncomplicated adult ADHD.

In patients who do not respond to or cannot tolerate bupropion but express a preference for monotherapy, noradrenergic antidepressants, particularly venlafaxine, desipramine, and nortriptyline, are alternative choices. Of these, only desipramine has supporting RCT data in adult ADHD. However, because of its side effect profile and concerns regarding safety, it should be considered a second-line treatment. This is also true for venlafaxine, for which there are only open-label data in adult ADHD.

In patients who are accepting of combination therapy, combining an antidepressant that has a low propensity for drug-drug interactions (eg, escitalopram or sertraline) with a first-line treatment for adult ADHD, such as a long-acting stimulant, may be considered as a first-line option. Similarly, depending on availability and patient preference, combining an antidepressant with first-line psychotherapy for ADHD is another first-line alternative. Given positive findings from recent RCTs of adjunctive CBT in adult ADHD, coupled with extensive level 1 evidence for CBT in the treatment of depression, we would recommend considering this modality in MDD+ADHD early in treatment planning if available. However, although CBT is increasingly available for MDD, this is not yet the case for ADHD.

Short-acting stimulants, atomoxetine, and lisdexamfetamine may be considered as third-line add-ons to effective antidepressant agents. Atomoxetine should not be coadministered with SSRIs, which inhibit the cytochrome P450 2D6 isoenzyme because of the potential for pharmacokinetic interactions.

EUTHYMIC PATIENTS WITH ADHD. In situations where MDD has remitted but ADHD symptoms persist, we suggest following the CADDRA guidelines for adult ADHD, which recommend long-acting stimulants or atomoxetine as first-line treatments. These agents may be added to ongoing antidepressant treatments in patients receiving maintenance therapy. Demoralization and other mild depressive symptoms that often are directly associated with ADHD in the absence of a concurrent major depressive episode would be expected to improve with effective treatment of ADHD. ■

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