The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders

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BACKGROUND: Comorbid mood and anxiety disorders are commonly seen in clinical practice. The goal of this article is to review the available literature on the epidemiologic, etiologic, clinical, and management aspects of this comorbidity and formulate a set of evidence- and consensus-based recommendations. This article is part of a set of Canadian Network for Mood and Anxiety Treatments (CANMAT) Comorbidity Task Force papers.

METHODS: We conducted a PubMed search of all English-language articles published between January 1966 and November 2010. The search terms were *bipolar disorder* and *major depressive disorder,* cross-referenced with *anxiety disorders/symptoms, panic disorder, agoraphobia, generalized anxiety disorder, social phobia, obsessive-compulsive disorder,* and *posttraumatic stress disorder*. Levels of evidence for specific interventions were assigned based on a priori determined criteria, and recommendations were developed by integrating the level of evidence and clinical opinion of the authors.

RESULTS: Comorbid anxiety symptoms and disorders have a significant impact on the clinical presentation and treatment approach for patients with mood disorders. A set of recommendations are provided for the management of bipolar disorder (BD) with comorbid anxiety and major depressive disorder (MDD) with comorbid anxiety with a focus on comorbid posttraumatic stress disorder, use of cognitive-behavioral therapy across mood and anxiety disorders, and youth with mood and anxiety disorders.

CONCLUSIONS: Careful attention should be given to correctly identifying anxiety comorbidities in patients with BD or MDD. Consideration of evidence- or consensus-based treatment recommendations for the management of both mood and anxiety symptoms is warranted.

INTRODUCTION

Comorbid mood and anxiety disorders are commonly seen in clinical practice. This article reviews the available literature on the comorbidity of mood and anxiety disorders, with an emphasis on examining etiologic processes, clinical implications, and treatment issues associated with these comorbidities. A series of evidence-based (when available) and consensus-based treatment recommendations are outlined.

These recommendations are part of a series of articles published by the Canadian Network for Mood and Anxiety Treatments (CANMAT) as recommendations for the management of patients with major depressive disorder (MDD) or bipolar disorder (BD) and comorbid medical or psychiatric conditions (subsequently referred to as the CANMAT Comorbidity Task Force recommendations). CANMAT comprises a group of clinical researchers with experience and expertise in various aspects of mood and anxiety disorders, who have published guidelines for the management of MDD and BD.[1,2] Readers are encouraged to review the accompanying introductory article in this issue of *Annals of Clinical Psychiatry (ACP)*, which outlines the overarching aims and principles of the CANMAT Comorbidity Task Force recommendations.

Mood and anxiety disorders are highly prevalent conditions associated with a tremendous public health burden. This combination of symptom clusters will be familiar to most mental health treatment providers. Many people with either BD or MDD experience significant symptoms of anxiety and may meet criteria for one or more anxiety disorders, including panic disorder (PD), social phobia (SP), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD).

Given the many possible combinations of specific mood and anxiety disorders, we have chosen to highlight what we believe are the most clinically challenging comorbidities that have not been the focus of previous CANMAT guidelines,[1,2] and/or those that had been sufficiently studied to permit evidence-based recommendations to be made. Based on these principles, this article

somewhat more heavily emphasizes anxiety comorbidity in the context of BD than MDD. MDD and comorbid anxiety have been extensively studied, and recently published treatment guidelines[1,3] have provided evidence-based recommendations. The overall conclusions indicate that the presence of anxiety in patients with MDD generally has less impact on the management plan than anxiety associated with BD. Prior reviews of the BD and anxiety comorbidity have been published[4,5] and identify limitations of the available literature. The current CANMAT Task Force builds on these reviews by including more up-to-date studies, broadening the focus to include specific anxiety disorders and age groups, and more comprehensively outlining specific recommendations that are both evidence- and consensus-based.

Within MDD, we have placed the emphasis on particular comorbid anxiety scenarios, including MDD and PTSD, MDD and anxiety in youth, and cognitive-behavioral therapy (CBT) for comorbid mood and anxiety disorders. The comorbidity of BD and broadly defined anxiety is reviewed in detail, with special emphasis on BD with OCD, PD, and PTSD.

The detailed methodology for the literature review and development of treatment recommendations has been outlined in the introductory article to this set of articles (see page 2 of this issue of *ACP*). When available, levels of evidence for specific interventions were determined using a priori criteria, and management recommendations were based on integration of level of evidence and clinical opinion of the authors.

Bipolar disorder and anxiety symptoms/ disorders

Prevalence. While modern diagnostic classification systems facilitate the recording of comorbid disorders, the link between BD (or earlier diagnostic labels for the illness) and anxiety symptoms has been reported for centuries.[6] Recent epidemiologic surveys have estimated that 52% to 75% of adult respondents with BD self-report a lifetime history of an anxiety disorder.[7-9] Numerous clinical samples have confirmed high rates of comorbidity, with approximately 24% to 56% of BD patients meeting criteria for a comorbid anxiety disorder.[10-18] While comorbidity rates vary for specific anxiety disorders, most studies report that a substantial number of patients have >1 anxiety disorder. Data from the Stanley Foundation Network suggest that comorbid anxiety may be more common in female than male patients with BD.[17] BD sub-

types I and II both are commonly associated with anxiety, with no clear difference between subtypes.[19]

Clinical manifestations. The epidemiologic and clinical literature is consistent in reporting the negative impact of comorbid anxiety among patients with BD. Comorbid anxiety symptoms or disorders have been associated with earlier age of onset of BD, greater burden of depressive symptoms, increased number of total mood episodes, mixed episodes, increased irritability, greater risk of substance use disorders, increased psychological distress, lower functioning and quality of life, poorer treatment response, longer time to remission, risk of earlier relapse, more severe medication side effects, nonadherence to treatment, and increased health care utilization.[9-12,16,20-29]

More suicidal ideation and greater risk of a suicide attempt also have been associated with comorbid anxiety in BD, with preliminary data suggesting that this association may be partially mediated through increased rumination[30] and through higher rates of cluster B personality disorders.[14] Importantly, effects of comorbid anxiety on decreased quality of life, decreased role functioning, and increased symptom burden appear generally to be independent of clinical state and other comorbidities.[31] This supports the inclusion of comorbid anxiety in the diagnostic classification of BD subtypes.[32,33] Along these lines, the DSM-5 committee has proposed the inclusion of an anxiety dimension rating for all patients diagnosed with a mood disorder.[34] This step forward would further support much needed clinical and research attention focused on this commonly observed comorbidity.

Etiology. Although there is no comprehensive etiologic model to fully explain BD and anxiety comorbidity, a number of clinical and biologic lines of research have provided key findings. First, the relationship between BD and anxiety appears to vary across the life span. For instance, data suggest SP most often precedes mania and then resolves, while other comorbid anxiety disorders tend to persist.[35] A staging model has been proposed in which anxiety disorders appear as an early manifestation of psychopathology in high-risk youth who go on to develop bipolar illness.[36]

Further research has supported the idea that anxiety symptoms are a manifestation of BD itself for some patients, rather than a separate condition. For instance, BD patients with a family history of BD appear more likely to have comorbid panic,[37] with evidence for shared genetic risk (outlined in the section on BD and PD).

There also is emerging functional neuroimaging data on specific neurobiological correlates of both state and trait anxiety symptoms among patients with BD, even when controlling for the severity of depressive symptoms. Although the limbic structures—including anterior cingulate, amygdala, and hippocampus—have been the primary focus, the full extent of the involved network remains to be elucidated.[38,39]

Examination of the independent role of anxiety in the neurobiology of BD is informative, because the relationship between anxiety and BD appears to be only partially mediated by depression.[40] An interplay between neurotransmitters and neuromodulators contributing to the overlap of BD and anxiety has been speculated, but there are no direct data addressing this possibility.[6]

Treatment studies. Three types of treatment studies have examined outcomes in patients with BD and anxiety:

1. Treatment of anxiety symptoms in patients with BD and an a priori diagnosed comorbid anxiety disorder

2. Reports on change in anxiety symptoms based on secondary analyses among BD patients treated for a mood episode

3. Examination of anxiety symptoms as predictors of response or nonresponse to specific treatments for BD.

See **TABLE 1** and **TABLE 2** for summaries of levels of evidence and recommendations for pharmacologic treatments for BD with comorbid anxiety.

TREATMENT OF ANXIETY SYMPTOMS IN PATIENTS WITH BD AND A COMORBID ANXIETY DISORDER. Two randomized controlled trials (RCTs) have specifically examined treatment of BD patients with an a priori established comorbid anxiety disorder. In a 12-week, randomized, single-blind pilot study, lithium-treated euthymic BD I or BD II patients with a current anxiety disorder were randomized to adjunctive olanzapine (mean dose, 7.7 mg) or lamotrigine (mean dose, 96.7 mg). Both medications significantly reduced total Hamilton Anxiety Rating Scale (HAM-A) scores, with olanzapine (part of level 1) significantly more effective in several secondary outcomes. Modest dosing and slow titration of lamotrigine (level 2) may have been a factor, but the study provided supportive evidence for use of either add-on treatment.[41] In the other RCT, risperidone monotherapy (mean dose, 2.5 mg) was found to be no more effective than placebo in reducing anxiety symptoms for patients with BD I, BD II, or BD not otherwise specified (NOS) and comorbid GAD or PD (N = 111)[42] (level 2 – negative).

<u>STUDIES REPORTING CHANGE IN ANXIETY SYMPTOMS AMONG BD PATIENTS TREATED FOR A MOOD EPISODE</u>. A number of studies examining atypical antipsychotics and anticonvulsants for treating bipolar depression have reported on change in anxiety symptoms. Quetiapine and olanzapine both have been found to reduce anxiety symptoms in this context. Four large RCTs of quetiapine monotherapy (300 or 600 mg) for patients with BD I or BD II depression reported a significantly greater reduction in total HAM-A scores compared with placebo as early as week 1 of treatment[43-45] (level 1). Both 300-mg and 600-mg doses appeared to exhibit similar anxiolytic effects. The 2 studies that included an active comparator arm (paroxetine,[44] lithium[45]) found a numerical, but not significantly greater, decline in anxiety symptoms in the quetiapine groups compared with active comparator groups. However, these studies were not powered for this comparison, and modest dosing of comparator arms may have impacted the results. Paroxetine treatment was associated with significantly greater reduction in anxiety symptoms compared with placebo (level 2).

In a large 8-week RCT, olanzapine (part of level 1) and olanzapine-fluoxetine combination (OFC) (level 2) were both found to be more effective than placebo in reducing total HAM-A scores among patients treated for BD I depression. There was a nonsignificant trend toward greater anxiolytic effect with OFC compared with olanzapine.[46] In a Canadian naturalistic observational study, BD patients receiving treatment with olanzapine experienced greater reduction in anxiety symptoms compared with patients receiving other treatments.[47]

Several smaller studies have examined the potential anxiolytic effects of anticonvulsants for patients with bipolar depression. In a large case series (N = 43), adjunctive gabapentin (mean dose, 1,270 mg) was reported to have both anxiolytic and antidepressant effects (level 3).[48] Two studies of valproic acid have also suggested anxiolytic effects with monotherapy treatment for patients with BD I or rapid-cycling BD (level 2).[49,50]

In 2 small BD maintenance studies, neither adjunctive gabapentin[51] nor oxcarbazepine[52] exhibited a clear effect on anxiety ratings compared with adjunctive placebo.

<u>EXAMINATION OF ANXIETY SYMPTOMS AS PREDICTORS OF RESPONSE OR NONRESPONSE TO TREATMENT FOR BD</u>. As outlined earlier, the presence of anxiety symptoms or disorders has been associated with poorer response to treatment for BD. Several studies have examined differences in medication-specific treatment response, based on subtypes

TABLE 1

Levels of evidence for specific pharmacotherapies for treatment of comorbid anxiety symptoms/ disorders in adult patients with bipolar disorder

Level of evidence	Pharmacologic agent
Level 1 (≥2 RCTs or meta-analysis)	Quetiapine[a,b] Olanzapine[a,b]
Level 2 (1 RCT)	Divalproex sodium[a,b,c] Lamotrigine[a,b] Serotonergic antidepressants[d] Olanzapine-fluoxetine combination[a]
Level 3 (prospective open-label trial with n ≥ 10)	Gabapentin[a] Lithium[a,b] Risperidone[b,e] Aripiprazole[b]
Level 4 (anecdotal data or expert opinion)	Benzodiazepines[f] Pregabalin[f]

Regardless of study design or sample size, medications that were assessed in noncomorbid patients were assigned level 4 status.

[a]Evidence relates to comorbid anxiety symptoms.
[b]Level 3 evidence specific to comorbid OCD.
[c]Evidence specific to comorbid PD.
[d]Evidence specific to paroxetine.
[e]Risperidone has level 2 (negative) data for comorbid anxiety symptoms.
[f]No published data. Level 4 based on the authors' clinical opinion.

OCD: obsessive-compulsive disorder; PD: panic disorder; RCT: randomized controlled trial.

of anxious or nonanxious BD. For instance, Passmore et al[53] found that lamotrigine responders were more likely to have experienced panic attacks than lithium responders. In a separate study of a large inpatient BD sample, anticonvulsants, but not lithium (level 3), were less effective in patients with comorbid anxiety.[13] Data from Young et al[54] showed a trend toward poorer response to lithium in patients with anxious vs nonanxious BD. The overall results are therefore equivocal, and further evidence is required before clear conclusions can be drawn as to whether anxiety comorbidity is predictive of response to specific mood stabilizers.

Antidepressants for patients with BD and comorbid anxiety. Although serotonergic antidepressants are the mainstay of pharmacologic treatment for anxiety disorders,[21] using these medications in patients with BD poses known risks of illness destabilization.[2] Because anxiety disorders generally are associated with chronic symptom burden, rather than discrete episodes, long-term antidepressant use may result in even greater risk of illness destabilization compared with short-term use for discrete episodes of depression.

TABLE 2

Recommendations for the pharmacologic treatment of comorbid anxiety symptoms/ disorders in adult patients with bipolar disorder

Level of recommendation	Pharmacologic agent
First line[a]	Gabapentin,[b] quetiapine[c]
Second line	Divalproex sodium, lamotrigine, serotonergic antidepressants,[d] olanzapine,[c] olanzapine-fluoxetine combination[c]
Third line	Lithium, risperidone,[c] aripiprazole,[c] pregabalin, medium- or long-acting benzodiazepines[e]

[a]Ensuring adequate mood stabilization before considering specific treatments for anxiety symptoms is advisable.

[b]Despite only level 3 evidence, was given first-line recommendation based on data in primary anxiety disorders and positive risk-benefit profile with benign side effect profile noted in clinical experience.

[c]Risk of metabolic adverse effects must be considered, and all patients prescribed atypical antipsychotics should undergo baseline and follow-up, guideline-based weight and metabolic monitoring.

[d]The decision of whether to use an antidepressant must weigh efficacy data for noncomorbid primary anxiety disorders vs known risk of illness destabilization, especially among adult patients with BD I and youth with any form of BD. Antidepressants should be considered only for patients receiving adequate anti-(hypo)manic mood stabilization (as required). Among serotonergic antidepressants, SNRIs have been associated with higher risk of manic switch than SSRIs, and their use should be limited.

[e]In the absence of data, the decision of whether to use a benzodiazepine must weigh short- and long-term anxiolytic efficacy data/opinion for anxiety symptoms and primary anxiety disorders vs known risks of dependence or abuse, especially among high-risk patients. While short-term, rapid alleviation of anxiety symptoms with benzodiazepines clearly is evident in clinical practice, clinicians should vigilantly monitor for any early signs of abuse and for evidence of physiological or psychological dependence.

BD: bipolar disorder; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors.

Somewhat surprisingly, antidepressant trials for BD depression generally have not reported on the impact of anxiety comorbidity or change in anxiety symptoms. Although several of these antidepressant trials have a sample size sufficient to address the issue, we did not find any reports on the impact of anxiety symptoms in antidepressant RCTs for bipolar depression,[55-57] other than those in which paroxetine was studied as an active comparator (level 2). Furthermore, there are no studies specifically focusing on patients with BD and a comorbid anxiety disorder.

Notwithstanding the absence of controlled trials, antidepressants commonly are prescribed to BD patients for treating anxiety symptoms. A large epidemiologic analysis found the presence of a comorbid anxiety disorder to be the strongest predictor of antidepressant use among patients with BD (odds ratio >2), even more than the presence of depressive episodes, and most were receiving antidepressant monotherapy, rather than in combination with antimanic medications.[20] Similarly, in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) clinical sample, BD patients with comorbid anxiety disorder were more likely to receive treatment with an antidepressant (44% vs 33%) or benzodiazepine (29% vs 15%) than BD patients without anxiety.[58]

This finding also highlights the common use of benzodiazepines to treat anxiety symptoms for BD patients (level 4). This clinical practice has not been extensively studied, despite the regular use of benzodiazepines as "rescue medications" in registration trials with numerous mood stabilizer agents.

Bipolar disorder and specific comorbid anxiety disorders

Bipolar disorder and obsessive-compulsive disorder. An estimated 21% to 25% of BD I and BD II respondents in the Epidemiologic Catchment Area (ECA) survey and National Comorbidity Survey Replication (NCS-R) met lifetime criteria for comorbid OCD.[7,59] Lower rates (4%) were reported for patients with subthreshold BD. In large outpatient clinical samples, 10% to 16% of BD patients had comorbid OCD,[60-63] whereas an inpatient study reported OCD comorbidity rates of 35% at the time of hospital admission,[64] but only 7% when patients were euthymic.[65]

The temporal association between BD and OCD also was examined in the NCS-R, with OCD developing first in 37% of patients, mood episodes developing first in 52% of patients, and onset of both in the same year in 11% of patients.[66] Small clinical studies have conflicting results, with a report of low rates of OCD present at the time of first mania[67] and other findings that OCD predominantly preceded the mood disorder in a female BD sample.[68]

These studies highlight the relevance of a longitudinal approach to understanding the interplay between BD and OCD, because symptoms of OCD may not be present throughout the course of BD illness. At a practical level, this suggests that treatment providers should be cognizant that the lack of syndromal OCD at time of first assessment should not be taken as evidence that OCD symptoms may not develop later in the course of illness, and vice versa. Furthermore, symptoms of OCD most often are present during periods of depression or euthymia, and patients may not exhibit symptoms when presenting with mania. Given the high rates of comorbid-

ity in both epidemiologic and clinical samples, careful screening and ongoing monitoring for OCD symptoms among patients with BD is warranted.

The presence of comorbid OCD among patients with BD has been associated with female sex, rapid cycling, a more chronic illness course, alcohol dependence, personality disorders, greater risk of suicide attempt, lower quality of life, longer period of untreated illness, and greater nonadherence to treatment compared with BD patients without OCD.[61,62,65,69] The type of OCD symptoms also may vary depending on the presence or absence of BD, with some evidence of higher rates of sexual and religious obsessions, and lower rates of checking rituals among patients with BD/OCD compared with OCD only.[70]

Treatment of BD with comorbid OCD is a significant challenge, with a very limited evidentiary base for specific pharmacologic or psychotherapeutic modalities. There are no RCTs testing interventions for BD with OCD. Small case series or case reports suggest the potential benefit of lithium,[71] anticonvulsants,[71,72] olanzapine,[73,74] risperidone,[75,76] quetiapine,[77] or aripiprazole[78] to manage both mood and OCD symptoms (level 3 for each). In the largest clinical sample to date (N = 68), Perugi et al[79] reported that most patients with BD/OCD had received antidepressant treatment, including clomipramine and selective serotonin reuptake inhibitors (SSRIs). Switch rates during short-term follow-up were 10.5%, with previous antidepressant-induced (hypo)mania seen in 39% of patients on an antidepressant alone, compared with 9% among patients receiving an antidepressant and a mood stabilizer. Combinations of mood stabilizer(s) and/or atypical antipsychotics were used for nearly half of the patients (42%).

Bipolar disorder and panic disorder. Results from the ECA survey suggest greater lifetime prevalence of PD among patients with BD (21%) compared with only 10% of MDD patients having PD.[59] Clinical samples of BD outpatients also have reported comorbid PD rates in the range of 14% to 27%.[10,63,80,81] Not surprisingly, rates of comorbid panic attack are even higher, up to 35% in BD respondents to the National Comorbidity Survey (NCS),[82] and 47% in a large clinical sample.[83] The presence of PD among patients with BD has been associated with female sex, more frequent and severe depressive episodes, rapid cycling, mixed episodes, greater likelihood of having depression as the first mood episode, other psychiatric comorbidities, higher scores on harm-avoidance mea-

TABLE 3

Treatment of bipolar disorder with comorbid anxiety symptoms/disorders

Summary

- Few treatment studies have focused exclusively on BD with comorbid anxiety symptoms/disorders, but there is a growing body of literature that can inform management decisions for patients with BD and anxiety (**TABLE 1**).

- Given the relative scarcity of treatment data, the different levels of evidence and recommendations are very much influenced by the studies that have been conducted. Very few comparative studies are available, leaving clinicians with a list of reasonable treatment options, but without clear treatment algorithms.

- Medications such as atypical antipsychotics or gabapentin also have evidence for use in primary anxiety disorders, which further supports their use in treating anxiety symptoms in BD patients.

- Other medications with efficacy in primary anxiety disorders (eg, pregabalin) have not been studied in BD patients with anxiety; therefore, recommendations are based solely on clinical opinion.

- There is a paucity of information on any possible differences in the burden of side effects and adverse treatment outcomes when treating BD with anxiety compared with BD alone.

Overall recommendations

- An overall strategy of first ensuring adequate mood stabilization before considering specific treatments for anxiety symptoms is advisable. This "stepwise" approach should be used when selecting primary mood-stabilizer treatments as well as when considering concomitant use of psychological or pharmacologic therapies.

- Several anticonvulsants and atypical antipsychotics have sufficient evidence and clinically observed benefit to be recommended as first- or second-line treatment for patients with BD and comorbid anxiety (**TABLE 2**).

- Caution is recommended when considering antidepressants for this indication. Although clinical experience suggests that some BD patients benefit from the anxiolytic properties of serotonergic antidepressants, there is clear potential risk of illness destabilization, especially among younger patients. When antidepressants are used, ensuring adequate mood stabilization and close monitoring for treatment-emergent manic symptoms is warranted.

- Although short-term, rapid alleviation of anxiety symptoms with benzodiazepines is an important clinical tool, clinicians should vigilantly monitor for any early signs of abuse/dependence.

- CBT should be considered as a first-line treatment option for management of anxiety in youth with BD.

Standard risk-benefit analyses and accepted treatment monitoring guidelines (eg, metabolic monitoring for atypical antipsychotic use) are applicable when utilizing any treatments for BD with anxiety.

BD: bipolar disorder; CBT: cognitive-behavioral therapy.

sures, and greater likelihood of a family history of mood disorders.[82-88] A comprehensive review[89] confirmed the finding of increased suicidality among patients with BD/PD compared with BD only.

Etiology. An interesting body of literature has examined the possible shared genetic risk for BD and PD. In a cohort of familial BD, MacKinnon et al[81] found some evidence of shared genetic risk for the 2 conditions. Other data also have supported the hypothesis of a genetic subtype of BD and panic,[90,91] and in a bipolar family-genetic study, PD was present almost exclusively in family members with BD, again suggesting a close association with bipolar illness.[92] MacKinnon and Zamoiski have proposed a novel explanatory model for the linkage between BD and PD that centers on putative deficits in plasticity-dependent processes of conditioning, associated with abnormal functioning of the amygdala.[93] Furthermore, CO_2 hypersensitivity has been implicated as a possible shared vulnerability between BD and PD.[94] Although further data are required to support these hypotheses, the approach to studying the neurobiological correlates of complex phenotypes that incorporate common comorbidities promises to improve our understanding of these ubiquitous clinical presentations.

In addition to neurobiological processes, psychological factors may predispose individuals to developing this comorbidity. Elevated levels of anxiety sensitivity during a period of manic symptoms have been shown to be one mediating factor in the development of comorbid PD among patients with BD.[95]

Treatment. There are limited data on pharmacotherapeutic approaches for patients with BD and PD. In the largest treatment study, lifetime panic spectrum among BD I patients (N = 66) was associated with a significantly longer median time to remission of the index mood episode (44 vs 17 weeks)[84] for participants in a clinical trial involving algorithm-based pharmacotherapy plus either intensive clinical management or interpersonal and social rhythm therapy.[84]

Two open-label studies have examined valproate for the treatment of BD with PD (level 3). A 3-year, open-label, add-on study of valproate (mean dose, 687 mg/d) among patients with comorbid BD II and PD (n = 35) already receiving treatment with a tricyclic antidepressant or paroxetine reported 89% remission rates for panic symptoms at some point in the study, with 49% experiencing a subsequent relapse.[96] An 8-week, open-label study of the addition of divalproex sodium in 5 patients

with BD II reported improved panic symptoms in the majority of patients.[97] A case report of add-on olanzapine reported resolution of PD in a patient with BD II.[98]

Bipolar disorder and posttraumatic stress disorder

Epidemiology and clinical implications. Patients with BD report elevated rates of lifetime PTSD ranging from 16% to 39%.[7,99] Similar to the 2:1 ratio of PTSD favoring women over men, women with BD (both BD I and II) are nearly twice as likely to have PTSD as men with BD.[100] The comorbidity of BD and PTSD is particularly important because of the role of early stress in the initiation and relapsing course of bipolar illness. Adult comorbid BD and PTSD is significantly associated with childhood sexual abuse, adult sexual assault, and adult survival of the suicide, homicide, or accidental death of a close friend or relative. BD adults with severe childhood adversity have a more severe course of bipolar illness than those without such a history. Patients with BD and early childhood adversity or trauma have an earlier age of onset and experience a greater number of subsequent manic or depressive episodes, a faster cycling pattern, more suicide attempts, and an increased number of additional psychiatric and medical disorders, including a higher incidence of alcohol or substance abuse.[100-103]

Patients with BD are at high risk of trauma exposure. Trauma might result from impulsive or erratic behavior associated with psychosis or mania, and traumatic events that occur during manic or hypomanic episodes have a higher likelihood of inducing PTSD symptoms.[101] BD patients are at increased risk of childhood trauma,[102-104] and are more likely to have a family member with BD, which may heighten trauma exposure. Childhood abuse has been shown to have occurred in as many as one-half of adult patients with BD,[105] although possible links between childhood trauma and subsequent PTSD in this population are not fully understood. A history of early trauma may be related to both the etiology and course of BD,[99] and severe trauma, such as sexual assault, has been associated with a poor BD prognosis.[106]

Treatment. No studies have specifically examined treatment of comorbid BD and PTSD. In the absence of data, it is reasonable that BD, when it co-occurs with PTSD, should be managed in a "stepwise" approach, with the initial use of mood stabilizers, such as lithium, antipsychotics, or anticonvulsants. There are limited data on the efficacy of anticonvulsants for treating PTSD

and somewhat more evidence for the use of atypical antipsychotics used in combination with an antidepressant. Mood stabilization should take precedence over other treatment approaches, and managing significant anxiety in the short term with medium- to long-acting benzodiazepines such as clonazepam or lorazepam is an appropriate treatment option. Once mood stability is established, and if anxiety is a focus of clinical concern, then use of combination mood stabilizers with or without an SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant can be undertaken with caution.

Comorbid anxiety disorders among children and adolescents with bipolar disorder

Burden of comorbid anxiety. Estimates regarding the prevalence of anxiety disorders among youth with BD are broad, ranging from 14% to 49% in large-scale observational studies.[107-110] Correlates of anxiety among youth with BD include higher rates of suicide attempts and psychiatric hospitalization, more BD II, and more severe depressive symptoms. A positive family history of depression also is more likely in this population.[104,111,112] Preliminary findings suggest that these clinical features may have neuropsychological and neuroanatomic underpinnings.[113,114] A 12-month prospective study of 71 adolescents with BD following their first hospitalization for a manic or mixed episode found that comorbid anxiety disorders were associated with a significantly lower likelihood of syndromic recovery.[115]

Treatment response. A recent secondary analysis of 3 open-label olanzapine studies in pediatric BD found the antimanic response among patients with comorbid OCD (n = 20) was significantly poorer than patients without comorbid OCD (n = 32). Response was observed in 25% of youth with comorbid OCD vs 63% of those without comorbid OCD.[116] Another recent study found that the *absence* of GAD was significantly associated with nonresponse to mood stabilizers.[117] No published randomized controlled studies to date, however, have explicitly examined the impact of comorbid anxiety disorders on treatment response of BD in youth.

Treatment-emergent hypomania. A study of 43 outpatient adolescents with BD found that 36% of those with comorbid anxiety disorders, but none of those without comorbid anxiety disorders, had a history of treatment-emergent hypomania.[80] A subsequent study found that treatment-emergent hypomania was somewhat more common among children and adolescents with comorbid

OCD (30% vs 22% without OCD).[118] A third study found a markedly increased risk of treatment-emergent mania among BD youth with antecedent anxiety disorders.[119] In each of these studies, youth were naturalistically treated with mood-stabilizing medication. Recent treatment guidelines advise caution in light of the increased risk of treatment-emergent manic episodes and/or the induction of rapid cycling, but do not address the differential treatment of BD with comorbid anxiety.[120] Moreover, in light of evidence that anxiety disorders often predate BD,[121] particularly among high-risk offspring of adults with BD,[122] careful screening for a history of manic or hypomanic symptoms is warranted before treatment with antidepressants. Pending further research on this topic, CBT may offer the best risk-benefit ratio in the treatment of anxiety among youth with BD. Similarly, CBT should be considered among first-line treatment options for depressed offspring of adults with BD. However, because SSRIs are efficacious for anxiety disorders among youth, particularly when combined with CBT,[123] this class of medications is an important option to consider when treating bipolar offspring with anxiety disorders, albeit with close prospective monitoring. Factors to consider when estimating the risk of treatment-emergent mania among offspring of adults with BD include the degree of familial loading for BD[122] and presence of comorbid anxiety in the parent with BD.[124]

See **TABLE 3** for a summary and recommendations for treating BD with comorbid anxiety.

Major depressive disorder with comorbid anxiety symptoms/disorders

Overview of MDD and anxiety. Depressive and anxiety disorders are among the most prevalent mental health problems,[125,126] and 30% to 50% of adults with MDD have a comorbid anxiety disorder.[127] Approximately one-half of adults with an anxiety disorder have a diagnosable depressive disorder.[128] Comorbid anxious and depressive disorders often are recurrent, chronic illnesses that have significant associated morbidity and mortality.[129-133] In general, adults with anxiety and depression have an increased risk of academic, occupational, and interpersonal difficulties, often persisting after the acute episode has resolved.[134-138]

MDD and anxiety symptoms/disorders: Pharmacologic treatments. Some data suggest that patients with MDD and comorbid anxiety have a poorer response to pharmacotherapy than patients with MDD alone.[139,140] A secondary analysis of Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study data

TABLE 4

Treatment of major depressive disorder with comorbid anxiety symptoms/disorders

Summary
• There is no strong basis for significantly altering the pharmacotherapeutic treatment of MDD when it is comorbid with anxiety.
• There are a number of RCTs examining the effects of CBT for comorbid depression and anxiety disorders, often using dimensional scale scores (eg, BDI scores) rather than a full DSM-IV-TR mood diagnosis.
• For patients with comorbid depression and SP or OCD, higher depression levels at pretreatment predict worse response to CBT.
• For patients with comorbid depression and PD/A or GAD, the moderating influence of depression on response to CBT is equivocal.
• There is a small body of literature suggesting that post-CBT depression scores may confer vulnerability for risk of relapse and recurrence of the anxiety disorder if the depression is not fully treated.
• There are limited data examining the treatment of mood or anxiety symptoms in patients with mood disorders and comorbid PTSD. Several first-line treatments for noncomorbid PTSD can, however, be recommended for patients with MDD and PTSD, based on strong noncomorbid data for each diagnosis and positive clinical experience.
• Anxiety appears to be a negative predictor of outcome in the treatment of adolescent MDD.
Overall recommendations
• Recent Canadian and US treatment guidelines for MDD are applicable to patients with comorbid anxiety, with some evidence to support first-line use of serotonin reuptake inhibitors (SSRIs/SNRIs).
• Taking a "start low, go slow, aim high" approach to antidepressant treatment is advisable; this may take ≥12 weeks.
• For patients who receive CBT for comorbid depression and an anxiety disorder, if depression is in the severe range and/or meets the diagnostic threshold, consider treating the depression first to enhance engagement, the successful completion of exposure-based tasks, and between-session homework. The anxiety disorder would then be treated in the second instance. If depression is in the mild to moderate range of severity and subthreshold diagnostically, then proceed with the CBT treatment of the primary anxiety disorder with minimal adjustment. However, following the successful treatment of the anxiety disorder, the aim should be to directly treat the secondary depressive episode or reduce residual symptoms of depression to the status of remission to reduce risk of relapse and recurrence.
• For patients with depression and comorbid PTSD, CBT (with a focus on prolonged exposure), SSRI or SNRI antidepressant, or a combination of SSRI/SNRI plus CBT are recommended first-line treatments.
• For patients with depression and comorbid PTSD who are nonresponders to first-line treatment, clinical opinion of the authors (in the absence of data) suggests that use of adjunctive atypical antipsychotics or anticonvulsants should be considered, especially in the context of high levels of anger, irritability, and distress.
• EMDR should not be considered a primary treatment for comorbid PTSD and depression.
• Combination pharmacotherapy and CBT may offer enhanced benefits among adolescents with treatment-resistant MDD along with comorbid anxiety.

BDI: Beck Depression Inventory; CBT: cognitive-behavioral therapy; EMDR: eye movement desensitization and reprocessing; GAD: generalized anxiety disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PD/A: panic disorder with agoraphobia; PTSD: posttraumatic stress disorder; RCTs: randomized controlled trials; SNRI: serotonin-norepinephrine reuptake inhibitor; SP: social phobia; SSRI: selective serotonin reuptake inhibitor.

reported lower response rates, longer time to improvement, and greater side effect burden among patients with anxious depression.[141] However, not all studies have found differences in treatment response,[142-146] and there is no strong evidentiary base for significantly altering the treatment of MDD when comorbid anxiety symptoms are present. Panzer[147] reviewed 28 randomized trials of antidepressant medications and found no differences among medications in reducing depression and anxiety symptoms in patients with MDD who have moderate to severe anxiety symptoms.

The CANMAT guidelines for pharmacologic management of adults with MDD were published in 2009.[148]

This article will not repeat the principles and recommendations contained in the CANMAT guidelines that, in summary, did not find evidence to substantially alter treatment for MDD among patients with comorbid anxiety symptoms. The 2010 American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder (third edition)[3] also reviewed the evidence for treatment of MDD with comorbid anxiety. The principal finding was that both depressive and anxiety symptoms can respond well to antidepressant pharmacotherapy. Clinical pearls of starting with a low dose to avoid early exacerbation of anxiety and then slowly increasing the dose as tolerable were

reiterated. Acknowledgement of the adjunctive role of benzodiazepines also was addressed.

Add-on treatments, such as atypical antipsychotics, gabapentin, pregabalin, and other anticonvulsants, have been studied as adjunctive treatments for both depressive and anxiety symptoms. Although there are limited data on their use for patients with MDD and comorbid anxiety symptoms, the recent guidelines considered these medications to be reasonable options for patients who do not respond to first-line antidepressant pharmacotherapy.

With regard to specific comorbidities, some data suggest differences among medications. For example, sertraline was found to be as effective and more tolerable than imipramine for patients with MDD and PD.[149] Sertraline also was found to be more efficacious than desipramine among patients with MDD and OCD. With extensive evidence for use of serotonergic antidepressants for treating primary anxiety symptoms,[150] first-line use of SSRI/SNRI medications for patients with comorbid depression and anxiety appears warranted.

MDD and PTSD

Epidemiology and clinical implications. More than 80% of individuals with PTSD also have another psychiatric disorder, including MDD or BD.[151-156] From 21% to 94% of PTSD patients have comorbid depression,[157-161] 39% to 97% have comorbid anxiety,[160,162-164] and 11% to 67% have anxiety, depression, and PTSD.[165]

Several comorbidity models have been reported in the literature. There are data to support at least 4 types of interaction between depression and PTSD, including: 1) PTSD increasing the risk of depression; 2) depression increasing the risk of PTSD; 3) shared risk factors; and 4) symptom overlap. The exact nature of the interaction between depression and PTSD varies among patient types, but the implications for understanding etiologic factors, determining prognosis, and planning treatment are important to consider. In most circumstances, PTSD is the dominant disorder following traumatic events, which then leads to the development of comorbid anxiety and MDD.[166]

The addition of another psychiatric disorder worsens the prognosis for PTSD and raises substantial treatment challenges.[156] Patients with MDD and PTSD comorbidity have been shown to experience more severe PTSD and depression symptoms, difficulty with psychosocial adjustment, more dysfunctional sleep patterns, and more disability days.[157,166-170] Both epidemiologic and

clinical studies have found that among anxiety disorders, PTSD is more strongly predictive of suicidal ideation and attempt.[171-173]

Etiology. It is likely that the combination of genetics, early life adversity, and ongoing psychosocial stressors create a vulnerability to developing MDD and PTSD.[174] Some of the same neuroanatomic and neurochemical alterations associated with chronic PTSD also are found in patients with recurrent MDD. Depression and PTSD animal stress models have been shown to suppress growth and survival of neurons in the hippocampus, with these changes occurring almost immediately after the stressful experience.[175,176] Hippocampal suppression has been reversed using antidepressants and other depression treatments, including exercise,[177-184] however, the impact on clinical presentation is not fully understood. As a result, this work should be interpreted cautiously. It is not clear how medication or psychotherapy might affect neurogenesis differently, depending on whether a patient has a diagnosis of PTSD, MDD, or both, but there are enough clues to support a possible causative link between these disorders.[185]

A meta-analysis of all published structural MRI studies of patients with PTSD reported smaller hippocampal volumes compared with normal controls.[186] Some adult studies have shown that reduced hippocampal volumes are not specific to PTSD and mirror the findings from similar studies in depressed patients.[187-189] Studies in children have not shown a correlation between hippocampal volume and PTSD.[190,191] Other findings in studies of traumatic exposure include decreased function in the hippocampus.[192] Several studies have shown that patients with PTSD have deficits in hippocampal activation while performing a verbal declarative memory task.[193,194]

Treatment. The usual treatment recommendations for PTSD include psychological and pharmacologic strategies.[150] Unfortunately, remission rates for PTSD are poor, even when treatments considered "first line" are employed. A systematic review published in 2008 identified 1,583 citations regarding treatments for PTSD,[195] yet there is limited empiric data directly examining the management of PTSD that presents with a comorbid mood disorder. Levels of evidence of various treatments therefore are not reported here, because they do not apply directly to treating the comorbidity.

CBT, notably with prolonged exposure, is the psychotherapeutic modality with the most empirical evidence for treating PTSD. However, other strategies are considered

useful by some, including interpersonal therapy and mindfulness-based cognitive therapy. A recent Cochrane systematic review[196] concluded that psychological treatment can reduce traumatic stress symptoms and secondary depressive symptoms, and that trauma-focused CBT and eye movement desensitization and reprocessing (EMDR) currently have the best evidence for efficacy and should be made available to PTSD patients; however, only marginal effects of EMDR have been evident in clinical practice.

Several reviews have concluded that there is no clear evidence to show that any class of antidepressant is more effective or better tolerated than any other for treating PTSD. However, the largest studies and the greatest number of trials showing efficacy until now have been with SSRIs.[197] Treatment with SSRIs results in response rates that rarely exceed 60%, with 20% to 30% of patients achieving remission.[195] Studies using the SNRIs venlafaxine and duloxetine are promising; however, although response and remission rates were as good as or better than the SSRI studies, venlafaxine did not improve the hyperarousal cluster of symptoms significantly.[198,199] In a small prospective trial, electroconvulsive therapy (ECT) improved the core symptoms of PTSD independent of improvement in depression, and the authors suggested ECT may be a useful treatment option for patients with severe, chronic, medication- and CBT-refractory PTSD.[200] Of note, this literature focuses on pharmacotherapy for treating PTSD symptoms, rather than mood symptoms/episodes. As noted above, there have been no published clinical trials examining the treatment of mood episodes specifically in patients with comorbid PTSD.

There are relatively few studies that assess the benefits of combining or switching medications to manage patients with PTSD who did not respond adequately to first-line treatments. There is good clinical but limited empiric evidence to suggest that treatment of chronic PTSD should include a combination of an SSRI (or SNRI) and CBT.[201] This combination is thought to enhance treatment outcomes, and exposure therapy might be more tolerable, and therefore effective, if a medication was used along with CBT.[202] A recent Cochrane review, however, did not identify enough evidence to determine whether added benefit exists for combination treatment for PTSD.[203]

As is the case with other anxiety disorders (eg, OCD, PD) comorbid with depression, the required dosing of antidepressants for comorbid PTSD and MDD generally is higher or exceeds the standard recommended range. Patients with PTSD commonly have many somatic complaints (eg, body/joint aches, headaches, gastrointestinal distress) and might be sensitive to adverse effects of medications, particularly early in the treatment course, when side effects are most likely to occur. Taking a "start low, go slow, aim high" approach to treatment meets the dual needs of limiting adverse effects but attaining doses more likely to be effective in this challenging population. As with other anxiety disorder medication trials, response and remission usually take longer than when treating MDD alone. An adequate antidepressant trial for PTSD, when optimizing titration is occurring, may take >12 weeks.

The presence of residual symptoms following treatment is common; therefore, combining treatments generally is the rule rather than the exception for PTSD, and this is particularly true with the presence of comorbid MDD.[167] There is growing evidence supporting use of antipsychotics and/or anticonvulsants for treating PTSD, but there are few studies examining their use specifically in PTSD patients with a comorbid mood disorder. Clinically, pharmacotherapeutic combinations often used for patients with depression and PTSD are similar to those used for treatment-resistant depression (2 antidepressants or the addition of a second-generation antipsychotic or anticonvulsant), and because of the high levels of anger, agitation, irritability, and distress associated with these comorbid conditions, the addition of antipsychotics and anticonvulsants is a common clinical practice.

MDD and anxiety: Cognitive-behavioral therapy

There is broad clinical and research consensus on the pivotal role of CBT in the management of depressive and anxiety disorders. We chose not to repeat the findings from prior guidelines,[2,150,204] but rather to focus on the principal question of the role of CBT in treatment of comorbid MDD and individual anxiety disorders.

Generalized anxiety disorder. There are conflicting data on the impact of comorbid depression and GAD on outcomes for CBT, with some evidence of worse initial outcomes and higher relapse rates. Mitte[205] conducted a meta-analysis of 65 studies (most were RCTs; all had controls) comparing medication with CBT and reported that CBT was better than no treatment or placebo in reducing anxiety and depressive symptoms (level 1), as well as improving quality-of-life measures. The comparisons between CBT and pharmacotherapy yielded inconsistent findings: analyses that included only studies directly comparing CBT and pharmacotherapy found

no significant differences in efficacy between treatment approaches.[205] As with pharmacotherapy, CBT treatment can lead to improvement in both GAD and depressive symptoms. In summary, the results were equivocal, with some studies suggesting that comorbid depression and GAD reduce the efficacy of CBT, and others suggesting that outcomes are unaffected or even enhanced.

Panic disorder (with and without agoraphobia). Similar to GAD, there are inconsistent data on the effect of PD and MDD comorbidity on response to CBT. Rief et al[206] looked at the effect of group CBT for those with PD with and without comorbid MDD (N = 80; 44% with comorbid MDD). Despite having higher pretreatment and posttreatment scores, treatment response for those with PD with MDD was similar to that with PD alone. Another study examined outpatients with PD with agoraphobia (PD/A) with or without comorbid anxiety and/or depression who were being treated with CBT. The study found that although all 3 groups improved, those with comorbid depression were less likely to remit.[207] Results of a recent meta-analysis found that CBT was no better than placebo in reducing secondary depression in PD.[208] In summary, preliminary research does not suggest that comorbid depression diminishes clinical outcomes to CBT for PD/A, but improvements in depressive symptoms may not be as robust.

Social phobia. Studies have suggested that the presence of comorbid depression and SP is a strong predictor of nonresponse to CBT treatment.[209] In terms of depression reduction, 2 meta-analytic reviews[210] reported that CBT treatment for comorbid MDD and SP yielded moderate to large effects on secondary depression when social anxiety is the primary treatment target (effect sizes = 0.67 and 0.70). In a Canadian study of patients with MDD and SP, improvements in social anxiety mediated 91% of the improvements in depression over time. Conversely, decreases in depression accounted for only 6% of the decreases in social anxiety.[211] In summary, the data suggest that the presence of comorbid depression and SP negatively affects outcomes of CBT treatment. However, unlike PD/A treatment, the successful reduction of social anxiety also appears to convert into moderate to large treatment effects on depression. However, little research has reported on whether these reductions lead to remission of MDD.

Obsessive-compulsive disorder. Studies examining the effectiveness of CBT (ie, exposure-response prevention [ERP]) with depressed OCD patients have generated results pointing to significantly reduced efficacy for this group.[212] It has been argued that depression negatively impacts response to CBT by: 1) inducing greater reactivity during exposure exercises, 2) preventing the natural course of habituation to stimuli both within and between sessions, and 3) reducing motivation for demanding CBT treatment. These putative mechanisms of interference may be especially operative at higher levels of depression severity. One study found that nondepressed, mildly, and moderately depressed OCD groups demonstrated significant treatment effects, whereas the severely depressed OCD group (Beck Depression Inventory score $\geq$30) had comparatively poor outcomes, and none were deemed treatment "responders."[23] Overbeek et al[213] studied the sequenced use of pharmacotherapy followed by ERP for patients with OCD with and without depression, and found that although both groups responded to combined treatment, those with both disorders had more residual symptoms. In summary, considerable evidence exists to suggest that the presence of depressive symptoms or a diagnosis of MDD impacts treatment outcomes to CBT treatment of OCD. Little research has addressed whether comorbid depression improves after successful CBT treatment of OCD.

Comorbid anxiety disorders among children and adolescents with MDD

Burden of comorbid anxiety. Approximately 25% to 50% of depressed youth have comorbid anxiety disorders, with rates somewhat higher in treatment-resistant populations and those with moderate to severe depression than in those with mild to moderate depression.[214-216] Most observational studies have found that anxiety disorders do not influence duration, recovery, or relapse among depressed youth.[217-219] However, some contradictory observational data also have been reported,[220] and indeed data from large-scale RCTs suggest that anxiety complicates MDD treatment.[214,215] In contrast to comorbid substance abuse and disruptive behavior disorders, comorbid anxiety has not been consistently shown to affect risk of suicide or suicidality among youth with MDD.[221,222] PD may, however, be independently associated with suicidality among youth.[222]

Treatment response. The importance of addressing comorbid anxiety among youth with MDD has long been acknowledged.[223] Several initial psychosocial treatment studies provided a signal that comorbid anxiety is a predictor or moderator of response to treatment for MDD.[224-226] However, 2 recent large-scale RCTs warrant particular attention. The Treatment for Adolescents with Depression Study

(TADS) randomized 439 adolescents to fluoxetine, placebo, CBT, or combined CBT and fluoxetine.[227] Comorbid anxiety at intake in TADS was a negative predictor of treatment response; however, treatment group did not moderate the impact of anxiety on outcome. In the Treatment of Selective Serotonin Reuptake Inhibitor–Resistant Depression in Adolescents (TORDIA) study, 334 patients were randomized to a different SSRI, venlafaxine, CBT in addition to a different SSRI, or CBT in addition to venlafaxine.[214] Anxiety at intake and at 12 weeks were each associated with lower likelihood of remission after 24 weeks.[228] The impact of CBT (in addition to a second SSRI or venlafaxine) on depressive symptoms at 12 weeks was nearly 3-fold greater among youth with vs without comorbid anxiety.[229] In summary, anxiety appears to be a negative predictor of outcome in the treatment of adolescents with MDD, and combination pharmacotherapy and CBT may offer enhanced benefits among adolescents with treatment-resistant MDD with comorbid anxiety.

See **TABLE 4** for a summary and recommendations for treating MDD with comorbid anxiety.

CONCLUSIONS

This article reviews the available information on the etiology, clinical manifestations, and treatment approaches for comorbid mood and anxiety disorders. Although much more data are needed, there is growing recognition of the urgent requirement for better understanding of these complex patients. We recommend that careful attention be given to correctly identifying anxiety comorbidities in patients with BD or MDD, as well as adoption of an evidence-based and clinically sensible approach to management of both mood and anxiety symptoms in these patients. ■

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