Treating Nonspecific Anxiety and Anxiety Disorders in Patients With Bipolar Disorder: A Review

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Objective: To review the evidence for treating anxiety in patients with bipolar disorder.

Data Sources: A literature search from 1950 to week 1 of August 2009 was conducted via OVID and the National Institutes of Health's clinical trials online databases. Search terms included *anxiety*, *anxiety disorders*, *bipolar disorder*, *panic disorder*, *generalized anxiety disorder*, *social phobia*, *social anxiety*, *obsessive compulsive disorder*, *specific phobia*, *posttraumatic stress disorder*, and *treatment*. Reference lists of identified articles were also searched.

Study Selection: Fourteen treatment studies that included patients with bipolar disorder with either a syndrome-defined anxiety disorder or nonspecific anxiety were selected.

Data Extraction: Sample size, bipolar disorder subtype, comorbid anxiety disorders, baseline anxiety, treatment interventions, and outcome measurements were extracted.

Results: The majority of studies focus on treating anxiety disorders and nonspecific anxiety occurring during bipolar mood episodes. Studies of syndrome-defined anxiety disorders reveal that risperidone monotherapy did not separate from placebo and that olanzapine was superior to lamotrigine when used to augment lithium treatment. A study using open-label divalproex sodium and an uncontrolled study of group cognitive-behavioral therapy both suggest some benefit from these treatments in patients with bipolar disorder with panic disorder.

Studies of nonspecific anxiety reveal some benefit for divalproex, quetiapine, olanzapine, and olanzapine-fluoxetine combination. Weaker evidence supports the use of Mindfulness-Based Cognitive Therapy, and observational studies suggest potential efficacy for gabapentin and valproate.

Conclusions: Nonspecific anxiety symptoms occurring during a mood episode improve with treatment of the mood disturbance, though divalproex may be the mood stabilizer of choice for anxious patients with bipolar disorder. Given their reduced risk for manic induction and episode cycling, psychotherapy, benzodiazepines, and certain atypical antipsychotics are recommended for treatment of anxiety disorders present in patients with bipolar disorder not currently experiencing an acute mood episode.

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Bipolar disorder and anxiety disorders (including panic disorder, generalized anxiety disorder [GAD], social phobia, specific phobia, obsessive-compulsive disorder [OCD], and posttraumatic stress disorder [PTSD]) are psychiatric illnesses that individually cause significant mortality and morbidity, reflected in suicide rates,[1–3] substance abuse rates,[4,5] total medical burden,[6–8] economic costs,[9,10] and quality of life.[11,12] All of these consequences are increased in severity when an anxiety disorder is comorbid with bipolar disorder. Compared to those with uncomplicated bipolar disorder, this combination of psychiatric illnesses is associated with increased suicide attempts and ideation,[13–17] substance abuse,[13–15,17,18] worse severity of mood episodes,[16,19] more mood episodes,[16,18,19] possibly decreased lithium responsiveness,[15] longer recovery times,[19–21] and an earlier age at onset of bipolar illness.[13,14,22] Depending on the sample (clinical[13,23] vs community[24]) and the type of bipolar disorder (I[24] vs combined I and II[13,23]), the prevalence of any lifetime co-occurring anxiety disorder ranges from 42%–93%. Moreover, many patients with bipolar disorder type I and II without comorbid anxiety disorders have high levels of nonspecific anxiety symptoms during acute mood episodes.[25]

Remarkably, despite the high levels of comorbidity and consequent increases in illness severity, there has been very little controlled research into treatment of patients with both bipolar disorder and an anxiety disorder. This dearth of research is reflected in current bipolar practice guidelines that minimally, if at all, address treatment for this population.[26–32] The most recent set of guidelines, Canadian Network for Mood and Anxiety Treatments (CANMAT) 2009,[29] identify only a positive study using either lamotrigine or olanzapine and a negative study using risperidone. Given the overall lack of attention to this topic, it is not surprising that patients with bipolar disorder with anxiety disorders often receive inadequate treatment for anxiety disorders.[33]

Standard anxiolytic agents proven effective in trials of patients with primary anxiety disorder may be of value in treating anxiety in patients with bipolar disorder. However, there are several reasons for caution when extending findings from such trials to patients with bipolar disorder with comorbid anxiety.

First, clinical trials of treatments for anxiety disorders almost universally exclude patients with bipolar disorder, so generalizability to patients with bipolar disorder cannot be assured. Limits to generalizability to patients with bipolar disorder have been demonstrated in clinical trials evaluating treatments for depression. For example, paroxetine, a selective serotonin reuptake inhibitor (SSRI), has shown benefit in unipolar depression[34,35] but has failed to separate from placebo in studies of bipolar disorder depression.[36,37] Similarly, medications proven effective for anxiety disorders cannot be assured to have similar benefits among patients with bipolar disorder with anxiety.

Second, family studies reveal anxiety disorders and bipolar disorder cosegregate among relatives of probands afflicted with both illnesses, and it may be that the biologic basis of anxiety disorders in patients with bipolar disorder differs from that of non–bipolar disorder patients with anxiety.[38,39] Third, antimanic and mood-stabilizing medications may have anxiolytic properties in themselves, such that the need for specific antianxiety medication may not be necessary. Fourth, antidepressant medications effective in the treatment of anxiety disorders may induce mania or increase episode cycling[40–44]; though this remains controversial,[45,46] with little data examining this risk specifically in patients with bipolar disorder with anxiety disorders. This risk may be significantly less for patients with bipolar disorder type II.[47–49] Antidepressants, such as bupropion, may actually increase anxiety, agitation, or panic, leading to an iatrogenic worsening of anxiety for these patients.[50] Finally, significant drug-drug interactions may occur between anxiolytics and the mood-stabilizing medications used to treat bipolar disorder. Examples of these interactions would include cytochrome P450 (CYP) 3A4 induction by carbamazepine, reducing plasma levels of medications such as clonazepam,[51] alprazolam,[52] and buspirone.[53]

Patients with bipolar disorder experiencing mixed episodes (either a depressed mixed state or mixed mania) may be a particular concern. These patients report higher levels of inner tension and agitation when compared to samples of purely depressed patients with bipolar disorder[54,55] and higher levels of inner tension, anxiety, phobia, and obsessive-compulsive symptoms when compared to samples of purely manic patients.[55–57] Antidepressants may be prescribed to treat these symptoms, which puts patients at risk for developing worse agitation and manic symptom severity and for attempting suicide.[58,59]

A limitation of most published studies of co-occurring anxiety and bipolar disorder is that anxiety is often defined nonspecifically and not based on syndrome criteria. Most commonly, a cutoff score on an anxiety symptom scale, such as the Hamilton Anxiety Rating Scale (HARS),[60] is used to classify patients as having comorbid anxiety. This approach is in contrast to the clinical practice of diagnosing a specific anxiety disorder based on the presence of *Diagnostic and Statistical Manual*, Fourth Edition, Text Revision (*DSM-IV-TR*) symptom criteria. These nonspecific anxiety symptoms may be part of a syndrome-defined anxiety disorder or reflect particular aspects of the biology or measurement of the mood disturbance. For example, the symptoms may represent confounding of overlapping symptoms listed on the HARS scale and those on the commonly used measure of mania severity, the Young Mania Rating Scale (YMRS),[61] as demonstrated in Table 1. Though experienced clinicians may be able to clarify the nuanced differences between these item constructs, assessment of these symptoms in clinical trials by less experienced raters may produce elevated scores on both the HARS and the YMRS. Although HARS data from bipolar disorder trials are rarely published, 1 study showed that patients with bipolar disorder with higher baseline mean HARS scores also had higher mean YMRS scores compared to the patients with lower mean HARS scores.[62] Additionally, patients with bipolar disorder with high scores on the HARS or patients with anxiety disorder with high scores on the YMRS may represent severe presentations of bipolar disorder or anxiety disorder, respectively, instead of representing patients with 2 separate, co-occurring disorders. As demonstrated in Table 2, similar anxiety and depressive symptoms are rated on the HARS and on the Hamilton Depression Rating Scale[63] and Montgomery-Asberg Depression Rating Scale,[64] 2 commonly used depression severity scales. As a result, HARS scores might be elevated in the absence of symptoms unique to anxiety states and improve with resolution of the depressive episode, with the result that the medication is inappropriately interpreted to have significant anxiolytic activity. Raters may also inappropriately categorize other physiologic or psychiatric symptoms as anxiety, leading to higher HARS scores. Examples include autonomic activation from medications such as SSRIs, agitation fueled by symptoms such as paranoid delusions or suicidal ideation, and akathisia, a sense of inner restlessness, typically caused by antipsychotic medications.

Table 1. Related but Different Symptom Constructs on Items of the Young Mania Rating Scale (YMRS) and the Hamilton Anxiety Rating Scale (HARS)

YMRS Item No.	YMRS Item	HARS Item No.	HARS Item
2	Increased motor activity	14	Behavior at interview
4	Sleep decreased	4	Sleep
5	Irritability	1	Psychic anxiety
7	Language-thought disorder	6	Concentration

This article aims to comprehensively review the available evidence for treating anxiety in patients with bipolar disorder, with an emphasis on separating studies of syndrome-defined anxiety disorders from studies of nonspecific anxiety.

METHOD

A literature search for all reports (randomized clinical trials, post hoc analyses, observational studies, case reports) of the treatment of comorbid anxiety and bipolar disorder from 1950 to week 1 of August 2009 was conducted via

Table 2. Similar Symptoms on Items of the Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), and the Hamilton Anxiety Rating Scale (HARS)

HDRS Item No.	HDRS Item	MADRS Item No.	MADRS Item	HARS Item No.	HARS Item
1	Depressed mood	1, 2	Reported sadness, observed sadness	6	Depressed mood
4, 5, 6	Initial/middle/late insomnia	4	Reduced sleep	4	Insomnia
7	Work and activities	8	Inability to feel	6	Depressed mood
9	Agitation			14	Behavior at interview
10	Anxiety psychic	3	Inner tension	1, 2	Anxious mood, tension
11	Somatic anxiety			9, 10, 11, 12, 13	Cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic symptoms
13	Somatic symptoms general	7	Lassitude	7, 8	Somatic (muscular)/somatic (sensory)
14	Genital symptoms			12	Genitourinary symptoms
15	Hypochondriasis			1	Anxious mood
16	Loss of weight			11	Gastrointestinal symptoms
		6	Concentration difficulties	5	Intellectual

OVID online computerized database. The search terms used included: *anxiety*, *anxiety disorders*, *bipolar disorder*, *panic disorder*, *generalized anxiety disorder*, *social phobia*, *social anxiety*, *obsessive compulsive disorder*, *specific phobia*, *post-traumatic stress disorder*, and *treatment*. Additionally, the reference lists of all identified articles were reviewed to search for other potentially relevant studies. The same search terms were also entered into the United States National Institutes of Health's clinical trials online database, www.clinicaltrials.gov. Principal investigators were contacted for updates on the progress and findings of their trials.

Several studies evaluating pharmacologic and psychotherapeutic tools were identified. These results were categorized based on the manner in which researchers defined their subjects' anxiety. The categories include "syndrome-defined anxiety" (anxiety that is part of a *DSM-IV-TR* anxiety disorder symptom constellation) and "nonspecific anxiety" (anxiety measured via a cross-sectionally administered rating scale or described qualitatively but not meeting syndrome criteria). In total, 14 randomized controlled trials, post hoc analyses, and observational studies were reviewed.

RESULTS

Syndrome-Defined Anxiety Disorders

Currently, there is only 1 published double-blind, randomized, placebo-controlled clinical trial[65] for which the primary aim was to evaluate the treatment of anxiety in patients with bipolar disorder (Table 3). Risperidone dosed at 0.5–4 mg/d or placebo was given to 111 patients with bipolar I, II, or NOS who also had a lifetime history of panic disorder or GAD and had current, at least moderately severe anxiety, defined as a Clinical Global Impressions-Severity of Illness scale score of greater than or equal to 4. Although patients did not have to be euthymic to be included in the study, their mood symptoms could not be more than moderately severe, defined as a score of less than or equal to 4 on the Clinical Global Impressions-Severity of Illness scale. The primary outcome measure was the Clinician Global Improvement Scale for Anxiety, and the Hamilton Anxiety Rating Scale (HARS) was used as a secondary outcome measure. After 8 weeks of treatment, there were no significant differences on either the Clinician Global Improvement Scale for Anxiety or HARS among all patients receiving risperidone and placebo. However, a secondary analysis revealed that among the patients with panic disorder, placebo treatment produced a significantly lower HARS score (mean ± SD = 11.9 ± 9.1) at endpoint than risperidone treatment (18.4 ± 10.7, $P < .007$). Fifty percent of the patients in the risperidone group dropped out of the study before completion as compared to 63% of those in the placebo group. The incidence of akathisia among both groups was low and similar. Two patients in the risperidone group discontinued due to an adverse advent (pregnancy, worsening anxiety), compared to 1 placebo patient who discontinued due to complaining of multiple symptoms (hair loss, word slurring, and fluid retention). Similar proportions of patients in both groups (approximately 20%) withdrew due to lack of efficacy.

Maina and colleagues[66] conducted a single-blind, active comparator study of 49 patients with euthymic bipolar disorder I and II, all of whom met criteria for a current syndrome-defined anxiety disorder and had a HARS score ≥ 12. All patients were taking lithium (levels 0.6–1.2 mEq/L) and randomized to 12 weeks of either adjunctive olanzapine 5 to 10 mg/d or lamotrigine 50 to 200 mg/d. The most common anxiety diagnosis in the sample was a current diagnosis of GAD, though social phobia, specific phobia, OCD, and panic disorder with and without agoraphobia were also present in the sample. On the intent-to-treat analysis, patients randomized to olanzapine had a significantly greater mean ± SD reduction in HARS score as compared to those randomized to lamotrigine (−9.1 ± 3.8 vs −5.0 ± 6.2, $P = .008$). Differences in response and remission rates did not reach statistical significance (responders: olanzapine = 63.6%, lamotrigine = 38.9%, $P = .119$; remitters: olanzapine = 54.5%, lamotrigine = 27.8%, $P = .088$).

Two uncontrolled studies of the efficacy of treatments for patients with primary anxiety disorders have reported post hoc analyses of the subset of enrolled patients with bipolar disorder. Baetz and Bowen[67] reported on 10 patients

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Table 3. Published Randomized Controlled Studies Assessing the Efficacy of Interventions for Bipolar Patients With Comorbid Anxiety Disorders or Nonspecific Anxiety Symptoms

Author, Year	Trial Design	Patient Population	Anxiety Definition	Sample Size	Intervention	Duration	Anxiety Outcome Measure	Result	Comment
Studies of *DSM-IV*–defined anxiety disorders									
Maina et al,[66] 2008	Single-blind, active comparator trial	Bipolar disorder type I or II, euthymic	HARS score of 12 or greater with or without an anxiety disorder	49	Olanzapine + lithium vs lamotrigine + lithium	12 wk	HARS	Olanzapine > lamotrigine, $P < .008$	All patients had a current anxiety disorder
Sheehan et al,[65] 2009	Double-blind, placebo-controlled trial	Bipolar disorder type I, II, or NOS, with CGI-S for bipolar illness less than 5	Lifetime GAD or panic disorder and with current moderate anxiety	111	Risperidone monotherapy vs placebo monotherapy	8 wk	CGI-21 Anxiety	No significant difference	Risperidone significantly worsened outcomes in panic disorder patients vs placebo
Studies of nonspecific anxiety symptoms									
Davis et al,[75] 2005	Double-blind, placebo-controlled trial	Bipolar disorder type I, in current depressive episode	None	25	Divalproex monotherapy vs placebo monotherapy	8 wk	HARS	Divalproex > placebo, $P < .0001$	No comorbid anxiety disorders; mostly male population
Hirschfeld et al,[25] 2006	Post hoc analysis of double-blind, placebo-controlled trial	Bipolar disorder type I or II, in current depressive episode	None	539	Quetiapine monotherapy vs placebo monotherapy	8 wk	HARS total	Quetiapine > placebo; bipolar disorder type I: $P < .001$; bipolar disorder type II: $P = .47$	No comorbid anxiety disorders; HARS mean score at baseline was 19 for both groups
Ghaemi et al,[76] 2007	Double-blind, placebo-controlled trial	Bipolar disorder type I, II, or NOS, in current depressive episode	None	18	Divalproex monotherapy vs placebo monotherapy	6 wk	HARS	No significant between-group difference; divalproex within-group change, $P < .0001$	Sample stratified by rapid-cycling status, bipolar subtype, and length of current major depressive episode
Tohen et al,[62] 2007	Post hoc analysis of double-blind, placebo-controlled trial	Bipolar disorder type I, in current depressive episode	HARS score > 17	833	Olanzapine-fluoxetine vs olanzapine vs placebo	8 wk	HARS	Olanzapine-fluoxetine > placebo, $P < .002$; olanzapine > placebo, $P < .002$	Presence of syndrome-defined anxiety disorders not reported
Williams et al,[80] 2008	Post hoc analysis of unblinded, waitlist-controlled trial	Bipolar disorder type I or II, not in current mood episode, with current anxiety symptoms	None	14	MBCT vs waitlist control group	8 wk	BAI	MCBT > waitlist control group, $P < .014$	Subset of 68 total patients enrolled with history of major depressive episode and current anxiety symptoms

Abbreviations: BAI = Beck Anxiety Inventory, CGI-21 Anxiety = 21-item Clinician Global Improvement Scale for Anxiety, CGI-S = Clinical Global Impressions–Severity of Illness scale, GAD = generalized anxiety disorder, HARS = Hamilton Anxiety Rating Scale, MBCT = Mindfulness-Based Cognitive Therapy, NOS = not otherwise specified.

with primary panic disorder and self-reported mood instability diagnosed with bipolar disorder II who completed 8 weeks of open-label divalproex sodium treatment. Patients improved in panic frequency (8.3 ± 2.5 attacks per week at baseline vs 2.6 ± 0.9 attacks per week at endpoint, $P = .03$), HARS scores (26.2 ± 2.1 at baseline vs 13.1 ± 2.7 at endpoint, $P = .0001$), and Beck Anxiety Inventory scores (53.7 ± 2.3 at baseline vs 38.0 ± 2.4, $P = .003$). All patients in this trial had failed to respond to both cognitive-behavioral therapy (CBT) and at least 1 medication trial for panic disorder, and several were taking other psychiatric medications during the study.

A second uncontrolled study that employed group CBT for the treatment of patients with primary panic disorder suggested this treatment may be effective for panic disorder in patients with (n = 18) and without (n = 38) symptoms of hypomania.[68] Patients were allowed to take concomitant medications and attended the therapy program until they and the therapist agreed that they had reached the full benefit of the treatment (number of sessions and total time in treatment not reported). No primary outcome was designated; however, the final analysis showed that over time in treatment, both groups of patients had significant improvements on anxiety measures (Phobic Anxiety subscale of the Brief Symptom Inventory) and functional scales. Those with hypomanic symptoms demonstrated continuing improvement between the sixth- and twelfth-month follow-up on measures of general function but deteriorated on the anxiety-related measures.

In their review on PTSD and bipolar illness, Otto et al[69] describe an observed benefit in their randomized trial of CBT treatment for patients with PTSD and bipolar disorder, though these results are yet to be published (written communication with Michael Otto, PhD, July 2009).

In case reports, 2 patients with bipolar disorder type I with OCD were reported to have a sustained remission from OCD after 30–51 sessions of behavioral therapy.[70] Obsessive-compulsive disorder in patients with comorbid bipolar disorder type I and II has also been reported to respond to mood stabilizer monotherapy or combination treatment with a mood stabilizer plus antipsychotic[71] and olanzapine monotherapy.[72] One case report suggests benefit with oxcarbazepine in the treatment of PTSD in a patient with bipolar disorder type II.[73] Quetiapine monotherapy was successful in the treatment of social phobia in a patient with rapid-cycling bipolar disorder II.[74]

Nonspecific Anxiety

There are 2 randomized, placebo-controlled trials that report HARS scores as secondary outcomes in patients with bipolar disorder treated with divalproex. Davis and colleagues[75] enrolled 25, mostly male, bipolar disorder I depressed outpatients in a single-site, 8-week, double-blind, placebo-controlled study. None of these patients had comorbid anxiety disorders based on a structured diagnostic interview. Patients receiving divalproex (mean serum valproic acid level = 81 μg/mL) had a greater mean percent change on the HARS as compared to patients receiving placebo (−35.2 vs −5.3, $P = .0001$). Ghaemi and colleagues[76] randomized 18 acutely depressed outpatients with bipolar disorder I, II, or NOS to 6 weeks of treatment with divalproex monotherapy (serum valproic acid level = 70–90 ng/dL) or placebo. Hamilton Anxiety Rating Scale scores improved significantly within the divalproex-treated group (baseline = 22.4 vs week 6 = 10.9, $P < .0001$), but the observed 8-point difference in mean HARS score change between divalproex and placebo did not meet statistical significance ($P = .13$).

Two published post hoc analyses examined anxiety symptoms in patients with bipolar depression. Hirschfeld and colleagues[25] examined data from a multicenter, double-blind, randomized, placebo-controlled clinical trial investigating the efficacy of 8 weeks of quetiapine monotherapy (300 mg/d and 600 mg/d) in 539 depressed outpatients with bipolar disorder type I or II currently experiencing a major depressive episode. None of these patients had comorbid anxiety disorders based on structured diagnostic interviews. Mean (SD) baseline HARS scores for the quetiapine (pooling patients in the 300 and 600 mg/d arms) and placebo treatment groups were 18.7 (7.3) and 18.9 (7.2), respectively. Patients with bipolar disorder type I treated with quetiapine had a significantly greater change in HARS than those randomized to placebo (−10.4 vs −5.1, $P < .001$), as well as significant changes on several other secondary measures of anxiety. However, among patients with bipolar disorder type II, quetiapine did not show a significant difference in the change in HARS total score as compared to those randomized to placebo (−9.8 vs −9.0, $P = .473$). On the other hand, among patients with bipolar disorder type II, a significant difference was present for change on the HARS item 1 (anxious mood), Montgomery-Asberg Depression Rating Scale item 3 (inner tension), and the Hamilton Depression Rating Scale item 10 (psychic anxiety) (all $P < .01$ vs placebo).

A second post hoc analysis was conducted from the results of a study randomizing 833 depressed patients with bipolar disorder type I to 8 weeks of flexible-dose treatment with olanzapine monotherapy (OLZ) 5 to 20 mg/d; olanzapine-fluoxetine combination (OFC) 6/25, 6/50, or 12/50 mg/d in a flexible dose; or placebo.[62] The authors do not report the presence or absence of comorbid anxiety disorders. Patients with a HARS score greater than or equal to 18 were categorized as having comorbid anxiety. Olanzapine and OFC significantly reduced HARS scores as compared to placebo (OLZ: −15, OFC: −16.6, placebo: −11; $P = .002$ for OFC vs placebo and for OLZ vs placebo). Response was defined as a 50% reduction in HARS score from baseline to endpoint, while remission was defined as a HARS score ≤ 7. Using generalized linear models, the likelihood of HARS response for patients treated with OFC was 2 times greater compared to placebo and 1.69 times greater compared to OLZ, while the likelihood of HARS remission for those treated with OFC or OLZ was between 2 and 3 times greater relative to placebo (all with $P < .01$).

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Two large case series have assessed the value of adjunctive gabapentin up to 2,400 mg/d for anxious versus nonanxious patients with bipolar disorder. Of 22 patients with bipolar disorder type I or II with subsyndromal mood symptoms, approximately 60% reported subjective improvement in anxiety symptoms after 12 weeks of treatment with adjunctive gabapentin.[77] Among 43 patients with bipolar disorder experiencing an active mood episode, adjunctive gabapentin for 8 weeks resulted in significantly greater reductions in the Anxiety-Somatization factor on the Hamilton Depression Rating Scale, compared to the other dimensions on that scale.[78] However, in both studies, patients were treated with a variety of concomitant medications, including mood stabilizers, benzodiazepines, antidepressants, and neuroleptics. Consequently, interpretation of these findings is limited.

In a study of 55 patients with rapid-cycling bipolar disorder, Calabrese and Delucchi[79] reported open-label valproate monotherapy or valproate combined with other drugs effectively reduced panic attacks in 21 of 22 patients who reported panic attacks at baseline.

The efficacy of Mindfulness-Based Cognitive Therapy was assessed in a randomized trial of 68 patients with a history of a major depressive episode and who reported current anxiety symptoms. The 8-week course of therapy focused on continuing depressive and anxiety symptoms in patients not in a current mood episode. Of the 14 patients with bipolar disorder I or II who had follow-up data, 7 each were assigned to the Mindfulness-Based Cognitive Therapy and waitlist conditions. Endpoint scores on the Beck Anxiety Inventory reveal that therapy significantly reduced anxiety symptoms as compared to the waitlist condition (mean ± SD = 6.8 ± 5.7 vs 20.6 ± 11.3, $P = .014$).[80]

Future Studies

The www.clinicaltrials.gov Web site lists 4 active studies investigating the treatment of syndrome-defined anxiety disorders in patients with bipolar disorder. These include placebo-controlled trials of (1) combined quetiapine SR and divalproex sodium ER for patients with bipolar disorder with panic disorder and/or GAD; (2) quetiapine XR monotherapy in patients with bipolar disorder with comorbid GAD; and (3) risperidone monotherapy for patients with bipolar disorder with a lifetime history of panic disorder or GAD. Additionally, there is an ongoing study of CBT for PTSD in patients with comorbid serious mental illness. A trial to evaluate ziprasidone in the treatment of GAD in patients with bipolar disorder was terminated early due to slow recruitment. (www.clinicaltrials.gov; accessed August 11, 2009).

DISCUSSION

Despite the clinical significance of anxiety disorders and their high rates of comorbidity in patients with bipolar disorder, there is little controlled research data to help guide clinicians who treat these patients. Only 1 placebo-controlled study of syndrome-defined anxiety disorders in patients with bipolar disorder has been published, finding that monotherapy with risperidone did not improve overall anxiety symptoms more than placebo, worsened outcomes in patients with bipolar disorder with panic disorder versus placebo, and was less well tolerated than placebo. A single-blind active comparator study found olanzapine was superior to lamotrigine when used to augment lithium treatment of patients with bipolar disorder with an anxiety disorder. A study using open-label divalproex sodium and an uncontrolled study of group CBT both suggest some benefit from these treatments in patients with bipolar disorder with panic disorder.

With regard to studies of nonspecific anxiety in patients with bipolar disorder, secondary analyses of existing double-blind, placebo-controlled data sets evaluating outcomes in patients based on the baseline cross-sectional level of nonspecific anxiety symptoms have shown benefit for divalproex and some atypical antipsychotics. Quetiapine, olanzapine, and olanzapine-fluoxetine combination treatment all reduced anxiety symptoms more than placebo in short-term trials in samples of patients with no identified comorbid anxiety disorders. A randomized trial of Mindfulness-Based Cognitive Therapy showed some efficacy in reducing anxiety symptoms in a small number of patients with bipolar disorder as compared to the waitlist control group. Additionally, observational studies suggest potential efficacy for gabapentin or valproate for anxiety symptoms in patients with bipolar disorder.

Overall, the data summarized here do not provide strong guidance for clinicians. Studies evaluating syndrome-defined anxiety and those focusing on nonspecific anxiety in patients with bipolar disorder are rare. Those that do exist suffer from a variety of limitations. The majority of these studies focus on treating nonspecific anxiety and anxiety disorders during bipolar mood episodes, rather than during periods of euthymia. Some are post hoc assessments of secondary measures or of small subgroups of patients with bipolar disorder. Some allow concomitant medications to be used, which confound the true effect of the agent being evaluated. Most lack placebo control groups, which prevent detection of improvements due to nonspecific treatment experiences and the effect of time in treatment. Additionally, although most of these studies report nonspecific anxiety, they do not always explicitly report the presence or absence of a concurrent syndrome-defined anxiety disorder. Even in those studies that do identify syndromal anxiety disorders, multiple anxiety disorders are grouped together in the treatment arms. This limitation is evident in the double-blind trial of risperidone monotherapy, in which the antipsychotic produced divergent results in patients with bipolar disorder with GAD (ineffective) versus those with panic disorder (actively harmful).

To our knowledge, no survey of clinician approaches to treating anxiety disorders or nonspecific anxiety in patients with bipolar disorder has been published. Current

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approaches to treatment seem to take 1 of the following forms:

- Extrapolate to patients with bipolar disorder treatment indications for drugs proven to treat anxiety disorders in non–bipolar disorder patients, ie, augment mood stabilizer treatment with antidepressants or benzodiazepines.
- Augment mood stabilizer treatment with psychotherapy, in particular CBT.
- Employ mood stabilizer monotherapy or combination therapy (2 mood stabilizers or a mood stabilizer and an atypical antipsychotic). This strategy is based on the secondary data analysis cited in this review and on data from studies of primary anxiety disorders suggesting that divalproex, gabapentin, quetiapine, olanzapine, risperidone, aripiprazole, and ziprasidone may have efficacy in these disorders.[81–87]

Each of these options carries risk or limitations. Serotonin norepinephrine reuptake inhibitors and to a lesser extent SSRIs carry risk of cycle induction or manic switching, particularly in bipolar disorder type I and with longer treatment periods.[43,44] As previously mentioned, this risk remains controversial. Benzodiazepines can provide useful adjunctive mood-stabilization properties but carry an abuse potential and therefore may be relatively contraindicated in many patients with bipolar disorder. Additional risks include cognitive dulling, anterograde amnesia, the potential to induce depression, ataxia, and disinhibition in patients with executive dysfunction.[88] Furthermore, there is a lack of long-term data with benzodiazepines in bipolar disorder beyond their use in acute mania. Cognitive-behavioral therapy carries little risk, but access to quality providers may be limited by cost or therapist availability. Individual mood stabilizers, which often carry their own significant side effect burden (including rashes, weight gain, thyroid dysfunction, hepatotoxicity, and nephrotoxicity among others), may lead to a higher incidence of side effects when used in combination. Certain atypical antipsychotics may even worsen anxiety, as found in a subgroup of patients with panic disorder randomized to risperidone monotherapy. Moreover, weight gain and the potential for medically significant metabolic disease[89] warrant clinicians to pause before combining these agents in pursuit of mitigating anxiety symptoms.

Surprisingly, no controlled data have been published regarding the efficacy of CBT in patients with bipolar disorder with anxiety disorders. Psychotherapy studies of anxiety disorders that permitted inclusion of subjects with euthymic bipolar disorder or with mild mood symptoms suggest that psychotherapy approaches may be efficacious, but the number of bipolar disorder subjects reported from these studies is small.

In choosing between these options, some additional questions may provide guidance for the clinician weighing the risks and benefits of each treatment option. These questions include:

1. What is the clinical impact of the anxiety disorder in relation to the bipolar disorder? For instance, anxiety disorders may be mild and have minimal impact, such as nongeneralized social phobia in a patient with bipolar disorder I, or they may carry greater clinical significance, such as in a patient with bipolar disorder II who has severe PTSD from combat trauma. In patients with a history of substance abuse, anxiety symptoms may increase the likelihood of the patient relapsing in order to reduce anxiety-related distress.
2. How long should treatment continue? Anxiety disorders with a waxing and waning course (eg, GAD, panic disorder)[90,91] may have a different risk-benefit ratio for sustained treatment than more persistent anxiety disorders (eg, OCD, PTSD, social phobia).[92,93] The risk of adverse effects, including mood switching or increased cycling, must be balanced against the risk of anxiety disorder relapse. Other adverse effects worthy of consideration are weight gain, metabolic changes, movement disorders, and sexual functioning.
3. Would targeting anxiety symptoms improve the patient's treatment adherence? Patients with bipolar disorder may not experience significant distress from their episodes of mood elevation compared to the distress associated with anxiety. Forging a treatment alliance around relieving anxiety may serve to improve patient adherence.

There is significant need for more controlled data to guide clinicians in treating these complicated patients. One way data could be generated quickly is by reanalyzing existing datasets of phase II and III placebo-controlled studies of bipolar disorder. The secondary analyses reviewed in this article assessed only cross-sectional baseline anxiety levels, which may be reflective of the state of the mood disturbance, and not an anxiety disorder per se. These and other similar datasets could be reanalyzed through evaluating the screening visit structured interview diagnoses to evaluate the effect of *DSM-IV* criteria anxiety disorders on outcomes, particularly for long-term maintenance studies.

Additionally, long-term studies are needed comparing the impact of treating syndrome-defined anxiety disorders and nonspecific anxiety on many important clinical bipolar disorder outcomes, such as time to remission, time to relapse, severity of episodes, quality of life, suicide ideation and attempts, family history, and other comorbidities. Such data could clarify whether cross-sectional nonspecific anxiety level at baseline produces a different clinical course than full syndromal comorbid anxiety disorders. Cross-sectional anxiety, as noted in mixed episodes, may be part of the bipolar disease process, phenomenologically different than

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the anxiety experienced in an anxiety disorder[58] and occurring cyclically with onset of the mood episode. On the other hand, syndrome-defined anxiety may be separate from the bipolar illness, existing independently of mood episodes and requiring additional treatment.

For patients with bipolar disorder with nonspecific anxiety, effective treatment of the mood episode through the use of classic mood stabilizers (lithium, valproate, carbamazepine, lamotrigine) may suffice, though this remains to be proven. Divalproex may be the mood stabilizer of choice for these patients, given its reported efficacy in treating both mood and anxiety symptoms simultaneously and its proGABAergic effect.[94] Though the data show quetiapine and OLZ monotherapy to also be effective in treating mood and anxiety, there are less data establishing a role for these medications as mood stabilizers compared to lithium and anticonvulsants. Moreover, considering their significant metabolic risks, quetiapine and OLZ monotherapy are more appropriate as second- or third-line choices.

Regarding anxiety disorders, given the absence of compelling efficacy data to guide treatment choice, we believe that psychotherapeutic approaches, with their low level of risk and proven efficacy in non–bipolar disorder populations, should be the first-line treatment in patients with bipolar disorder. Should this approach fail or be impractical, medication approaches should be used. Given their efficacy in nonspecific anxiety and anxiety disorders (GAD, social phobia, panic disorder) and their use as adjunctive antimanic agents, benzodiazepines probably provide the best overall risk-benefit ratio among medications for use in patients with bipolar disorder without a history of substance abuse. In patients for whom benzodiazepines are contraindicated or ineffective (PTSD, OCD), the decision of whether to treat the anxiety by adding an SSRI or an atypical antipsychotic depends on the particular clinical situation of the patient.

Drug names: alprazolam (Xanax, Niravam, and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), divalproex (Depakote and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), valproate sodium (Depacon and others), ziprasidone (Geodon).

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