Pharmacologic Treatment Considerations in Co-Occurring Bipolar and Anxiety Disorders

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Background: Anxiety disorders are among the most commonly co-occurring psychiatric syndromes with bipolar disorder. The presence of co-occurring anxiety disorders has important prognostic and treatment implications. ***Method:*** Using the PaperChase database augmented by a manual search of the literature, we identified 122 publications that consisted of reports regarding pharmacologic agents used in the treatment of bipolar disorder also assessing the efficacy of these agents in anxiety disorders, treatment studies of patients with comorbid bipolar disorder and specific anxiety disorders, and studies of novel antiepileptic agents in the treatment of anxiety symptoms or disorders. ***Results:*** No randomized controlled trials have been conducted in patients with bipolar disorder and any co-occurring anxiety disorder. Among agents with antimanic or mood-stabilizing effects, evidence of efficacy from placebo-controlled trials exists for valproate in the treatment of panic disorder; lamotrigine, risperidone, and olanzapine in posttraumatic stress disorder; and risperidone, olanzapine, and quetiapine as adjunctive treatment in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Antidepressants from virtually every class have efficacy in the treatment of most anxiety disorders but present the challenge of minimizing switch risk when used in conjunction with a moodstabilizer. Among novel antiepileptic agents without proven thymoleptic properties studied in randomized controlled trials in anxiety disorders, gabapentin and pregabalin had efficacy in the treatment of social anxiety disorder, and pregabalin in the treatment of generalized anxiety disorder. ***Conclusion:*** In the absence of controlled trials in patients with comorbid bipolar and anxiety disorders, the initial goals of treatment include mood stabilization and selection of thymoleptic agents with efficacy in the co-occurring anxiety disorder. *(J Clin Psychiatry 2006;67[suppl 1]:8–15)*

Anxiety disorders are the most prevalent co-occurring illnesses in patients with bipolar disorder.[1–18] The high lifetime prevalence rate of anxiety disorders in bipolar disorder is remarkable in that bipolar disorder itself is frequently comorbid with a number of other psychiatric and medical disorders as discussed in this supplement. Moreover, the lifetime prevalence rates of each specific anxiety disorder are elevated in patients with bipolar disorder.[7–10,18] The presence of co-occurring anxiety disorders in patients with bipolar disorder is associated with earlier age at onset of mood symptoms[5,15,16]; greater number of depressive episodes,[15] severity of illness,[5,6,16] and suicidal behavior[16,19]; higher rates of disability[15,16] and subsyndromal symptoms[12]; lower self-reported mental and physical function[15,16]; and greater comorbidity of substance use[12,15,16,19] and eating disorders.[6] Not surprisingly, comorbid anxiety disorders are associated with a poor response to acute and maintenance treatment and overall worse course of illness.[19–22]

In particular, the presence of panic or generalized anxiety disorder seems to be associated with a lower likelihood of response to lithium[19,22] or anticonvulsants.[21] Some investigators have recently postulated that bipolar disorder co-occurring with panic and/or generalized anxiety disorders, or with social anxiety disorder, may constitute specific endophenotypic forms of bipolar disorder.[17,22–26] Given the negative prognostic significance of comorbid anxiety disorders in patients with bipolar disorder, identifying pharmacologic treatment approaches that address both disorders without exacerbating one by treating the other is an important clinical challenge.[27]

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METHOD

We conducted a literature review using the PaperChase database with the following key words: *bipolar disorder*, *anxiety*, *anxiety disorder*, *panic disorder*, *generalized anxiety disorder*, *posttraumatic stress disorder*, *social anxiety disorder*, *social phobia*, *obsessive-compulsive disorder*, *lithium*, *antiepileptics*, *valproate*, *divalproex*, *carbamazepine*, *oxcarbazepine*, *lamotrigine*, *topiramate*, *gabapentin*, *pregabalin*, *levetiracetam*, *atypical antipsychotics*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, and *aripiprazole* to identify pharmacologic treatment reports of these agents in patients with comorbid bipolar disorder and specific anxiety disorders and of these agents in the treatment of anxiety symptoms or disorders. The search was limited to studies appearing between 1966 and 2005 published in English.

In addition, we manually searched each citation identified by the PaperChase search for additional references. This search yielded 122 reports. Below, we summarize the findings from this body of literature.

RESULTS

Studies of Antimanic or Mood-Stabilizing Agents in Anxiety Disorders

Lithium. There are no randomized controlled trials of lithium monotherapy in the treatment of any anxiety disorder. Lithium was not superior to placebo as an augmentation strategy to serotonin reuptake inhibitor treatment in 2 trials in patients with obsessive-compulsive disorder.[28,29] In contrast, lithium was reported to be beneficial in case reports of patients with obsessive-compulsive disorder with associated mood instability.[30,31] Other open-label trials[32] and case reports[33,34] have described therapeutic effects of lithium in patients with symptoms of posttraumatic stress disorder. Lastly, one case report suggested that lithium might have efficacy in the treatment of panic disorder.[35] Taken together, this meager body of literature does not provide compelling evidence of therapeutic benefit of lithium in the treatment of anxiety disorder symptoms.

These preliminary findings are consistent with reports suggesting that patients with bipolar disorder with high anxiety ratings were less likely to respond to lithium.[19,22] They are also consistent with observations that patients with mixed episodes, which are frequently characterized by high levels of anxiety, are less likely to respond to lithium.[36]

Valproate. Lum et al.[37] conducted the only placebo-controlled trial of valproate in any anxiety disorder, a crossover trial in 12 patients with panic disorder. During valproate treatment, patients displayed significantly greater improvement in Clinical Global Impressions-Severity of Illness and -Improvement and Hamilton Rating Scale for Anxiety scores compared with the placebo phase of treatment. The results of this small randomized controlled trial are consistent with a number of open-label studies[38–40] and case reports[41,42] suggesting that valproate exerts antipanic effects at therapeutic concentrations. Valproate has also been demonstrated to block lactate-induced panic attacks in patients with panic disorder.[43]

Valproate has been reported to have potential efficacy in the treatment of posttraumatic stress disorder in case reports[44–46] and most open-label trials.[47–49] In these reports, which included mostly patients with combat-related posttraumatic stress disorder, valproate-treated patients displayed improvement primarily in hyperarousal and intrusive symptoms, with mixed results in avoidant symptoms and general lack of improvement in reexperiencing symptoms. Valproate was also associated with improvement in sleep disturbance. In contrast, one recent open-label trial in patients with non–combat-related posttraumatic stress disorder did not find significant improvement with valproate in any symptom cluster.[50]

Only a small number of case reports exist describing the effects of valproate in the treatment of other anxiety disorders.[51] Two reports suggest that valproate may have some efficacy in patients as an adjunctive treatment with serotonergic drugs in patients with obsessive-compulsive disorder who could not tolerate initial anxiety symptoms associated with the initiation of treatment with serotonin reuptake inhibitors.[52,53] These beneficial effects appeared limited to a reduction of overall generalized anxiety symptoms rather than specific anti–obsessive-compulsive disorder effects. Two open-label trials of valproate in the treatment of social anxiety disorder yielded mixed results, with one study reporting no significant improvement in 16 patients[54] and another describing a 41% responder rate among 17 patients.[55]

Carbamazepine. Carbamazepine has been studied in 1 randomized, placebo-controlled trial of 14 patients with, panic disorder.[56] In this study, carbamazepine did not produce significantly greater improvement compared with placebo. These findings were in contrast to an open-label trial of 34 patients with panic disorder, which found that 58% of patients had substantial reductions in the frequency of panic attacks and marked improvement in avoidance behavior and adaptive functioning.[57]

Several open-label studies suggest that carbamazepine may be useful for the treatment of some symptoms of posttraumatic stress disorder.[45,58–61] Carbamazepine appeared to be efficacious in ameliorating the frequency and intensity of flashbacks, nightmares, and intrusive thoughts in these studies. These preliminary results require confirmation in randomized controlled trials.

Open-label descriptions of carbamazepine's efficacy in the treatment of patients with obsessive-compulsive disorder have been mixed. Some reports described beneficial effects of carbamazepine in patients with obsessive-

compulsive symptoms in conjunction with epileptiform presentations[61–63] and in augmentation of serotonergic agents,[64] but in other case series of patients without epileptiform activity carbamazepine monotherapy was not found to exert significant therapeutic benefit.[65] There are no reports, to our knowledge, of carbamazepine in the treatment of generalized or social anxiety disorders.

Lamotrigine. The potential efficacy of lamotrigine in the treatment of posttraumatic stress disorder has been examined in 1 preliminary 12-week, placebo-controlled trial of 15 patients.[66] The response rate was significantly higher for patients receiving lamotrigine (50%) compared with placebo (25%). Lamotrigine-treated patients displayed greater improvement in reexperiencing and avoidance/numbness symptoms compared with patients receiving placebo. In the only other report to date of lamotrigine in the treatment of patients with anxiety disorders, Kumar and Khanna[67] augmented selective serotonin reuptake inhibitor (SSRI) treatment of patients with obsessive-compulsive disorder and found that only 1 of 8 patients appeared to benefit.

Risperidone. Risperidone has been studied in combination with SSRIs in 3 placebo-controlled trials in patients with SSRI-refractory obsessive-compulsive disorder.[68–70]

All 3 trials found significantly higher response rates in patients receiving risperidone compared with placebo. These results confirmed other case reports and case series suggesting the efficacy of adjunctive risperidone in SSRI-refractory patients with obsessive-compulsive disorder.[71–77]

Three placebo-controlled trials have also been reported using risperidone as monotherapy or adjunctive therapy in patients with posttraumatic stress disorder.[78–80] In these trials, risperidone was superior to placebo in reduction of irritability,[78] intrusive thoughts,[78,79] and hyperarousal.[80] These findings were consistent with case reports describing improvement in flashbacks/nightmares,[81] hyperarousal, and irritability[82] in patients receiving risperidone for posttraumatic stress disorder. To our knowledge, there are no reports of the use of risperidone in panic, social, or generalized anxiety disorders.

Olanzapine. Olanzapine has been reported to be effective in 2 case series of patients with treatment-refractory panic disorder[83,84] but also to precipitate panic attacks in a patient with schizophrenia.[85] In the largest case series of 10 patients, olanzapine treatment was associated with substantial reductions in the frequency of panic attacks and anticipatory anxiety and with remission of panic attacks.[83]

As with risperidone, the addition of olanzapine to SSRIs in patients with SSRI-refractory obsessive-compulsive disorder has been studied in 2 placebo-controlled trials.[86,87] Shapira et al.[86] found no significant difference between the olanzapine and placebo groups, but the placebo response rate was high in this trial. In contrast, Bystritsky et al.[87] reported significantly greater improvement in measures of obsessive-compulsive symptoms and in response rates in patients receiving olanzapine augmentation of SSRIs compared with placebo. In addition, a large number of open-label trials[88–92] and case series[93–95] have reported beneficial effects of adding olanzapine to SSRIs in patients with SSRI-refractory obsessive-compulsive disorder.

Olanzapine has been studied as adjunctive[96] and monotherapy treatment[97] of symptoms of posttraumatic stress disorder in randomized controlled trials. Stein et al.[96] randomly assigned 19 patients with posttraumatic stress disorder who were minimally responsive to treatment with an SSRI at maximum tolerated dose to an 8-week trial of adjunctive olanzapine or placebo. Patients in the olanzapine treatment arm displayed significantly greater reduction in specific measures of posttraumatic stress symptoms, depressive symptoms, and sleep disturbance. Pivac et al.[97] conducted a 6-week open, randomized comparison of fluphenazine with olanzapine in 55 male veterans with psychotic symptoms associated with posttraumatic stress disorder. Although the results were limited by the lack of a placebo group, after 3 and 6 weeks of treatment, patients receiving olanzapine displayed significantly greater improvement in positive and negative symptoms of psychosis and in avoidance and arousal symptoms. States and St.Dennis[98] reported the results of a case series of 7 patients with posttraumatic stress disorder treated with olanzapine, describing significant improvement in sleep, in reduction of nightmares, and across other symptom clusters. These findings were consistent with those reported in 2 other case series.[99,100] Lastly, Barnett et al.[101] reported beneficial effects of olanzapine in a pilot trial of patients with social anxiety disorder. To our knowledge, there are no reports of olanzapine in the treatment of generalized anxiety disorder.

Quetiapine. Denys et al.[102] conducted the only placebo-controlled trial of quetiapine, as adjunctive treatment, in patients with treatment-refractory obsessive-compulsive disorder to date. Forty patients were randomly assigned to quetiapine or placebo added to SSRIs in patients with SSRI-refractory symptoms for up to 8 weeks. Patients receiving quetiapine had significantly greater reductions in obsessive-compulsive symptoms and significantly higher responder rates compared with patients receiving adjunctive placebo. These findings were consistent with 5 other open-label reports and case series.[103–107] In contrast, Sevincok and Topuz[108] reported that only 2 of 8 patients with SSRI-refractory obsessive-compulsive disorder responded to the addition of quetiapine. However, only low-dose (150 mg/day) quetiapine was used in this case series, which may have significantly limited the efficacy of quetiapine.

Hamner et al.[109] reported the results of a 6-week open-label trial of quetiapine in 19 patients with combat-related posttraumatic stress disorder. Overall patients displayed significant improvement in psychotic, depressive, and posttraumatic stress symptom clusters. In other reports,

quetiapine was described as ameliorating panic attacks in 3 patients with comorbid schizophrenia[110] and as exerting significant improvement in 13 patients with social anxiety disorder.[111]

Aripiprazole. Three case series describing beneficial effects of aripiprazole as monotherapy[112] in patients with treatment-refractory obsessive-compulsive disorder, or as adjunctive therapy with SSRIs in the treatment of residual anxiety and depressive symptoms in patients with major depressive disorder or a variety of anxiety disorders, have appeared to date.[113–114]

There are no published randomized controlled trials of aripiprazole in the treatment of anxiety disorders to our knowledge to date.

Ziprasidone. We could not locate any published reports of the use of ziprasidone in patients with anxiety disorders.

Atypical Antipsychotics and Exacerbation of Obsessive-Compulsive Symptoms

A number of case reports (reviewed and analyzed in Sareen et al.[115] and Lykouras et al.[116]) have described exacerbation or new onset of obsessive-compulsive symptoms with exposure to atypical antipsychotics in patients with psychotic disorders. These observations are in contrast to the positive findings of atypical antipsychotic augmentation of SSRIs in placebo-controlled trials in patients with obsessive-compulsive disorder. Sareen et al.[115] hypothesized that the exacerbation or induction of obsessive-compulsive symptoms in patients with psychotic disorders may be due to a predominance of 5-HT_2 over D_2 receptor blockade by atypical antipsychotics when administered at lower doses. In other words, 5-HT_2 antagonism may induce or exacerbate obsessive-compulsive symptoms, whereas D_2 antagonism may augment the therapeutic effects of SSRIs. Thus, they suggest increasing the dose of an atypical antipsychotic when obsessive-compulsive symptoms occur or adding an SSRI. It is possible that some patients with apparent psychotic disorders in fact had bipolar manic or mixed episodes with psychotic symptoms, and with resolution of the psychotic manic or mixed episode in response to treatment with an atypical agent, they switched into a depressive episode marked by obsessive-compulsive symptoms.

Studies of Antidepressants in Anxiety Disorders

There is a substantial body of evidence indicating that antidepressant agents from virtually every class have efficacy in the treatment of most anxiety disorders.[117,118] The one exception may be obsessive-compulsive disorder, for which SSRIs appear to be more effective than nonserotonergic antidepressants.[118] The established efficacy of these unimodal antidepressants in the treatment of anxiety disorders presents the dilemma of balancing the therapeutic effects of these agents in patients with bipolar disorder and co-occurring anxiety disorders with the switch risk associated with combining such agents with mood-stabilizing or antimanic medications.

Studies of Other Antiepileptics in Anxiety Disorders

In this section, we review studies of antiepileptic agents with unproven efficacy in the treatment of bipolar disorder, but which have been studied in the treatment of anxiety disorders.

Topiramate. Topiramate has been reported to be effective in case reports and preliminary open-label trials in patients with generalized social anxiety[119] and posttraumatic stress disorder[120,121] and as adjunctive treatment with SSRIs in patients with SSRI-refractory obsessive-compulsive disorder.[122] In contrast, topiramate was reported to be associated with new-onset panic attacks in a patient with bipolar disorder[123] and new-onset obsessive-compulsive symptoms in a patient treated for epilepsy[124] in case reports. These preliminary observations and reports require further study in randomized controlled trials.

Gabapentin. Gabapentin has been evaluated in placebo-controlled trials in the treatment of panic disorder[125] and social phobia.[126] In the panic disorder trial, 103 patients were randomly assigned to receive gabapentin (600–3600 mg/day) or placebo for 8 weeks.[125] There were no significant differences between the gabapentin and placebo groups on the primary outcome measure, the Panic and Agoraphobia Scale. These findings were in contrast to the beneficial effects of adjunctive gabapentin use in a patient with refractory panic disorder.[127] In the 14-week social phobia trial,[126] patients receiving gabapentin (900–3600 mg/day) displayed significantly greater reduction in symptoms of social phobia at study endpoint.

The remaining literature regarding gabapentin in the treatment of anxiety disorders consists of case reports and case series suggesting that the adjunctive use of gabapentin was helpful in individual patients with SSRI-refractory obsessive-compulsive disorder[128] and posttraumatic stress disorder,[129–132] with particular improvement in sleep quality and reduction of nightmares in the latter.

Pregabalin. Pregabalin has been examined in placebo-controlled trials for the treatment of generalized anxiety disorder[133,134] and social phobia.[135] In the first generalized anxiety disorder trial, 271 patients were randomly assigned to pregabalin 50 mg t.i.d., pregabalin 200 mg t.i.d., lorazepam 2 mg t.i.d., or placebo for 4 weeks.[133] Patients receiving pregabalin 200 mg t.i.d. and lorazepam 2 mg t.i.d. displayed significantly greater reductions in anxiety symptoms compared with placebo at study endpoint. The group receiving pregabalin 50 mg t.i.d. did not show a significantly greater improvement compared with the placebo group. The second generalized anxiety disorder trial compared pregabalin 100 mg b.i.d., pregabalin 200 mg b.i.d., and pregabalin 150 mg t.i.d. with placebo in 341 patients over 6 weeks.[134]

All 3 pregabalin treatment groups displayed significantly greater improvement in anxiety symptoms compared with the placebo group, with no difference between the b.i.d. and t.i.d. administration groups.

In the social phobia trial, 135 patients were randomly assigned to 10 weeks of treatment with pregabalin 150 mg/day, pregabalin 600 mg/day, or placebo.[135] The pregabalin 600 mg/day group had significantly greater improvement in social phobic symptoms at study endpoint compared with the placebo group; the pregabalin 150 mg/day group did not separate from placebo.

Oxcarbazepine. There are no controlled trials of oxcarbazepine in the treatment of anxiety disorders. The available literature consists of case reports suggesting beneficial effects in patients with treatment-refractory posttraumatic stress disorder,[136,137] obsessive-compulsive disorder,[138] and panic attacks occurring in patients with epilepsy.[139]

Levetiracetam. Simon et al.[140] reported significant reductions in symptoms of social anxiety in 20 patients treated with levetiracetam (to 3000 mg/day). There were also significant reductions in anxiety symptoms overall.

Studies of Patients With Bipolar Disorder and Co-Occurring Anxiety Disorders

Unfortunately, there are no randomized controlled trials examining the treatment response of patients with bipolar disorder and a co-occurring anxiety disorder. Only 1 open-label trial of divalproex in 55 patients with rapid-cycling bipolar disorder simultaneously assessed response in co-occurring panic disorder or generalized anxiety disorder.[141] Patients were followed for an average of approximately 8 months, and the majority achieved decreases in or remission of anxiety symptoms. Small open-label trials of topiramate[142] and gabapentin[143] in patients with bipolar disorder have yielded modest evidence of improvement in co-occurring anxiety.

PHARMACOLOGIC TREATMENT IMPLICATIONS FOR COMORBID BIPOLAR AND ANXIETY DISORDERS

From the literature reviewed above, there is modest evidence that valproate may exert beneficial effects in panic and anxiety symptoms. Preliminary findings suggest that lamotrigine may ameliorate some symptoms of posttraumatic stress disorder, as may adjunctive treatment with risperidone, olanzapine, and quetiapine. Risperidone, olanzapine, and quetiapine have all been demonstrated to augment the effects of SSRIs in patients with SSRI-refractory OCD in at least one acute randomized controlled trial. Among other antiepileptic agents, some evidence suggests that gabapentin may be useful in social anxiety disorder, and perhaps in reducing overall symptoms of anxiety. Data from randomized controlled trials indicate that pregabalin appears to have efficacy in the treatment of generalized and social anxiety disorders. Neither gabapentin nor pregabalin appear to have antimanic properties, although Perugi et al.[144] have speculated that improvement reported in patients with bipolar disorder in open-label trials of gabapentin may have been due to improvement in co-occurring anxiety disorders.

Most classes of antidepressants have demonstrated efficacy in the treatment of anxiety disorders, with SSRIs being most efficacious for obsessive-compulsive disorder.

In the recent Expert Consensus Guidelines Series for Bipolar Disorder,[145] divalproex, gabapentin, quetiapine, and olanzapine were endorsed as among the first-line agents for patients with co-occurring anxiety disorders. Similarly, the Canadian Network for Mood and Anxiety Treatments (CANMAT)[146] guidelines for the management of patients with bipolar disorder mentioned atypical antipsychotics, antidepressants, and benzodiazepines as agents showing efficacy in reducing anxiety symptoms.

The initial goal in pharmacologic management of patients with bipolar disorder and a co-occurring anxiety disorder is mood stabilization.[147] The recommendation of an antimanic or mood-stabilizing agent would, in part, be influenced by the specific co-occurring anxiety disorder. Ideally, an agent that provides both mood-stabilizing effects and addresses the co-occurring anxiety disorder would be chosen if available. Given the limited data regarding the efficacy of thymoleptic agents used in bipolar disorder and their efficacy in anxiety disorders, this goal presents a common clinical challenge.

Drug names: aripiprazole (Abilify), carbamazepine (Tegretol and others), divalproex (Depakote), fluphenazine (Prolixin and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), levetiracetam (Keppra), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), pregabalin (Lyrica), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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