

Treatment of anxiety disorders in patients with comorbid bipolar disorder

Carol A. Ott, PharmD, BCPP¹

How to cite: Ott CA. Treatment of anxiety disorders in patients with comorbid bipolar disorder. Ment Health Clin [Internet]. 2018;8(6):256-63. DOI: 10.9740/mhc.2018.11.256.

Abstract

Anxiety disorders are the most prevalent comorbid diagnoses in patients with bipolar disorder (BD). A comorbid anxiety diagnosis can significantly impact the severity of bipolar symptoms, increase the risk of suicidality, and decrease psychosocial functioning and quality of life. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force published recommendations for treatment in 2012 suggesting that specific anticonvulsant mood stabilizers and second-generation antipsychotics are the medications of choice to treat these comorbidities. Serotonergic antidepressant medications are first-line medications for the treatment of most anxiety disorders; however, this can be problematic for a patient with BD. Antidepressant use in BD has been associated with a risk of manic switch as well as potential destabilization of mood. Mood stabilizer therapy should be established for patients with comorbid BD and an anxiety disorder before other medications are added to address the anxiety disorder. While benzodiazepine medications are recommended as third-line therapy in the CANMAT task force recommendations, their use should be avoided in patients with comorbid BD, posttraumatic stress disorder, and substance use disorders. The use of benzodiazepines should in general be avoided for all patients if possible, based upon current clinical research. Interpersonal, cognitive behavioral, and relaxation therapy are effective for the treatment of anxiety symptoms, especially emotional experiences, in patients who are euthymic.

Keywords: bipolar disorder, anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, mood stabilizers, antidepressants, antipsychotics, psychotherapy

¹ (Corresponding author) Clinical Professor of Pharmacy Practice, Department of Pharmacy Practice, Purdue University College of Pharmacy, Indianapolis, Indiana; Clinical Pharmacy Specialist, Outpatient Psychiatry, Prevention and Recovery Center for Early Psychosis, Mood Disorders Clinic, Midtown Community Mental Health, Eskenazi Health, Indianapolis, Indiana, caott@iupui.edu, ORCID: <http://orcid.org/0000-0003-2719-3845>

Disclosures: I have nothing personal to disclose. Psychopharmacology Pearls are review articles intended to highlight both the evidence base available and/or controversial areas of clinical care for psychiatric and neurologic conditions as well as strategies of clinical decision making used by expert clinicians. As pearls, articles reflect the views and practice of each author as substantiated with evidence-based facts as well as opinion and experience. Articles are edited by members of the Psychopharmacology Pearls Editorial Board as well as peer reviewed by MHC reviewers. This article was developed as part of the 2018 Psychopharmacology Pearls product for BCPP recertification credit. The course information and testing center is at cnp.org/353267.

Introduction

Anxiety disorders are the most prevalent comorbid diagnoses in patients with bipolar disorder (BD). The lifetime prevalence of anxiety disorders is 45% when BD is present; patients with BD are 3 to 7 times more likely to meet criteria for diagnosis of an anxiety disorder than the general population.^{1,2} Panic, posttraumatic stress (PTSD), and generalized anxiety disorders (GAD) are the most common (13% to 60%), followed by obsessive compulsive disorder (OCD; 10%).¹⁻³ Anxiety disorders and compulsive disorders, specifically OCD, will be addressed as a group because of the similar approaches used in treatment outside of the context of BD. For the purposes of this review, the terms *anxiety* and/or *anxiety symptoms* can be interpreted to also include obsessive and compulsive symptoms. Comorbid anxiety symptoms have a significant impact on the treatment of BD leading to increased

Take Home Points

1. Bipolar disorder (BD) with comorbid anxiety disorders is very prevalent and can lead to a higher illness burden, greater risk of residual symptoms upon resolution of the mood episode, and decreased medication adherence.
2. There are limited clinical trials to provide evidence for medication and other treatments for comorbid BD and anxiety disorders. Mood stabilization is generally the first priority before addressing the anxiety disorder.
3. Polypharmacy is the rule in the treatment of comorbid bipolar and anxiety disorders. Mood stabilizer monotherapy is unlikely to be effective for all symptoms. Recognition of the need for effective treatment of the anxiety disorder is paramount in improving quality of life and minimizing suicidality.
4. Although serotonergic antidepressants, specifically selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, are first-line medication treatments for anxiety disorders, the use of antidepressants in BD may lead to destabilization of mood and a risk of manic switch, especially when used for long-term treatment. Serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants have been associated with a greater risk of manic switch than selective serotonin reuptake inhibitors and bupropion. Mood stabilizers and second-generation antipsychotics should be used as initial treatment before treatment with antidepressants. Lithium may be more protective against manic switch than other mood stabilizers. If antidepressant therapy is warranted, it should be undertaken with caution and close monitoring.

severity of bipolar symptoms and use of mental health services, more frequent and severe depressive episodes, non-adherence to treatment, and decreased functioning and quality of life (Table 1).⁴⁻⁶

The goals of treatment for patients with comorbid anxiety and BD are remission of symptoms and a return to baseline functioning. Anxiety commonly occurs during a depressive episode, which partly reflects the prevalence of the comorbid diagnoses of anxiety and mood disorders but does not explain anxiety symptoms occurring during euthymia.⁴ Anxiety symptoms may not commonly remit with resolution of the mood episode; this leads to a progressive decrease in functioning and quality of life, even in euthymia. Residual anxiety symptoms may be a risk factor for limited success in the treatment of mood symptoms and may be predictive of mood symptom relapse. In a recent study evaluating the effectiveness of

TABLE 1: Risk factors and impact of comorbid anxiety disorders and bipolar disorder^{4,5}

Risk factors for comorbid anxiety disorders and bipolar disorder
Earlier age of onset of bipolar disorder (early symptoms of anxiety in high-risk youth)
Family history of mood disorders
Female gender
Childhood sexual abuse
Adult sexual assault
Comorbid personality disorder
Impact of comorbid anxiety disorders and bipolar disorder
↑ # mood episodes
↑ rate of depression as first episode
↑ rate of mixed episodes
↑ rate of rapid cycling
↑ frequency/severity of mood episodes
↑ periods of untreated illness
↑ time to remission
↑ suicidality
↑ risk of substance use
↑ severity of medication adverse events
↑ health care use
↑ psychological distress
↓ response to treatment
↓ adherence to treatment
↓ functioning and quality of life

venlafaxine versus lithium monotherapy in acute ($n = 129$, duration 12 weeks) and continuation ($n = 55$, duration 6 months) treatment of BD II depression, the investigators evaluated the impact of comorbid anxiety symptoms on depression relapse. Venlafaxine was more effective than lithium on depressive symptoms ($P < .0001$), but was less likely to improve symptoms of anxiety ($P < .027$). The rate of manic switch was not reported in this study. Residual anxiety symptoms, especially uncontrollable worry, were a stronger predictor of depression relapse than residual depressive symptoms. The investigators concluded that remission of anxiety symptoms in bipolar depression may be protective against depressive relapse.⁷

The recognition and treatment of comorbid anxiety and BD remains an understudied area. Most published literature is descriptive in nature; few clinical trials exist related to pharmacologic and behavioral treatments.⁸ The cases presented in this article will highlight treatment choices for medications and psychotherapy, the risk of manic switch when using antidepressants, the *with anxious distress* specifier, and the need for mood stabilization prior to initiation of antidepressant treatment for patients with BD and comorbid anxiety disorders.

TABLE 2: Canadian Network for Mood and Anxiety Treatments task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders⁵

Recommendations

First line: gabapentin, quetiapine

Second line: divalproex sodium, lamotrigine, serotonergic antidepressants, olanzapine, olanzapine-fluoxetine combination

Third line: lithium, risperidone, aripiprazole, pregabalin, medium- or long-acting benzodiazepines

Adolescents: cognitive behavioral therapy is the first-line recommendation for the management of anxiety

Summary comments

Second generation antipsychotics and gabapentin have evidence for use in primary anxiety disorders

Pregabalin has not been studied in bipolar disorder; use should be based on clinical opinion

Side effect burden has not been studied for patients with comorbid anxiety and bipolar disorder for these medications

Ensure adequate mood stabilization before considering specific options for anxiety disorders

Use caution when considering antidepressants; clear risk of destabilization of bipolar mood symptoms

Use of benzodiazepines for rapid treatment of anxiety symptoms should take into account risk of substance misuse

Case 1: OCD

A 28-year-old patient with a 6-year history of BD, most recent episode depressed, and OCD presents to the outpatient mood disorders clinic for a medication evaluation. Current medications include lithium 900 mg orally at bedtime and sertraline 150 mg orally once daily. The most recent lithium level, obtained 2 months ago, was 0.8 mEq/L. All other laboratory parameters are within normal limits. The patient denies suicidal ideation or any symptoms of hypomania or mania, however, continues to feel sad and hopeless, and is in bed about 14 h/d, often not sleeping. Obsessive compulsive disorder symptoms include obsessional thinking about the safety of family members, with associated rituals performed every 2 hours. These symptoms have not improved since the initiation of sertraline and dose increases over the past 6 months. Medications are taken as prescribed with rarely missed doses and no side effects.

Treatment Considerations for Comorbid BD and OCD

Obsessive compulsive disorder symptoms that present only during episodes of depression may be secondary to the mood episode.^{5,9} The patient in Case 1 is taking a mood stabilizer and a selective serotonin reuptake inhibitor (SSRI) antidepressant without any improvement in depressive or OCD symptoms. There is limited evidence for the efficacy of medications in the treatment of comorbid BD and OCD. Case reports and case series have suggested lithium, anticonvulsant mood stabilizers, olanzapine, risperidone, quetiapine, or aripiprazole for this comorbidity.^{5,9} Serotonergic antidepressant medication should only be used in combination with appropriate effective mood stabilizer treatment to avoid decompensation of bipolar symptoms.⁵ A systematic review of the treatment of BD and OCD reported a high rate of nonresponse to pharmacologic treatment, common use

of polypharmacy, and a risk of manic/hypomanic mood switch if conventional treatment for OCD, such as SSRI therapy, was used.¹⁰ Mood stabilizer monotherapy is unlikely to be effective for both disorders; combination treatment with a mood stabilizer and a second-generation antipsychotic (SGA) or 2 mood stabilizers is recommended.^{10,11} A case series reported on 3 patients with comorbid BD and OCD taking a mood stabilizer and adjunctive aripiprazole 15 mg to 25 mg daily.¹² A decrease in the Yale Brown Obsessive Compulsive Scale (YBOCS) score was observed for all patients. All 3 patients tolerated aripiprazole with no reported side effects, including akathisia. In a placebo-controlled study of adjunctive quetiapine in patients with treatment-refractory OCD (n = 40), the YBOCS score decreased by ~25%.¹³ A comparison trial of aripiprazole (n = 6) and quetiapine (n = 12) as augmentation treatment in refractory OCD resulted in more participants moderately responding to quetiapine (~55%) than aripiprazole (~28%) with similar decreases in YBOCS scores ($P = .01$ for quetiapine, not statistically significant for aripiprazole).¹⁴

In the case of the 28-year-old patient with continuing symptoms of bipolar depression and OCD, medication changes are warranted. Lithium is recommended as third-line therapy in the Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations.⁵ Table 2 provides a review of the recommendations from the CANMAT task force.⁵ Selective serotonin reuptake inhibitor drug therapy should not be used without effective mood stabilizer therapy; sertraline is not effective for either depressive or OCD symptoms for this patient. The case does not clarify if the patient has taken other SSRI antidepressant therapy, therefore a switch to a different SSRI may be an option. Aripiprazole, risperidone, and quetiapine have evidence of efficacy as augmentation agents for SSRI treatment for OCD symptoms specifically in randomized controlled trials of

OCD without BD.¹³⁻¹⁵ Other SGAs that have been studied for bipolar depression, such as lurasidone or olanzapine, may be considered although clinical evidence is limited for effectiveness for OCD symptoms. For this patient, options include transition to another SSRI or to an atypical antipsychotic while continuing lithium treatment. If the patient prefers another SSRI, paroxetine may help with sleep. It can be initiated either by direct switch or cross-titration as tolerated by the patient. If the patient prefers an atypical antipsychotic, then the sertraline should be tapered over 1 to 4 weeks, as tolerated, while initiating either quetiapine (if sedation desired) or aripiprazole (if sedation is not desired). Combination treatment with either an SSRI and mood stabilizer or SGA and mood stabilizer were most commonly used in a systematic review of the treatment of BD and OCD.⁵

The use of psychotherapy in comorbid BD and OCD has been shown to be effective in clinical trials. Interpersonal therapy, cognitive behavioral therapy (CBT), mindfulness-based CBT, and relaxation therapy may be employed in combination with medication treatment.¹⁵⁻¹⁷ Psychoeducation is not effective, and CBT is more effective for OCD symptoms when the patient is euthymic.^{18,19} Comorbid OCD can have a significant impact on recovery for both bipolar and OCD symptoms, with a decreased social quality of life, higher risk of rapid cycling, suicide attempts, alcohol use, and a decreased likelihood of remission of bipolar symptoms in the first year of treatment with mood stabilizers.¹⁸⁻²⁰

Case 2: GAD

A 34-year-old patient with BD I diagnosed approximately 10 years ago following the first manic episode, presents to the outpatient mood disorders clinic for a medication evaluation. While there have been no subsequent manic episodes, the first episode of depression was about 6 years ago with incomplete remission of symptoms. Additionally, GAD was diagnosed 5 years ago based on symptoms of uncontrollable worry. The patient has had 2 depressive episodes in the past year and 2 past suicide attempts by medication overdose. Substance use includes 3 to 4 beers each evening but no use of other substances including tobacco. Current medications are divalproex sodium extended release 1500 mg orally at bedtime and duloxetine 90 mg orally daily (dose increased about 4 weeks ago from 60 mg daily). The most recent valproate level was 85 mcg/mL approximately 3 months ago. All other laboratory parameters are within normal limits. Current symptoms of hypomania include decreased sleep (4 hours per night vs normal 6 to 8 hours), pressured speech and racing thoughts.

Risk of Manic Switch: Use of Antidepressants in BD

Symptoms of anxiety disorders are regarded as chronic throughout treatment, often necessitating long-term medication treatment. The SSRI antidepressants are recommended as first-line drug therapy for the treatment of anxiety disorders. Selective serotonin reuptake inhibitors and bupropion are believed to have a lower risk of manic switch than serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants.^{21,22} The risk of antidepressant treatment-emergent hypomania or mania (ATEM) has been a long-standing concern about the use of these medications to treat bipolar depression. The CANMAT task force recommendations for the treatment of anxiety disorders with comorbid BD suggest serotonergic antidepressants are second-line therapy, with the caution that patients should be taking effective mood stabilizer treatment as a foundational therapy.⁵ Predictors of manic switch were evaluated in a study using a sample of participants (n=1720) in the Systematic Treatment Program for Bipolar Disorder trials.²³ According to this study, baseline variables for an increased risk of manic switch include younger age (17 to 22 years) at onset of BD, a previous history of rapid cycling, severe manic symptoms, suicide attempts, or amphetamine use.²³ A higher switch rate is possible if there is a history of manic switch using SSRIs in general and specifically with the use of fluoxetine, sertraline, or paroxetine.²³ A lower risk is conferred if the patient has a history of participation in psychotherapy.²³ The number of past manic episodes overall may also contribute to the risk of ATEM. A study of depressed bipolar patients (n=1242) taking a mood stabilizer and a recently initiated antidepressant for 1 month observed 4.8% (n=60) of study participants experienced a manic switch. Patients who had at least 4 lifetime manic episodes and a history of ATEM were at 2.84 times greater risk of manic switch.²⁴ Switch rates during a study of acute treatment comparing lithium monotherapy (n=49), sertraline monotherapy (n=45), and the combination (n=48) were estimated to be approximately 14%, with no difference between the treatment arms.²⁵ Two studies focused on evaluating the correlates and rates of switch using a strict definition of ATEM.^{26,27} Study participants who had ATEM (n=44) had different baseline Young Mania Rating Scale (YMRS) scores compared to those who had and had not responded to antidepressant treatment but did not have ATEM (n=128). The baseline YMRS scores for participants with ATEM was 3.7 versus those without ATEM (1.8 to 2.5). The YMRS scores for motor activity and speech were increased and the item for language-thought disorder was positive.²⁶ The authors²⁶ recommend evaluating patients for the presence of minimal baseline manic symptoms (specifically motor activation, pressured speech, and racing thoughts) to identify individuals at risk for ATEM

prior to initiating antidepressant therapy. A study²⁷ (n = 210) using strict criteria for ATEM differentiated odds ratios (OR) of risk for ATEM based upon gender. For men (n = 95), increased risk was found for alcohol use/substance use disorder (OR 6.37), history of suicide attempt (OR 4.19), and increased number of depressive episodes per year (OR 1.71). For women (n = 125), history of thyroid disorder (OR 3.23), family history of BD I (OR 2.68), and depression as the first mood episode (OR 2.01) conferred greater risk of ATEM.²⁷

Treatment Considerations for Comorbid BD and GAD

The point prevalence for GAD with comorbid BD is estimated to be 12% with a lifetime prevalence of 15%.²⁸ This comorbidity leads to a more severe course of illness and increased suicidality.²⁸ Quality of life in patients with BD and comorbid anxiety disorders who are euthymic is poorer overall in both BD I and II, but the greater negative effect is found in BD I.²⁹ Olanzapine, lamotrigine, divalproex sodium, and olanzapine/fluoxetine combination have been found to be effective in the treatment of nonspecific anxiety symptoms that are comorbid with BD.^{3,30,31} Lithium is not likely to be effective as monotherapy; augmentation of lithium with lamotrigine or olanzapine may improve efficacy.^{3,30} Risperidone is not effective for nonspecific anxiety symptoms. Ziprasidone monotherapy was not associated with improved panic disorder or GAD symptoms in patients with BD (n = 49); increased abnormal involuntary movements were noted over the 8-week study.³² Benzodiazepines may be considered if the patient is not experiencing an acute depressive episode.^{3,30}

Quetiapine extended-release has been studied as monotherapy versus placebo and divalproex sodium extended-release, with conflicting results relative to effectiveness.^{33,34} In a study³³ evaluating patients (n = 100) with acute bipolar I or bipolar II depression with comorbid GAD, quetiapine extended-release, at an average study dose of 276 mg/d, was not superior to placebo in treating anxiety symptoms. A trial³⁴ evaluating quetiapine extended-release monotherapy (n = 49), divalproex sodium extended-release monotherapy (n = 49), and placebo (n = 51) observed quetiapine extended-release, at an average study dose of 186 mg/d, provided rapid sustained improvement in anxiety symptoms (Hamilton Anxiety Rating Scale, $P < .05$ vs divalproex and placebo) in bipolar patients and was superior to both divalproex sodium extended-release and placebo.

Cognitive behavioral therapy has been shown to be beneficial for patients experiencing BD with comorbid GAD.³⁵ The Unified Protocol for Emotional Disorders was used as the basis for CBT developed to address common

core symptoms of emotional lability and maladaptive attempts to control or avoid emotional experiences in patients with BD and comorbid anxiety disorders (n = 29). Greater reductions in anxiety (Hamilton Anxiety Rating Scale, $P = .03$) and depressive (Hamilton Depression Rating Scale, $P = .01$) symptoms were observed in study participants.³⁵

In the case of the 34-year-old patient with BD and comorbid GAD, the patient seems to be experiencing a hypomanic episode due to antidepressant treatment. Symptoms of depression and GAD are not well controlled on the combination of divalproex sodium extended-release and duloxetine. Duloxetine should be discontinued and the hypomanic symptoms evaluated for resolution. Discontinuation of duloxetine for this patient may be achieved via a dose taper over a few weeks since this patient is hypomanic. If this patient was manic and met criteria for hospitalization, duloxetine should be discontinued without a taper with monitoring for antidepressant discontinuation syndrome. The efficacy of divalproex sodium in the past should be evaluated. It would be useful to obtain another serum concentration of divalproex to evaluate adherence to medication and for possible dose adjustments. Since the patient has not had effective treatment of GAD and depression symptoms, an SGA such as quetiapine or olanzapine should be considered as adjunctive therapy. Quetiapine is the preferred choice for this patient, based on the limited clinical trial evidence for efficacy. The CANMAT task force recommends quetiapine as first-line treatment and the sedative side effect may be helpful for this patient. Olanzapine/fluoxetine is a second-line treatment recommendation and may be considered with caution if quetiapine is not effective.

Case 3: PTSD and the *With Anxious Distress Specifier*

A 38-year-old with BD I, most recent episode depressed, with anxious distress and PTSD presents to the outpatient mood disorders clinic for medication evaluation and follow-up. History includes two prior manic episodes requiring hospitalization, the most recent 8 years ago. Social history includes domestic violence in the home as a child and sexual assault as an adult. Residual symptoms of depression have not improved since the previous visit 3 months ago. Sleep is “okay”, about 6 hours per night, with the aid of over-the-counter doxylamine 25 mg nightly. The patient is able to get out of the house to go to work but does not participate in many activities with family or friends and expresses uncontrollable worry about life events and being outside the comfort of home for an extended time. Active substance use consists of one-half of a bottle of wine every evening and 1 pack per

TABLE 3: *Diagnostic and Statistical Manual for Mental Disorders, 5th edition, criteria for the with anxious distress specifier*³⁶

At least 2 of the following symptoms present during most days of the current mood episode:

- Feeling on edge or nervous
- Feeling abnormally restless
- Worry leading to difficulty concentrating
- Fear that something bad may happen
- Feeling that the individual may lose control of himself or herself

Specify current severity:

- Mild: 2 symptoms
- Moderate: 3 symptoms
- Moderate-Severe: 4 to 5 symptoms
- Severe: 4 to 5 symptoms with motor agitation

Note: Anxious distress has been noted as a prominent feature of both bipolar and major depressive disorder in both primary care and specialty mental health settings. High levels of anxiety have been associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse. As a result, it is clinically useful to specify accurately the presence and severity levels of anxious distress for treatment planning and monitoring of response to treatment.

day of tobacco. Previous ineffective medication trials include lithium, sertraline, topiramate, and alprazolam. Current medications are quetiapine extended-release 400 mg orally at bedtime and fluoxetine 40 mg orally once daily. According to the pharmacy, medications are filled about every 45 days, indicating poor adherence to the medication regimen.

With Anxious Distress Specifier

Table 3 provides the diagnostic criteria for the *with anxious distress* specifier.³⁶ This specifier was added to the *Diagnostic and Statistical Manual for Mental Disorders, 5th edition*³⁶ because of greater recognition that anxiety symptoms and disorders are common comorbidities in mood disorders. Anxiety symptoms lead to a greater burden of depressive symptoms, increased total number of depressive episodes, and a longer time to remission.⁵ The use of the *with anxious distress* specifier reminds health care professionals to evaluate anxiety symptoms and appropriate treatment in addition to evaluation of other mental health diagnoses.

Treatment Considerations for Comorbid BD and PTSD

Patients with comorbid BD and PTSD have a higher risk of psychosis upon hospitalization (13%, $P < .001$), personality disorder diagnosis (42%, $P = .002$), and suicide attempts (75%, $P < .001$).^{6,37} Poorer quality of life, accelerated illness progression, and high rates of functional impairment also characterize patients with this comorbidity,

with a higher symptom burden compared to either illness alone.^{6,38,39}

Non-adherence to treatment in BD increases the risk of rapid cycling, suicide attempts, current anxiety, and alcohol use disorder.⁴⁰ Non-adherence at 3 month follow-up is predictive of less improvement in bipolar symptoms than non-adherence at 12 month follow-up.⁴⁰ Patients with non-adherence to treatment for comorbid BD and PTSD may have childhood or other trauma that created a negative or distrustful impression of physicians, health care providers, and medication treatment.⁴¹ Traumatic outcomes resulting from dangerous behaviors that occur during a manic episode may trigger the reemergence of PTSD symptoms. Posttraumatic stress disorder nightmares could impact the sleep-wake cycle, leading to decreased sleep and a greater risk for a manic episode.⁴¹

The CANMAT task force recommendations recognize that there have been no clinical trials of drug therapy for comorbid BD and PTSD. The recommendations suggest initial medication therapy should be a mood stabilizer, followed by the combination of an SGA and an antidepressant.⁵ Once mood stabilizer treatment is initiated, then SSRI or SNRI antidepressant therapy may be used with caution for residual PTSD anxiety symptoms. Posttraumatic stress disorder may be less likely to respond to lithium treatment; therefore risperidone, lamotrigine, gabapentin, and oxcarbazepine may be considered.^{11,30,42} The level of evidence for the efficacy of anticonvulsants and antipsychotics for the treatment of PTSD is limited. Mood stabilization remains the priority; once this is established, medication combinations including anticonvulsants, antipsychotics, and antidepressants may be considered.⁵ Benzodiazepines appear as a third-line recommendation in the CANMAT task force recommendations, but these medications are generally considered to be ineffective for PTSD and carry a risk of developing further PTSD symptoms after recent trauma, worsening psychotherapy outcomes, and developing substance use disorders in PTSD.⁴³ Divalproex sodium may be considered for the *with anxious distress* and general anxiety symptoms in BD.³⁰

In the case of the 38-year-old patient currently prescribed quetiapine extended-release and fluoxetine with questionable adherence to treatment, the patient should be asked about the reasons for not taking medications appropriately as well as the overall perception of medication therapy. A priority for this patient is to evaluate if this combination of medications has been effective in the past. If so, patient factors related to non-adherence should be addressed, and the patient should be encouraged to restart this medication regimen. Risperidone has positive evidence of effectiveness and may be considered if

quetiapine is discontinued. If fluoxetine is discontinued, switching to an SNRI, such as venlafaxine, could be considered after mood stabilizer therapy has been established with increased monitoring for the risk of manic switch. The use of benzodiazepines should be avoided for this patient. Other common medications and treatments for PTSD, such as prazosin for nightmares and psychotherapy or CBT may also be considered. Studies evaluating CBT, including psychoeducation, coping skills, cognitive restructuring, and relaxation training, have included patients with comorbid BD and PTSD.¹⁸ While the results of these studies have preliminarily shown improvement in anxiety symptoms for CBT focused on PTSD with comorbid BD, retention rates in these studies has been low.¹⁸

Conclusion

Bipolar disorder with comorbid anxiety disorders is very common. The burden of illness with this comorbidity leads to prolonged mood episodes, residual anxiety and depressive symptoms, decreased quality of life, and negative treatment outcomes. There is limited clinical evidence for appropriate use of medications that are effective specifically for these comorbidities, leading clinicians to attempt to treat each disorder separately based upon treatment guidelines. The CANMAT task force recommendations are currently the only guidance that focuses on the treatment of comorbid bipolar and anxiety disorders, which highlights the need for further research in this area. It is important to recognize the limited ability of medications to treat these comorbidities and advocate for the use of psychotherapy and CBT as complementary treatment options. Polypharmacy is the rule when treating BD with comorbid anxiety disorders; close monitoring for medication adherence, effectiveness, and side effects is required.

References

1. Lee JH, Dunner DL. The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders. *Depress Anxiety*. 2008; 25(2):91-7. DOI: [10.1002/da.20279](https://doi.org/10.1002/da.20279). PubMed PMID: [17311265](https://pubmed.ncbi.nlm.nih.gov/17311265/).
2. Pavlova B, Perlis RH, Alda M, Uher R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry*. 2015;2(8):710-17. DOI: [10.1016/S2215-0366\(15\)00112-1](https://doi.org/10.1016/S2215-0366(15)00112-1). PubMed PMID: [26249302](https://pubmed.ncbi.nlm.nih.gov/26249302/).
3. Vázquez GH, Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. *Depress Anxiety*. 2014;31(3):196-206. DOI: [10.1002/da.22248](https://doi.org/10.1002/da.22248). PubMed PMID: [24610817](https://pubmed.ncbi.nlm.nih.gov/24610817/).
4. Sala R, Goldstein BI, Morcillo C, Liu S-M, Castellanos M, Blanco C. Course of comorbid anxiety disorders among adults with bipolar disorder in the U.S. population. *J Psychiatr Res*. 2012; 46(7):865-72. DOI: [10.1016/j.jpsychires.2012.03.024](https://doi.org/10.1016/j.jpsychires.2012.03.024). PubMed PMID: [22534180](https://pubmed.ncbi.nlm.nih.gov/22534180/).
5. Schaffer A, McIntosh D, Goldstein BI, Rector NA, McIntyre RS, Beaulieu S, et al. The CANMAT task force recommendations for

the management of patients with mood disorders and comorbid anxiety disorders. *Ann Clin Psychiatry*. 2012;24(1):6-22. PubMed PMID: [22303519](https://pubmed.ncbi.nlm.nih.gov/22303519/).

6. Reddy MK, Meyer TD, Wittlin NM, Miller IW, Weinstock LM. Bipolar I disorder with comorbid PTSD: demographic and clinical correlates in a sample of hospitalized patients. *Compr Psychiatry*. 2017;72:13-17. DOI: [10.1016/j.comppsy.2016.08.007](https://doi.org/10.1016/j.comppsy.2016.08.007). PubMed PMID: [27693886](https://pubmed.ncbi.nlm.nih.gov/27693886/).
7. Lorenzo-Luaces L, Amsterdam JD, DeRubeis RJ. Residual anxiety may be associated with depressive relapse during continuation therapy of bipolar II depression. *J Affect Disord*. 2018;227:379-83. DOI: [10.1016/j.jad.2017.11.028](https://doi.org/10.1016/j.jad.2017.11.028). PubMed PMID: [29149756](https://pubmed.ncbi.nlm.nih.gov/29149756/).
8. Provencher MD, Guimond A-J, Hawke LD. Comorbid anxiety in bipolar spectrum disorders: a neglected research and treatment issue? *J Affect Disord*. 2012;137(1-3):161-4. DOI: [10.1016/j.jad.2011.12.001](https://doi.org/10.1016/j.jad.2011.12.001). PubMed PMID: [22209124](https://pubmed.ncbi.nlm.nih.gov/22209124/).
9. Amerio A, Stubbs B, Odone A, Tonna M, Marchesi C, Ghaemi SN. The prevalence and predictors of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review and meta-analysis. *J Affect Disord*. 2015;186:99-109. DOI: [10.1016/j.jad.2015.06.005](https://doi.org/10.1016/j.jad.2015.06.005). PubMed PMID: [26233320](https://pubmed.ncbi.nlm.nih.gov/26233320/).
10. Amerio A, Odone A, Marchesi C, Ghaemi SN. Treatment of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. *J Affect Disord*. 2014;166:258-63. DOI: [10.1016/j.jad.2014.05.026](https://doi.org/10.1016/j.jad.2014.05.026). PubMed PMID: [25012439](https://pubmed.ncbi.nlm.nih.gov/25012439/).
11. Keck PE, Strawn JR, McElroy SL. Pharmacologic treatment considerations in co-occurring bipolar and anxiety disorders. *J Clin Psychiatry*. 2006;67 Suppl 1:8-15. PubMed PMID: [16426111](https://pubmed.ncbi.nlm.nih.gov/16426111/).
12. Uguz F. Successful treatment of comorbid obsessive-compulsive disorder with aripiprazole in three patients with bipolar disorder. *Gen Hosp Psychiatry*. 2010;32(5):556-8. DOI: [10.1016/j.genhosppsy.2010.07.004](https://doi.org/10.1016/j.genhosppsy.2010.07.004). PubMed PMID: [20851277](https://pubmed.ncbi.nlm.nih.gov/20851277/).
13. Carey PD, Lochner C, Kidd M, van Ameringen M, Stein DJ, Denys D. Quetiapine augmentation of serotonin reuptake inhibitors in treatment-refractory obsessive-compulsive disorder: is response to treatment predictable? *Int Clin Psychopharmacol*. 2012;27(6): 321-5. DOI: [10.1097/YIC.0b013e3283576881](https://doi.org/10.1097/YIC.0b013e3283576881). PubMed PMID: [22859064](https://pubmed.ncbi.nlm.nih.gov/22859064/).
14. Shoja Shafiq S, Kaviani H. Aripiprazole versus quetiapine in treatment-resistant obsessive-compulsive disorder: a double-blind clinical trial. *Ther Adv Psychopharmacol*. 2015;5(1):32-7. DOI: [10.1177/2045125314560739](https://doi.org/10.1177/2045125314560739). PubMed PMID: [25653829](https://pubmed.ncbi.nlm.nih.gov/25653829/).
15. Deckersbach T, Peters AT, Sylvia L, Urdahl A, Magalhães PVS, Otto MW, et al. Do comorbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? Results from STEP-BD. *Am J Psychiatry*. 2014;171(2):178-86. DOI: [10.1176/appi.ajp.2013.13020225](https://doi.org/10.1176/appi.ajp.2013.13020225). PubMed PMID: [24077657](https://pubmed.ncbi.nlm.nih.gov/24077657/).
16. Provencher MD, Hawke LD, Thienot E. Psychotherapies for comorbid anxiety in bipolar spectrum disorders. *J Affect Disord*. 2011;133(3):371-80. DOI: [10.1016/j.jad.2010.10.040](https://doi.org/10.1016/j.jad.2010.10.040). PubMed PMID: [21093062](https://pubmed.ncbi.nlm.nih.gov/21093062/).
17. Stratford HJ, Cooper MJ, Di Simplicio M, Blackwell SE, Holmes EA. Psychological therapy for anxiety in bipolar spectrum disorders: a systematic review. *Clin Psychol Rev*. 2015;35:19-34. DOI: [10.1016/j.cpr.2014.11.002](https://doi.org/10.1016/j.cpr.2014.11.002). PubMed PMID: [25462111](https://pubmed.ncbi.nlm.nih.gov/25462111/).
18. Magalhães PVS, Kapczinski NS, Kapczinski F. Correlates and impact of obsessive-compulsive comorbidity in bipolar disorder. *Compr Psychiatry*. 2010;51(4):353-6. DOI: [10.1016/j.comppsy.2009.11.001](https://doi.org/10.1016/j.comppsy.2009.11.001). PubMed PMID: [20579506](https://pubmed.ncbi.nlm.nih.gov/20579506/).
19. Kim S-W, Berk L, Kulkarni J, Dodd S, de Castella A, Fitzgerald PB, et al. Impact of comorbid anxiety disorders and obsessive-compulsive disorder on 24-month clinical outcomes of bipolar I disorder. *J Affect Disord*. 2014;166:243-8. DOI: [10.1016/j.jad.2014.05.017](https://doi.org/10.1016/j.jad.2014.05.017). PubMed PMID: [25012437](https://pubmed.ncbi.nlm.nih.gov/25012437/).
20. Abdel-Ahad P, Kazour F. Non-antidepressant pharmacological treatment of obsessive compulsive disorder: a comprehensive

- review. *Curr Clin Pharmacol*. 2015;10(2):97-111. DOI: [10.2174/15748847113089990060](https://doi.org/10.2174/15748847113089990060). PubMed PMID: [23438726](https://pubmed.ncbi.nlm.nih.gov/23438726/).
21. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry*. 2013;170(11):1249-62. DOI: [10.1176/appi.ajp.2013.13020185](https://doi.org/10.1176/appi.ajp.2013.13020185). PubMed PMID: [24030475](https://pubmed.ncbi.nlm.nih.gov/24030475/).
 22. Fornaro M, Anastasia A, Novello S, Fusco A, Solmi M, Monaco F, et al. Incidence, prevalence and clinical correlates of antidepressant-emergent mania in bipolar depression: a systematic review and meta-analysis. *Bipolar Disord*. 2018;20(3):195-227. DOI: [10.1111/bdi.12612](https://doi.org/10.1111/bdi.12612). PubMed PMID: [29441650](https://pubmed.ncbi.nlm.nih.gov/29441650/).
 23. Niitsu T, Fabbri C, Serretti A. Predictors of switch from depression to mania in bipolar disorder. *J Psychiatr Res*. 2015;66-67:45-53. DOI: [10.1016/j.jpsychires.2015.04.014](https://doi.org/10.1016/j.jpsychires.2015.04.014). PubMed PMID: [25937504](https://pubmed.ncbi.nlm.nih.gov/25937504/).
 24. Gorwood P, Richard-Devantoy S, Sentissi O, Le Strat Y, Olié JP. The number of past manic episodes is the best predictor of antidepressant-emergent manic switch in a cohort of bipolar depressed patients. *Psychiatry Res*. 2016;240:288-94. DOI: [10.1016/j.psychres.2016.04.071](https://doi.org/10.1016/j.psychres.2016.04.071). PubMed PMID: [27138820](https://pubmed.ncbi.nlm.nih.gov/27138820/).
 25. Altshuler LL, Sugar CA, McElroy SL, Calimlim B, Gitlin M, Keck PE, et al. Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. *Am J Psychiatry*. 2017;174(3):266-76. DOI: [10.1176/appi.ajp.2016.15040558](https://doi.org/10.1176/appi.ajp.2016.15040558). PubMed PMID: [28135846](https://pubmed.ncbi.nlm.nih.gov/28135846/).
 26. Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PE, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry*. 2009;166(2):164-72. DOI: [10.1176/appi.ajp.2008.08030322](https://doi.org/10.1176/appi.ajp.2008.08030322). PubMed PMID: [19015231](https://pubmed.ncbi.nlm.nih.gov/19015231/).
 27. Scott J, Brichant-Petitjean C, Etain B, Henry C, Kahn J-P, Azorin J-M, et al. A re-examination of antidepressant treatment-emergent mania in bipolar disorders: evidence of gender differences. *Acta Psychiatr Scand*. 2017;135(5):479-88. DOI: [10.1111/acps.12728](https://doi.org/10.1111/acps.12728). PubMed PMID: [28369709](https://pubmed.ncbi.nlm.nih.gov/28369709/).
 28. Preti A, Vrublevska J, Veroniki AA, Huedo-Medina TB, Fountoulakis KN. Prevalence, impact and treatment of generalised anxiety disorder in bipolar disorder: a systematic review and meta-analysis. *Evid Based Ment Health*. 2016;19(3):73-81. DOI: [10.1136/eb-2016-102412](https://doi.org/10.1136/eb-2016-102412). PubMed PMID: [27405742](https://pubmed.ncbi.nlm.nih.gov/27405742/).
 29. Albert U, Rosso G, Maina G, Bogetto F. Impact of anxiety disorder comorbidity on quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes. *J Affect Disord*. 2008;105(1-3):297-303. DOI: [10.1016/j.jad.2007.05.020](https://doi.org/10.1016/j.jad.2007.05.020). PubMed PMID: [17617468](https://pubmed.ncbi.nlm.nih.gov/17617468/).
 30. Rakofsky JJ, Dunlop BW. Treating nonspecific anxiety and anxiety disorders in patients with bipolar disorder: a review. *J Clin Psychiatry*. 2011;72(1):81-90. DOI: [10.4088/JCP.09ro5815gre](https://doi.org/10.4088/JCP.09ro5815gre). PubMed PMID: [21208580](https://pubmed.ncbi.nlm.nih.gov/21208580/).
 31. Maina G, Albert U, Rosso G, Bogetto F. Olanzapine or lamotrigine addition to lithium in remitted bipolar disorder patients with anxiety disorder comorbidity: a randomized, single-blind, pilot study. *J Clin Psychiatry*. 2008;69(4):609-16. PubMed PMID: [18294024](https://pubmed.ncbi.nlm.nih.gov/18294024/).
 32. Suppes T, McElroy SL, Sheehan DV, Hidalgo RB, Cosgrove VE, Gwizdowski IS, et al. A randomized, double-blind, placebo-controlled study of ziprasidone monotherapy in bipolar disorder with co-occurring lifetime panic or generalized anxiety disorder. *J Clin Psychiatry*. 2014;75(1):77-84. DOI: [10.4088/JCP.12mo8297](https://doi.org/10.4088/JCP.12mo8297). PubMed PMID: [24345758](https://pubmed.ncbi.nlm.nih.gov/24345758/).
 33. Gao K, Wu R, Kemp DE, Chen J, Karberg E, Conroy C, et al. Efficacy and safety of quetiapine-XR as monotherapy or adjunctive therapy to a mood stabilizer in acute bipolar depression with generalized anxiety disorder and other comorbidities: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2014;75(10):1062-8. DOI: [10.4088/JCP.13mo8847](https://doi.org/10.4088/JCP.13mo8847). PubMed PMID: [25007003](https://pubmed.ncbi.nlm.nih.gov/25007003/).
 34. Sheehan DV, Harnett-Sheehan K, Hidalgo RB, Janavs J, McElroy SL, Amado D, et al. Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient. *J Affect Disord*. 2013;145(1):83-94. DOI: [10.1016/j.jad.2012.07.016](https://doi.org/10.1016/j.jad.2012.07.016). PubMed PMID: [22920718](https://pubmed.ncbi.nlm.nih.gov/22920718/).
 35. Ellard KK, Bernstein EE, Hearing C, Baek JH, Sylvia LG, Nierenberg AA, et al. Transdiagnostic treatment of bipolar disorder and comorbid anxiety using the Unified Protocol for Emotional Disorders: a pilot feasibility and acceptability trial. *J Affect Disord*. 2017;219:209-21. DOI: [10.1016/j.jad.2017.05.011](https://doi.org/10.1016/j.jad.2017.05.011). PubMed PMID: [28577505](https://pubmed.ncbi.nlm.nih.gov/28577505/).
 36. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
 37. Goldstein BJ, Levitt AJ. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. *Bipolar Disord*. 2008;10(1):67-78. DOI: [10.1111/j.1399-5618.2008.00461.x](https://doi.org/10.1111/j.1399-5618.2008.00461.x). PubMed PMID: [18199243](https://pubmed.ncbi.nlm.nih.gov/18199243/).
 38. Passos IC, Jansen K, de Cardoso TA, Colpo GD, Zeni CP, Quevedo J, et al. Clinical outcomes associated with comorbid posttraumatic stress disorder among patients with bipolar disorder. *J Clin Psychiatry*. 2016;77(5):e555-60. DOI: [10.4088/JCP.15mo9935](https://doi.org/10.4088/JCP.15mo9935). PubMed PMID: [27135375](https://pubmed.ncbi.nlm.nih.gov/27135375/).
 39. Cerimele JM, Bauer AM, Fortney JC, Bauer MS. Patients with co-occurring bipolar disorder and posttraumatic stress disorder: a rapid review of the literature. *J Clin Psychiatry*. 2017;78(5):e506-14. DOI: [10.4088/JCP.16r10897](https://doi.org/10.4088/JCP.16r10897). PubMed PMID: [28570791](https://pubmed.ncbi.nlm.nih.gov/28570791/).
 40. Perlis RH, Ostacher MJ, Miklowitz DJ, Hay A, Nierenberg AA, Thase ME, et al. Clinical features associated with poor pharmacologic adherence in bipolar disorder: results from the STEP-BD study. *J Clin Psychiatry*. 2010;71(3):296-303. DOI: [10.4088/JCP.09mo5514yel](https://doi.org/10.4088/JCP.09mo5514yel). PubMed PMID: [20331931](https://pubmed.ncbi.nlm.nih.gov/20331931/).
 41. Rakofsky JJ, Levy ST, Dunlop BW. Conceptualizing treatment nonadherence in patients with bipolar disorder and PTSD. *CNS Spectr*. 2011;16(1):11-20. DOI: [10.1017/S1092852912000119](https://doi.org/10.1017/S1092852912000119). PubMed PMID: [24725297](https://pubmed.ncbi.nlm.nih.gov/24725297/).
 42. Kauer-Sant'Anna M, Kapczinski F, Vieta E. Epidemiology and management of anxiety in patients with bipolar disorder. *CNS Drugs*. 2009;23(11):953-64. DOI: [10.2165/11310850-000000000-00000](https://doi.org/10.2165/11310850-000000000-00000). PubMed PMID: [19845416](https://pubmed.ncbi.nlm.nih.gov/19845416/).
 43. Guina J, Rossetter SR, DeRhodes BJ, Nahhas RW, Welton RS. Benzodiazepines for PTSD: a systematic review and meta-analysis. *J Psychiatr Pract*. 2015;21(4):281-303. DOI: [10.1097/PRA.000000000000091](https://doi.org/10.1097/PRA.000000000000091). PubMed PMID: [26164054](https://pubmed.ncbi.nlm.nih.gov/26164054/).