Update on Bipolar Disorder, Part 2: Bipolar Depression and Cyclothymic Disorder

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This article reviews DSM-5 changes to symptom criteria for bipolar disorder with a focus on treatment of bipolar depression and cyclothymic disorder.

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This activity offers CE credits for:
1. Physicians (CME)
2. Other

ACTIVITY GOAL
This article reviews DSM-5 changes to symptom criteria for bipolar disorder. The primary focus is on treatment of bipolar depression and cyclothymic disorder.

LEARNING OBJECTIVES
At the end of this CE activity, participants should be able to:
• Identify the 4 FDA-approved medications for bipolar depression
• Identify FDA-approved medication for maintenance therapy of depression in bipolar disorder
• Distinguish which antidepressants to avoid to minimize the risk of mood destabilization

TARGET AUDIENCE
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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Diagnosis of bipolar depression

It is difficult to distinguish MDD from bipolar depression early in the course of illness. Many bipolar patients will initially present with one or more depressive episodes before experiencing mania or hypomania. This can delay proper diagnosis and appropriate treatment, worsen the long-term prognosis, and increase the cost of treatment.

Several demographic and clinical characteristics may help differentiate the 2 disorders. Factors such as a family history of bipolar disorder; earlier onset of illness; a seasonal component to mood changes; mixed episode presentations (ie, also experience 3 or more criteria for mania/hypomania [see Part 1, Table 1]); mood reactivity; psychotic features; reverse neurovegetative symptoms, such as hypersomnia and increased appetite; a history of suicide attempts; and antidepressant "misadventures," such as mood switches, may indicate a greater likelihood of bipolar depression.

More recent findings suggest that statistical models may further help delineate MDD from bipolar depression. For example, one study using a probabilistic model found that younger depressed individuals with psychomotor retardation, psychosis, or mixed features had an increased risk of bipolar disorder.

Management of bipolar depression

The irony in treating bipolar I and II disorders is that depression is much more prevalent than mania or hypomania, but there is far less evidence from controlled trials to guide its management. Bipolar depression is associated with high morbidity and mortality; it is often chronic, persisting in refractory or subsyndromal forms; and it increases the risk of suicide. While the existing evidence is limited and at times inconsistent, it indicates benefit for acute management with the combination of olanzapine-fluoxetine, quetiapine monotherapy, or lurasidone as a monotherapy or an adjunct to lithium or valproate (Table). These 3 FDA-approved acute bipolar depression therapies appear to have similar efficacy profiles, but they differ substantially in terms of tolerability.

A recent summary calculated the likelihood to help or harm, which considers the ratio of the number needed to treat and the number needed to harm for the olanzapine-fluoxetine combination, quetiapine, and lurasidone. Although the overall results supported lurasidone, multiple factors may shift the balance in favor of olanzapine-fluoxetine or quetiapine (eg, good response with acceptable tolerability, extensive clinical experience, better maintenance data, lower cost).

Lamotrigine shows benefit for maintenance management, particularly in preventing depressive episodes, and is FDA-approved for this indication. Other treatment strategies commonly used but with less evidence to support their use include lithium, valproate, carbamazepine, antidepressants, and ECT.

The Figure illustrates the treatment strategy for acute bipolar depression.

**Antipsychotics**

**Olanzapine-fluoxetine combination**

The FDA initially approved the combination of olanzapine plus fluoxetine as the first treatment for adults with acute bipolar depression. This indication is supported by a systematic review and meta-analysis of controlled trials (N = 1330) showing that olanzapine-fluoxetine improved responses compared with olanzapine monotherapy and placebo. As a result, this combination is often considered a first-line treatment for moderate to severe episodes.

The positive results from a randomized, double-blind, placebo-controlled trial (N = 255) with olanzapine-fluoxetine (6/25 to 12/50 mg/d) in children and adolescents with bipolar I depression supported an additional FDA approval for patients aged 10 to 17 years. An important concern, however, is the risk of weight gain and related metabolic complications associated with ongoing treatment, particularly in younger patients.

**Olanzapine monotherapy**
Some data support olanzapine monotherapy for acute bipolar depression, although the drug is not approved for this indication. Two placebo-controlled studies (N = 1214) demonstrated that olanzapine was effective for bipolar I depression, regardless of the presence of concurrent manic symptoms, and that melancholic features might predict a better outcome with this agent.\(^6,7\)

In a double-blind placebo-controlled study (N = 68) olanzapine monotherapy was superior to placebo in treating bipolar I depression but was associated with significant metabolic adverse effects.\(^8\)

Finally, results from a 12-month naturalistic observational study (N = 51) showed that olanzapine monotherapy was superior to lamotrigine in preventing bipolar depression relapses.\(^9\)

**Olanzapine**

Substantial evidence from controlled trials supports the role of quetiapine in bipolar depression as either a monotherapy or in combination with lithium or valproate. Statistical superiority for quetiapine monotherapy or combination therapy (300 or 600 mg/d) over placebo for acute bipolar I or II depression was reported in a systematic review and meta-analysis (11 randomized clinical trials [RCTs]; N = 3488).\(^10\) Quetiapine had a lower switch rate into mania/hypomania than placebo but a higher incidence of adverse effects such as extrapyramidal symptoms, sedation, increased appetite, and weight gain. Two of these studies involved pediatric populations; however, the data were insufficient to support its use in this age group.

In an analysis of 2 randomized controlled maintenance trials (N = 1326), quetiapine combined with either lithium or valproate was superior to placebo in bipolar I patients in preventing a recurrence of either mania or depression.\(^11\) Another analysis from 2 placebo-controlled maintenance trials (N = 584) with quetiapine monotherapy in bipolar I and II depressed patients showed similar results.\(^12\) These outcomes, however, should be tempered by the potential for cardiometabolic risks with longer-term exposure.

**Lurasidone**

This is the most recent agent to receive FDA approval for acute bipolar I depression as both a monotherapy and in combination with lithium or valproate.\(^13\) Its purported mechanism(s) of antidepressant action include serotonin (5-HT)-1A agonism; and 5-HT2A and norepinephrine alpha-1 antagonism.\(^14\) The data also indicate comparable benefit in mixed episodes.\(^15\) Note that its adverse-effect profile indicates minimal risk of weight gain, dyslipidemia, or electrocardiographic abnormalities. The most common adverse effects associated with lurasidone were mild to moderate and included gastrointestinal disturbances, extrapyramidal symptoms, akathisia, and somnolence.

**Anticonvulsants**

Certain anticonvulsants have demonstrated a role in treating acute depressive episodes, as well as preventing relapse in stabilized bipolar patients.

**Valproate**

Valproate has consistent, albeit limited support for acute management of bipolar depression. One meta-analysis of 4 RCTs (N = 142) found valproate superior to placebo in reducing depressive symptoms, and the proportion of patients who achieved at least a 50% improvement in symptoms; tolerability was similar to that of placebo.\(^16\) Despite the small sample sizes, which preclude a more definitive conclusion about this agent’s usefulness in treating bipolar depression, it is a first- or second-line treatment recommendation as monotherapy or adjunctive therapy.

**Carbamazepine**

While there are preliminary encouraging results, this agent requires further study, particularly in light of its adverse-effect and drug-interaction profiles, which are more problematic than existing alternatives.

**Lamotrigine**

The mechanism of action for this agent in the context of treating bipolar disorder appears to involve modulation of glutamate, particularly at cortical projections to the ventral striatal-limbic areas. This may be related to its inhibition of voltage-sensitive Na+ channels, blockade of calcium channels, and weak 5-HT3 receptor inhibition. The half-life of lamotrigine is 15 to 30 hours but may be accelerated by enzyme induction with agents such as carbamazepine, phenytoin, and estrogen or prolonged (ie, 30 to 90 hours) by agents such as valproate and sertraline. The latter scenario requires a lower lamotrigine starting dose (12.5 mg) and a slower titration schedule to reduce the risk of serious skin reactions (eg, Stevens-Johnson syndrome). Elimination occurs through glucuronidation and subsequent renal excretion (90%). Overall, the safety and tolerability profile of lamotrigine compares favorably to that of alternative therapies for bipolar depression. The most common adverse effects associated with lamotrigine are headache, nausea, and mild rash. More severe skin reactions are the most important potential serious risk, estimated to occur in fewer than 0.2% of cases.\(^17\) This complication can be minimized by
an initial low dose (eg, 25 mg/d) and slow titration schedule (eg, increase every 2 weeks) over several weeks. While the results for acute management are inconsistent, there is evidence for a potential role (usually in combination with other mood stabilizers) in more severe depressive episodes in bipolar I and II. These studies involved comparisons to or combinations with agents such as placebo, lithium, valproate, citalopram, gabapentin, risperidone, and the olanzapine-fluoxetine combination. Typical daily dosing ranged from 50 to 200 mg, but the necessity to titrate slowly limits the usefulness of lamotrigine in more severe acute episodes. As noted, if combined with valproate, the lamotrigine dose should be half the recommended amount and the titration schedule slower. In contrast to the trial data for acute management, there is more consistent evidence for its role in preventing a mood relapse, particularly into depression. Two 18-month, placebo-controlled studies (N = 638) assessed the benefit of lamotrigine or lithium maintenance therapy compared with placebo in bipolar I patients (either recently manic/hypomanic or depressed) initially stabilized with open-label lamotrigine. In each trial, both active drugs were superior to placebo in prolonging time to intervention for any mood episode; lamotrigine was superior to placebo in time to intervention for a depressive episode; and lithium (but not lamotrigine) was superior to placebo in time to intervention for manic, hypomanic, or mixed episodes. In terms of safety and tolerability, no serious rashes occurred and lamotrigine’s overall adverse-effect profile was similar to placebo in these trials.

**Lithium**

Although lithium is often used to treat acute bipolar depression either alone or as an adjunct with other mood-stabilizing strategies (eg, lithium plus lamotrigine), the evidence to support this approach is presently inadequate. However, an open-label, proof of concept trial (N = 31) found that with lithium monotherapy, lower serum levels (< 0.5 mEq/L) were as effective as higher levels (> 0.5 mEq/L) in achieving robust remission rates (ie, 62%). Moreover, lower levels were better tolerated. A potential advantage is lithium’s anti-suicidal properties that may be further enhanced by concurrent use of various adjuncts such as psychoeducation, bright light therapy, and sleep deprivation.

Most guidelines for the long-term management of bipolar depression recommend lithium as first-line maintenance therapy. Since early studies of lithium do not meet present-day criteria for adequacy, this is primarily based on more recent placebo-controlled trials in which lithium was used as an active comparator (eg, lamotrigine, quetiapine). Two meta-analyses that included data from these trials concluded that lithium was superior to placebo in preventing both manic and depressive episodes for up to 2 years. The data came from lithium non-enriched samples, making this finding even more noteworthy; however, this finding must be weighed against the potential renal complications associated with prolonged lithium exposure.

**Antidepressants**

While antidepressants are frequently used in clinical practice, there are limited data to support their short-term benefit in bipolar depressed or mixed episodes. Indeed, in a report of their meta-analysis, Sidor and Macqueen concluded that although antidepressant augmentation was generally safe, relative to placebo it did not improve response or remission rates more than mood stabilizers alone. Furthermore, there is concern that these agents may worsen the course of illness (eg, promote mood switches or cycle acceleration). Thus, their role for treatment of bipolar depression is controversial and yet to be resolved. Given these circumstances, reasonable recommendations include:

- Avoid antidepressants when possible for the treatment of acute depression; particularly in bipolar I patients, those with mixed episodes, rapid cyclers, and patients with comorbid substance abuse/dependence
- If antidepressants are used, it should only be after better-supported approaches (eg, olanzapine-fluoxetine, or quetiapine, or lurasidone) prove insufficient and then, only in combination with a mood stabilizer
- To minimize the risk of mood switches, bupropion or SSRIs (eg, paroxetine, sertraline) may be preferable to TCAs, tetracyclics, or dual-acting agents (eg, venlafaxine)
- Consider ECT (and possibly transcranial magnetic stimulation [TMS]) in more severe episodes of depression, when there are insufficient benefits from medications or medication intolerance
- After a patient is stabilized, frequently reassess the need to continue the antidepressant in lieu of maintenance with a mood stabilizer(s) only

**Cyclothymic disorder**

**Diagnosis**

While there is far less evidence regarding the diagnosis and management of cyclothymic disorder,
this is a prevalent, often underdiagnosed, and highly impairing condition. This disorder involves mild to moderate fluctuations in mood, thinking, and activity for at least 2 years (1 year in children or adolescents) that do not meet full criteria for a major depression or hypomania (see Part 1, Table 21). In addition, there is often a family history of bipolar disorder. Theories on the basis of these cyclical “subsyndromal” mood swings range from characterological, with individuals seen as temperamentally or unreliable; a prodromal phase prior to the development of bipolar disorder (particularly bipolar II) with a greater propensity to rapid cycling and greater reactivity to environmental factors; or a distinct clinical phenotype along a continuum of bipolar spectrum disorders.

Management
In the context of treating cyclothymic disorder, recommendations and concerns about mood destabilization with antidepressants parallel those for bipolar disorder, particularly type II. The existing literature, however, more equally considers pharmacological (eg, lithium, anticonvulsants, quetiapine) and psychotherapeutic approaches (eg, cognitive behavioral therapy [CBT], mindfulness-based cognitive therapy, psychosocial, psychoeducational) for at least acute treatment. There are no FDA-approved medications with an indication for cyclothymic disorder.

The role of psychotherapy
Paralleling the experience with other major disorders such as schizophrenia, environmental factors substantially contribute to the long-term course and prognosis of bipolar disorder. In this context, various adjunctive psychotherapeutic interventions can help enhance acute response, decrease the risk of relapse or recurrence, improve functionality, and facilitate recovery. While more extensively studied for MDD, there is growing evidence supporting adjunctive psychotherapy (eg, psychoeducation, CBT, family-focused therapy, interpersonal and social rhythm therapy) for bipolar disorder. The goals for these approaches are to:

• Provide education about the illness
• Facilitate appropriate interventions with early signs of a pending relapse
• Reduce psychosocial stressors and family conflict
• Regulate social and circadian rhythms
• Treat comorbid substance abuse
• Improve medication adherence

To accomplish this successfully, it is crucial to achieve an effective working alliance with patients and their families early in the course of treatment. During an acute manic or mixed episode, the role for various psychotherapeutic interventions is limited. Thus, there is much more information regarding psychotherapy in mildly ill patients as part of a maintenance strategy that focuses on the management of depressive symptoms in the context of bipolar disorder. However, psychotherapy may help patients and their families better manage mania.

A recent functional MRI study compared 12 patients (ages 13 to 17) with mood dysregulation who were also at familial risk for bipolar disorder with 12 healthy controls. After 4 months of psychotherapy, the investigators observed a normalization of brain frontal executive control regions in the patient group that correlated with improvement in their manic symptoms. Another study utilized a collaborative care model that included group psychoeducation to enhance bipolar patients’ self-management skills.26,27 This approach improved long-term clinical outcomes, particularly in reducing the duration of manic episodes.

Most psychotherapy studies, however, involve more chronic patients who were euthymic or mildly ill and focused on management of residual subsyndromal symptoms and prevention of relapse or recurrence. Acutely symptomatic patients were usually in a depressed phase, since acutely ill manic patients are more difficult to engage. In one study, stabilized bipolar I (n = 115) or bipolar II (n = 45) patients were assessed for up to 72 weeks while receiving standard pharmacotherapy and manualized, evidence-based psychosocial treatment (ie, CBT or psychoeducation). The data showed that 65% remained euthymic over this period. Those who became symptomatic primarily experienced subsyndromal depression with relapses averaging every 7.5 months. The researchers concluded that these patients had an improved course of illness compared with the results of earlier trials that assessed the long-term, natural history of this illness. These results are consistent with data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) that followed 293 depressed bipolar patients randomized to an intensive psychosocial intervention (ie, 30 sessions of CBT, family-focused therapy, or interpersonal and social rhythm therapy) or 3 sessions of psychoeducation.29 Patients were also receiving standard pharmacotherapy, including antidepressants for some. At the end of the 6-month acute treatment phase, the intensive psychosocial group was 15% more likely to have achieved symptom remission.
Future directions
Ideally, therapies should be based on a clear understanding of underlying pathoetiology. Unfortunately, as in other areas of psychiatry, this is not the case. Thus, our theories often “work back” from the purported mechanisms of drug actions to help decipher the disease’s origins. Increasingly, however, work in several areas (e.g., genetics, neuroimaging, the immune system, biological rhythms) is providing a better understanding of bipolar disorder and offers the hope for new and more effective treatment approaches.

The increased risk of inflammatory processes in bipolar disorder may explain its higher comorbidity with various medical disorders (e.g., cardiovascular disease, diabetes). This leads to consideration of a dysfunctional immune system and what role the observed elevations in pro-inflammatory cytokines play in the development and neuroprogression of bipolar disorder. For example, they may be used as markers for this disorder, as well as potential targets for novel treatments. Indicators of increased oxidative stress are also found in bipolar patients. A recent meta-analysis reported that markers of stress such as lipid peroxidation, DNA/RNA damage, and nitric oxide were significantly increased in bipolar patients compared with controls. This finding may indicate that there is a potential role for antioxidant therapies; however, more research is needed.

Disruptions in biological rhythms (e.g., sleep-wake cycle, seasonality of symptoms) are common in bipolar disorder and may play an important role in its pathophysiology. In particular, it has been postulated that an abnormally shifted or arrhythmic circadian system is common in bipolar disorder. Abnormal sleep patterns are even seen in bipolar patients with symptom remission. Support for this hypothesis also comes from studies demonstrating the therapeutic potential for chronotherapies such as sleep deprivation, bright light therapy, and CBT for insomnia. The role of dopamine in the pathology of bipolar disorder is supported in part by the number of agents that act at its receptors and have approved indications for this illness, as well as the impact of this neurotransmitter on mood and reward systems. Recently, cariprazine, a partial agonist at the D2 and D3 receptors, demonstrated efficacy for the treatment of bipolar mood symptoms, which raises the question of whether other dopamine agonists could serve as adjuncts for the treatment of bipolar disorder.

Another hypothesis is based on the potential contributions of the glutamate excitatory neurotransmitter system to the pathophysiology of bipolar disorder. A meta-analysis of MRI spectroscopy studies found that the levels of glutamine (the precursor to glutamate) were elevated in bipolar patients. Further support involves the study of gene variants and their possible contribution to bipolar susceptibility. In this context, the SLC1A2 gene encodes the excitatory amino acid transporter 2, which is responsible for clearing glutamate from the synaptic cleft. Certain variations in this gene are associated with both schizophrenia and bipolar disorder, perhaps increasing susceptibility to them.

One potential therapeutic application is the use of the glutamate N-methyl-D-aspartate (NMDA) ionotropic receptor antagonist, memantine. A recent 3-year naturalistic study (N = 30) showed that when used as an augmentation strategy in patients with treatment-resistant bipolar I or II disorder, memantine (20 to 30 mg/d) provided substantial long-term benefits. Data from MDD and bipolar depression trials show a short-term, rapid and robust antidepressant, anxiolytic, and anti-suicidal effect with a single intravenous infusion of ketamine (e.g., 0.5 mg/kg), a more potent NMDA receptor antagonist. While this strategy holds the promise of a more rapidly effective antidepressant effect, it presently remains investigational and requires more data regarding both the mid-term and long-term benefits, as well as the potential for adverse effects (e.g., psychotomimetic reactions; abuse potential).

When algorithm-based pharmacological strategies prove insufficient, ECT can be beneficial. Although an effective therapy for more severe episodes of mania and depression in the context of bipolar disorder, there are several disadvantages to consider in terms of an overall risk-to-benefit evaluation. These include its limited availability in many areas, cognitive disruption, high relapse rates, a negative public image, and cost. Therefore, alternative therapeutic and neuromodulation strategies are being considered. For example, preliminary data support the use of adjunctive TMS in bipolar depressed patients for acute and maintenance purposes. Studies with vagus nerve stimulation and deep brain stimulation have also shown initial promise.

Important questions to be addressed in future studies include the value of introducing psychotherapy early in the course of illness; clarifying which components of the various therapies are most helpful; determining which patients are more likely to benefit from a specific approach; and the potential role of alternate psychotherapeutic approaches such as mindfulness-based cognitive therapy, systematic care management, and cognitive or functional remediation. Given that only a
small proportion of patients presently utilize psychotherapy, strategies to increase its use are necessary.

Conclusion
Both bipolar depression and cyclothymic disorder are often difficult to properly diagnose. Even when they are identified correctly, there is limited guidance on how to manage them. There are only 4 FDA-approved medications for the treatment of bipolar depression (3 for acute episodes; 1 for maintenance); their therapeutic effects are modest, and they carry substantial risks. There are no approved treatments for cyclothymic disorder. There are, however, several initiatives to improve diagnosis and to develop novel therapeutics for bipolar disorder. Some of the more promising are based on genetic and neuroimaging findings and include exploration of the immune system and related inflammatory processes; the role of oxidative stress; the dopamine and glutamate systems; and disruptions in biological rhythms. The emergence of novel therapeutic neuromodulation techniques and more refined psychotherapeutic approaches also bode well for more effective treatment of bipolar disorder.

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Disclosures:
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Links: