Recognition and Management of Bipolar Depression

Emily Schroeder, BS, Yonglin Gao, MD, R. Jeannie Roberts, MD, and Rif S. El-Mallakh, MD

ABSTRACT

- **Objective:** To review identification and treatment of bipolar depression.
- **Methods:** Literature review.
- **Results:** Bipolar depression is a common mood state in patients with both bipolar I and II disorders. Identification of bipolar depression depends on screening for both mania and hypomania. While it seems clear that treatment should generally minimize the use of antidepressants, there is a dearth of alternatives demonstrated to be both effective and safe. Avoidance of agents that increase synaptic serotonin appears to be a reasonable goal. While use of second-generation antipsychotic agents has increased, their utility may be more in reducing associated anxiety.
- **Conclusions:** Identification and treatment of bipolar depression remains challenging with an inadequate database to properly guide treatment decisions.

Bipolar disorder is a severe psychiatric illness that affects 2% to 5% of the population. It is associated with significant morbidity with social, occupational, and legal consequences [1], and greater dysfunction than unipolar depression [2,3]. When dysfunction occurs in bipolar illness, it appears to be more specifically related to the depressive state [3–5]. Furthermore, depression and depressive symptoms occupy more of patients’ lifetime than hypomania, mania, and euthymia [6,7]. Specifically, patients experience depressive symptoms approximately one-third of the time in type I illness and over half of the time in type II illness [6,7]. Additionally, dysthymia has a lifetime prevalence of 15.5% to 26.6% in bipolar patients [8], adding to the overall depressive load. Over the last decade, new insights into the diagnosis and treatment of bipolar depression have altered the approach to this condition. This paper reviews these advances and puts forward best practice recommendations for optimizing treatment of patients with bipolar illness.

DIAGNOSIS OF BIPOLAR DEPRESSION

Identification and treatment of bipolar disorder is frequently challenging. Nearly two-thirds of patients with an ultimate bipolar disorder are initially diagnosed with a different axis I disorder, and over one-third do not receive the bipolar diagnosis until about 10 years after the initial presentation [9]. Misdiagnoses most commonly involve overdiagnosis of unipolar major depressive disorder [9,10]. In the clinical setting, substance abuse may be frequently misdiagnosed as bipolar disorder [11,12]. Misdiagnoses result in inadequate or inappropriate management of the disorder, with consequent poorer outcome and prognosis [13].

There are no unique criteria for the diagnosis of bipolar depression, so clinicians cannot readily differentiate bipolar and unipolar patients [14]. Instead, the identification of a bipolar depression is dependent on the identification of past mania, hypomania, or mixed states. Frequently, these are difficult to identify because the patient may not recognize them, or the clinician may not search adequately. Several authors have put forward clues as to how to identify past manic/hypomanic episodes. These include screening for decreased need for sleep [15,16], increased goal-directed activity [14,17], or family history of bipolar disorder [17]. Frequently, obtaining collateral information from family members can provide critical information for the diagnosis. The Mood Disorders Questionnaire (MDQ) has been proposed to be a reasonable screening tool and is useful [18,19], but its sensitivity drops in patients with poor insight [20], the same population that is difficult to diagnose.

In addition to the screening for mania/hypomania, a clinician needs to be aware of dimensional differences in the presentation of bipolar depression compared with
unipolar depression. The presentation of bipolar depression tends to be more “atypical,” with hypersomnia, hyperphagia, weight gain, and severe psychomotor slowing with leaden paralysis [14]. Depressive episodes tend to be shorter than in unipolar depression but more frequent and with an earlier age of onset [14].

A recent phenomenon has been the adoption of bipolar spectrum diagnosis in patients who do poorly with antidepressants [21]. This may be accurate for a large number of patients, but it should be remembered that cycle acceleration secondary to antidepressants is related to possession of the gene for the short form of the serotonin transporter [22], which is not specifically associated with bipolar disorder [23].

While not useful for current practice, promising studies suggest that diagnosis of type I bipolar disorder with a blood test may be available to clinicians in the not too distant future [24,25].

TREATMENT OF BIPOLAR DEPRESSION: PSYCHOPHARMACOLOGY

Antidepressants

The use of antidepressants in bipolar depression remains controversial, with some reviews finding that antidepressants may be safe and effective in bipolar depression [26] and others finding lack of efficacy [27]. In the 1990s, 50% to 80% of patients with bipolar illness were on antidepressants [28,29]; by 2005, that number dropped to 34% [30]. The change was due in part to the release of the Expert Treatment Guidelines in 2000 [31] and new treatment guidelines by the American Psychiatric Association in 2002, both of which relegated antidepressants to second-line agents after optimization of mood stabilizers [32]. These changes were due to the realization that bipolar depression may be different than unipolar depression, that patients with bipolar illness may have cycle acceleration with antidepressant treatment [33], and the emergence of a possible alternative treatment—lamotrigine [34].

Several randomized, placebo-controlled studies in which antidepressants or placebo are added to a mood stabilizer have been performed. All of these studies found that adding an antidepressant to a mood stabilizer does not provide any additional benefit compared with adding placebo to a mood stabilizer [35–38]. The only exception is fluoxetine. When added to olanzapine, it was effective compared with placebo alone, placebo added to olanzapine [39], as well as lamotrigine alone [40]. Some open or monotherapy studies, particularly with type II bipolar illness, suggest that antidepressant monotherapy is effective for improving depression [41,42]. These data can be summarized by stating that antidepressants may be helpful over the short term for bipolar depression when given as monotherapy or added to low-dose antipsychotic, but are not particularly effective if added to a mood stabilizer [43].

Even if antidepressants are useful over the short term, they appear to be problematic for most bipolar patients over the long term. Antidepressants cause 3 distinct problems in bipolar patients: they increase manic switch rate [36], accelerate cycling in bipolar patients [33,37], and increase the likelihood of depression by nearly threefold [44] and irritable dysphoric syndrome by about ninefold in rapid-cycling bipolar patients [45]. These effects of antidepressants happen despite ongoing mood stabilizer treatment. However, not everyone experiences worsening with antidepressants, and over the long term (6 months), approximately one-quarter of patients continue to experience benefit from antidepressant treatment [37]. It may be that one of the predictors of doing poorly is having at least 1 allele of the short form of the serotonin transporter (a variant of the gene for the serotonin reuptake pump) [22,46–48]. Obviously, other as yet unknown factors must also contribute to the antidepressant response.

Antipsychotics

Four second-generation antipsychotics have been examined for bipolar depression in large, placebo-controlled trials: quetiapine, olanzapine, aripiprazole, and ziprasidone. Of these, quetiapine and olanzapine have gained Food and Drug Administration (FDA) approval for treatment of bipolar depression (Table).

Olanzapine is approved for use in combination with fluoxetine, but its effect alone is small and clinically insignificant [39]. Quetiapine has demonstrated efficacy as monotherapy in both type I and type II bipolar patients at doses of 300 and 600 mg daily [49]. Furthermore, in a large long-term study (2 years), quetiapine added to either lithium or divalproex reduces the likelihood of depressive relapse approximately threefold compared with placebo added to lithium or divalproex [50]. The mechanism of action of quetiapine is believed to be mediated in part through the ability of the active metabolite N-desalkyl-quetiapine to inhibit norepinephrine reuptake and block the post-synaptic serotonin 5HT_{1A} and 5HT_{2} [51].
Aripiprazole and ziprasidone have both been examined in large, placebo-controlled trials as potential monotherapy for bipolar depression. Ziprasidone was examined in 2 unpublished studies [52,53]. Both studies did not show efficacy, but some of the depression scale items improved at low doses of ziprasidone (20–40 mg/day) [52,53]. Aripiprazole significantly improved depressive symptoms in the first 6 weeks of treatment in 2 large placebo-controlled studies of depressed bipolar subjects, but the effect was lost in the last 2 weeks of treatment [54]. This biphasic effect is believed to be due to accumulation of both the parent drug and the active metabolite, dehydroaripiprazole, creating more relative dopamine D2 blockade over time. If this is true, then lower doses of aripiprazole may be effective, but this has not yet been examined.

Other antipsychotics have been examined in smaller case series and uncontrolled studies. No conclusions can be drawn from those studies. Risperidone has been examined in the control of anxiety symptoms in bipolar patients with comorbid generalized anxiety disorder and found to be ineffective in reducing anxiety symptoms at doses below 4 mg daily [55]. Augmentation with risperidone was also ineffective [56]. Quetiapine was examined in patients with only generalized anxiety disorder (not comorbid with bipolar disorder) and found to be effective both as monotherapy [57] and adjunctive treatment to antidepressant [58].

**Mood Stabilizers**

Anticonvulsants and lithium have some antidepressant activity. The American Psychiatric Association’s practice guidelines recommend “optimizing” mood stabilizers prior to moving on to second-line interventions [32].

A meta-analysis of the 5 placebo-controlled studies with lamotrigine in bipolar depression documents the efficacy of this antiepileptic in acutely depressed patients [59]. Moreover, the drug is significantly more effective in more severely ill bipolar patients (Hamilton Depression Rating > 24) [59]. Additionally, in long-term studies (18 months) lamotrigine prevents depressive relapse to a degree greater than lithium and greater than lamotrigine’s own ability to prevent manic relapse [60]. Interestingly, lamotrigine is the only agent that has been studied as monotherapy in placebo-controlled design for rapid-cycling bipolar patients [61]. Forty-one percent of lamotrigine patients versus 26% of placebo patients (p = 0.03) were stable without relapse for 6 months of monotherapy [61]. All of these studies suggest that lamotrigine is the preferred agent for patients with a predominant depressive illness, including rapid-cycling patients.

Lithium clearly has an antidepressant action in depressed bipolar patients [62]. Optimization of lithium in bipolar depression typically includes increasing the dose (and level) until response is achieved. It is important to monitor the patient through this process as significant side effects may occur, particularly since higher doses are frequently more effective [62]. Furthermore it is important to monitor the thyroid status in lithium-treated patients since subsyndromal hypothyroidism may be associated with an increased risk for depressive relapse [63,64].

Five small placebo-controlled studies of valproic acid in bipolar depression have been performed. Meta-analysis of the 4 earlier studies finds that divalproex monotherapy is weakly effective with response rates that are nearly double those of placebo (39.3% vs. 17.5%) and remission rates that are 1.6 times greater than placebo (40.6% for divalproex and 24.3% for placebo) [65]. An additional study in 54 mood stabilizer–naive type I and II bipolar patients published after the meta-analysis found that both response (38.5% for divalproex versus 10.7% for placebo) and remission were more than twice as likely in

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<th>Table. Agents That Display Efficacy in the Treatment of Bipolar Depression in Randomized, Placebo-Controlled Trials</th>
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<td><strong>Agent</strong></td>
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*Lamotrigine reduces rapid cycling in type II bipolar patients.

†Mean effective dose 1.7 mg/day.

‡Mean effective dose 177 mg/day.

§Post hoc analyses of type II bipolar patients included in placebo-controlled trials of unipolar major depressive illness before the creation of the type II bipolar diagnostic category. In these studies, manic induction could appear as improvement in depressive illness.
divalproex-treated versus placebo-treated subjects (23.1% for divalproex versus 10.7% for placebo, \( P = \text{ns} \)) [66]. While higher levels clearly increase the efficacy of divalproex in mania [67], it is unclear if a similar relationship exists for bipolar depression.

Carbamazepine may have antidepressant efficacy in bipolar disorder but is generally not well studied [68,69]. A recent study comparing immediate-release carbamazepine with extended-release capsules combined with standard treatment found no difference between the 2 formulations in depressed bipolar patients, and all patients improved significantly compared with baseline [70]. Oxcarbazepine has not been studied in bipolar depression. Gabapentin showed no efficacy in a blind, randomized monotherapy study [71].

**Novel Agents**

All clinicians who treat bipolar patients realize that current treatment options are not adequate and novel agents are needed. There have been several new approaches that are useful for depressed bipolar patients.

Pramipexole is a dopamine D\(_2\) and D\(_3\) agonist [72] that is approved for the treatment of Parkinson’s disease [73] and restless legs syndrome [74]. Two small randomized, placebo-controlled studies in depressed type I and II bipolar patients have shown that pramipexole, added on to standard treatment (0.5–2 mg/day), is superior to placebo added to standard treatment [75,76]. A naturalistic open study reported that ongoing use of pramipexole, for an average of over 6 months is associated with maintenance of antidepressant response [77].

Modafinil and armodafinil are novel agents that are indicated for improving alertness in narcolepsy [78], sleep apnea [79], jet lag [80], and shift workers [81,82]. Armodafinil is the enantiopure form of the racemic drug modafinil, consisting of just the active R (or “−” or “D”) enantiomer [83]. The mechanism of action is unknown but probably involves increasing electrical coupling of the reticular activating system [84], possibly through blockade of dopamine reuptake [85] or activation of histamine [86]. In 2 small randomized, placebo-controlled studies of depressed bipolar I and II patients treated with modafinil [87] or armodafinil [88] versus placebo, the active drug was associated with a significantly greater improvement in depression.

Other stimulants have only been studied in open studies. A small open study with methylphenidate suggests it may be useful and safe for both type I and II bipolar patients [89]. In children with bipolar illness and attention deficit hyperactivity disorder, coadministration of methylphenidate or placebo with mood stabilizers [90] or aripiprazole [91] are equally safe, ie, methylphenidate does not increase manic or other mood symptoms compared with placebo.

Interestingly, ketamine, an N-methyl-D-aspartate antagonist, has been studied in treatment-resistant depressed bipolar subjects. When administered as a single intravenous dose (0.5 mg/kg), it is significantly superior to placebo [92]. The effect is marked, rapid, and persists approximately 7 to 10 days [92]. However, since ketamine is a dissociative anaesthetic [93], it may be difficult to use as a therapeutic agent other than in inpatient settings.

**TREATMENT OF BIPOLAR DEPRESSION: PSYCHOTHERAPY**

There is an overwhelming deficit of clinically significant research utilizing psychotherapy as a form of monotherapy for the treatment of bipolar depression. In addition, there is also a lack of large-sample, controlled studies that allow for definitive conclusions to be drawn about psychotherapy’s efficacy in treating depression in bipolar patients. However, there are important suggestions made by certain studies that are necessary to consider when identifying the most effective treatment for a bipolar patient in the depressive stage of their illness. The majority of this research looks at the effects of therapy as an adjunct treatment with medication in alleviating depressive symptoms. Therapies with the aim to improve social support, educate the patient and family, and help increase mood awareness have been shown to be associated with improvement in relapse prevention and quality of life measures for patients and their caretakers. The most prominent of these therapies found in the literature are family-focused therapy, interpersonal and social rhythm therapy, and cognitive behavioral therapy [94].

**Family-Focused Therapy**

As bipolar patients often express extreme and persistent symptoms, the burden placed on family members and caretakers of the patient is significant. The stress placed on those closest to the patient causes interpersonal conflict and contributes to the patient’s depressive symptoms [95]. Studies implicate the importance of psychoeducation in this particular therapy where the
family unit is educated about the stages and projected mood disturbances of bipolar illness. In addition, members are encouraged to speak with other caretakers experiencing similar stress in order to encourage social support of their own. In FFT, family members are counseled on techniques to plan for manic or depressive episodes, understand the process and need for hospitalization and learn to accept the disorder in the patient they are caring for. It is likely that when family members are empowered with a better understanding of the illness and the ability to identify important risk factors in the patient, they feel more at ease with the individual and are able to interact in a more supportive manner. This, in turn, alleviates interpersonal conflict between the patient and their caretaker and has the ability to open important lines of communication [96]. When caregivers were provided 90 minutes of psychoeducation, bipolar patients with whom they live had a fourfold prolongation of time to mood episode over the subsequent 12 months compared with control families who did not receive psychoeducation (n = 113 patients) [97]. In a study following bipolar patients 2 years post clinical episode, FFT in conjunction with medication was more effective in decreasing patient’s depressive mood symptoms compared to a less involved “crisis management” control group. FFT also provided greater drug adherence capabilities and led to fewer symptomatic relapses over the 2-year period. The authors indicate that increasing communication among the family unit and emphasizing problem-solving skills helped the patient and caretaker adjust to their mood symptoms and work more efficiently through mood fluctuations [98]. More recently, Perlick et al [99] performed an efficacy study on the data presented above where sessions focused on skill building to help manage the patient’s illness as well as the increased awareness of the families own stress in response to their caretaking responsibilities. Results support previous research identifying a clear correlation between mood instability of family members with depressive symptoms in patients with bipolar illness [99]. When FFT was provided to families of adolescents, significant improvements in depressive symptoms of the adolescent patients were observed over the 2-year follow-up period [100] with the greatest improvements occurring in families rated as having high levels of expressed emotion [101]. Family psychoeducation reduces perceived burden [102] but seems to have its greatest impact on patients in earlier stages of bipolar illness, and a much reduced impact on patients with advanced disease [103].

Psychoeducation

Psychoeducation is also beneficial when provided to the patient. For example, psychoeducation is associated with better compliance with medication as evidenced by higher and more consistent lithium levels in patients undergoing psychoeducation compared with a control group [104]. That is probably one of the reasons that psychoeducation (provided in a group setting) was associated with reductions in recurrences (over a 60-week follow-up) [105] of both manic and depressive episodes and reduced number of hospitalizations compared with usual treatment (over a 5-year follow-up) [106]. The effect is true for both types of bipolar disorder [106,107]. These combine to produce a significant cost saving by significantly cutting the number of inpatient days [108].

Interpersonal and Social Rhythm Therapy

Interpersonal and social rhythm therapy (ISRT) is based on the foundation that our social interactions as well as our circadian rhythms both contribute to symptomatology of individuals prone to major mood disorders. Professionals in the field of IPSRT theorize 3 major factors that maintain symptoms in bipolar patients: medication nonadherence, response to stressful life events, and the disruption of social rhythms (eg, daily routines) [109]. A randomized trial comparing IPSRT with intensive clinical management (ICM) at either an acute or maintenance stage of the disorder followed 175 acutely ill patients with either depression or mania. Each patient received either IPSRT, ICM, or a combination of the 2 at acute or maintenance stages. All therapies were used in collaboration with medication treatment provided by study physicians. Acute measures were taken weekly until the patient stabilized, at which point the maintenance phase began and continued for the 2-year duration. Results of this study showed no significant difference in time to stabilization between the 2 therapies. However, in the acute phase, IPSRT was significantly better than ICM in prolonging the onset of new affective mood disorders. This indicates the IPSRT likely provides benefits in symptom awareness and control. Secondly, IPSRT was more beneficial in the adaptation to social rhythms, where patients
were able to implement structured daily routines and adaptive social interaction into their daily functioning. Finally, in the maintenance phase of this study, IPSRT showed overall improvement in general functioning over ICM, where patients displayed the ability to maintain adherence to their medication as well as continued adaptive social functioning [110].

Cognitive Behavioral Therapy

An additional psychotherapy that has shown promising results in the area of bipolar depression is cognitive behavioral therapy (CBT). CBT therapy has been recognized for its ability to decrease recurrence of depressive episodes as well as increase bipolar patient’s ability to adhere to their medication. Tenets of CBT include the important connection between thoughts and behaviors. In a depressive bipolar population, therapy focuses on the ability to identify and appropriately manage automatic thoughts that contribute to depressive feelings and behaviors. Increasing the client’s awareness of their moods is important in preventing relapse symptoms and hospitalization for bipolar patients [111,112]. A pilot study conducted nearly 10 years ago was one of the first comparing CBT as a treatment for bipolar and unipolar depression. In this study, 22 patients (11 meeting clinical criteria for bipolar and 11 meeting criteria for unipolar depression) were treated with CBT as an adjunct to their medication prescribed by a psychiatrist. Both populations were treated with a manualized CBT protocol by a doctorate level psychologist that worked on goal-directed behaviors as well as the ability to identify affective mood change. Results indicated that bipolar patients in the depressive stage of their illness responded as well as unipolar patients on scale scores of depression and anxiety. This indicates that CBT may be as effective in treating depressive symptoms in bipolar patients as it has been in treating those with unipolar depression. However, CBT was not as effective in changing the more pervasive symptoms of bipolar depression that include the general dysfunctional attitude in these patients. The authors concluded that CBT is helpful when used in collaboration with a medication routine, but it may be more beneficial when directed at identifying and changing underlying attitudes that are unique to bipolar depression [113]. Since this preliminary research, additional studies have begun to specialize treatment emphasis that is more illness specific and likely more beneficial to bipolar patients. In a recent study comparing CBT with a control psychoeducation “PE” group, 163 outpatient bipolar patients acknowledged via self-report that they experienced 50% fewer days with depressive symptoms than did the group receiving only psychoeducation. In addition, CBT therapy was more effective in improving daily mood ratings for the 6-month study than was the PE control. Finally, when assessing the need for antidepressant medication patients receiving CBT from licensed psychologists required less medication treatment throughout the study than did the PE group. The authors conclude that CBT is likely an effective supplement to medication in subsyndromal bipolar patients, but caution that these results may not be generalizable to patients experiencing clinically acute bipolar symptoms [114]. While comparative data are rare and frequently difficult to interpret, in a study of depressed bipolar patients randomized to CBT alone or CBT plus psychoeducation the patients assigned to combined treatment experienced 50% fewer depressed days over the subsequent year, suggesting that effects of different types of psychotherapy may be additive [114]. When the available literature is combined in a meta-analysis, the overall effectiveness of CBT in depressive symptoms associated with bipolar illness is somewhat modest (mean weighted Cohen’s d of −0.29 relative to treatment as usual) [115].

While there are surprisingly few studies of psychosocial interventions in the treatment of bipolar disorder, the available data are consistent that combination treatment is more effective than either medication alone or psychotherapy alone [116]. Furthermore, the use of psychotherapy reduces hospitalization, functional impairment, and overall cost [117].

CONCLUSION

The practitioner faces a number of challenges in the appropriate treatment of bipolar depression. These include making the correct diagnosis, the frequent use of antidepressants, and the dearth of adequate studies to guide treatment decisions. Nonetheless, there is an emerging consensus that antidepressants may destabilize the course of bipolar disorder and do not appear to be effective when added to a mood stabilizer. Alternative agents are becoming more available and include quetiapine, lamotrigine, modafinil and armodafinil, and pramipexole. Unfortunately, with the exception of quetiapine and lamotrigine, there is little information about the long-term consequences of using these agents. Psychosocial interventions have been documented to reduce the likelihood of depressive relapse and are probably underutilized.
We present our approach to treating bipolar depression in the Figure. In our model, utilization of the serotoninergic system is generally avoided or minimized while dopaminergic or noradrenergic approaches are employed preferentially.

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**Figure.** Schematic for approach to the treatment of bipolar depression.


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