SUPPLEMENT TO
Current PSYCHIATRY
OCTOBER 2013 / VOL 12, NO 10
Available at CurrentPsychiatry.com

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Managing Bipolar Depression: An Evidence-Based Approach

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CME/CE Information

Release Date: November 1, 2013
Expiration Date: November 1, 2014
Estimated Time to Complete This Activity: 1 Hour

Overview

This article includes a state-of-the-art review of the diagnostic and treatment challenges in bipolar depression (BD) and of recent clinical data on the efficacy and safety of atypical antipsychotics, mood stabilizers, antidepressants, and novel treatments, organized according to the level of available evidence. The article also includes a discussion on the role of neuromodulatory or psychosocial interventions with pharmacotherapy in enhancing mood and quality-of-life outcomes.

Target Audience

This activity has been designed to meet the educational needs of physicians, physician assistants, nurse practitioners, and registered nurses who care for patients with BD.

Educational Objectives

After completing this activity, the participant should be better able to:

- Discuss evidence-based treatments for the management of patients with BD
- Individualize treatment choices, giving consideration to efficacy, safety, long-term data, and unique patient characteristics of patients with BD
- Select appropriate treatment regimens that consider the emergence of new investigative agents
- Provide appropriate care and counsel for patients and their families

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This activity is supported by an independent educational grant from Sunovion Pharmaceuticals.

Bipolar disorder is characterized by the cyclical occurrence of elevated (manic or hypomanic) and depressed mood states. The illness, which includes the bipolar I and bipolar II subtypes, exacts a heavy toll in terms of quality of life, functioning, morbidity, comorbidity, and mortality.[1] Depressive episodes and symptoms deserve particular attention: Not only do they dominate the long-term course of the illness; they are associated with similar or greater psychosocial impairment than corresponding levels of manic or hypomanic symptoms.[1]

Bipolar depression also poses special challenges for diagnosis and treatment; however, until recently, the scientific literature primarily focused on the management of manic episodes and symptoms.[2] Although numerous agents targeting the manic phase of bipolar disorder have received Food and Drug Administration (FDA) approval, there has long been an unmet need for FDA-approved agents in the treatment of bipolar depression (***Figure 1***). The olanzapine-fluoxetine combination (OFC) and quetiapine IR were FDA-approved for the acute treatment of bipolar depression in 2003 and 2006, respectively. However, treatment options have only very recently expanded with the 2013 approval of lurasidone as monotherapy and adjunctive therapy for patients with bipolar I depression. This article discusses new developments in the diagnosis and treatment of bipolar depression in an effort to help physicians follow an evidence-based approach to managing bipolar depression.

Diagnosis

Based on the *DSM-IV-TR* and *DSM-5* criteria, the diagnosis of bipolar I disorder requires at least one full manic or mixed episode, whereas bipolar II disorder requires depressive and hypomanic episodes.[3,4] In practice, patients display a complex constellation of symptoms during different phases of the illness, increasing the likelihood of misdiagnosis. Changes introduced in the new *DSM-5* diagnostic criteria are intended to enhance the accuracy of diagnosis and facilitate earlier detection.[4] A separate chapter is now devoted to bipolar and related disorders.

Other notable changes include:

- "mixed episode" has been eliminated; the "with mixed features" specifier has been added to mania or hypomania when depressive features are present, and to depressive episodes in the context of major depressive disorder (unipolar depression) or bipolar disorder when features of mania/hypomania are present;
- antidepressant switching: full manic/hypomanic episode emerging during antidepressant treatment and persisting beyond physiological treatment effect to meet episode criteria is now sufficient to qualify as a manic/hypomanic episode diagnosis;
- the "with anxious distress" specifier has been added for manic, hypomanic, and major depressive episodes.[4]

It remains to be seen how the *DSM-5* changes will impact the diagnosis of bipolar illness and bipolar depression. The *DSM-5* does not address

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some longstanding challenges (such as not utilizing information regarding age of onset, illness course, family history of bipolar disorder, and prior responses to medications to improve diagnostic accuracy) and may even complicate diagnosis. As an example of the latter, major depressive episodes with mixed features can now occur both in unipolar depression and in bipolar disorder, which may add to the difficulty of distinguishing unipolar from bipolar depression.

The challenge of diagnosing bipolar II disorder is particularly well recognized[5] and will likely persist, owing in part to the difficulty of identifying hypomanic episodes retrospectively. Very often, hypomanic episodes are not experienced by patients as abnormal.[2] Patients typically appear in the physician's office when they are depressed and may have yet to experience a hypomanic episode, or may not recall having experienced one, in part because the majority of hypomanic episodes have mixed (hypomanic and depressive) symptoms.[6] Hypomania is particularly difficult to diagnose retrospectively without history from a significant other.

The failure to diagnose bipolar depression has serious consequences because morbidity and mortality are greater in bipolar depression than in major depressive disorder, and the treatments are distinctly different. In view of the challenges of distinguishing between unipolar and bipolar depression, a consensus has developed in support of a "probabilistic" approach that enables physicians to identify characteristics that may indicate a greater likelihood of bipolar depression.[7] As summarized in ***Table 1***, these include early onset of first depression (<25 years), multiple prior episodes of depression, positive family history of bipolar disorder, and postpartum depression.[2,7,8]

FIGURE 1

FDA-Approved Agents for Bipolar Disorder

Acute Mania	Acute Depression	Maintenance
1970 Lithium	2003 Olanzapine + fluoxetine combination	1974 Lithium
1973 Chlorpromazine	2006 Quetiapine IR, XR (2008)	2003 Lamotrigine
1994 Divalproex, ER (2005)	2013 Lurasidone*	2004 Olanzapine
2000 Olanzapine*	Important unmet needs: well-tolerated treatments for acute depression and maintenance	2005 Aripiprazole*
2003 Risperidone*		2008 Quetiapine IR and XR (adjunct)
2004 Quetiapine IR, XR (2008)*		2009 Risperidone LAI*
2004 Ziprasidone		2009 Ziprasidone (adjunct)
2004 Aripiprazole*		
2004 Carbamazepine ERC		
2009 Asenapine*		

*Adjunctive and monotherapy.

ER: extended release; ERC: ER capsule; IR, immediate release; LAI: long-acting injectable; XR: extended release.

Adapted from Ketter TA (ed). *Handbook of Diagnosis and Treatment of Bipolar Disorder*. American Psychiatric Publishing, Inc., Washington, DC, 2010.

Management Considerations

Optimal management of bipolar depression entails selecting treatments that result in the fewest, briefest, or mildest episodes and side effects, and do not induce switching into mood elevation. Major therapeutic objectives include treating depressive symptoms to remission, preventing recurrences, and restoring function. The treatment of bipolar depression poses special challenges in part because pharmacotherapeutic strategies carried over from unipolar depression may not be effective. Therapy with at least two drugs is often required during acute and maintenance treatment but, to date there are fewer studies of combination therapy than of monotherapy. Non-medication treatments, such as electroconvulsive therapy (ECT) and psychotherapy, can prove to be helpful adjuncts to pharmacotherapy.

Pharmacotherapy

In clinical practice, the pharmacotherapy of bipolar depression includes combinations of mood stabilizers (lithium and anticonvulsants), atypical antipsychotics (eg, olanzapine, quetiapine), and antidepressants (eg, fluoxetine). According to treatment guidelines, antidepressants should not be prescribed in the absence of antimanic agents in bipolar depression because they lack evidence for efficacy and may induce mania or mood instability.[9,10] However, as shown in a recent study that evaluated gaps in clinical knowledge and practice, 54% of 200 US-based psychiatrists reported that they would prescribe antidepressant monotherapy even in patients with depression and risk factors for bipolar I disorder.[10] Although previous randomized, controlled acute bipolar depression trials were extremely limited, there is now further research expanding the potential for evidence-based management, thereby helping patients attain better outcomes in terms of symptoms, functional states, and quality of life. The following discussion is organized according to the level of available evidence.

Approved agents for acute bipolar depression

In 2003, OFC was approved by the FDA, based on an 8-week, placebo-controlled trial that examined the use of olanzapine monotherapy (5-20 mg/d) and OFC (olanzapine 6 and fluoxetine 25 mg/d, olanzapine 6 and fluoxetine 50 mg/d, or olanzapine 12 and fluoxetine 50 mg/d) to treat bipolar I depression.[11] OFC and olanzapine monotherapy were both significantly superior to placebo on the primary outcome measure, which was improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) total score.

An important secondary outcome, the response rate (percentage of patients with at least 50% MADRS decrease) for the olanzapine monotherapy group, was significantly higher than placebo; however, the OFC group's response rate was 56% (***Figure 2***), which was significantly higher than both the placebo group (P <.001) and the olanzapine monotherapy group (P =.006).[11] The remission rate (percentage of patients completing at least 4 weeks, with final MADRS ≤12) for the OFC group was also significantly higher than those of the placebo and olanzapine monotherapy groups. The incidence of treatment-emergent mania was low, with no statistically significant difference among groups (P =.86).[11]

Adverse events for both olanzapine and OFC were similar for somnolence, weight gain, and increased appetite,

TABLE 1 Depressive Presentations at Increased Risk for Bipolar Outcome

- Acute onset, abrupt offset of depression
- Early onset of first depression (age 25 or younger)
- Family history of bipolar disorder
- Postpartum depression
- Seasonal affective disorder
- Antidepressant-induced hypomania or mania[a]
- Recurrent depressions
- Atypical depression

[a]Counts toward bipolar diagnosis if persists beyond expected physiological antidepressant duration (*DSM-5*, but not *DSM-IV-TR*).

Bowden CL. *Psychiatr Serv.* 2001;52:51-55; Mitchell PB, et al. *Bipolar Disord*. 2008;10:144-152; Sharma V, Pope CJ. *J Clin Psychiatry*. 2012;73:1447-1455.

but the combination treatment included statistically higher rates of nausea and diarrhea than olanzapine monotherapy.[11] In addition, in this 8-week study, the percentage of patients with at least 7% weight gain was significantly greater for the OFC (19.5%) and olanzapine monotherapy (18.7%) groups compared with the placebo group (0.3%).[11]

In 2006, the FDA approved quetiapine IR monotherapy for bipolar (I or II) depression based on the 2 BOLDER (BipOLar DEpRession) trials. Additional confirmation of the efficacy of quetiapine monotherapy in bipolar depression was provided by the two large, placebo- and active-controlled EMBOLDEN (Efficacy of Monotherapy Seroquel in BipOLar DEpressioN) trials.[12,13] In BOLDER I, patients with bipolar I disorder or bipolar II disorder experiencing a major depressive episode were randomly assigned to 8 weeks of quetiapine (600 mg/d or 300 mg/d) or placebo.[14]

Both doses of quetiapine monotherapy were significantly superior to placebo on the primary efficacy measure, which was mean change from baseline to Week 8 in the MADRS total score. In addition, about 58% of patients treated with either dose of quetiapine were responders (with at least a 50% decrease in final MADRS score) compared with 36.1% of placebo patients (P <.001).[14] Similarly, the percentage of patients meeting remission criteria (final MADRS score ≤12) was 52.9% in both quetiapine groups, significantly higher than the placebo rate of 28.4% in each group (P <.001). Treatment improved nearly all MADRS individual items that corresponded to core symptoms of depression.[14]

The BOLDER II trial produced similar efficacy results, with improvements in MADRS response and remission rates that were significantly greater in both quetiapine dosage groups compared with placebo.[15] The combined efficacy results from both studies are shown in ***Figure 2;*** in this pooled analysis, the number needed to treat (NNT) for response compared with placebo was six (that is, six participants would need to be treated to obtain one more response compared with placebo).[16] In both trials, adverse events such as dry mouth, sedation, somnolence, dizziness, and constipation were reported more than with placebo, while the incidence of treatment-emergent mania or hypomania was lower with quetiapine than with placebo. Importantly, in a pooled analysis that combined both of these 8-week trials, as well as the two quetiapine dosage groups, a significantly higher percentage of patients taking quetiapine monotherapy (30.4%) experienced sedation compared with patients taking placebo (8.1%).[17]

In June 2013, the FDA approved lurasidone as monotherapy and adjunctive therapy (added to background treatment with lithium or valproate) in adult patients with bipolar I depression. These new indications are supported by the two PREVAIL (PRogram to Evaluate the Antidepressant Impact of Lurasidone) trials, for which the prespecified primary end point was reduction in depressive symptoms as measured by change from baseline in the MADRS total score at Week 6.[18,19]

In the study of lurasidone monotherapy (PREVAIL 2), 505 subjects meeting *DSM-IV-TR* criteria for bipolar I depression were randomized to 6 weeks of double-blind treatment with lurasidone 20-60 mg/d or 80-120 mg/d, or placebo.[18] Overall (pooling the two lurasidone dosage groups) at Week 6, response (≥50% MADRS decrease) was seen in 52% of patients taking lurasidone compared with 30% of patients taking placebo (***Figure 3***). Based on this study, lurasidone monotherapy compared favorably with quetiapine and OFC in terms of response (NNT for response = 5).

The most common adverse reactions were akathisia and nausea (numbers needed to harm [NNH] were 15 and 17, respectively). Importantly, lurasidone was relatively weight-neutral (NNH for at least 7% weight gain was -493). The second study (PREVAIL 1) evaluated lurasidone 20-120 mg/d as adjunctive treatment in patients with bipolar I disorder who did not respond to adequate dosages and duration of lithium or valproate, and also found significant benefit (NNT = 7) and comparable tolerability (NNH of 16 for nausea, 30 for akathisia, 19 for somnolence, and -51 for at least 7% weight gain), compared with placebo.[19]

Lurasidone has also been evaluated in the context of co-occurring bipolar I depression and subsyndromal hypomania. The "real-world" presentation of bipolar I depression is often characterized by the admixture of depressive and subsyndromal hypomanic features, as captured by the new *DSM-5* "mixed features" specifier.[20] A post-hoc analysis evaluated whether the presence of subsyndromal hypomanic features influences efficacy and safety outcomes with lurasidone in the treatment of bipolar I depression, and found that lurasidone was superior to placebo in adults presenting with or without clinically significant subsyndromal hypomanic features.[20] Moreover, in the subsyndromal hypomania subgroup, treatment with lurasidone was associated with a reduction in mean Young Mania Rating Scale scores and a slightly lower incidence of treatment-emergent mania.[20]

Bipolar disorder is often complicated by such physical comorbidities as diabetes and cardiovascular disease, as well as associated cognitive impairments.[21] Ideally, clinicians should choose evidence-based medications that are less likely to add to these burdens. Antipsychotic drugs as a class have been associated with metabolic side effects; however, each drug has a specific risk profile that physicians must consider when making treatment decisions.[22] For example, some recent reports have indicated that both quetiapine and olanzapine may be linked to fatal diabetic ketoacidosis,[23] and quetiapine has been associated with negative cognitive side effects.[24] As seen in ***Table 2,*** lurasidone does not

increase lipid parameters and measures of glycemic control compared with placebo, and may be safer than some other drugs in the same class, which carry an increased risk for hyperglycemia, metabolic syndrome, and diabetes.[22] However, other less metabolically based side effects (such as nausea and akathisia) have been noted with lurasidone.

Unapproved agents with some evidence of efficacy in acute bipolar depression

Lithium is not FDA-approved for acute bipolar depression but is a mainstay of treatment for acute mania and for the maintenance phase for bipolar disorder.[25] For example, in a study in 360 patients with bipolar I disorder or bipolar II disorder, the benefits of long-term lithium treatment included reductions of episode frequency by 56% overall; on average, episode frequency was reduced somewhat more for mania (64%) than for bipolar depression (46%).[25] Comparable reductions in the proportion of time in mania and in depression were also achieved (61% vs 53%); however, the average duration of episodes was reduced substantially more for depression than for mania (32.4% vs 19.4%), which likely reflects the longer duration of depressive episodes compared with manic episodes prior to lithium treatment.[25] The study also found that participants with bipolar II disorder benefited slightly more than those with bipolar I disorder.[25]

There are also observational data showing substantial reductions of suicide risks with lithium-maintenance therapy in bipolar disorders to overall levels approximating the general population rate.[26] Although useful in the long-term management of bipolar disorder, lithium has a narrow therapeutic index and can have adverse effects (including hand tremor and weight gain, as well as renal toxicity over the long term) that require careful monitoring.

Data for the anticonvulsant lamotrigine for acute bipolar depression are equivocal. Five controlled, parallel-group monotherapy studies examined the efficacy of lamotrigine in acute bipolar depression; of these, four of five showed no evidence of benefit, although one study showed evidence of efficacy on a secondary outcome measure.[27] However, a systematic review and meta-analysis of individual patient data from randomized, controlled trials comparing lamotrigine with placebo showed a modest but significant benefit for lamotrigine overall. Moreover, this meta-analysis showed that lamotrigine was superior to placebo in more severely depressed patients.[28] Lamotrigine has good data for preventing relapses and recurrences, particularly of bipolar depression, and has demonstrated efficacy as an adjunct to lithium in patients with acute bipolar depression.[29,30]

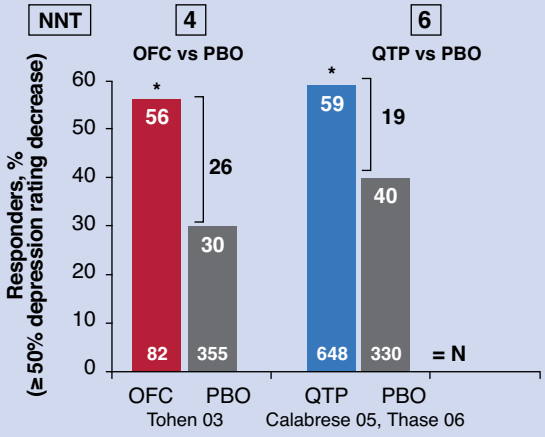
Valproate is a commonly used mood stabilizer for bipolar disorder; however, evidence regarding its efficacy as monotherapy for bipolar depression remains meager. Three of four small, placebo-controlled studies in bipolar depression supported its antidepressant effects, as did a recent meta-analysis.[31] However, the total sample size for the depression studies combined was small; larger controlled studies are warranted to provide a more complete picture of the role of valproate in bipolar depression.

Common side effects of valproate include dizziness, somnolence, weight gain, and nausea. The major concern with lamotrigine is Stevens-Johnson syndrome, a potentially life-threatening rash, although this is rare and the risk may be minimized by careful, slow titration.

FIGURE 2

QTP and OFC in Acute Bipolar Depression

NNT for Response, Rates Approved Treatments



*P < .0001 vs PBO.
OFC, olanzapine + fluoxetine; OLZ, olanzapine.

Keter TA, ed. *Handbook of Diagnosis and Treatment of Bipolar Disorder*. American Psychiatric Publishing, Inc., Washington, DC; 2010.

Some novel agents show promise as add-on treatment (augmentation), including armodafinil, modafinil, and pramipexole. An 8-week, double-blind trial of adjunctive armodafinil in acute bipolar I depression randomized patients to armodafinil 150 mg/d or placebo added to bipolar maintenance therapies. The primary outcome measure was mean change in score from baseline to Week 8 in the 30-Item Inventory of Depressive Symptomatology-Clinician-rated (IDS-C_{30}).[32] At the Week 8 end point, armodafinil compared with placebo yielded a significantly greater decrease in mean IDS-C_{30} total score and a significantly higher response (≥50% decrease from baseline) rate (46.2% vs 34.2%; P =.015; NNT for response = 9). Adverse events associated with armodafinil included headache, insomnia, diarrhea, and nausea. At final visit, 1.65% of armodafinil and 4.4% of placebo patients experienced ≥7% weight gain from baseline (NNH = -37) and 5.6% of armodafinil patients discontinued due to adverse events compared with 3.5% of placebo patients (NNH = 50).[32]

A 6-week study of modafinil added to lithium, valproate, or ongoing antidepressants in bipolar depression showed that the baseline-to-end point change in IDS score was significantly greater in the modafinil group compared with the placebo group.[33] Two small, randomized, controlled trials showed that pramipexole added to lithium or valproate had significant antidepressant effects in patients with bipolar depression.[34,35]

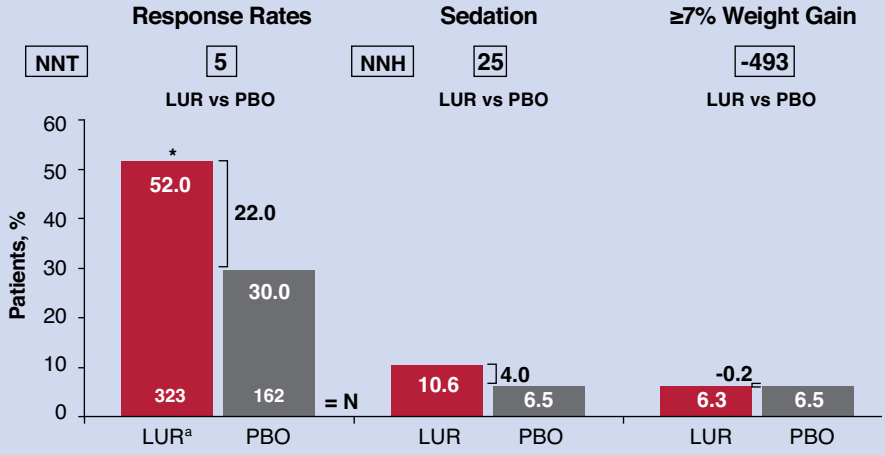
Unapproved agents lacking substantive efficacy evidence in acute bipolar depression

As noted above, studies have not established efficacy for antidepressants in bipolar depression, and there are

FIGURE 3

6-Week Randomized Double-Blind Lurasidone Monotherapy in Acute Bipolar I Depression

Approved Treatment of Acute Bipolar Depression as Monotherapy and Adjunctive Therapy



*P<.0001 vs PBO; [a]LUR = 20-60 or 80-120 mg/d. LUR, lurasidone.

Adapted from Loebel A, et al. 165th Annual APA Meeting; Philadelphia, PA; May 5-9, 2012.

doubts about their efficacy as adjunctive therapy.[13,36] Antidepressants can induce hypomania or mania in bipolar disorder patients, particularly when given without an antimanic agent. Older tricyclic antidepressants have been shown to confer a risk of switching into mood elevation, and their use is further limited by somatic and psychiatric (mood switch) tolerability concerns.[37] A study comparing the adjunctive use of the newer antidepressants venlafaxine, bupropion, and sertraline found comparable response and remission rates, but there was a significantly increased risk of switching into hypomania or mania during acute treatment with venlafaxine.[38]

Although mood stabilizers may reduce the risk of antidepressant-induced mania,[39] comparative evidence is not available regarding the best choice of mood stabilizer.

Given that many clinicians continue to use antidepressants to manage severe bipolar depression, a study sought to identify the correlates of treatment-emergent mania associated with the use of antidepressants in bipolar depression.[40] The study found that minimal manic symptoms, such as increased motor activity, speech, and thought disorder, coexisting with syndromal bipolar depression were associated with subsequent antidepressant-induced mania or hypomania.[40] A careful examination for such minimal manic symptoms may help physicians decide whether or not to prescribe antidepressants in particular patients.

Unapproved agents with negative evidence in acute bipolar depression

Although there is clear evidence for the efficacy of quetiapine and lurasidone—and, to a lesser extent, olanzapine monotherapy—two other antipsychotics have failed to show efficacy in acute bipolar depression. In two randomized, placebo-controlled studies of aripiprazole monotherapy in bipolar I depression, statistically significant differences were observed in Weeks 1 to 6, but aripiprazole monotherapy was not more effective than placebo at end point (Week 8).[41] Ziprasidone 40 and 160 mg/d did not show superiority over placebo in two 6-week, randomized, double-blind studies in bipolar I depression.[42] In a randomized, double-blind, placebo-controlled trial of adjunctive ziprasidone for acute treatment of bipolar I disorder, ziprasidone failed to separate from mood stabilizer alone.[43]

Adjunctive Nonpharmacologic Treatments

Because medications alone are not always sufficient, other evidence-based treatments have been integrated into the management of bipolar depression, including neuromodulatory and psychosocial interventions.

Adjunctive neuromodulatory treatments

A recent meta-analysis showed that ECT was equally effective in both unipolar and bipolar depression, with a remission rate of 53.2% for patients with bipolar depression.[44]

A study of deep brain stimulation (DBS) in patients with treatment-resistant depression in the context of either unipolar or bipolar II disorder found a significant decrease in depression and an increase in functioning. Efficacy was similar in patients with unipolar depression and those with bipolar depression.[45]

Although most studies of transcranial magnetic stimulation (TMS) have been conducted in unipolar depression, a small study showed benefit of repetitive TMS (rTMS) in drug-resistant bipolar depressive patients. These results are preliminary, as the study is limited by an open-label design and lack of a sham-controlled group.[46]

TABLE 2 **Antipsychotics: Adverse Events**

Adverse Event	ARI	ASE	CLZ	ILE	LUR	OLZ	QTP	RIS	ZIP
Metabolic									
Weight gain	+/0	+/0	++++	++	+/0	+++	++	++	+/0
Dyslipidemia	0	0	++	0	0	+++	++	+	0
Glucose dysregulation	0	0	++	0	0	++	++	+	0
Neurological									
Somnolence/sedation	+	0/+	++++	+	+	+++	+++	++	+
Extrapyramidal symptoms	+	0	0	0	0/+	+	0	++	+
Hormonal									
Hyperprolactinemia	0	0	0	0	0	+/0	0	++	0

ARI, aripiprazole; ASE, asenapine; CLZ, clozapine; ILE, iloperidone; LUR, lurasidone; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; ZIP, ziprasidone.

Adapted from Cha DS, McIntyre RS. *Expert Opin Pharmacother*. 2012;13:1587-1598.

There is less evidence for vagus nerve stimulation (VNS) in bipolar depression patients, but a post hoc analysis showed that the short- and long-term effects of VNS on bipolar and unipolar treatment-resistant depression were similar.[47]

Despite the possible role of these interventions, their use is limited by issues of tolerability and/or by financial constraints.

Adjunctive psychosocial interventions

Psychosocial interventions in conjunction with medications have been shown to improve outcomes in bipolar disorder. These interventions include cognitive-behavior therapy, family-focused therapy, interpersonal and social-rhythm therapy, and group psychoeducation.[48] It should be noted that multiple psychotherapy studies have looked at relapse prevention (bipolar maintenance treatment), but data for acute bipolar depression are limited.

Accordingly, a 1-year study demonstrated the benefit of 6 months of cognitive therapy in preventing relapses, alleviating symptoms, and promoting social functioning in patients with bipolar disorder who had experienced relapses despite mood stabilizers.[49] A follow-up study looked at effects over 30 months and found that cognitive-therapy patients had significantly better outcomes in terms of time to relapse, but that the overall effect of relapse prevention was strongest during the first 12 months.[50] There was also a significant effect in prevention of depression symptoms but not in prevention of mania/hypomania.[50] According to investigators, these results suggest the need for cognitive-therapy booster sessions or maintenance therapy to maintain benefit.

A randomized, blinded clinical trial of interpersonal and social-rhythm therapy in the acute and maintenance treatment of persons with bipolar I disorder found a reduced likelihood of recurrence during the maintenance phase but was not powered to detect efficacy in depressed patients.[51] In a study of group psychoeducation in bipolar disorder, all patients received standard psychiatric care with pharmacotherapy, but the experimental group received additional group psychoeducation, whereas the control group attended nonstructured group meetings. Group psychoeducation significantly reduced the number of relapsed patients and the number of recurrences per patient and increased the time to recurrences, including depressive recurrences.[52]

In contrast to the above-mentioned psychosocial intervention bipolar maintenance studies, a one-year STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) trial focused specifically on bipolar depressed patients in evaluating the benefits of three intensive, structured psychotherapies, compared with a control intervention in conjunction with pharmacotherapy on time to recovery and the likelihood of remaining well following an episode of bipolar depression.[48] Patients with acute bipolar depression were randomized to receive intensive psychosocial intervention (as many as 30 sessions of cognitive-behavior therapy, interpersonal and social-rhythm therapy, or family-focused therapy in 9 months) or minimal psychosocial intervention consisting of collaborative care (three sessions in 6 weeks). Patients with acute bipolar depression who received intensive psychotherapy in conjunction with medication had a higher recovery rate than patients in collaborative care (64.5% vs 51.5%; P =.01), as well as shorter time to recovery. There were no statistically significant differences between the intensive modalities in terms of outcomes, although the study appeared to have been underpowered to detect such differences.[48]

Conclusions

Bipolar depression is an extremely debilitating illness, frequently difficult to differentiate from unipolar depression. However, diagnostic accuracy can be enhanced by looking for characteristics that suggest an increased likelihood of bipolar depression, such as age of onset, illness course, family history of bipolar disorder, and prior responses to medications.

In addition to efficacy, physicians must also carefully weigh safety, tolerability, and the risk of treatment-emergent mania/hypomania when selecting among treatment options. Older, effective treatments for bipolar depression, such as quetiapine and OFC, have substantial tolerability limitations. However, lurasidone, a more recently FDA-approved option for bipolar depression, has similar efficacy and superior tolerability compared with these older agents. Importantly, in many cases, combining neuromodulatory or psychosocial interventions with pharmacotherapy can enhance mood and quality-of-life outcomes.

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