Evaluating Treatment Decisions in Bipolar Depression CME

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Release Date: July 30, 2003; **Valid for credit through July 30, 2004**

Target Audience

This activity is intended for physicians, pharmacists, nurses, psychologists, and healthcare professionals.

Goal

The goal of this activity is to provide clinicians with the latest scientific and clinical information in the treatment of bipolar depression.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Review the salient issues in diagnosing bipolar disorder depression.
2. Evaluate the current scientific data on psychopharmacologic approaches in the treatment of bipolar depression.
3. Discuss the current nonpharmacologic interventions in bipolar depression.

Credits Available

Physicians - up to 1.0 AMA PRA category 1 credit(s);
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Contents of This CME Activity

Introduction

In recent years, there has been a much-needed resurgence of interest in the treatment of bipolar depression.[1] This renewed interest has been driven, in part, by research indicating that depressive symptoms and episodes account for greater morbidity and disability than previously appreciated,[2,3] and by pharmacologic and psychotherapeutic treatment advances.[1,4] Moreover, other studies indicate that bipolar depression continues to be underrecognized and frequently misdiagnosed, leading to inadequate or improper treatment.[5,6] In this review, new data regarding the recognition, diagnosis, and treatment of bipolar depression that bear on treatment decisions for bipolar depression are discussed.

Recognition

Bipolar depression is an important diagnostic consideration in the differential assessment of patients presenting for treatment of a depressive episode.[7] Several recent studies indicate that a substantial number of patients with bipolar depression, especially bipolar II depression, are initially diagnosed with unipolar major depressive disorder. For example, Ghaemi and colleagues [7] found that bipolar disorder was misdiagnosed as unipolar depression in 37% of patients who initially sought treatment with a mental health clinician following their first manic or hypomanic episode. Consequently, antidepressants were used earlier and more commonly than mood-stabilizers in these patients, resulting in new or worsening rapid cycling in 23%. In a survey of members of the Depression and Bipolar Support Alliance (DBSA), Hirschfeld and colleagues [6] found that 60% of respondents with bipolar disorder had initially been diagnosed with unipolar depression.

Moreover, an average of 10 years elapsed between the onset of mood symptoms and accurate diagnosis of bipolar disorder. Why is bipolar depression so difficult to diagnose? First, hypomanic and even manic episodes may go unreported by patients. Second, more than 50% of patients with bipolar disorder experience a depressive episode as their first mood episode.[2] Third, although atypical depressive symptoms (eg, hyperphagia, hypersomnia, profound fatigue, and psychomotor retardation) may occur more commonly in bipolar depression, they are not pathognomic symptoms for bipolar depression and can occur in unipolar depression as well. Fourth, the diagnosis of bipolar II disorder, bipolar disorder NOS, and cyclothymia can be difficult to diagnose because the brief and relatively mild excursions into hypomania may be difficult for patients to recall or characterize as abnormal, and therefore difficult for clinicians to elicit.

With these diagnostic pitfalls in mind, there are fortunately several ways of improving diagnostic sensitivity for bipolar depression. Two screening instruments for bipolar disorder have recently been devised with reliable psychometric properties: the Mood Disorder Questionnaire (MDQ)[8,9] and the Bipolar Spectrum Diagnostic Scale (BSDS).[10] Both scales can be provided to patients and family members or friends to increase the diagnostic suspicion of bipolar spectrum disorders. Manning and colleagues[11] provided clues for detecting hypomania (Table 1) and suggested questions for eliciting evidence of hypomania (Table 2). In addition, they also identified clues for the detection of subtle presentations of bipolar disorder (Table 3) and mixed states (Table 4).

Table 1. Detecting Hypomania[11]

Characteristics of Hypomania

- No adequate cause of grossly disproportionate emotional reaction to a situation
- Labile affect, appearing and disappearing suddenly (bipolar switching)
- Can be dysphoric in drivenness, although mood is typically elated
- May lead to substance abuse
- Tends to impair social judgment
- Typically preceded or followed by retarded depression
- A recurrent condition
- If the typical features are present, 48 hours duration is sufficient to make the diagnosis
- Not psychotic

Table 2. Suggested Questions for Uncovering Hypomania [11]

1. Do you have days of energy or ideas that come and go *abruptly*?

2. On those days of energy, are you productive? Creative? Feel uncomfortable? Convinced of your self-worth, talents, abilities? Positive about the future? Talkative? Distinctly more social? Irritable?

3. On those days of energy, do your thoughts feel as if they are racing?

4. At night during this period of energy, do you need less sleep? Continue to be productive? Get ideas or make plans for the future?

5. How many consecutive days does this period of increased energy and change in mood last?

6. Do others notice the change in your mood or energy level?

7. During these "up" times, do you do things that you later regret? Make plans you find impossible to follow through with? Take on tasks that you later suddenly lose interest in or find you are without energy or desire to complete?

8. Are you particularly more depressed or lethargic immediately before or after the cessation of these periods of energy? Does it feel like you "crash"? Does your body seem as if it is made of lead? Do you need excessive sleep?

Table 3. Detecting Subtle Bipolarity [11]

1. Established bipolar family history, or lithium-responsive illness in first-degree relative, or both, or loaded 3-generational family history of mood disorder

2. Pharmacologically induced mania or hypomania

3. History of mixed states

4. Spontaneous episodes of hypomania, even when "adaptive"

5. Premorbid hyperthymia, cyclothymia, irritable, or dysthymic temperament

6. Periodic depression with abrupt onset and termination or seasonal pattern, especially with psychomotor retardation and hypersomnia

7. Psychotic depression in a teenager or young adult

Table 4. Detecting Mixed States[11]

1. Unrelenting dysphoria or irascibility
2. Severe agitation
3. Refractory anxiety
4. Unendurable sexual excitement
5. Intractable insomnia
6. Suicidal obsessions
7. "Histrionic" demeanor yet with genuine expressions of intense suffering

Diagnosis

The importance of making the diagnosis of bipolar depression and distinguishing it from unipolar depression is self-evident, but also highlighted by the findings of several recent outcome studies. First, bipolar spectrum disorder (bipolar I, II, and NOS disorders as well as cyclothymia) is common and a global public health problem.[12,13] Using the MDQ to screen for bipolar spectrum disorder in a US national community sample, Hirschfeld and colleagues[13] found that the lifetime prevalence was 3.4%. Individuals with bipolar spectrum disorder in this survey reported significantly more difficulties with work-related performance, social and leisure time activities, and family and interpersonal interactions than nonspectrum respondents.[14] Women with bipolar spectrum disorder reported significantly more disruption in family and social life, and men reported significantly more frequent time in jail, arrested, or convicted for criminal behavior.

MacQueen and colleagues [15] reported that the number of bipolar depressive, but not manic, episodes was the strongest determinant of functioning and well-being in patients with bipolar disorder. Similarly, Altshuler and colleagues [16] found that chronic subsyndromal depressive symptoms were the strongest predictor of functional impairment in bipolar disorder. The problem of persistent subsyndromal depressive symptoms in patients with bipolar disorder was also identified in 2 other studies. [17,18] Judd and colleagues,[17] in a longitudinal follow-up study of 86 patients with bipolar II disorder, assessed weekly for an average of 13 years, found that most patients spent most of the time not manic, depressed, or well, but rather experiencing subsyndromal depressive symptoms. Benazir [18] reported that 45% of patients with bipolar II disorder had residual depressive symptoms for more than 2 years from their index depressive episode. These persistent residual depressive symptoms were significantly correlated with illness duration and number of mood episode recurrences.

Since mood episodes are likely to recur in bipolar disorder, identifying signs of depressive episode recurrence can assist in rapid intervention. Two studies recently examined prodromal depressive symptoms in bipolar disorder.[19,20] Jackson and colleagues[19] found the 4 most common prodromal symptoms of bipolar depression reported in the literature to be mood change (48%), psychomotor symptoms (41%), increased anxiety (36%), and appetite change (36%). Keitner and colleagues [20] interviewed 74 patients with bipolar I disorder and their families to identify prodromal symptoms of bipolar depression. They found some interesting similarities and differences in perception and recognition of such symptoms, summarized in Table 5.

Table 5. Patient and Family Identification of Prodromal Bipolar Depressive Symptoms [20]

Category	Patient	Family
Behavioral	Quiet, withdrawn	Quiet
	Self-neglect	Less responsible

Cognitive	Poor concentration	Worried
	Can't make decisions	Down on self
Mood	Crying	Sad
	Irritable and angry	Irritable
Social	Withdrawal from friends	Less affectionate
Neurobehavioral	Poor sleep	Sleeps more
	Loss of appetite & energy	Low energy

In summary, the diagnosis of bipolar depression is an important consideration in patients presenting with depressive symptoms. The importance of accurate diagnosis rests not only with providing appropriate treatment, but also in avoiding potentially destabilizing treatment. Screening tools and careful diagnostic personal and family history can increase the sensitivity for detecting bipolar depression. Treating to full remission of depressive symptoms is especially critical to avoid the long-term debilitating effects of chronic, residual subsyndromal depression

Pharmacologic Treatment

Although the acute and long-term treatment of bipolar depression remains a remarkably understudied area, new data from randomized, controlled trials and naturalistic studies have expanded the treatments available for bipolar depression and expanded our understanding of the balance between treatment of depression and risk of switching into mania or hypomania.

Mood-Stabilizer Monotherapy

Most guidelines for the acute treatment of bipolar depression emphasize initiating treatment of patients with acute bipolar depression with a mood-stabilizer.[21,22] This recommendation is based on the assumption that mood-stabilizers will exert at least some antidepressant effect and have negligible risks of inducing switches or rapid cycling.[23] Among the mood-stabilizers, lithium has been the most well studied in randomized, controlled trials in acute bipolar depression.[24] In pooled data from these studies, lithium response rates were 79%, although only 36% displayed a marked antidepressant response.[24]

Two recent randomized, controlled, parallel-group trials also examined lithium's efficacy in acute bipolar depression.[25,26] Nemeroff and colleagues[25] compared paroxetine and imipramine with placebo added to lithium in patients with breakthrough depression. Patients receiving lithium at serum concentrations >/= 0.8 mmol/L experienced no significant benefit from the addition of either antidepressant compared with placebo. However, in patients with lithium levels of < 0.8 mmol/L, the addition of paroxetine provided superior antidepressant efficacy compared with placebo. One interpretation of these findings is that in mid-to-upper therapeutic serum concentrations, lithium provided substantial antidepressant benefit, but that the addition of paroxetine was most evident in patients who could not tolerate such lithium concentrations. In the second trial, Young and colleagues[26] also addressed the question of what treatment to add for breakthrough bipolar depression in patients maintained on a mood-stabilizer -- in this case, either lithium or valproate. They randomized patients to receive the alternative mood-stabilizer or paroxetine. There was no significant difference in antidepressant efficacy between the two treatment groups (mood-stabilizer combination vs paroxetine-mood-stabilizer), and both showed significant improvement from baseline. This study was limited by the small sample size (n = 27), which made it difficult to detect significant differences between the two active treatments. Of note, there were no significant differences in switch rates between the two groups.

To date, divalproex (and other formulations of valproic acid) have not been well studied in acute bipolar depression. Sachs and Collins [27] did not find significant differences in efficacy between divalproex and placebo in a small trial in acute bipolar depression.

Olanzapine had significantly greater efficacy than placebo in a recently completed 8-week trial in bipolar depression, with differences in efficacy evident by the first week of treatment. [28] There were no significant differences in switch rates between the two groups.

Three small placebo-controlled trials examined the efficacy of carbamazepine in acute bipolar depression. [1] Nearly all patients had treatment-refractory bipolar depression and pooled response rates were approximately 34%.

Antidepressant Monotherapy

A randomized, placebo-controlled trial found significant efficacy for lamotrigine in acute bipolar depression.[29,30] In a 7-week, parallel-group study, Calabrese and colleagues[29] observed significantly greater efficacy for lamotrigine 50 mg/day and 200 mg/day over placebo in mean reduction in Montgomery-Asberg Depression Rating Scale total scores. There were no significant differences in switch rates among the 3 treatment arms. There was also a trend toward greater efficacy of the 200 mg/day group, which did not receive the full 200 mg/day dose until the fourth week of the study because of the slow titration required of lamotrigine. It is possible that significantly greater efficacy would have been apparent in this group had the study been longer. In a second study of treatment-refractory rapid-cycling bipolar I and II patients, Frye and colleagues [30] compared lamotrigine, gabapentin, and placebo in a series of 6-week crossover trials. The lamotrigine group, but not the gabapentin group, displayed significantly greater improvement in depressive symptoms compared with placebo. In contrast to these positive trials, a second placebo-controlled parallel-group trial did not find significantly greater efficacy for lamotrigine over placebo in patients with bipolar I and II disorders, largely due to a high placebo response rate. [31]

There are relatively few other studies of unimodal antidepressant treatment of bipolar depression, no doubt because of the risk of switch induction. Tranylcypromine was superior to imipramine in a study of patients with anergic bipolar depression, with switch rates of approximately 25% in both groups. [32] However, the severity of switching was qualitatively less in the tranylcypromine group. Thase and Sachs, in a recent review of antidepressant trials in bipolar depression, observed that no "single antidepressant medication, nor even a particular class of antidepressant, has been demonstrated to be effective in at least 2 adequately powered, placebo-controlled clinical trials (p.558)."[22] We will return to this issue in the discussion of switch rates associated with different antidepressants.

Mood-Stabilizer/Antidepressant Combinations

Two combination therapy trials involving paroxetine were summarized above.[25,26] The combination of olanzapine-fluoxetine (OFC) was superior to placebo beginning at week 1 and throughout an 8-week trial.[28] In addition, OFC was superior to olanzapine monotherapy from weeks 4-8 in this study. There were no significant differences in switch rates among all 3 treatment arms.

Goldberg and colleagues [33] reported significantly greater efficacy for pramipexole, a dopamine agonist, compared with placebo added to mood-stabilizers in 24 patients with bipolar depression, with no significant differences in switch rates. McIntyre and colleagues [34] compared topiramate with bupropion added to mood-stabilizers in an 8-week single-blind study and found comparable efficacy between agents. However, the study was not powered to find a significant difference in efficacy. Two studies of omega-3 fatty acids yielded mixed results. [35, 36] Stoll and colleagues [35]

found significantly greater efficacy for a preparation containing EPA/DHA compared with placebo in a 4-month trial in patients with bipolar depression. In contrast, Keck and colleagues [36] found no significant differences in efficacy between EPA 6 g/day and placebo added to mood-stabilizers in a trial of similar design.

With the possible exception of superior efficacy of tranylcypromine over imipramine, there are no data to date that indicate that one antidepressant or class of antidepressant has greater efficacy compared with another in bipolar depression. Similarly, there are no compelling data to suggest that antidepressants administered with mood stabilizers are less effective in bipolar I compared with unipolar depression. [37]

The findings of 2 recent studies suggested that subclinical hypothyroidism (eg, low FTI and high TSH, or low T_4) was associated with slower antidepressant treatment response [38] and more mood episodes and greater severity of depression. [39]

Long-term Treatment of Bipolar Depression

Mood-Stabilizer Monotherapy

Placebo-controlled maintenance studies of lithium conducted in the late 1960s and early 1970s found that lithium reduced the risk of mood episode relapse fourfold compared with placebo at 6 months and 1 year.[40] Lithium was comparable to olanzapine in preventing relapse into bipolar depression in a recently reported 1-year maintenance trial, but olanzapine was superior to lithium in preventing relapse into a manic episode and need for hospitalization.[41] Olanzapine was superior to placebo in prevention of relapse into both manic and depressive episodes in another recently reported randomized, controlled maintenance study.[42]

Two studies examined the efficacy of divalproex in the maintenance treatment of bipolar disorder.[43,44] In the only placebo-controlled trial, neither divalproex nor lithium were superior to placebo in time to relapse into any mood episode by 1 year.[43] However, in a post hoc analysis, patients who received divalproex during an open-label stabilization phase prior to randomization, and who were then randomized to divalproex or placebo, demonstrated significantly lower relapse rates in the divalproex group. In the second study, patients who responded to divalproex or olanzapine in a 3-week acute bipolar mania trial were followed for an additional 44 weeks to examine maintenance of efficacy. [44] At the end of the 47-week study, there were no significant differences between the 2 agents in manic or depressive symptom reduction, although there was a trend for superior efficacy in depressive symptom improvement in the olanzapine group.

Two large, placebo-controlled, 18-month maintenance trials compared the efficacy of lamotrigine (200-400 mg/day) with lithium following stabilization after either a manic or depressive episode. [45, 46] The results of these 2 studies were remarkably consistent: lamotrigine but not lithium was superior to placebo in time to relapse into a depressive episode, whereas lithium but not lamotrigine was superior to placebo in time to relapse into a manic episode. One implication of these findings is that the combination of lithium and lamotrigine might be especially efficacious in preventing relapse into both manic and depressive episodes, although this has not yet been tested in a randomized, controlled trial. The efficacy of lamotrigine was also examined in the relapse prevention of patients with bipolar I and II disorders with rapid cycling. [47] In this 6-month trial, Calabrese and colleagues did not find significant differences in efficacy in relapse prevention between lamotrigine and placebo. However, in a post hoc analysis, there was a trend for superior efficacy for lamotrigine in the bipolar II group of patients.

Mood-Stabilizer Combination Therapy

The majority of patients with bipolar I disorder are treated with at least 2 medications in maintenance treatment. Despite this commonplace and clinically necessary practice, there are only 2 randomized, controlled trials that have assessed the efficacy of combination compared with mood-stabilizer monotherapy treatment.[48,49] Solomon and colleagues[48] compared the efficacy of valproate vs placebo added to lithium in a 1-year pilot study. Patients receiving the combination experienced significantly lower relapse rates compared with patients receiving lithium and placebo. Not unexpectedly, the combination therapy group reported twice the side effect rate.

In the second study, Tohen and colleagues [49] randomized patients who responded to the combination of olanzapine with lithium or divalproex for acute mania to remain on the combination or revert to monotherapy with lithium or divalproex. They then followed patients for 18 months. As in the study by Solomon and colleagues, [48] the combination therapy group displayed significantly lower relapse rates compared with the monotherapy group. However, the advantage of combination therapy was primarily in the prevention of manic relapse (combination therapy, 15% vs monotherapy, 35%). There was no significant difference in efficacy between the 2 groups in time to depressive relapse, although, again, a trend favored the combination therapy group.

Treatment Decisions: Balancing the Switch Risk Vs Risk of Depression

Although, as reviewed above, mood stabilizer monotherapy can be expected to produce significant improvement in bipolar depression in some patients, for others, improvement will be insufficient. For patients who have an inadequate antidepressant response to mood stabilizer monotherapy, antidepressants are often added. This common clinical situation raises at least 3 important considerations:

1. Are there differential risks of switching among the available antidepressants when added to mood stabilizers?

2. How protective are mood stabilizers against the risk of switching?

3. After a patient experiences a marked response to a mood stabilizer-antidepressant combination, what are the risks of continuing this combination on switching, compared with the risk of discontinuing the antidepressant and depressive relapse?

Risk of Switching

Calabrese and colleagues [50] recently reviewed the reported switch rates from randomized controlled trials in acute bipolar depression (Table 6). Overall, these studies suggest that the lowest switch rates were associated with lithium, lamotrigine, olanzapine, OFC, and paroxetine (administered with a mood stabilizer).

Table 6. Switch Rates in Controlled Trials in Acute Bipolar Depression [50]

Drug	Switch Rates (%)	Design
Lithium	0	Mostly crossover trials
Olanzapine	6	8 week parallel
OFC	6	8 week parallel
Placebo	3.3	6 week parallel
	4.6	7 week parallel

	2	10 week parallel
	6	8 week parallel
Lamotrigine	5.4	7 week parallel
Paroxetine	0	6 week parallel with MS
	0	10 week parallel with MS
Bupropion	11	8 week parallel with MS
Tranylcypromine	20	6 week parallel
Tricyclics	0-50	Variable

OFC, olanzapine-fluoxetine; MS, mood stabilizer

Three recent studies examined the efficacy of mood stabilizers in preventing switching with the addition of an antidepressant for bipolar depression.[51-53] Bottlender and colleagues[51] reported an overall switch rate of 25% in a cohort of 158 inpatients treated for bipolar depression. Risk factors for switching were administration of a tricyclic antidepressant, particularly without a mood stabilizer. Patients who switched were significantly less likely to be receiving a concomitant mood stabilizer. These findings were consistent with earlier reports that described a reduction in switch risk by approximately 50% if an antidepressant was added to a mood stabilizer compared with no mood stabilizer.[54,55] Henry and colleagues[52] also found a relatively low switch rate of 27% in a cohort of 44 patients receiving antidepressants in naturalistic trials. Patients receiving a mood stabilizer, particularly lithium, were at one third the risk of switching over the 6 week treatment interval. Post and colleagues [53] examined switch rates in an interim analysis of an ongoing trial comparing the addition of bupropion, sertraline, and venlafaxine to mood stabilizers over an acute 10-week period, followed by 1 year of maintenance treatment in responders. The switch rate was 14% in the acute treatment trials (mania 6%, hypomania 7%) and 33% during the one year follow-up (mania 13%, hypomania 21%). No antidepressant was associated with a significantly higher switch rate.

These studies indicate that concomitant administration of an antidepressant with a mood stabilizer does not eliminate but does significantly reduce the risk of switching. The studies of Henry and colleagues [52] and Post and colleagues [53] found that hypomanic rather than manic switches were quite common.

The long-term treatment of bipolar depression raises the final question of how long to maintain an antidepressant once a patient has experienced a remission of symptoms, balancing the risk of depressive relapse with the risk of switching. Two studies by Altshuler and colleagues [56, 57] recently examined this question. The first study compared relapse rates of 25 patients who discontinued antidepressants (administered with mood stabilizers) with 19 patients who continued on antidepressants (with mood stabilizers). [56]

The group that discontinued antidepressants had a threefold higher risk of depressive relapse compared with the group that continued on antidepressants. In contrast, the group that continued antidepressants did not have a significantly higher switch risk. The second study examined the same issue in a cohort of 84 patients from the Stanley Foundation Bipolar Treatment Network.[53,57] At 1-year follow-up, patients who discontinued antidepressants within 6 months of achieving remission from depression were twice as likely to experience a depressive relapse with antidepressant discontinuation compared with patients who continued these agents (bupropion, sertraline, venlafaxine). There was no significant difference in depressive relapse rates between the 2 groups. These 2 studies suggest that the risk of depressive relapse with antidepressant

discontinuation was high relative to the risk of switching with antidepressant continuation. Two cautionary notes to consider, however, are that these findings do not necessarily generalize to rapid cycling patients, and the comparatively low switch rates may have been attributable to the use of antidepressants with low switch rates themselves. [1]

Psychotherapy

Several studies have recently reported beneficial effects of psychotherapies targeted for bipolar disorder on long-term outcome. [58-60] Zaretsky and colleagues [58] investigated individual cognitive therapy in 11 patients with bipolar depression and 11 patients with unipolar depression also receiving pharmacotherapy. Both groups displayed significant improvement in depressive symptoms; however, the bipolar group did not display comparable degrees of improvement on measures of pervasive dysfunctional attitudes.

Lam and colleagues[59] randomized 103 patients with bipolar I disorder who experienced frequent relapses to cognitive therapy or treatment as usual in addition to mood stabilizer medications. The cognitive therapy group received an average of 14 sessions during the first 6 months plus 2 booster sessions in the second 6 months. During the 12-month period, the cognitive therapy group had significantly fewer bipolar episodes, days in bipolar episodes, and number of admissions for episodes, as well as higher social functioning. Colom and colleagues[60] randomized 120 patients with bipolar I or II disorder who were in remission for at least 6 months to 21 sessions of group psychoeducation or 21 sessions of nonstructured group meetings. Group psychoeducation significantly reduced the number of relapses and increased the time to depression, manic, hypomanic, and mixed episodes. The number of hospital admissions was also significantly reduced in this group.

Summary

There have been a number of important advances in the treatment of bipolar depression. Recent research has underscored that bipolar depression remains underdiagnosed, but has also provided new methods of screening to improve diagnostic sensitivity. New medications have been found to be efficacious in short- and long-term trials, including lamotrigine and olanzapine. Combination therapy appears to improve both short- and long-term treatment response while reducing the risk of switching.

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