Bipolar major depression in adults: General principles of treatment

AUTHORS: William V Bobo, MD, MPH, Richard C Shelton, MD
SECTION EDITOR: Paul Keck, MD
DEPUTY EDITOR: David Solomon, MD

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INTRODUCTION

Bipolar disorder is marked by episodes of mania (table 1) and hypomania (table 2) and nearly always includes episodes of major depression (table 3) [1]. Observational studies consistently show that depressive episodes predominate the clinical course of bipolar disorder [2,3]. Compared with manic and hypomanic episodes, bipolar depressive episodes and residual bipolar depressive symptoms account for a greater proportion of long-term morbidity, impaired functioning, and risk of suicide [4,5].

As a result, improved treatment of bipolar major depression is a patient priority. In an internet based survey from 11 countries, which asked patients with bipolar disorder (n = 1300) which aspects of care they would most like to see improved, better treatment of depression was endorsed by the largest number (>40 percent) [6]. The second and third leading aspects of care that patients would most like to see improved were avoiding weight gain and preventing relapse of depressive episodes.

This topic reviews the general principles of treating bipolar major depression. Other topics discuss choosing treatment for adults with bipolar major depression, the efficacy and adverse effects of antidepressants and second generation antipsychotics for bipolar major depression in adults, investigational approaches to treating bipolar major depression in adults, choosing pharmacotherapy for adults with acute mania and hypomania, choosing maintenance treatment for adults, and choosing pharmacotherapy for pediatric bipolar major depression:

- (See "Bipolar major depression in adults: Choosing treatment".)
- (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)
- (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics".)
- (See "Bipolar major depression in adults: Investigational and nonstandard approaches to treatment".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment".)
- (See "Pediatric bipolar major depression: Choosing treatment".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is a mood disorder that is characterized by periods of pathologic mood elevation (mania or hypomania) [1]. Patients with bipolar I disorder experience manic episodes (table 1) and nearly always experience both hypomanic episodes (table 2) and major depressive episodes (table 3). Bipolar II disorder is characterized by at least one episode of hypomania (table 2) and one or more major depressive episodes. In addition, psychotic features such as delusions and hallucinations frequently accompany bipolar depressive episodes, particularly in patients with bipolar I disorder [7].

Additional information about the clinical features and diagnosis of bipolar disorder, including bipolar major depression, is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis".)

GENERAL PRINCIPLES

Initial assessment — Treatment of acute bipolar depressive episodes begins with a psychiatric and general medical history, mental status and physical examination, and focused laboratory and imaging studies as clinically indicated. Clinicians should assess current and past:

- Depressive symptoms and episodes (table 3), including suicidal ideation and behavior
- Manic and hypomanic symptoms and episodes (table 1 and table 2)
- Psychotic features such as delusions and/or hallucinations
- Substance abuse
- Treatment responses, including treatment-limiting adverse effects
- Patient preferences regarding treatment

Establishing a clear history of mania or hypomania meeting full diagnostic criteria is essential. Additional information about assessing patients for bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Assessment'.)

Goals — The goals of acute treatment for bipolar depressive episodes is remission, defined as resolution of mood symptoms or improvement to the point that few symptoms of only mild intensity persist, and restored functioning [8,9]. However, remission can require several weeks or longer to occur; thus, a reasonable interim goal is response [8,9], defined as stabilization of the patient's safety with clinically significant reduction in the number and severity of mood symptoms. Response includes resolution of suicidal ideation and psychotic features, when present. In addition, improvement in depressive symptoms should occur without precipitating treatment-emergent manic/hypomanic episodes or rapid cycling. In many studies that use rating scales to monitor response to treatment, response is defined as reduction of baseline symptoms ≥50 percent.

Setting — Hospitalization may be required for the safety and stabilization of patients with severe bipolar depression accompanied by [10]:

- Suicidal ideation with a plan and intent to kill oneself. (See "Suicidal ideation and behavior in adults".)
- Delusions or hallucinations that threaten the patient's safety, such as command auditory hallucinations involving suicide. (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)
- Severe agitation. (See "Assessment and emergency management of the acutely agitated or violent adult".)
- Loss of functioning such that patients can no longer adequately care for themselves – As an example, patients may become dehydrated and malnourished due to refusal of liquids and food.

Patients with acute but moderate bipolar depression (such as those with fleeting suicidal ideation without suicidal intent or plan) can be treated in a partial hospitalization or intensive outpatient treatment program. Otherwise, most patients with bipolar depression can be managed as outpatients.

Pharmacotherapy — Choosing a specific medication regimen for acute episodes of bipolar I or II major depression is discussed separately. (See "Bipolar major depression in adults: Choosing treatment".)

In selecting pharmacotherapy for patients with bipolar major depression, clinicians should understand that they are likely selecting a maintenance regimen as well, because medications that successfully resolve acute bipolar episodes are generally continued [11,12]. Maintenance treatment of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment".)

For patients with bipolar major depression who receive a second-generation antipsychotic as monotherapy, efficacy is often comparable for low doses and high doses, whereas discontinuation of treatment due to adverse effects may occur less often with low doses. As an example, a meta-analysis of four randomized trials (n >1600 patients) compared fixed doses of quetiapine 300 mg/day with quetiapine 600 mg/day and found that symptomatic improvement, response (reduction of baseline symptoms ≥50 percent), and remission were each comparable for the two groups [13]. However, discontinuation of treatment due to adverse effects occurred less often with quetiapine 300 mg/day.

Nearly all of the high quality evidence that guides choosing a medication regimen consists of randomized trials that compared an active drug with placebo. Few head-to-head trials have compared different active drugs.

If patients respond poorly to a medication regimen that includes multiple drugs, we change one medication at a time.

Duration of an adequate drug trial — Based upon literature reviews [14] and multiple randomized trials [15], the duration of an adequate medication trial for patients with bipolar I or II major depression is usually six to eight weeks. Nearly all of the studies were conducted with outpatients.

However, in clinically urgent situations, such as inpatient hospitalization, it is typically not feasible to wait six to eight weeks to determine if a drug trial has sufficiently relieved symptoms. For these patients, if there is minimal improvement (eg, reduction of baseline symptoms <20 percent) within the first few weeks (eg, two to three) of treatment with a specific medication, it may be acceptable to decide that response is unlikely to occur [16,17].

Using absence of early improvement to predict nonresponse is supported by a study of four randomized trials in which an active medication regimen was superior to placebo in bipolar I or II major depression (n > 2000 patients) [18]. The active drugs consisted of lamotrigine, olanzapine plus fluoxetine, or quetiapine; the trials lasted seven or eight weeks; early improvement was defined as reduction of baseline symptoms ≥20 percent at week 2, and response was defined as reduction of baseline symptoms ≥50 percent. The analyses pooled the negative predictive values, which represented the probability that patients would not respond

at the end of the study if they had not demonstrated early improvement. The pooled negative predictive value was high (74 percent) and the false positive rate was low (14 percent); these results were interpreted to mean that absence of early improvement was a highly reliable predictor of subsequent nonresponse. By contrast, the presence of early improvement did not reliably predict eventual response.

Monitoring — We recommend that clinicians monitor depressive symptoms, treatment response and adverse effects, and adherence to treatment at each visit [16,19]. Assessment frequency depends upon the severity of depressive symptoms, treatment setting, suicide risk, presence of psychotic features and comorbid psychopathology, and functional impairment. Hospitalized patients are assessed at least daily, and symptoms of suicidality or psychosis may necessitate constant monitoring. Outpatients who have responded well to treatment can be followed less frequently (typically every one to three weeks, depending upon residual symptom severity) until they achieve remission. Once remission is achieved and adequate medication tolerability and adherence are established, office visits can be scheduled less frequently (eg, every one to six months), depending upon factors such as prior course of illness, including the duration of the most recent depressive episode; duration of current remission; and current level of psychosocial functioning.

Patients treated for bipolar major depression should also be monitored for symptoms of hypomania and mania. The course of illness is such that depressed patients can spontaneously develop concurrent symptoms of hypomania/mania (mixed features), or switch from depression to hypomania/mania, despite the use of antimanic drugs such as lithium, second-generation antipsychotics, and valproate. In addition, some patients may be vulnerable to hypomania/mania induced by antidepressants. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants", section on 'Risk of switching to mania'.)

Measurement based care is the systematic and quantitative assessment of symptoms with rating scales during treatment. Rating scales that can be used to monitor depressive syndromes include the Patient Health Questionnaire – Nine Item (PHQ-9) (table 4) [20] and the Quick Inventory of Depressive Symptomatology – Self-Report 16 Item (QIDS-SR_{16}) (table 5) [21,22], which are self-report instruments that have good psychometric properties and were developed for use in patients with unipolar major depression. Additional information about these instruments is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item'.)

Routine monitoring with rating scales may identify nonresponders, detect residual or prodromal symptoms, and help patients recognize improvement; however, the use of rating scales is not standard clinical practice. There is no evidence demonstrating that measurement

based care improves outcomes for bipolar major depression; this may be due in part to the scarce literature.

For patients who are treated with second-generation antipsychotics, especially quetiapine or olanzapine, we suggest monitoring metabolic parameters (table 6) to help patients avoid weight gain and the metabolic syndrome. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Metabolic syndrome'.)

Nonadherence — Clinicians should assess patients with bipolar disorder for nonadherence and address it when present [23]. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy".)

Adjunctive psychotherapy — Although the cornerstone of treatment for bipolar major depression is pharmacotherapy, we frequently prescribe adjunctive psychotherapy to:

- Educate patients about the illness, including symptoms, course of illness, treatment options, and sequelae
- Enhance acceptance of the diagnosis and adherence to pharmacotherapy
- Ameliorate symptoms
- Address comorbid psychiatric disorders (eg, personality disorders or substance use disorders)
- Promote self-management, which includes creating structure and adopting daily routines, being physically active, monitoring symptoms, and avoiding potentially mood destabilizing activities such as alcohol misuse and use of cannabis and other drugs
- Manage stress
- Address problems with relationships and work
- Develop a plan to cope with acute crises

Clinicians should educate and support all patients with bipolar major depression, as well as family members, caregivers, and supportive others, when appropriate. Using psychotherapy is consistent with recommendations in multiple treatment guidelines [9,19,23-27] and reviews [28,29]. Nevertheless, not all patients with bipolar major depression need psychotherapy, such as patients without comorbidity who are knowledgeable about bipolar disorder and adhere to treatment [30].

We often select cognitive-behavioral therapy (CBT) for bipolar major depression because it has been most widely studied, and in our experience is the most widely available. However, the specific choice of psychotherapy depends upon individual patient needs and preferences, as well as availability of services. As an example, patients with prominent dysfunctional thoughts and difficulties performing tasks may benefit from CBT [31], whereas patients with role disputes or role transitions may benefit from interpersonal psychotherapy [32], and patients with families that are characterized by frequent conflicts, high expressed emotion, and problems with communication and problem solving may benefit from family therapy [33,34]. Another reasonable option is group psychoeducation, which is readily comprehended by most patients and relatively easy to implement in most clinical settings.

Evidence supporting the use of psychotherapy for bipolar major depression includes a one-year randomized trial that compared adjunctive intensive psychotherapy with brief psychoeducation in patients with bipolar I or II major depression (n = 293) [35]. All patients were treated with pharmacotherapy. Patients assigned to intensive psychotherapy received CBT, family therapy, or interpersonal and social rhythm therapy on a weekly or biweekly basis for up to 30 sessions (mean number = 14) over nine months. Brief psychoeducation consisted of three sessions administered over six weeks. Recovery occurred in more patients treated with intensive psychotherapy than psychoeducation (64 versus 52 percent). In addition, functioning improved more with intensive psychotherapy. Study attrition for intensive psychotherapy and psychoeducation was comparable (36 and 31 percent). No statistically significant difference was observed in the rate of recovery among patients treated with CBT, family therapy, or interpersonal and social rhythm therapy.

Multiple randomized trials specifically support using CBT for bipolar major depression. As an example, a meta-analysis of four randomized trials (n = 305 patients) found that improvement of depressive symptoms was superior with adjunctive CBT than usual care, and the clinical effect was small to moderate [24,36].

Psychotherapy (eg, group psychoeducation or interpersonal social rhythm therapy) can also be effective for maintenance treatment of bipolar disorder [37]. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies".)

Comorbidity — Bipolar disorder is frequently accompanied by general medical and/or psychiatric comorbidity. (See "Bipolar disorder in adults: Clinical features", section on 'Comorbidity'.)

For patients with bipolar major depression and comorbidity (eg, substance use disorders), we suggest that clinicians attempt to treat both disorders concurrently [10,19,23,38].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (See "Patient education: Bipolar disorder (The Basics)" and "Patient education: Coping with high drug prices (The Basics)".)
- Beyond the Basics topics (See "Patient education: Bipolar disorder (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)".)

SUMMARY

- Treatment of acute bipolar depressive episodes begins with a psychiatric and general medical history, mental status and physical examination, and focused laboratory and imaging studies as clinically indicated. (See 'Initial assessment' above.)
- Hospitalization may be required for the safety and stabilization of severe bipolar depression, such as patients with suicidal ideation and behavior. Patients with moderate bipolar depression can be treated in a partial hospitalization or intensive outpatient treatment program. Most patients with bipolar depression can be managed in outpatient clinics. (See 'Setting' above.)

- In selecting pharmacotherapy for patients with bipolar major depression, clinicians should understand that they are likely selecting a maintenance regimen as well. For patients who receive a second-generation antipsychotic as monotherapy, efficacy is often comparable for low doses and high doses, whereas discontinuation of treatment due to adverse effects may occur less often with low doses. (See 'Pharmacotherapy' above.)

- The duration of an adequate medication trial for outpatients with bipolar I or II major depression is usually six to eight weeks. However, in clinically urgent situations, if there is minimal improvement within the first few weeks of treatment, it may be acceptable to decide that response is unlikely to occur. (See 'Duration of an adequate drug trial' above.)

- Clinicians should monitor depressive symptoms, treatment response and adverse effects, and adherence to treatment at each visit. (See 'Monitoring' above.)

- Although the cornerstone of treatment for bipolar major depression is pharmacotherapy, we often prescribe adjunctive psychotherapy. (See 'Adjunctive psychotherapy' above.)

- For patients with bipolar major depression and comorbidity, we suggest that clinicians attempt to treat all of disorders concurrently. (See 'Comorbidity' above.)

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