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Review Article

Treatment of acute bipolar depression

Yu-Chih Shen[a,b]*

[a]Department of Psychiatry, Buddhist Tzu Chi General Hospital, Hualien, Taiwan, [b]School of Medicine, Tzu Chi University, Hualien, Taiwan

Abstract

Depression is the predominant pole of disability in bipolar disorder and compared with mania/hypomania, has less systematic research guiding the development of treatment especially in its acute phase (acute bipolar depression). The deficiency in the management of the acute bipolar depression largely reflects the natural divergence of opinion resulting from significant knowledge gaps. At present, there are only 3 approved drug treatments for acute bipolar depression: olanzapine/fluoxetine combination, quetiapine (immediate or extended release), and lurasidone (monotherapy or adjunctive to lithium or valproate). Nonapproved agents and nonpharmacologic treatment such as lamotrigine, antidepressants, modafinil, pramipexole, ketamine, and electroconvulsive therapy are often prescribed to treat acute bipolar depression. This article discusses the challenges of diagnosing bipolar depression, and reviews above treatment options for acute bipolar depression.

Keywords: *Acute bipolar depression, Lurasidone, Olanzapine/fluoxetine combination, Quetiapine*

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Introduction

Bipolar disorder is a mental disorder that causes unusual changes in mood, energy, activity levels, and the ability to perform daily tasks [1]. The symptoms of bipolar disorder can manifest as manic, hypomanic, or major depressive episodes [1]. A manic episode is a period of extreme happiness, extrovert behavior, or extreme irritability associated with an increase in energy that usually lasts one or more weeks and can lead to hospitalization and cause problems at work or in personal life. A hypomanic episode has symptoms similar to those of a manic episode that lasts for at least 4 days and does not cause as many problems in the work or personal life as a manic episode. A major depressive episode typically lasts at least 2 weeks and includes several features of depression that interfere with work or relationships. A person in a major depressive episode may feel sad or desperate, withdraw from social situations and may also lose interest in the people and activities that they usually enjoy.

Bipolar disorder can occur in different ways depending on the type and intensity of mood episodes. Although there are inconsistencies in prevalence rates, studies suggest that the prevalence of manic/hypomanic episodes decreases and major depressive episodes increase at the extremities of life [1]. In fact, bipolar disorder can be conceptualized as a predominantly depressive disorder, based on the time during which patients are symptomatic of depression [2,3]. On average, the ratio of major depressive to manic/hypomanic episodes is 3:1 for bipolar I disorder (at least one manic episode necessary for diagnosis) [3], and the ratio of major depressive to hypomanic episodes is 39:1 for bipolar II disorder (at least one hypomanic episode and one major depressive episode necessary for diagnosis) [2].

Bipolar disorder is a disabling chronic disease in which depression usually presents a higher risk of long-term functional impairment than mania [4]. While early identification and treatment of bipolar disorder might improve prognosis, there are barriers to early intervention. For example, a delay of about 10 years between the first episode of illness and a diagnosis of bipolar disorder has been reported [5]. This is especially true for the many patients who initially present with major depressive episodes and much later with manic/hypomanic episodes, making a diagnosis of bipolar disorder impossible until later in the disease course.

Bipolar disorder is associated with a substantial burden of illness-related mental and medical problems. It is one of the most life-threatening psychiatric disorders since the life expectancy of patients with this disease is 9–13 years lower than that of individuals in the general population [6-8]. Increased mortality in patients is attributed to both unnatural (suicide and accidents) and natural (cardiovascular disorders, diabetes mellitus, chronic obstructive pulmonary disease, influenza, or

***Address for correspondence:**
Dr. Yu-Chih Shen,
Department of Psychiatry, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
E-mail: shengmp@gmail.com

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pneumonia) causes of death [7]. Of these causes, approximately 15%–19% of patients with bipolar disorder die from suicide [9]. The suicide rate of patients with this disease is 20–30 times higher than that of the general population [10]. Otherwise, the risk of suicide in mood disorders is 1.2 times higher in the case of bipolar disorder than in the case of major depressive disorder [11]. Suicidal behavior in patients with bipolar disorder occurs almost exclusively during the major depressive episode, less frequently in mixed-line mania, and very rarely during euphoric mania, hypomania, or euthymia [12].

Despite the devastating impact of bipolar depression on life, there has been a dearth of knowledge about its underlying etiology and the development of therapeutic strategies especially in its acute phase (acute bipolar depression). Currently, there are only 3 drug treatments approved for the acute bipolar depression: olanzapine/fluoxetine combination (OFC), quetiapine (immediate or extended release), and lurasidone (monotherapy or adjunctive to lithium or valproate). Nonapproved agents and nonpharmacologic treatment such as lamotrigine, antidepressants, modafinil, pramipexole, ketamine, and electroconvulsive therapy (ECT) are often prescribed to treat acute bipolar depression. This article discusses the challenges of diagnosing bipolar depression, and reviews above treatment options for acute bipolar depression.

Diagnosing bipolar depression

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition definition, patients with bipolar depression meet the criteria for a major depressive episode and a history of a specific episode meeting the criteria for mania or hypomania. Over-reliance on recall for the past episodes limits the reliability of diagnosis and largely explains the uncertainty inherent in the diagnosis of bipolar depression [13]. Repeated longitudinal assessment and the search for personal or family history of mania in assessing patients with acute depression are beneficial for improving diagnosis [14]. Otherwise, clear documentation in the medical record of an index episode of hypomania or mania may facilitate the management of bipolar depression.

With the exception of incomplete clinical history, many factors may complicate the diagnosis of bipolar depression, including patients' lack of insight, and the presence of high rates of psychiatric comorbidities such as substance use disorders and anxiety disorder [15]. Bipolar depression is often misdiagnosed as unipolar depression around 7.6% to 12.1% of cases have been reported [16]. Obtaining diagnostic certainty is crucial because the similarity of symptoms between bipolar depression and unipolar depression does not necessarily imply that the same treatments that are effective in one should be equally effective in the other [17].

Although there are no pathognomonic features of the major depressive episode in bipolar disorder compared to unipolar depressive disorder, some clinical features are more common in unipolar depressed patients who convert to bipolar disorder over time.

According to the International Society of Bipolar Disorders Working Group on Bipolar Depression, the greater likelihood of diagnosis of bipolar depression should be considered if ≥5 of the following characteristics are present [18] [Table 1]:

1. Family history: Positive for bipolar disorder
2. The course of illness: Early onset of first depression (<25 years), multiple prior episodes of depression (≥5 episodes)
3. Symptomatology: Hypersomnia and/or increased daytime napping, hyperphagia and/or increased weight, other atypical depressive symptoms such as leaden paralysis, psychomotor retardation, psychotic features and/or pathological guilt, and lability of mood.

Conversely, clinical features that have been consistently reported to be more frequent in unipolar depression patients than in those with bipolar depression if ≥4 of the following characteristics are present [18] [Table 1]:

1. Family history: Negative for bipolar disorder
2. The course of illness: Later onset of first depression (>25 years), long duration of current episode (>6 months)
3. Symptomatology: Initial insomnia/reduced sleep, appetite loss/weight loss, somatic complaints, and higher activity levels.

In the past, the management of bipolar depression was extrapolated from accumulated experience and research into the treatment of unipolar depression simply because there was no specific evidence for patients with bipolar depression. However, the appropriateness of these agents for patients with bipolar depression cannot be determined based on studies of unipolar depression [17]. Not only because the mechanisms by which these drugs act remain poorly understood, but also

Table 1: A probabilistic approach proposed for the diagnosis of bipolar depression in a person suffering from a major depressive episode without manifest previous mania episode (adapted from [18])

A probable diagnosis of bipolar depression should be considered if ≥5 of the following characteristics are present*	A probable diagnosis of unipolar depression should be considered if ≥4 of the following characteristics are present*
Family history	
Positive for bipolar disorder	Negative for bipolar disorder
Course of illness	
Early onset of first depression (<25 years)*	Later onset of first depression (>25 years)*
Multiple prior episodes of depression (≥5 episodes)*	Long duration of current episode (>6 months)*
Symptomatology	
Hypersomnia and/or increased daytime napping	Initial insomnia/reduced sleep
Hyperphagia and/or increased weight	Appetite loss/weight loss
Atypical depressive symptoms such as leaden paralysis	
Psychomotor retardation	Higher activity levels
Psychotic features and/or pathological guilt	Somatic complaints
Lability of mood	

*Confirmation of proposed numbers requires further study and consideration

because trials establishing the effectiveness of these agents generally exclude patients with bipolar depression.

Proven pharmacological treatment options

Despite the devastating impact of bipolar depression on life, there has been a dearth of knowledge about its underlying etiology and the development of therapeutic strategies especially in its acute phase (acute bipolar depression). Today, we only have three different approved agents to choose from: OFC, quetiapine (immediate or extended release), and lurasidone (monotherapy or adjunctive to lithium or valproate). Table 2 summarizes the proven studies of above three agents in acute bipolar depression [19-27].

There are a number of measures of the treatment effect that can be used to evaluate the clinical significance, but perhaps the most clinically intuitive is called number needed to treat (NNT) [28]. When considering adverse effects, the term number needed to harm (NNH) is used [28]. NNT is a count of how many people need to be treated in order for one person to benefit, while NNH is a measure of how many people need to be treated in order for one person to have a particular adverse effect.

Olanzapine/fluoxetine combination

The first approved treatment for acute bipolar depression is OFC. The initial study randomized patients with bipolar depression to receive OFC (6 and 25, 6 and 50, or 12 and 50 mg/day [n = 86]), olanzapine monotherapy (n = 370), or placebo (n = 377) for 8 weeks [19]. The OFC (mean daily dose 7.4 and 39.3) is superior to placebo in the response rate (56.1% vs. 30.4%, NNT = 4) and remission rate (48.8% vs. 24.5%, NNT = 5).

Olanzapine monotherapy (mean dose 9.7 mg/day) is also superior to placebo in the response rate (39.0% vs. 30.4%, NNT = 12) and remission rate (32.8% vs. 24.5%, NNT = 12) [19]. Later, a replication study revealed similar antidepressant efficacy for olanzapine (5–20 mg/day, n = 343) in a 6-week placebo-controlled trial (n = 171), the NNT for response (52.5% vs. 43.3%), and remission rate (38.5% vs. 29.2%) in this study is 11 [20].

OFC is associated with significant weight gain and metabolic dysregulation in patients with bipolar depression [19,29]. The proportion of patients with potentially clinically significant weight gain (≥7%) during OFC treatment is higher than in the placebo group (17.4% vs. 2.7%, NNH = 7) [29]. In addition, OFC is associated with an increased appetite that affects 12.8% of patients versus 5% of patients receiving placebo (NNH = 13) [29]. Furthermore, it has been shown that patients treated with OFC with bipolar depression experience clinically relevant diarrhea (18.6% vs. 6.6%, NNH = 9), tremor (9.3% vs. 2.4%, NNH = 15), asthenia (12.8% vs. 3.2%, NNH = 11), and dry mouth (16.3% vs. 6.1%, NNH = 10) when compared with placebo [29].

Quetiapine

Quetiapine has the largest evidence base among the 3 approved treatments for bipolar depression. Five placebo-controlled trials, involving >1800 patients with bipolar depression, demonstrated the efficacy of quetiapine [21-25].

The initial study randomized patients with bipolar depression to receive placebo (n = 181), quetiapine 300 mg (n = 181) or 600 mg/day (n = 180) for 8 weeks. Both doses of quetiapine resulted in a higher response rate (57.9% vs. 36.1%, NNT = 5) and remission rate (52.9% vs. 28.4%, NNT = 4) than placebo. Two subsequent studies used variations on the same design with the addition of lithium or paroxetine as an active control [23,24]. The results for the quetiapine and placebo groups are similar to the results of the previous study, but none of the active control groups differed from the placebo.

Sedation/somnolence has been shown to occur in approximately half of the patients enrolled in short-term bipolar depression studies compared to placebo (56.2% vs. 14.4%, NNH = 3) and it is the adverse event that most often led to premature discontinuation of treatment [21,22,25]. Quetiapine is also associated with weight gain in patients with bipolar depression (8.4% vs. 1.9%, NNH = 16) [21-25]. Furthermore, patients with bipolar depression treated with quetiapine have

Table 2: Proven drug studies for the treatment of acute bipolar depression

Treatment	Reference [number]	Dosage (mg)	Study duration (weeks)	Number treatment	Number placebo	NNT*
Olanzapine/fluoxetine	[19]	6-12/25-50	8	86	377	4
Olanzapine	[19]	5-20	8	370	377	12
	[20]	5-20	6	343	171	11
Quetiapine (immediate release)	[21]	300	8	181	181	4
	[21]	600	8	180	181	4
	[22]	300	8	155	161	7
	[22]	600	8	151	161	7
	[23]	300	8	245	121	10
	[23]	600	8	247	121	7
	[24]	300	8	255	129	7
	[24]	600	8	263	129	7
Quetiapine (extended release)	[25]	300	8	133	137	7
Lurasidone/lithium or valproate	[26]	20-120	6	183	165	7
Lurasidone	[27]	20-60	6	166	170	7
	[27]	80-120	6	169	170	7

*NNT for remission rate. NNT: Number needed to treat

been shown to have clinically relevant dry mouth (42.5% vs. 11.1%, NNH = 4), dizziness (16.8% vs. 8.0%, NNH = 12), constipation (9.9% vs. 4.5%, NNH = 19), extrapyramidal syndrome (8.6% vs. 3.3%, NNH = 19), and fatigue (9.6% vs. 6.0%, NNH = 28) when compared with placebo [21,22,25].

Lurasidone

The Program to Evaluate the Antidepressant Impact of Lurasidone (PREVAIL) evaluated the efficacy of lurasidone in bipolar depression. PREVAIL 1 recruited 348 depressed bipolar I patients treated with lithium or valproate who were randomized to receive adjunctive lurasidone 20–120 mg/day (n = 183) versus placebo (n = 165) for 6 weeks [26]. Compared to placebo, lurasidone is superior in response (57.0% vs. 42.2%, NNT = 7) and remission rates (50.3% vs. 35.4%, NNT = 7). The PREVAIL 2 study included 505 bipolar I depressed patients randomized to 6 weeks of lurasidone monotherapy (20–60 mg/day [n = 166] or 80–120 mg/day [n = 169]) or placebo (n = 170) [27]. Once again, compared to placebo, lurasidone is associated with a superior rates of response (52.0% vs. 30.2%, NNT = 5) and remission (40.9% vs. 24.7%, NNT = 7).

Adverse events are slightly more common at higher doses (80–120 mg/day) than at lower doses (20–60 mg/day) of lurasidone monotherapy compared with placebo: nausea (higher dose: 10.8% vs. 2.4%, NNH = 12; lower dose: 7.9% vs. 2.4%, NNH = 18), akathisia (higher dose: 17.4% vs. 7.7%, NNH = 11; lower dose: 10.4% vs. 7.7%, NNH = 39), somnolence (higher dose: 13.8% vs. 6.5%, NNH = 14; lower dose: 7.3% vs. 6.5%, NNH = 130), extrapyramidal syndrome (higher dose: 9.0% vs. 2.4%, NNH = 16 and lower dose: 4.9% vs. 2.4%, NNH = 40), and vomiting (higher dose: 6.0% vs. 1.8%, NNH = 24 and lower dose: 2.4% vs. 1.8%, NNH = 154) [30].

Lurasidone showed a low propensity to gain weight in studies of bipolar depression (monotherapy: 2.4% vs. 0.7%, NNH = 58; adjunctive to lithium or valproate: 3.1% vs. 0.3%, NNH = 36) [30].

Unproven pharmacological treatment options

Lamotrigine

Lamotrigine, a drug approved for the maintenance phase of bipolar I disorder, is not approved for acute bipolar depression. Calabrese *et al*. first demonstrated the efficacy of lamotrigine in the treatment of acute bipolar depression [31], but subsequent studies sponsored by Glaxo resulted in failed trials. However, a meta-analysis (lamotrigine monotherapy) and one placebo-controlled study (adjunctive to lithium) suggested possible efficacy in acute bipolar depression [32,33].

This meta-analysis enrolled 5 placebo-controlled trials (n = 1072) of variable study duration (7–10 weeks) and dosing regimens (fixed dose, 50 mg/day vs. 200 mg/day; flexible dosing 100–400 mg/day) [32]. The NNT for a response greater than what would have been observed on the placebo is 13. A planned subgroup analysis revealed a greater treatment effect in patients with severe depression (NNT = 7). Remission rates are inconsistent with lamotrigine relative to placebo. In another 8 weeks, placebo-controlled trial involving 124 lithium-maintained patients with acute bipolar depression, adjuvant therapy with 200 mg/day of lamotrigine resulted in a higher response rate than placebo (51.6% vs. 31.7%, NNT = 5) [33].

Many clinicians are concerned about the potential for a serious rash as an adverse effect of lamotrigine; however, the prevalence of severe rash in patients treated with lamotrigine is low (1 in 1000–2000), and placebo-controlled studies on lamotrigine for bipolar depression gave an NNH for a mild rash of 44 [34].

Antidepressants

Although antidepressants are commonly used for acute bipolar depression, they are generally lacking (apart from OFC) multicenter, randomized controlled trials demonstrating their efficacy. The initial study randomized patients with acute bipolar depression treated with lithium to double-blind adjunctive therapy with placebo (n = 43), paroxetine (n = 35), or imipramine (n = 39) [35]. Overall, this study showed that neither paroxetine nor imipramine had any advantage over placebo over any efficacy measure.

The largest placebo-controlled study of antidepressants in acute bipolar depression was performed by the STEP-BD study. Three hundred and thirty-six patients were randomized to receive treatment with mood stabilizer and adjuvant antidepressant therapy (bupropion or paroxetine) (n = 179) or placebo (n = 187) [36]. There were no group differences in the likelihood of individuals achieving sustainable recovery or other outcome measures.

A meta-analysis of 6 double-blind placebo-controlled studies of primarily adjuvant antidepressants in acute bipolar depression included 416 patients taking antidepressants and 610 taking a placebo [37]. This analysis concluded that antidepressants were not statistically superior to placebo or other current standard treatments for acute bipolar depression. The NNT versus placebo for response is 29.

The main adverse effects associated with antidepressant use vary by antidepressant class and sometimes by medication in each class. On a warning note, although the risk of a mood change with antidepressants is relatively low (NNH vs. placebo for a mood switch is 200), a switch to mania can have profound negative psychosocial consequences [37].

Modafinil

Modafinil and its active R-enantiomer, armodafinil are approved for treating narcolepsy, obstructive sleep apnea, and shift-work sleep disorder. Previous studies have been conducted to evaluate the efficacy and safety of adjunctive modafinil or armodafinil in bipolar depression, which is often characterized by excessive drowsiness and fatigue [38-40]. The first report randomized 85 patients with bipolar depression with an inadequate response to a mood stabilizer, then added either placebo (n = 44) or modafinil (n = 41) for 6 weeks [40]. The response and remission rates are significantly higher in the modafinil group than in the placebo group (44% vs. 23%, 39% vs. 18%, NNT = 5, respectively). During the 6-week study period, there is no difference between groups in cases of hypomania or mania (15% vs. 11%, NNH = 31).

Subsequent studies on armodafinil have yielded inconsistent results. Two studies evaluate the efficacy and safety of armodafinil when used adjunctively in patients with bipolar depression [38,39]. Positive results are only obtained in a few primary outcome measures at a few moments. Armodafinil is generally well tolerated and is not associated with increased incidence and/or severity of suicidality, depression or mania, or changes in metabolic profile measures.

Pramipexole

Pramipexole is a D2/D3 dopamine receptor agonist approved for the treatment of Parkinson's disease and restless legs syndrome. Two small studies have examined the efficacy of pramipexole in the treatment of bipolar depression [41,42]. The first report randomized 22 patients with bipolar depression with an inadequate response to existing mood stabilizers, and then added either pramipexole (n = 12) or placebo (n = 10) for 6 weeks [41]. The response rate is significantly higher in the pramipexole group than in the placebo group (67% vs. 20%, NNT = 2), but not in the remission rate (20% vs. 16%, NNT = 30). Another report randomized 21 patients with bipolar depression with a similar study design and gave a higher response and remission rates in the pramipexole group than in the placebo group (60% vs. 9%, NNT = 2; 40% vs. 9%, NNT = 3, respectively) [42]. Pramipexole is generally well tolerated and is not associated with an increased incidence of hypomania/mania.

Ketamine

Ketamine is an anesthetic drug that acts as an N-methyl-D-aspartate receptor antagonist and targets glutamate. Rapid resolution of depression and suicidal ideation after single intravenous infusions of low doses of ketamine has been reported in patients with bipolar depression [43-45]. A meta-analysis of 3 double-blind placebo-controlled studies in 69 patients with bipolar depression showed a significant improvement in mean primary depression scores in the ketamine group versus the placebo group [46]. The onset of antidepressant effects is observed within 40 min and is maintained for several days. The NNT versus placebo for response is 1.5. None of the individuals had serious side effects, and the side effects are similar between the ketamine and placebo groups. The results for ketamine are very encouraging, but there is still potential that some of the putative antidepressant effects may be due to the small sample size.

Nonpharmacological treatment options

Electroconvulsive therapy

ECT is the longest-standing biologic intervention in psychiatry and remains the most effective treatment available for major depressive disorder or bipolar disorder [47]. Regarding bipolar disorder, ECT is one of the few treatments with therapeutic properties in the acute treatment of bipolar depression or mania [47]. This first multicenter randomized controlled trial was conducted in 73 bipolar disorder patients with treatment-resistant depression [48]. These patients were randomly assigned to receive either ECT or algorithm-based pharmacological treatment. The outcome was evaluated by blind evaluators after 6 weeks. The response rate was significantly higher in the ECT group than in the group that received algorithm-based pharmacological treatment (73.9% vs. 35.0%, NNT = 3). However, there was no difference in the remission rate, suggesting that ECT may have been terminated before full benefit.

The main limitations of ECT use are its side effects and relapse rates. There is always the concern that treating the patient in bipolar depression with ECT will cause hypomania or mania. The incidence of hypomania/mania in patients with bipolar depression during ECT is relatively frequent at 24.8% [49]. Some practitioners will continue treatment if the symptoms are mild. Some would end the course of ECT, observe the patient, and institute a pharmacological regime if severe manic symptoms appeared. In addition, long-term adverse effects of ECT on memory have been documented. Previous studies have shown that methods of administering ECT differ considerably in their impact on the degree of retrograde amnesia observed 6 months after treatment [50-52]. For example, the introduction of ultrabrief pulse stimulation, when coupled with the unilateral placement of the right electrode, significantly reduces cognitive effects at all time points [52]. Furthermore, relapse is common following ECT-induced remission. Recent studies indicate that approximately 50% of remitting patients recur despite prolonged aggressive treatment with pharmacologic agents or ECT [53,54]. However, the longevity of benefits appears to be a general problem in the management of depression, regardless of whether pharmacological agents or ECT are received [55].

Are these treatment options approved for maintenance treatment?

At present, lithium, lamotrigine, olanzapine, aripiprazole, quetiapine, long-acting injectable risperidone and aripiprazole, and ziprasidone (in combination with lithium or valproate) are approved for maintenance therapy for bipolar disorder. Most patients with bipolar disorder have a polarity, relapsing more often in mania or depression [56]. The polarity of the patient influences the choice of maintenance treatment. For patients with depressive polarity, the recommended therapies are lamotrigine or quetiapine [56].

Conclusion

Bipolar depression remains a clinical challenge. Treatment options are limited especially in managing the acute phase of bipolar depression. At present, there are only three approved drug treatments including OFC, quetiapine (immediate or extended release), and lurasidone (monotherapy or adjunctive to lithium or valproate). All three agents have similar efficacy profiles, but they differ in terms of tolerability. Nonapproved agents and nonpharmacologic treatment such as lamotrigine, antidepressants, modafinil, pramipexole, ketamine, and ECT are often prescribed to treat acute bipolar depression. To individualize treatment decisions, it will be necessary to consider the different potential adverse effects that are more likely to occur with each treatment. While the number of treatment options for bipolar depression has been significantly lower than for the manic and maintenance phases, trials of new effective side effects are warranted in the future.

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Conflicts of interest

There are no conflicts of interest.

References

1. Anderson IM, Haddad PM, Scott J. Bipolar disorder. BMJ 2012;345:e8508.
2. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261-9.
3. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530-7.
4. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: A prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005;62:1322-30.
5. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: How far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003;64:161-74.
6. Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life span in bipolar disorder. J Affect Disord 2015;180:142-7.
7. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: A Swedish national cohort study. JAMA Psychiatry 2013;70:931-9.
8. Chang CK, Hayes RD, Perera G, Broadbent MT, Fernandes AC, Lee WE, et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. PLoS One 2011;6:e19590.
9. Abreu LN, Lafer B, Baca-Garcia E, Oquendo MA. Suicidal ideation and suicide attempts in bipolar disorder type I: An update for the clinician. Rev Bras Psiquiatr 2009;31:271-80.
10. Pompili M, Gonda X, Serafini G, Innamorati M, Sher L, Amore M, et al. Epidemiology of suicide in bipolar disorders: A systematic review of the literature. Bipolar Disord 2013;15:457-90.
11. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry 2011;68:1058-64.
12. Schaffer A, Isometsä ET, Tondo L, Moreno DH, Turecki G, Reis C, et al. International Society for Bipolar Disorders Task Force on Suicide: Meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar Disord 2015;17:1-6.
13. Takayanagi Y, Spira AP, Roth KB, Gallo JJ, Eaton WW, Mojtabai R, et al. Accuracy of reports of lifetime mental and physical disorders: Results from the Baltimore Epidemiological Catchment Area Study. JAMA Psychiatry 2014;71:273-80.
14. Bowden CL. Strategies to reduce misdiagnosis of bipolar depression. Psychiatr Serv 2001;52:51-5.
15. Schaffer A, Cairney J, Veldhuizen S, Kurdyak P, Cheung A, Levitt A, et al. A population-based analysis of distinguishers of bipolar disorder from major depressive disorder. J Affect Disord 2010;125:103-10.
16. Li CT, Bai YM, Huang YL, Chen YS, Chen TJ, Cheng JY, et al. Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: Cohort study. Br J Psychiatry 2012;200:45-51.
17. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry 2010;11:81-109.
18. Mitchell PB, Goodwin GM, Johnson GF, Hirschfeld RM. Diagnostic guidelines for bipolar depression: A probabilistic approach. Bipolar Disord 2008;10:144-52.
19. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079-88.
20. Tohen M, McDonnell DP, Case M, Kanba S, Ha K, Fang YR, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. Br J Psychiatry 2012;201:376-82.
21. Calabrese JR, Keck PE Jr., Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162:1351-60.
22. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: A double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006;26:600-9.
23. McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry 2010;71:163-74.
24. Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry 2010;71:150-62.
25. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J Affect Disord 2010;121:106-15.
26. Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: A randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014;171:169-77.
27. Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, et al. Lurasidone monotherapy in the treatment of bipolar I depression: A randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014;171:160-8.
28. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract 2013;67:407-11.
29. Citrome L. Olanzapine-fluoxetine combination for the treatment of bipolar depression. Expert Opin Pharmacother 2011;12:2751-8.
30. Citrome L, Ketter TA, Cucchiaro J, Loebel A. Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. J Affect Disord 2014;155:20-7.
31. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry 1999;60:79-88.
32. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: Independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry 2009;194:4-9.
33. van der Loos ML, Mulder PG, Hartong EG, Blom MB, Vergouwen AC, de Keyzer HJ, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: A multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:223-31.
34. Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, et al. Lamotrigine in the acute treatment of bipolar depression: Results of five double-blind, placebo-controlled clinical trials. Bipolar Disord 2008;10:323-33.

35. Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906-12.
36. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007;356:1711-22.
37. Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: A systematic review and meta-analysis. J Clin Psychiatry 2011;72:156-67.
38. Calabrese JR, Frye MA, Yang R, Ketter TA; Armodafinil Treatment Trial Study Network. Efficacy and safety of adjunctive armodafinil in adults with major depressive episodes associated with bipolar I disorder: A randomized, double-blind, placebo-controlled, multicenter trial. J Clin Psychiatry 2014;75:1054-61.
39. Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA, et al. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: A randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry 2010;71:1363-70.
40. Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr., Walden J, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry 2007;164:1242-9.
41. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004;161:564-6.
42. Zarate CA Jr., Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, et al. Pramipexole for bipolar II depression: A placebo-controlled proof of concept study. Biol Psychiatry 2004;56:54-60.
43. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010;67:793-802.
44. Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA, et al. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. Transl Psychiatry 2014;4:e469.
45. Zarate CA Jr., Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial. Biol Psychiatry 2012;71:939-46.
46. Parsaik AK, Singh B, Khosh-Chashm D, Mascarenhas SS. Efficacy of ketamine in bipolar depression: Systematic review and meta-analysis. J Psychiatr Pract 2015;21:427-35.
47. Rasmussen K. The practice of electroconvulsive therapy: Recommendations for treatment, training, and privileging (second edition). J ECT 2002;18:58-9.
48. Schoeyen HK, Kessler U, Andreassen OA, Auestad BH, Bergsholm P, Malt UF, et al. Treatment-resistant bipolar depression: A randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. Am J Psychiatry 2015;172:41-51.
49. Bost-Baxter E, Reti IM, Payne JL. ECT in bipolar disorder: Incidence of switch from depression to hypomania or mania. J Depress Anxiety 2012;1:123.
50. Sackeim HA. Autobiographical memory and electroconvulsive therapy: Do not throw out the baby. J ECT 2014;30:177-86.
51. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M, et al. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 2007;32:244-54.
52. Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul 2008;1:71-83.
53. Jelovac A, Kolshus E, McLoughlin DM. Relapse following successful electroconvulsive therapy for major depression: A meta-analysis. Neuropsychopharmacology 2013;38:2467-74.
54. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, et al. Continuation electroconvulsive therapy vs. pharmacotherapy for relapse prevention in major depression: A multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 2006;63:1337-44.
55. Rush AJ. STAR*D: What have we learned? Am J Psychiatry 2007;164:201-4.
56. Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E, et al. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur Neuropsychopharmacol 2012;22:339-46.