IN THE NAME OF GOD

TREATMENT OF BIPOLAR DEPRESSION

PRESENTED BY
MEHRAN ZARGHAMI

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Department of Psychiatry, Faculty of Medicine

&

Psychiatry and behavioral sciences research center, Addiction Institute;

Mazandaran University of Medical Sciences

The management of bipolar depression is complex & should be differentiated from management of unipolar depression.

–Nivoli, Alessandra M.A., Colom, Francesc, Murru, Andrea, Pacchiarotti, Isabella, Castro-Loli, Piero, González-Pinto, Ana, Fountoulakis, Kostas N., Vieta, Eduard, Journal of Affective Disorders. New treatment guidelines for acute bipolar depression: A systematic review. Journal of Affective Disorders 2011: 129, (1–3):14-26

The prevalence of

manic/hypomanic episodes

decreases

&

major depressive episodes

increase

at the extremities of life.

-Anderson IM, Haddad PM, Scott J. Bipolar disorder. BMJ. 2012;345:e8508.

On average, the ratio of major depressive to manic/hypomanic episodes is

3:1 for BID,

and the ratio of major depressive to hypomanic episodes is

39:1 for BIID.

- 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.

Depression is the

predominant pole of disability

in BMD.

- Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18

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.

- 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.

- 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.

- 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.

Increased mortality in patients is attributed to both

unnatural (suicide & accidents) & natural (cardiovascular disorders, diabetes mellitus, chronic obstructive pulmonary disease, influenza, or pneumonia) causes of death.

-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.

Of these causes, approximately

15%–19%

of patients with

BMD die from

suicide.

-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.

The suicide rate is 20–30 times higher than that of the general population.

The risk of suicide is 1.2 times higher in the case of BMD than in the case of MDD.

Suicidal behavior in patients with BMD occurs almost exclusively during the MD episode,

less frequently in mixed-line mania, and very rarely during euphoric mania, hypomania, or euthymia.

-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. [PubMed] [Google Scholar]

-Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry. 2011;68:1058–64. [PubMed] [Google Scholar]

-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.

- 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. 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 BMD impossible until later in the disease course.

-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.

DIAGNOSIS OF BIPOLAR DEPRESSION

Bipolar depression is often misdiagnosed as unipolar depression around 7.6% to 12.1% of cases have been reported.

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.

. 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. [PubMed] [Google Scholar]

- 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.

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.

Repeated longitudinal assessment and the search for personal or family history of mania in assessing patients with acute depression are beneficial for improving diagnosis.

Otherwise, clear documentation in the medical record of an index episode of hypomania or mania may facilitate the management of bipolar depression.

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.

Bowden CL. Strategies to reduce misdiagnosis of bipolar depression. Psychiatr Serv. 2001;52:51–5.

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.

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.

Although there are

no pathognomonic features

of the major depressive episode in MBD compared to MDD,

some clinical features

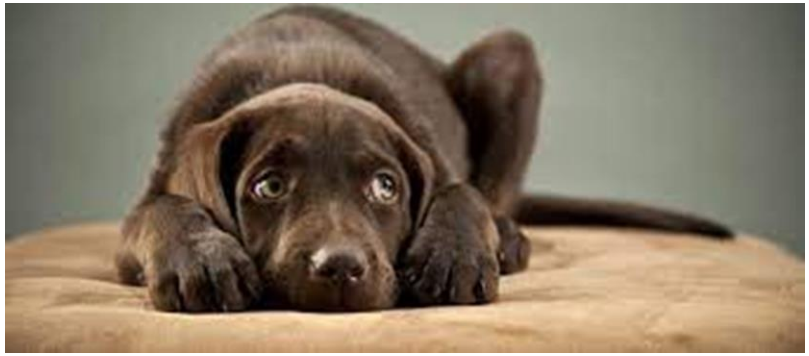
are more common in unipolar depressed patients who convert to bipolar disorder over time.

Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18

A PROBABLE DIAGNOSIS OF BMD SHOULD BE CONSIDERED IF ≥5 OF THE FOLLOWING CHARACTERISTICS ARE PRESENT	A PROBABLE DIAGNOSIS OF MDD SHOULD BE CONSIDERED IF ≥4 OF THE FOLLOWING CHARACTERISTICS ARE PRESENT
Family history	
Positive for BMD	Negative for BMD
Course of illness	
Early onset of first depression (<25 years)	Later onset of first depression (>25 years)
Multiple prior episodes of depression episodes (≥5)	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	

Mitchell PB, Goodwin GM, Johnson GF, Hirschfeld RM. Diagnostic guidelines for bipolar depression: A probabilistic approach. Bipolar Disord. 2008;10:144–52.

PROVEN PHARMACOLOGICAL TREATMENT OPTIONS



Currently, there are only 3 drug treatments approved for the acute bipolar depression:

olanzapine/fluoxetine combination (OFC),

quetiapine (immediate or extended release),

lurasidone (monotherapy or adjunctive to lithium or valproate).

Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18

MEASURES OF THE TREATMENT EFFECT

There are a number of measures of the treatment effect that can be used to evaluate the clinical significance:

- number needed to treat (NNT): a count of how many people need to be treated in order for one person to benefit

- number needed to harm (NNH): a measure of how many people need to be treated in order for one person to have a particular adverse effect

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.

Olanzapine/fluoxetine combination (OFC)

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.

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)

remission rate (48.8% vs. 24.5%, NNT = 5)

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.

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.

Olanzapine monotherapy (mean dose 9.7 mg/day) is also superior to placebo in the:

response rate (39.0% vs. 30.4%, NNT = 12)

remission rate (32.8% vs. 24.5%, NNT = 12).

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):

response rate (52.5% vs. 43.3%, NNT = 11)

remission rate (38.5% vs. 29.2%, NNT = 11)

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.

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.

OFC is associated with significant **weight gain** and **metabolic dysregulation** in patients with bipolar depression.

diarrhea (18.6% vs. 6.6%, NNH = 9),

tremor (9.3% vs. 2.4%, NNH = 15),

asthenia (12.8% vs. 3.2%, NNH = 11),

dry mouth (16.3% vs. 6.1%, NNH = 10)

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.

Citrome L. Olanzapine-fluoxetine combination for the treatment of bipolar depression. Expert Opin Pharmacother. 2011;12:2751–8.

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.

-Calabrese JR, Keck PE, Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH. 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.

-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.

-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.

-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.

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.

-Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18

Two subsequent studies used variations on the same design with the addition of

lithium or paroxetine as an active control.

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.

-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.

-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.

Sedation/somnolence

has been shown to occur in approximately

half of the patients

and it is the adverse event that most often led to premature discontinuation of treatment.

-Calabrese JR, Keck PE, Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH. 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.

-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. -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.

weight gain in patients with bipolar depression (8.4% vs. 1.9%, NNH = 16).

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),

fatigue (9.6% vs. 6.0%, NNH = 28) .

-Calabrese JR, Keck PE, Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH. 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. [PubMed] [Google Scholar]

-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. [PubMed] [Google Scholar]

-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. [PubMed] [Google Scholar]

-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. [PubMed] [Google Scholar]

-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.

Lurasidone

- 20 mg PO qDay initially; may increase dose if needed, not to exceed 120 mg/day
- In monotherapy study, higher dose range (80-120 mg/day) did **not** provide additional efficacy compared to the lower dose range (20-60 mg/day)

https://reference.medscape.com/drug/latuda-lurasidone-999605

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).

Another study: a superior rates of

response (52.0% vs. 30.2%, NNT = 5)

remission (40.9% vs. 24.7%, NNT = 7).

-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.

-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.

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),

vomiting (higher dose: 6.0% vs. 1.8%, NNH = 24 and lower dose: 2.4% vs. 1.8%, NNH = 154).

-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.

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).

-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.

UNPROVEN PHARMACOLOGICAL TREATMENT OPTIONS

Lamotrigine

Lamotrigine, a drug approved for the maintenance phase of BID, is not approved for acute bipolar depression.

Calabrese et al. first demonstrated the efficacy of lamotrigine in the treatment of acute bipolar depression,

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.

-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.

-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.

-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.

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).

-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.

Other Anticonvulsants

Evidence for

valproate & other anticonvulsants

(other than lamotrigine)

is limited.

Gabapentin & levetiracetam

are ineffective.

-Boland R, Verduin M. Kaplan and Sadock's Synopsis of Psychiatry. 2022. WoltersKluwer

Lithium

There is limited evidence for lithium in Bipolar depression.

-Boland R, Verduin M. Kaplan and Sadock's Synopsis of Psychiatry. 2022. WoltersKluwer

Antidepressants

Adjuvant to mood stabilizer: neither paroxetine nor imipramine nor bupropion had any advantage over placebo over any efficacy measure.

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. This analysis concluded that antidepressants were not statistically superior to placebo or other current standard treatments for acute bipolar depression. The NNT vs. placebo for response is 29.

-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. [PubMed] [Google Scholar]

-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. [PubMed] [Google Scholar]

-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.

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.

-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.

May induce

rapid cycling, mania, or hypomania.

The risk of inducing mania seems highest for

TCAs, MAOIs & SNRIs.

-Boland R, Verduin M. Kaplan and Sadock's Synopsis of Psychiatry. 2022. WoltersKluwer

Modafinil

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.

-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. [PubMed] [Google Scholar]

-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. [PubMed] [Google Scholar]

-Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE, Jr, Walden J. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry. 2007;164:1242–9.

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.

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).

-Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE, Jr, Walden J. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry. 2007;164:1242–9.

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:

Positive results are only obtained in a few primary outcome measures at a few moments.

-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. [PubMed] [Google Scholar]

-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.

Armodafinil is generally well tolerated &

is not associated with increased incidence and/or severity of suicidality, depression or mania, or changes in metabolic profile measures.

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Pramipexole

A 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.

The response rate was 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).

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.

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).

-Zarate CA, Jr, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD. Pramipexole for bipolar II depression: A placebo-controlled proof of concept study. Biol Psychiatry. 2004;56:54–60.

Pramipexole is generally well tolerated and is not associated with an increased incidence of hypomania/mania.

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Ketamine

Ketamine, is an anesthetic that has also been used for

many years

to treat depression.

Johns Hopkins Medicine. Esketamine for Treatment-Resistant Depression. Available From: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/esketamine-for-treatment-resistant-depression

Rapid resolution

of

depression & suicidal ideation

after single intravenous infusions of low doses of ketamine has been reported in patients with bipolar depression.

-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. [PMC free article] [PubMed] [Google Scholar]

-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. [PMC free article] [PubMed] [Google Scholar]

-Zarate CA, Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A. Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial. Biol Psychiatry. 2012;71:939–46.

The effect seems to be short-lived, and wears off after between 2-7days.

There are little data on longer term treatment as well as concern over associated adverse effects.

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Esketamine

(a more potent version of ketamine)

is made from ketamine.

Johns Hopkins Medicine. Esketamine for Treatment-Resistant Depression. Available From: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/esketamine-for-treatment-resistant-depression

More recently, esketamine in a

nasal spray formulation

was approved by the FDA for

treatment-resistant depression.

Given the abuse risk, it is only availably through a restricted distribution system.

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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.

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.

-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.

None of the individuals had

serious side effects,

& the side effects are similar between the ketamine and placebo groups.

-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.

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.

-Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18

Omega-3-fatty acid

Omega-3-fatty acid adjunctive therapy has conflicting evidence.

-Boland R, Verduin M. Kaplan and Sadock's Synopsis of Psychiatry. 2022. Wolters Kluwer

NONPHARMACOLOICAL TREATMENT OPTIONS

Electroconvulsive therapy (ECT)

Regarding bipolar disorder, ECT is one of the few treatments with therapeutic properties in the acute treatment of bipolar depression or mania.

- Rasmussen K. The practice of electroconvulsive therapy: Recommendations for treatment, training, and privileging (second edition) J ECT. 2002;18:58–9.

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%.

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.

-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.

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.

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.

-Sackeim HA. Autobiographical memory and electroconvulsive therapy: Do not throw out the baby. J ECT. 2014;30:177–86. [PMC free article] [PubMed] [Google Scholar]

-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. [PubMed] [Google Scholar]

-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.

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.

-Jelovac A, Kolshus E, McLoughlin DM. Relapse following successful electroconvulsive therapy for major depression: A meta-analysis. Neuropsychopharmacology. 2013;38:2467–74. [PMC free article] [PubMed] [Google Scholar]

-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.

In cases which

strong suicidal tendency

presents.

-Boland R, Verduin M. Kaplan and Sadock's Synopsis of Psychiatry. 2022. Wolters Kluwer

ARE THESE TREATMENT OPTIONS APPROVED FOR MAINTENANCE TREATMENT?

At present,

lithium,

lamotrigine,

olanzapine,

aripiprazole,

quetiapine,

long-acting injectable risperidone & aripiprazole,

ziprasidone (in combination with lithium or valproate)

are approved for maintenance therapy for BMD.

-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.

VALPROATE

Limited evidence supports the efficacy of valproate in the long-term treatment of bipolar disorder. Clinicians and patients should consider

acceptability & tolerability

profile when choosing between lithium and valproate—their combination or other agents—as long-term treatment for bipolar disorder.

-Cipriani A, Reid K, Young AH, Macritchie K, John Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database of Systematic Reviews Review – Intervention. Version published: 17 October 2013. https://doi.org/10.1002/14651858.CD003196.pub2

VALPROATE

Valproate was more effective than placebo in preventing new BMD episodes of mania or depression, and not significantly different from lithium, second-generation antipsychotics, or other anticonvulsants.

Overall benefits were nonsignificantly greater versus mania than bipolar depression.

-Yee CS, Vázquez GH, Hawken ER, Biorac A, Tondo L, Baldessarini RJ. Long-Term Treatment of Bipolar Disorder with Valproate: Updated Systematic Review and Meta-analyses. Harvard Review of Psychiatry: 5/6 2021. 29(3):188-95. doi: 10.1097/HRP.0000000000000292

Lithium, carbamazepine & valproic acid alone or in combination

are the most widely used agents for the long-term treatment of BMD.

-Boland R, Verduin M. Kaplan and Sadock's Synopsis of Psychiatry. 2022. Wolters Kluwer

Most patients with BMD have a polarity, relapsing more often in mania or depression.

The polarity of the patient influences the choice of maintenance treatment.

For patients with depressive polarity, the recommended therapies are:

lamotrigine or quetiapine.

-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.

CONCLUSION

Currently, there are only 3 drug treatments approved for the acute bipolar depression:

olanzapine/fluoxetine combination (OFC),

quetiapine (immediate or extended release),

lurasidone (monotherapy or adjunctive to lithium or valproate).

Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18

Nonapproved agents and nonpharmacologic treatment such as lamotrigine, antidepressants, modafinil, pramipexole, ketamine, and ECT are often prescribed to treat acute bipolar depression.

-Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18

To individualize treatment decisions, it will be necessary to consider the different potential

adverse effects

that are more likely to occur with each treatment.

-Shen Y-C. Treatment of acute bipolar depression. Tzu Chi Med J. 2018 Jul-Sep; 30(3): 141–147. doi: 10.4103/tcmj.tcmj_71_18