

The Challenge of Treatment in Bipolar Depression: Evidence from Clinical Guidelines, Treatment Recommendations and Complex Treatment Situations

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Abstract

Bipolar depression and its clinical presentation is a frequent but complex psychiatric disease. Despite the high prevalence and the clinical and economic relevance of bipolar depression, few treatments are proven to be highly and consistently effective. In practice, the treatment of bipolar depression typically includes complex treatment decision-making. The best evidence for a pharmacological treatment exists for quetiapine. Alternatives with limitations are lamotrigine (also in the combination with lithium), carbamazepine and olanzapine. The effectiveness and recommendation of antidepressants in the treatment of bipolar depression remains controversial. Initially, depressive episodes should be treated with one of the

named substances with antidepressant properties. In non-responders, a combination of lithium and lamotrigine, or antidepressants in combination with either lithium, an antiepileptic drug or atypical antipsychotics, may be necessary. If a depressive episode occurs under ongoing mood-stabilizing treatment, combination treatments of different substances, even with antidepressants, can be necessary. In the case of treatment-resistant depressive episodes, complex treatment strategies (combination therapies, MAO inhibitors) should be considered. This review describes the treatment recommendations of different guidelines for bipolar depression and emphasizes their differences. Furthermore, alternative pharmacological treatment strategies and complex treatment situations are discussed.

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Introduction

The treatment of depressive episodes in bipolar disorder is an important challenge for any psychiatrist. Depressive episodes predominate in bipolar disorder and are related to a high burden of disease [1]. However, there is limited evidence provided for the treatment options available in bipolar depression compared to unipolar depression [2]. Additionally, there is a certain diagnostic gap, as the diagnosis of bipolar depression is often delayed, or even misdiagnosed as unipolar depression. Following incorrect diagnosis as unipolar depression, there is often suboptimal treatment [3]. Looking at the BRIDGE study, roughly 12–59% of acutely depressed patients were diagnosed as bipolar, depending on the criteria applied [4]. There are important differences in the symptomatology and epidemiology of bipolar and unipolar depression, which help to discriminate between the 2 entities. For example, patients suffering from bipolar depression show a significantly higher rate of suicide attempts and com-

pleted suicides compared to unipolar depression [5]. Furthermore, patients with bipolar depression show an earlier onset of disease, bipolar depression is equally distributed between sexes, there is a higher rate of comorbidity, and there is a higher frequency of episodes as well as a higher number of atypical depressive symptoms such as hyperphagia, hypersomnia and a changed pattern of reaction to affective stimuli [6]. The differences between these 2 entities of depression are described briefly in **Table 1** [7]. There is also the entity of recurrent brief depression (RBD) with a relevant risk of suicidal behaviour and significant clinical impairment that also appears in bipolar disorders [8]. The recommendations for the treatment of bipolar depression given by the guidelines include pharmacological and non-pharmacological (e.g., psychotherapy, electroconvulsive therapy) therapy strategies. A detailed patient history of disease, especially the dominant mood pole, is essential before making a treatment decision [9]. The summary given in this article is limited to

Table 1 Differences between unipolar and bipolar depression.

	Unipolar Depression	Bipolar Depression
epidemiology	<ul style="list-style-type: none"> – life time prevalence: 16–18% [59] – 12 month-prevalence: 6.9% [60] – gender ratio f:m = 2:3 [60] 	<ul style="list-style-type: none"> – life time prevalence (bipolar disorder): 1–2% [59] – 12 month-prevalence (bipolar disorder): 0.9% [60] – gender ratio (bipolar disorder) f:m = 1:2 [60]
course of the disease	<ul style="list-style-type: none"> – age of onset: 30–40 years [61] – 10% onset after the age of 60 [61] 	<ul style="list-style-type: none"> – age of onset (bipolar disorder I + II): 15–24 years [1, 62] – delay of first treatment 5–10 years [63] – in 50% beginning with a depressive episode [61] – with a first manic/hypomanic episode following in 5 years after onset [61] – in a 12 year follow-up, patients with bipolar disorder were symptomatic 47.3% of the time: 31.9% in a depressive episode, 8.9% in a manic episode, and 5.9% in a mixed episode [64]
differences in course and symptomatology [6]	<ul style="list-style-type: none"> – usual onset after the age of 30 – longer duration of episodes during lifetime – insomnia (especially early morning awakening) and reduced appetite – loss of energy – diminished libido 	<ul style="list-style-type: none"> – family history of bipolar depression – onset of symptoms before the age of 25 – more frequent episodes with a shorter duration (i. e., <6 months) – hypersomnia and hyperphagia are more common in bipolar depression as well as presence of psychosis – diurnal mood variation
prognosis and complications	<ul style="list-style-type: none"> – life-time prevalence for suicide attempts: 15.9% [66] 	<ul style="list-style-type: none"> – life-time prevalence for suicide attempts [5]: BP I: 36.3%, BP II 32.4% – prevalence for completed suicide: 4–19% [65]

pharmacological treatment recommendations. These recommendations are mainly based on the German S3 guideline [10], the recently published Canadian guideline [11], the English NICE (National Institute for Health and Care Excellence) guideline [12], as well as the guideline of the WFSBP (The World Federation of Societies of Biological Psychiatry [13]). Furthermore, recommendations for complex treatment situations are given [14].

Effectiveness of the Pharmacological Therapy Strategies



Antidepressants

The treatment of bipolar depression with antidepressants is a common strategy, especially in Europe. However, there is little evidence from controlled trials. RCTs with antidepressants for treatment of bipolar depression are rare, vary in size and quality and their findings are inconsistent. Overall there are positive results for the use of fluoxetine and imipramine compared to placebo [15], as well as treatment with venlafaxine monotherapy compared with lithium monotherapy [16]. Conversely, several studies examining treatment with antidepressant drugs in bipolar depression showed no significant effect. Looking, e. g., at a recent methodologically high quality study (EMBOLDEN II), there was no difference between paroxetine treatment and placebo in the treatment of bipolar depression [17]. Sachs and colleagues found that combined treatment with the addition of either bupropion or paroxetine to a current treatment with lithium, valproate, carbamazepine or an atypical antipsychotic did not have a better treatment effect than adding placebo [18]. In contrast, a combination treatment of olanzapine and fluoxetine showed higher antidepressive effectiveness, compared to monotherapy with one of these medications alone [19].

Basically, it is necessary and helpful to distinguish between classes of antidepressants regarding their effectiveness in bipolar depression. However, there are only limited data for this purpose. Potentially, TCAs, venlafaxine and MAO inhibitors seem to be more effective than SSRIs or bupropion, which otherwise may increase the risk of switch into mania. There is also a discussion that antidepressants should be used primarily in patients with low serum lithium levels to have an additional positive effect [20].

Looking at a recent meta-analysis, no significant difference between antidepressants or placebo in the treatment of bipolar depression could be demonstrated. At best there was a statistical trend ($p < 0.1$) for the superiority of antidepressant drugs compared to placebo [21].

However, stronger effects of antidepressants in bipolar depression could be found in different studies. In a recent meta-analysis, the same efficacy of antidepressants was verified in treatment of unipolar and bipolar depression [22]. Additionally, in a naturalistic study with a high number of patients with bipolar and unipolar depression, the results of treatment with antidepressants are encouraging, demonstrating good response (bipolar II: 69.6%, bipolar I: 62.9%) and remission values (54.0% and 50.6%) [23].

Therefore, there is still an ongoing and controversial discussion of the effectiveness of antidepressants in bipolar depression. Specific clinical recommendations from treatment guidelines and expert consensus statements differ substantially in their assessments of the value and safety of antidepressants for the treatment of bipolar depression. The German S3 guideline states that the question of whether an antidepressant monotherapy should be used or not could not clearly be answered, and no clear recommendation could be given for the use of antidepressants alone or in combination. In contrast, the recently published Canadian guideline for the treatment of bipolar disorder recommends SSRIs (except paroxetine) or bupropion together with lithium, valproate or olanzapine as a first treatment step in acute bipolar depression. In the course of treatment, the antidepressant drug should be stopped after remission [11]. A similar recommendation is given by the NICE guideline which denotes SSRIs in combination with lithium or antiepileptic drugs as a possible treatment strategy [12]. In the guideline of the WFSBP, the poor evidence for antidepressant drugs is emphasized, along with the remark of the small but still existing risk of switching a bipolar depression into a manic episode by medication of this type [13].

The value of antidepressants to treat bipolar depression highly varies and reflects the limited and inconsistent state of available research based information [24]. Altogether, the current data do not yet allow for a final evaluation and recommendation of antidepressants in the treatment of bipolar depression.

The biggest concern of using antidepressants in bipolar depression is the antidepressant-induced mania. The data in this area

also demonstrate inconsistent results. In a recent meta-analysis, the risk of medication-induced switch was low with the highest switch risk shown for tricyclic antidepressants (12.5%) [25]. A parallel intake of antimanic medication like lithium, carbamazepine or valproate seems to reduce the risk of switching into mania, as shown in an older retrospective analysis [26]. The German S3 guideline concluded that in the end it is unclear how much antidepressants contribute to the risk of switching in general, which antidepressant agents are at particular risk, and for how long antidepressants should be applied. The only recommendation in the treatment with antidepressants that could be given is the lower switch risk of SSRIs or bupropion over tricyclic agents or venlafaxine. This conclusion could be found in other guidelines as well [11, 12].

Lithium

Lithium has proved its importance for bipolar disorder in many studies and is regarded as a main pillar in the treatment of acute mania and as a mood stabilizer. In the German S3 guideline it is the only agent which received a grade A recommendation as a mood stabilizer, and is the only drug which has an approval for bipolar disorder in Germany without restrictions.

Looking at the use of lithium as monotherapy in the treatment of bipolar depression, high quality evidence is lacking. In the EMBOLDEN I study lithium was not superior to placebo in the treatment of bipolar II patients in a depressive episode [27]. However, it should be noted that the lithium serum levels were too low for sufficient treatment in this indication. As mentioned, in another study lithium had a lower effect on depressive symptoms than venlafaxine [16]. Compared to lamotrigine, lithium showed an equal effectiveness for the treatment of bipolar depression [28]. Additionally, there is an ongoing discussion of a possible increasing effect of lithium monotherapy with higher serum lithium levels [20]. Low serum lithium levels were a major limitation of several studies examining lithium in the treatment of bipolar depression. Some argue that antidepressants should be added, especially to patients with low serum levels of lithium.

In summary, the German S3 guideline does not recommend the use of lithium monotherapy in the treatment of bipolar depression. A rather similar recommendation is given by the WFSBP guideline, which recognizes, however, the importance of lithium in the combination therapy of bipolar depression [13].

Nevertheless there are several aspects which favour the use of lithium in bipolar depression; its central role as mood stabilizer, which should be considered even in the acute treatment, its anti-manic potential, and its well proven anti-suicidal effectiveness [29]. This is the reason why lithium is still recommended as monotherapy in the treatment of bipolar depression in the Canadian guideline as well as in the NICE guideline [11, 12].

Lamotrigine

Lamotrigine has shown properties of preventing depressive relapses in bipolar disorders. The effectiveness of lamotrigine in bipolar depression is controversial and should be regarded critically. An RCT provided evidence for lamotrigine in the treatment of bipolar depression only in secondary outcomes [30]. A meta-analysis of 5 RCTs (4 of them without significant results) could show a significant but weak superiority (NNT=11) of lamotrigine against placebo in the treatment of bipolar depression [31]. Another drawback is the need for a slow increase in dosage with this agent because of the side effects (e.g., rash). To summarize, the German S3 guideline gives a mere "could recommendation"

for lamotrigine [10]. The WFSBP evaluates the existing data for lamotrigine critically (i.e., negative results in studies), but gives a recommendation for its use in this indication because of an overall positive meta-analysis, its effectiveness especially in severe depression, and the good clinical experience with this agent [13]. The Canadian guideline also recommends lamotrigine as single agent in the treatment of bipolar depression [11].

Valproate

The anti-manic properties of valproate are well proven by several high quality studies [32]. Looking at the use of valproate for phase prophylaxis, it could not show its effectiveness in the 2 existing double-blind RCTs [33, 34], which resulted in a 0 recommendation ("can be used") in the German S3 guideline.

Concerning bipolar depression, 4 RCTs found a positive effect of valproate compared to placebo in the acute treatment of bipolar depression [35, 36]. Summarized in 2 meta-analyses, the overall antidepressive effectiveness of valproate in bipolar disorder was weak [37, 38]. For this reason, the German S3 guideline does not recommend the use of valproate as a monotherapy in bipolar depression. However, the Canadian guideline gives a recommendation for the use of valproate as a second line therapy option in the treatment of bipolar depression [11]. The WFSBP claims improvement resulting from treatment with valproate in bipolar depression, and puts it on the same rank in the treatment recommendations as olanzapine and lamotrigine [13].

Carbamazepine

For treatment with carbamazepine there are some positive results in uncontrolled trials and one RCT [39], in which a significant superiority of carbamazepine against placebo was shown. In the German S3 guideline it is noted that carbamazepine can be used for the treatment of bipolar depression, but with limitations because of the side effects and the high drug interaction potential. Looking at the Canadian guideline, carbamazepine is recommended as monotherapy or in combination with other drugs as a second or third line treatment strategy [11]. However, the WFSBP guideline rates monotherapy with carbamazepine as "unconvincing" [13]. Regarding the short-acting or the delayed form of the medication, no differences could be described [40].

Atypical antipsychotics

In the last few years a growing number of studies were performed on atypical antipsychotics in the treatment of both manic and depressive episodes in bipolar disorder, however with different results. In a meta-analysis on bipolar depression including studies with atypical antipsychotics (5 studies with quetiapine, aripiprazole and olanzapine), the superiority of these substances compared to placebo was shown to be significant, however with large differences between the single drugs [41]. It can be concluded that the positive effects of atypical antipsychotics cannot be generalized to every atypical antipsychotic drug, which is not surprising given their differing pharmacological properties.

Quetiapine: Among the atypical antipsychotics, quetiapine has the best evidence for an antidepressant effect. 3 large RCTs and more explorative studies have shown a greater reduction of depressive symptoms and higher remission rates than placebo [42, 43]. Therefore the recommendations for quetiapine in treating bipolar depression are unanimous in the current guidelines [10, 11, 13].

Olanzapine: Olanzapine underwent research for this indication in 2 RCTs [19,44]. In both studies, relatively weak but statistically significantly stronger antidepressant effects compared to placebo were found. However, sleep and appetite improved in particular, which may not only be due to an antidepressive effect, but also due to the side effect profile of olanzapine, including sedation and increased appetite. A combination of olanzapine and fluoxetine showed even greater effects on depressive symptoms in bipolar depression [19]. Limitations in the use of olanzapine are the lack of approval for this indication in some countries (approved in the U.S.A. and U.K.), and its side effects, such as metabolic risks. The German S3 guideline therefore evaluates olanzapine as a possible therapeutic option, similar to the WFSBP and the NICE guidelines. However, the Canadian guideline suggests olanzapine, due to the aforementioned negative aspects, to be of inferior importance [10,11,13].

Aripiprazole and ziprasidone: Aripiprazole underwent research in 2 RCTs as well, looking at its properties in bipolar depression. Apart from initial signs indicating improvement in the first weeks

of treatment with aripiprazole, neither of the studies found a significant difference between the medication and placebo after 8 weeks of treatment [45]. Furthermore, the rate of drop-outs because of adverse drug effects among patients taking aripiprazole was twice the number of patients taking placebo.

In parallel with aripiprazole, ziprasidone could not show an additional beneficial effect to lithium, lamotrigine, or valproate compared to placebo in the treatment of bipolar depression in an RCT [46]. Both aripiprazole and ziprasidone did not get a recommendation for the treatment of bipolar depression in any of the current guidelines [10,11,13].

Lurasidone: More positive results for the treatment of bipolar depression are occurring for the novel antipsychotic lurasidone, phase III trials are currently being conducted. In 2 six-week RCTs lurasidone was superior to placebo in both monotherapy [47] and combination with lithium or valproate [48]. As a result, approval of lurasidone was proposed to the FDA, which may change treatment recommendation rapidly. These new data have already led to a recommendation by the Canadian guideline

Table 2 Summary of pharmacological treatment options in bipolar depression.

Pharmacological Agent	Evidence	Recommendation by guidelines	Further advice
quetiapine	– 3 RCTs [40,41] with positive results for a monotherapy compared to placebo in the dosage of 300 mg or 600 mg per day	– treatment recommendation in all cited guidelines	– provides also protection against a switch into mania – effective in both bipolar I and II depression
lamotrigine	– studies mainly negative (4/5 RCTs), but weak antidepressive effect shown in a meta-analysis [29]	– overall treatment recommendation by all the guidelines with remark for a rather weak antidepressant effect and associated limitations – potentially additional positive effects in combination with lithium	– additional mood stabilizing effect against depressive episodes – limitations by the need for a slow dosage increase and by the side effects (skin reaction)
lithium	– overall weak evidence for monotherapy with lithium (1 RCT without difference to placebo, 1 RCT lithium < venlafaxine), however with methodical deficits	– German S3 guideline as well as the WFSBP advise against monotherapy with lithium – NICE and the Canadian guideline see an overall indication for the use of lithium in bipolar depression	– long-term advantages for the treatment with lithium (mood stabilizing, anti-suicidal and anti-manic effects)
valproate	– 4 positive RCTs compared to placebo, however some negative results as well – 2 meta-analysis showed overall weak antidepressive effects	– German S3 guideline advises against a monotherapy – Canadian guideline sees valproate as a second-line medication, similar to the WFBP	– good anti-manic effectiveness but questionable mood stabilizing effects have to be taken into consideration for the long-time-use
carbamazepine	– one positive RCT [37] as well as several uncontrolled positive studies – overall weak evidence	– German S3-guideline: carbamazepine can be used – WFSB gives no recommendation – Canadian guideline sees carbamazepine as second or third line medication in monotherapy or combination	– limitations because of side effects and a high drug interaction potential – evidence for a better effectiveness in the combinatory treatment
olanzapine	– 2 RCTs with positive results compared to placebo – overall weak antidepressive effects	– German S3 guideline, NICE, WFSBP: olanzapine can be used and has a similar importance as lamotrigine – Canadian guideline: olanzapine is a third choice treatment option, because just weak antidepressant effects and because of the side effects	– combination treatment with olanzapine and fluoxetine with good results for bipolar depression – side effects such as sedation and weight gain have to be taken into consideration
antidepressants	– there are few positive RCTs (e.g., for fluoxetine, imipramine, venlafaxine) – overall small effects – but meta-analysis shows differential results regarding effectiveness	– German S3 guideline gives no recommendation for ADs – Canadian and NICE guideline: SSRI and bupropion can be given in combination with lithium, valproate or olanzapine – WFSBP: No sufficient evidence for a recommendation in favour for the treatment with ADs	– overall, there is a low risk of switching into mania (higher with TCAs and venlafaxine), but a low effectiveness against bipolar depression as well – if ADs are used, they should always be used in combination with an anti-manic drug – potentially different efficacy between AD sub-classes (MAO-inhibitors, venlafaxine, TCAs > SSRIs, bupropion)

for its use as monotherapy or in combination with either lithium or valproate in bipolar depression [11].

• **Table 2** gives a summary of the relevant pharmacological treatment options in bipolar depression.

Alternative Pharmacological Treatment Strategies

Besides the agents already discussed, there are other drugs, but with a low level of evidence so far. These experimental options will be discussed briefly in the following section.

The dopamine-agonist pramipexole, which is mainly used in the treatment of Parkinson's disease, demonstrated a positive effect on depressive symptoms in bipolar depression in 2 small RCTs [49,50]. In both studies pramipexole was used in combination with either lithium or an antiepileptic drug. The average dosage was 1.7 mg/d. In another small RCT, inositol (dosage 12 g/d) showed antidepressant effects [51]. Similarly, the stimulating drugs modafinil (dosage 100–200 mg/d) and armodafinil (150 mg/d) underwent research in acute bipolar depression in one placebo-controlled RCT each, where they were used in combination with either lithium, valproate or olanzapine [52,53]. In both studies, a significantly larger reduction of depressive symptoms compared to placebo was reported.

Another new approach is the i.v. administration of ketamine, which is mainly used as a narcotic agent. In one RCT, a single i.v. administration (dosage 0.5 mg/kg BW) showed a fast and stable antidepressant effect compared to placebo [54]. The anti-glutamatergic riluzole, in an open trial, as well as the anti-antimuscarinic scopolamine, in an RCT, demonstrated antidepressant effects [55,56]. Recently, one open uncontrolled trial showed positive effects for treatment with *N*-acetylcysteine [57].

All of the above named treatment strategies are only an option in the case of therapy failure of first and second line therapies and should be seen as experimental therapeutic trials. These experimental approaches are not recommended in the current guidelines.

Treatment Recommendations

In general, in mild depressive episodes occurring in bipolar disorders a specific antidepressant pharmacological treatment is not recommended, as the risk-benefit ratio is not favourable. A mood stabilizing medication should be started (if indicated) or an already existing one should be optimized and non-pharmacological strategies should be applied. Treatment recommendations for a more severe depressive episode in bipolar disorder are dependent on ongoing and previous pharmacological treatment strategies. 3 different scenarios have to be distinguished: (i) A depressive episode without ongoing treatment, such as mood stabilizers. (ii) A depressive episode during a treatment with mood stabilizers (“breakthrough-episode”). (iii) A treatment resistant depressive episode.

For the treatment of medication-naïve bipolar depression, the evidence from controlled trials for the different drugs was already shown above. To summarize briefly, quetiapine has the best evidence. Lamotrigine, olanzapine and carbamazepine, as well as SSRIs and bupropion, are alternatives.

If a combination treatment is necessary, the German S3 guideline recommends lithium and lamotrigine. Another treatment option is the combination with an antidepressant [14].

In a “breakthrough-episode” (ii), the serum levels of the mood-stabilizer should be checked and, if necessary, be raised. Furthermore, lamotrigine should be considered as an addition to ongoing lithium therapy. Effectiveness of antidepressants in bipolar depression is still controversial, but they can be used as a treatment strategy as an ongoing prophylaxis.

If there is no improvement with the recommended treatment (treatment resistance, iii), complex combinations as well as strategies which may be associated with a higher risk of switching into a manic episode may be considered. As examples, TCAs or venlafaxine can be named. In addition, MAO inhibitors and electroconvulsive therapy (ECT) are effective treatment options in bipolar depression [58].

Treatment of recurrent brief depression (RB) potentially differs from treatment of “classical” bipolar depression. However, there is a lack of treatment recommendations for this entity due to the lack of studies [8].

Conflict of Interest

Yes: TB received lecture fees from Lilly, Bristol-Myers-Squibb, Lundbeck, esparma and AstraZeneca.

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