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Psychopharmacology of Bipolar II Depression and Bipolar Depression with Mixed Features

Abstract: The lifetime prevalence of bipolar disorder (BD) is estimated at 1%−2%, with significant rates of associated impairment in social and occupational functioning (1, 2). Although there have been important advancements in the treatment of BD over the last few decades, most of this work has centered on BD type I, from the management of pure manic or pure depressive episodes to the maintenance of mood stability. In this article we focus on the aspects of BD that are difficult to treat clinically and that lie outside most research to date, but nonetheless represent a significant illness burden: BD II depression and BD depression with mixed features (3). We review the latest evidence-based treatment strategies and recommendations for these conditions, as well as outstanding questions that require further investigation. BD II depression raises considerations distinct from BD I depression; current evidence is strongest for quetiapine in its acute treatment and lithium for long-term maintenance, although significant gaps in our treatment knowledge remain. The appropriate role for antidepressants is still not determined for BD II depression. Similarly, BD depression with mixed features conveys clinical significance distinct from other BD mood episodes, and evidence suggests that antidepressant use should be monitored more closely in this context. Further research is needed to improve our phenomenologic understanding of BD and to increase specificity in treatment approaches.

Bipolar II Disorder: Clinical Context

Bipolar type II is defined by the presence of at least one depressive and one hypomanic episode over the course of a lifetime (3). The threshold to a bipolar type I diagnosis is determined by the characteristic features that distinguish a manic period from a hypomanic one: a marked degree of impairment in social or occupational functioning, need for hospitalization, the presence of psychotic features, and duration (at least 1 week for mania unless hospitalization is warranted or psychotic symptoms are present) (3). Hypomania, in turn, is distinguished from normal mood variation by a clear change in baseline functioning that is observable to others, but without significant social or occupational impairment during the episode, lasting at least 4 days (3). In the United States, lifetime prevalence of bipolar disorder (BD) II is estimated at 1.1% and BD I at 1.0% (1); in the world population, estimates of BD II prevalence have ranged from 0.4% to 11% (2, 4). Although BD I has been the primary focus of much research, both BD I and BD II subgroups are comparable in terms of severity of role impairment, magnitude of psychiatric comorbidities, and suicide risk (2, 5, 6). BD II is thus a significant contributor

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to the bipolar illness burden, despite disproportionate attention in the field on BD I course and treatment.

Prospective analyses indicate that the symptomatic course of BD II, like BD I, is predominantly characterized by depressive rather than hypo/manic mood states (7, 8). In one study, BD II patients were found to be depressed 37% of the time, versus hypomanic 10% of the time; this amounts to a depression-to-mania ratio of 3.8, similar to a ratio of 2.9 in BD I patients (8). A retrospective analysis, by contrast, found that BD II patients had an average of three times more depressive episodes than BD I patients over a 10-year period, a result that could be limited by the differential likelihood of retaining BD II versus BD I patients in follow-up (9). Nonetheless, these data indicate that treatment and prevention of depressive symptoms are likely to play an important role in alleviating disability and impairment from the disorder. Of note, an international survey study found that 50.6% of BD II patients reported suicidal ideation and 20.8% attempted suicide over a 12-month period (similar rates to BD I), further underscoring the imperative need for therapeutic interventions in these patients (2).

Most studies on the pharmacology of bipolar depression involved BD I patients, and with the lack of clear treatment guidelines for BD II, it has become common clinical practice to apply known BD I treatment strategies to BD II patients (10). Long-term studies, however, have shown there is high diagnostic stability of these BD subtypes, as well as differing psychopharmacologic responses, suggesting that BD I and II represent distinct disease processes, or distinct phenotypic expressions of a shared pathophysiologic mechanism (9 10–13). A diagnosis of BD II depression, therefore, merits its own treatment considerations distinct from BD I.

Bipolar II Depression: Treatment Strategies and Evidence

Quetiapine

Quetiapine was studied in two industry-sponsored, randomized, placebo-controlled, double-blind trials for acute bipolar depression, where BD II patients constituted about one-third of the study population (14, 15). Both trials found that quetiapine monotherapy improved depression rating scores in all treatment arms significantly, without any increase in treatment-emergent mania/hypomania (14, 15). Only one of the studies showed efficacy of quetiapine for BD II depressed patients as a subgroup; however, a post hoc analysis of BD II patients from both studies combined (351 patients total) found evidence of quetiapine efficacy in reducing depression symptoms, with a separation between medication and placebo as early as week one (16). A second post hoc analysis of these studies combined with two other similarly designed trials conducted worldwide (EMBOLDEN I and II studies, for a total of 776 patients) again showed treatment efficacy of quetiapine monotherapy in BD II depression, with an effect size of 0.44 for quetiapine 300 mg daily dose and 0.47 for 600 mg daily dose, both significantly different from placebo (17). Although there are several limitations to these pooled analyses (such as the post hoc nature of study methods and lack of follow-up beyond week eight of treatment), these trials nonetheless represent the largest group of BD II depressed patients studied in a randomized, placebo-controlled manner. Based on this evidence, quetiapine monotherapy is effective treatment for acute BD II depression.

In these analyses, the most common adverse events reported in quetiapine-treatment arms were dry mouth, somnolence, sedation, and dizziness (16, 17). Adverse events attributed to extrapyramidal symptoms occurred at a rate of 12.4%, 8.8%, and 6.1% in groups receiving quetiapine 300 mg daily dose, quetiapine 600 mg daily dose, or placebo, respectively (17). Rates of medication discontinuation due to an adverse event were higher in quetiapine-treatment arms than in placebo (12.1% and 17.9%, versus 5.1%) (17). Interestingly, the discontinuation rate due to adverse events was slightly higher in BD II than in BD I patient groups, in keeping with the historical notion that BD II patients may be more sensitive to medication side effects than BD I patients (16). Last, metabolic effects are well known to the atypical antipsychotic class and should be monitored. Although patients receiving quetiapine gained an average of 1 kg more in weight than placebo-treated patients at the end of these studies, the proportion of patients who gained at least 7% body weight was higher (17). In the long term, weight gain and metabolic abnormalities contribute to the risk of diabetes and cardiovascular disease (18).

Lamotrigine

The role of other medications in BD II depression is less established. Lamotrigine, which has a demonstrated role in preventing mood relapse in BD I (particularly with regard to depression episodes) (19), has been the subject of intense interest in the management of acute BD depression. Five randomized, double-blind, placebo-controlled trials were conducted examining the efficacy of lamotrigine in acute BD I and II depression, and one of these was an industry-sponsored

trial of 221 BD II depressed patients that was never published (20). None of the trials found any difference between lamotrigine and placebo in primary outcome measures (depression rating scales) (20). A meta-analysis and meta-regression of pooled data from all five trials showed a small but significant effect of lamotrigine in BD I and II depressed patients, although the effect was modest (estimated number needed to treat [NNT] of 11) (21). Interestingly, lamotrigine performed better against placebo in patients with more severe depression symptoms at baseline (Hamilton Depression Rating Scale [HAM-D] >24), although it is unclear how this result related to BD subtype divisions (21). Taken together, these studies suggest there may be weak efficacy of lamotrigine treatment in acute BD II depression. There have been a few studies of lamotrigine as adjunct to lithium or other mood stabilizers for acute BD depression that have been largely positive; however, these studies involved small numbers of patients and were not adequately powered to examine BD II specifically (22, 23). The use of lamotrigine in BD II depression can thus be considered a weak "second-line" strategy (10), perhaps as an option to consider in patients who are severely depressed or remain depressed on a mood stabilizer (to which lamotrigine can be added as adjunctive therapy).

Common adverse effects of lamotrigine include headache, nausea, and nonserious rash; notably, the rare side effect of Stevens-Johnson syndrome (or other serious rash requiring hospitalization) was not reported in these studies, although precautions must be taken in practice of an initial slow titration (20). Rates of medication discontinuation due to an adverse event were comparable between lamotrigine-treated and placebo arms (11% and 8% from all studies, respectively) (20). Last, the rates of treatment-emergent mania/hypomania were unaffected by lamotrigine. Although lamotrigine is also effective as a mood stabilizer for BD I depressed patients for up to 18 months (as demonstrated in a population enriched for lamotrigine responders) (19), a role for lamotrigine as maintenance therapy of BD II depression has not been adequately examined.

LITHIUM

Although historical data from combined BD I, II, and NOS subgroups suggests that lithium is more effective than placebo in treating acute BD depression (24), the precise efficacy of lithium remains unknown. A single-blind study comparing lithium to lamotrigine in acutely depressed BD II patients found no difference between the treatment arms in terms of mood improvement; however, this was an open-label study with no placebo-controlled group, and a high dropout rate (42%) (25). Perhaps the most informative study to date is the EMBOLDEN I trial, where lithium monotherapy was directly compared with placebo and quetiapine monotherapy arms in acutely depressed BD I and II patients (26). There was no separation between lithium and placebo groups throughout the 8 weeks of the study, although lithium levels were at the low end of the target range (mean of median concentrations was 0.61 mEq/L) (26). The use of lithium for acute BD II depression, therefore, is not well supported by the evidence.

By contrast, lithium has been studied extensively in bipolar maintenance. An open, uncontrolled, prospective study of lithium maintenance treatment found greater benefits for BD II than BD I patients. The average time to mood episode recurrence, for example, was increased from 8 months to 100 months in BD II patients after lithium therapy initiation, whereas time to recurrence increased from 8 months to only 17 months in BD I patients, respectively (27). There was also a greater proportional decrease in the percentage of time spent ill in BD II-treated versus BD I-treated patients, and a greater reduction in the frequency of depressive episodes (although BD II patients in this study had a greater burden of depression than BD I patients prior to and during lithium treatment) (27). It is important to note, however, that this specific study population of BD patients is known to be responsive to lithium. In BD II patients, a few older and smaller double-blind, placebo-controlled studies have shown the efficacy of lithium in preventing depressive episodes (28, 29). Thus, evidence exists for the use of lithium as maintenance therapy in BD II, and specifically for preventing BD II depression.

In the EMBOLDEN I study of acute BD I and II depression, the most common reported side effect of lithium was nausea, and the proportion of patients who discontinued lithium due to adverse events was 8.8%, which is similar to placebo (26). With long-term use, lithium has been associated with an enhanced risk of hypothyroidism, reduced urinary concentrating function, hyperparathyroidism, and weight gain (30).

ANTIDEPRESSANT ADJUNCTIVE THERAPY

Antidepressants have been studied in the treatment of acute BD depression, although their role remains controversial. While most guidelines recommend against the use of antidepressants as monotherapy or adjunctive therapy for BD depression due to the risk of treatment-emergent mania/hypomania, a prospective study (the Stanley Foundation Bipolar Network) of BD depressed patients treated with adjunctive

antidepressant therapy found a lower manic switch rate in BD II than in BD I patients (2%, or 1 out of 48 patients, versus 12%, or 16 out of 134 patients, respectively) (31). Furthermore, in a double-blind, placebo-controlled study of 240 BD I and 114 BD II depressed patients completed within the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) collaboration, there was no difference in the rate of treatment-emergent mania/hypomania between patients on adjunctive antidepressant medication (bupropion or paroxetine) versus placebo (32). A thorough discussion of the evidence surrounding antidepressant-associated affective switch is out of the scope of this article, as the phenomenon remains widely debated (33). Consensus within the field, however, is that treatment-emergent switches are less frequent in BD II than BD I patients, if they do in fact exist.

In the STEP-BD study of acutely depressed BD patients, no differences were observed in mood recovery (at 8 weeks) between antidepressant adjunct and placebo arms (32). Among BD II patients, there was actually an insignificant trend toward better mood recovery in patients receiving placebo. Two meta-analyses of antidepressant use for acute BD I and II depression have been performed (where the majority of patients were concurrently on a mood stabilizer) and arrived at opposing conclusions regarding antidepressant efficacy in this context (34, 35). However, these meta-analyses are difficult to interpret due to extensive methodological heterogeneity between the studies examined (35, 36). There are a few small, randomized studies of combined BD I and II depressed patients suggesting that antidepressant adjunctive use is as effective as lamotrigine or other mood stabilizer adjunct; however, the actual number of BD II patients examined was very low (<20) and there were no placebo controls in these studies (37, 38). To date, the STEP-BD trial remains the largest study to examine the efficacy of antidepressant adjunctive use in acute BD II depression, and the results do not support a clinical benefit of this treatment strategy. In fact, in patients who exhibit manic symptoms during the acutely depressed BD state, antidepressant adjunctive therapy was associated with a worsening of manic features, suggesting cautious monitoring when using this approach for a subgroup of BD patients (see Bipolar Depression with Mixed Features section below) (39, 40).

There is limited data examining the role of long-term antidepressant adjunctive use in BD II depression, as most studies in this area are continuation trials of patients already stabilized on adjunctive antidepressants, and the majority of patients examined had a BD I diagnosis. One prospective study followed 84 BD I and II depressed patients who achieved remission with antidepressant augmentation for 1 year, and found that patients who discontinued the antidepressant within 6 months of remission had a significantly higher rate of depressive relapse (70%) compared with those who continued their antidepressant (36%). Interestingly, the risk of manic relapse was also higher (41). It is important to note that this study was a nonrandomized study cohort. A study of 70 BD I and II depressed patients (within the STEP-BD collaboration) randomized responders of antidepressant adjunctive therapy to continuation versus discontinuation of antidepressants for 1–3 years (42). There was no difference observed in the primary outcome of depressive symptom ratings, although a mild delay in depressive episode relapse was observed in the continuation group (hazard ratio 2.13, 95% CI 1.00–4.56) (42). A BD II diagnosis did not predict a better response to antidepressant continuation (42). Current guidelines recommend that BD depressed patients who respond to antidepressant adjunctive therapy may be maintained on this regimen; however, the evidence supporting this remains limited (33).

ANTIDEPRESSANT MONOTHERAPY

Are antidepressants alone effective in treating acute BD II depression? An open-label study of fluoxetine use in BD II depressed patients found that mood symptoms improved similarly to fluoxetine-treated major depressive disorder (MDD) patients by week 12, with a 3.8% rate of treatment-emergent mania/hypomania; however, this was a lead-in phase for long-term studies and there was no placebo control (43). Another open-label study of BD II depressed patients randomized to venlafaxine versus lithium monotherapies found greater improvement in depression symptoms with venlafaxine treatment by week 12, but this study also lacked a placebo control (44). The most definitive investigation thus far is the EMBOLDEN II study of combined BD I and II depressed patient groups, which also examined paroxetine monotherapy as a treatment arm (45). While paroxetine improved anxiety symptoms over placebo, there was no difference in depression outcomes compared with placebo at the week 8 endpoint (45). Notably, the incidence of treatment-emergent hypo/mania in the paroxetine-only group was 10.7%, comparable to placebo (8.9%) but higher than the quetiapine-treated groups (2.1%–4.1%) (45).

If treatment-emergent hypomanic/manic switches are less frequent in BD II than BD I, could there be a long-term benefit to antidepressant monotherapy in BD II depressed patients that exceeds possible risk? In one study, patients who responded to fluoxetine monotherapy (81 BD II patients) were next

Table 1. Bipolar II Depression Treatment Strategies[a]

Medication	Acute Therapy		Maintenance Therapy	
Quetiapine	+	Post hoc analyses of 4 placebo-controlled studies	0	
Lamotrigine	+/−	Meta-analysis of 5 placebo-controlled studies	0	
Lithium	-	One placebo-controlled study (EMBOLDEN I)	+	Historical data, one open-label study
Antidepressant Adjunct	-	One placebo-controlled study (STEP-BD)	?	One uncontrolled study, but enriched for antidepressant-responders (STEP-BD)
Antidepressant Monotherapy	-	One placebo-controlled study (EMBOLDEN II)	?	One placebo-controlled study, but enriched for antidepressant-responders

[a] Summary of evidence for acute and maintenance therapy of BD II depression. Strength of recommendation is indicated in the left-sided subcolumns for each main column: +, strongly recommend based on evidence; +/−, weakly recommend based on evidence; -, do not recommend based on evidence; 0, absent or little evidence available to make a recommendation; ?, limited or controversial evidence exists but not enough to make a recommendation. The primary sources of these recommendations are indicated in the corresponding right-sided subcolumns.

randomized to lithium, placebo, or fluoxetine monotherapies for another 50 weeks, and those who continued fluoxetine demonstrated a significantly lower hazard ratio of depression relapse compared with lithium-treated patients, but not placebo (46). These results should be interpreted with extreme caution, however, before antidepressant monotherapy can be recommended as a mood stabilizer: the study population of this long-term continuation trial was enriched for fluoxetine-responders, and the primary outcome was relapse to depression instead of a mood stability measure without consideration of hypomanic symptoms (47). Thus, the evidence for antidepressant monotherapy in the maintenance treatment of BD II depression remains limited, and the safety of this treatment strategy is unknown.

Other classes

Additional drug classes have been examined as adjunctive therapies for acute BD II depression. A small study of pramipexole augmentation showed a significant effect on depressive symptoms in BD II depressed patients versus placebo (48). Modafinil adjunctive therapy may also be helpful in this regard (49). Further research will be needed before these or other novel treatment approaches can be recommended.

Bipolar II depression: recommendations, knowledge gaps, and future directions

In summary (Table 1), there is strong evidence for quetiapine use in acute BD II depression, and lithium use for the maintenance of BD II mood stability and preventing depressive episodes. The evidence for lamotrigine use in acute BD II depression suggests a weak effect. The use of antidepressants as adjunctive treatment for acute BD II depression is not supported by evidence. Although there are data suggesting that antidepressants may be helpful in preventing depression relapse, these studies have important limitations and we recommend caution in pursuing this strategy. It is also important to note that guidelines recommend avoiding venlafaxine, tricyclic, and tetracyclic antidepressant use in bipolar disorder, based on limited evidence that these drug classes may increase the risk of a manic switch compared with other antidepressants (33).

Significant gaps remain in our knowledge of treating BD II depression. The best evidence for treating acute BD II depression comes from post hoc analyses of quetiapine placebo-controlled studies, as most other treatment trials have focused on BD I depression exclusively. Would other atypical antipsychotics that are Federal Drug Administration (FDA)-approved for acute BD I depression, such as olanzapine/fluoxetine combination and the recently approved lurasidone, also be effective (or perhaps more effective) in acute BD II depression? There has also been little data investigating long-term maintenance use of an antipsychotic or anticonvulsant for BD II depression. Although lithium is the recommended maintenance medication, its efficacy in acute BD II depression has never been demonstrated. Last, antidepressant monotherapy in BD II depression remains an open topic of research, in need of large-scale efficacy studies, precise quantification of hypomanic/manic switch risk, and further direct comparison to other (antipsychotic, mood stabilizer) pharmacological strategies.

Another unanswered question is whether all BD II depressed patients should be treated pharmacologically. It is intriguing, for instance, that within the

placebo continuation group of the 50-week fluoxetine monotherapy study above (see Antidepressant Monotherapy section), only about half (52%) of the patients experienced a depression relapse, which is similar to the lithium-continuation group (58%) (46). Although the risk of hypomania in untreated BD II patients is real and must be adequately addressed, the question remains whether there is a subgroup of BD II depressed patients who may not need long-term pharmacotherapy to prevent depression relapse and could minimize relapse or recurrence using other treatment modalities. It is also important to note that for acute treatment of depressive symptoms, the placebo effect and its evolution is a well-recognized phenomenon in major depressive disorder (MDD) (50), but has not been closely examined in BD II.

Since antidepressants are first-line treatments for MDD, the possibility that antidepressants may be helpful in some cases of BD II depression brings to mind the hypothesis of a mood disorder spectrum from unipolar to bipolar depression and what this concept might imply about the nosology, phenomenology, and treatment of mood disorders (51, 52). In fact, there is evidence suggesting that patients with recurrent MDD report the existence of lifetime manic/hypomanic symptoms, which in turn relates to increased suicidal ideation (53). A 10-year prospective study of 488 MDD patients found that a significant portion (41%) had subthreshold hypomania (i.e., euphoric hypomania with an insufficient number of symptoms, or irritable hypomania not observable to others) (54). Further studies with more precise descriptions of a lifetime mood disorder [such as the DSM-5 subcategorical codes, e.g., short-duration hypomania (2–3 days) with major depressive episodes, hypomania with insufficient symptoms and major depressive episodes, etc. [3] may enhance our prognostic understanding of BD and the development of targeted BD treatment approaches.

Bipolar depression with mixed features: historical and clinical context

While the idea of a mood disorder spectrum has recently taken hold, the concept of a mood *state* spectrum has captured psychiatrists' attention for a long time. Emil Kraepelin (1856–1926) and Wilhelm Weygandt (1870–1939) described the concept of "mixed states" as simultaneous combinations of various depressed and manic features, such as "agitated depression" or "inhibited mania" (13, 52, 55). Kraepelin viewed these states as independent phenomena spanning a mood continuum; in the DSM this concept has evolved from a highly restrictive definition of co-occurring manic and depressive states (a "mixed episode" in DSM-IV), to a more inclusive mixed features specifier attached to predominantly manic or depressive mood episodes (DSM-5; Table 2) (3, 55). This nosological change occurred in the midst of increasing evidence suggesting a dimensional nature to mixed mood states, with implications for disorder prognosis, comorbidities, and treatment response (13, 52, 55, 56).

In previous DSM-IV-based studies, the most common depressive features associated with DSM-IV-defined mixed manic episodes include dysphoric mood, anxiety, guilt, and suicidality (57), whereas manic symptoms most commonly associated with bipolar depression included distractibility, racing thoughts, and psychomotor agitation (58). In the STEP-BD study of 1,380 acutely depressed BD patients, 54% of individuals exhibited 1–3 of these co-occurring manic symptoms (58). The DSM-5 mixed specifier, by contrast, avoided overlapping symptoms, so distractibility, irritability, and strict insomnia do not count toward the mixed specifier diagnosis (3). Agitation can occur at either pole and was therefore not included as a feature of the DSM-5 mixed specifier for depression (3). It is important to note that controversy continues to persist over this definition of a depressive episode with mixed features, and whether the DSM-5 criteria remain too restrictive by virtue of not including the overlapping but most commonly associated symptoms of mixity noted in STEP-BD and other studies (59, 60).

Multivariate analyses have been performed to describe mood symptom clusters, which appear to be better mapped along a coordinate system of orthogonal manic and depressive symptom axes, rather than a single linear spectrum from one mood polarity to the other (55, 56). In these analyses, the presence of mixed symptoms in either manic or depressed episodes of BD correlates with anxiety, suicidal behavior, and early onset of illness —for BD depression, the concurrent presence of at least three manic symptoms to define a mixed depressive episode resulted in a statistically significant difference in suicide attempt history between threshold and subthreshold episodes (56). There is also an association between mixed mood episodes and the presence of early-life stressors, stress-related disorders, and alcohol and substance abuse (55). The diagnosis of mixed states in BD, therefore, carries important clinical and safety considerations.

An additional clinical implication of a mixed depressive state is the possible link to a change in disorder diagnosis: a prospective study found that the concurrent presence of hypomanic features in an index MDD episode (most commonly, decreased

Table 2. DSM–5 Specifiers for Bipolar and Related Disorders[a]

With mixed features: The mixed features specifier can apply to the current manic, hypomanic, or depressive episode in bipolar I or bipolar II disorder:
Depressive episode, with mixed features:
A. Full criteria are met for a major depressive episode, and at least three of the following manic/hypomanic symptoms are present during the majority of days of the current or most recent episode of depression:
1. Elevated, expansive mood.
2. Inflated self-esteem or grandiosity.
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Increase in energy or goal-directed activity (either socially, at work or school, or sexually).
6. Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
7. Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).
B. Mixed symptoms are observable by others and represent a change from the person's usual behavior.
C. For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features.
D. The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment).

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need for sleep, high energy, and increased activity) was associated in some patients with later onset of hypomania/mania and thus subsequent diagnostic progression to bipolar disorder, more commonly BD II (61). It is important to note, however, that patients without report of hypomanic/manic symptoms also progressed to BD diagnosis; the authors argue that the presence of at least three such symptoms was a helpful specificity (not sensitivity) measure, although the positive predictive value for BD progression was only 42% (61). Whether a mixed depressive state is a marker for a distinct BD clinical subtype remains an open question.

Finally, the implications of these studies for the pathophysiological mechanism of mixed mood episodes remains unclear; whether mixed states represent the superimposition of distinct manic and depressive processes or the rapid oscillation between manic and depressive (or other mixed) states is unknown (55).

Bipolar depression with mixed features: treatment strategies and evidence

As the DSM-5 mixed specifier for depressive episodes is a new classification, there is little evidence available regarding specific treatment of these mood states. The STEP-BD trial followed bipolar depressed patients presenting with at least two concurrent manic symptoms, and found that antidepressant augmentation was associated with worse manic symptom severity at 3 months, versus placebo (39). There was no change in the probability of mood recovery at 3 months, however, suggesting that adjunctive antidepressant use may have simply exacerbated existing manic symptoms without affecting the overall course of the mood episode (31). These results are intriguing in light of another study specifically examining the risk of treatment-emergent mania: BD patients who became manic after adjunctive antidepressant treatment had worse baseline subthreshold hypomanic symptoms than patients who simply responded or did not respond to antidepressant augmentation (baseline symptoms included increased motor activity, pressured speech, and disorganized thought) (40).

Complicating this matter further is a post hoc analysis of olanzapine/fluoxetine combination treatment in 355 acutely BD I depressed patients, which found that patients with at least two baseline manic symptoms had a similar response rate to olanzapine/fluoxetine as to olanzapine monotherapy, with no difference in the manic switch rate (the most common manic symptoms noted were irritability, decreased need for sleep, pressured speech, and racing thoughts) (62). This discrepancy with prior findings (40) was attributed to the use of different mood-rating scales, exclusion of BD II patients in this study, and the use of different medications (fluoxetine as an antidepressant versus sertraline, bupropion, or venlafaxine; olanzapine as a mood stabilizer versus lithium or anticonvulsants) (62). Thus, while adjunctive antidepressant use in BD depression with mixed features

should be monitored carefully, further research is needed regarding the efficacy and risks of this treatment strategy.

Research on other treatment possibilities for BD depression with mixed features remains ongoing. One recent prospective double-blind study tested the efficacy of ziprasidone augmentation versus placebo in BD II and MDD depressed patients presenting with 2–3 manic features (73 patients total; the most common manic symptoms were flight of ideas, distractibility, and decreased need for sleep) (63). Ziprasidone augmentation significantly reduced depression rating scores over 6 weeks compared with placebo, and this effect was more prominent in BD II mixed-depressed rather than MDD mixed-depressed patients (63). Further research will be needed to confirm these preliminary findings.

Bipolar depression with mixed features: recommendations and future directions

Current treatment guidelines for bipolar mixed states recommend avoiding antidepressants however, the data behind this is preliminary and/or based on post hoc analyses, and more data are needed to determine precise efficacy (33). It may be possible to treat BD depression with mixed features as if treating a pure BD depressed episode, but with extreme care in follow-up and monitoring, as the presence of mixed features bears additional prognostic considerations. Studies involving detailed, prospective analysis of a mixed specifier population are needed. Furthermore, there is no long-term data on antidepressant safety within this population, and it remains unclear whether or not antidepressant augmentation in BD depression with mixed features is associated with distinct long-term outcomes.

Interestingly, the study of ziprasidone augmentation for BD II and MDD mixed-depressed patients suggests a possible future tension between treating a patient by mood *state* versus *disorder*, and whether to prioritize one over the other when managing these complex cases. BD and MDD mixed-depressed states may lie along a mood disorder spectrum, with a parallel gradation in antipsychotic responsiveness. Alternatively, treating mixed depression as a state may be an effective (and simpler) strategy. Larger-scale studies will be needed to explore these possibilities more fully.

Conclusions

We reviewed recent developments in the psychopharmacologic treatment of bipolar II depression and bipolar depression with mixed features, which are subtypes of BD that have not been well studied despite their significant illness burden. Further research, primarily in the form of large, randomized, placebo-controlled studies with long-term, prospective follow-up, which have so far been lacking for these BD subtypes, are needed to improve therapeutic options. In the long term, correlations between mood state and mood disorder definitions, treatment responses, and biological data (genetics, molecular/cellular phenotypes, functional neuroscience, and so forth) will be needed to further our understanding of bipolar disorder and to provide better psychopharmacological treatments for all patients.

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