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REVIEW ARTICLE

Treatment of bipolar depression

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Depressive symptoms and episodes dominate the long-term course of bipolar disorder and are associated with high levels of disability and an increased risk of suicide. However, the treatment of bipolar depression has been poorly investigated in comparison with that of manic episodes and unipolar major depressive disorder. The goal of treatment in bipolar depression is not only to achieve full remission of acute symptoms, but also to avoid long-term mood destabilization and to prevent relapses. A depressive presentation of bipolar disorder may often delay the appropriate management and, thus, worsen the long-term outcome. In these cases, an accurate screening for diagnostic indicators of a possible bipolar course of the illness should guide the therapeutic choices, and lead to prognostic improvement. Antidepressant use is still the most controversial issue in the treatment of bipolar depression. Despite inconclusive evidence of efficacy and tolerability, this class of agents is commonly prescribed in acute and long-term treatment, often in combination with mood stabilizers. In this article, we review available treatment options for bipolar depression, and we shall provide some suggestions for the management of the different presentations of depression in the course of bipolar disorder.

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Key words: Antidepressants, atypical antipsychotics, bipolar depression, bipolar spectrum, depressive mixed state, mood stabilizers, nonpharmacological treatment, pharmacological treatment.

FOCUS POINTS

- Recognize that a depressive episode belongs to the bipolar spectrum
- Provide an overview of treatment options currently available for bipolar depression
- Controversial issues concerning the use of antidepressants in bipolar depression
- Suggestions for the management of the different presentations of depression in the course of bipolar disorder.

Introduction

Bipolar disorder (BD) is a chronic, recurrent, and disabling illness, carrying an immense burden of both morbidity and all-cause mortality.[1] While past research was more focused on the manic phases of the disorder, in the last decade, several reports emphasized that depressive symptoms and episodes are the most prevalent dimension of the illness.[2,3] Bipolar patients spend three times more days of their lives in a depressed state than in any other mood episode, with a significant degree of psychosocial impairment and disability.[1,4] Incomplete remission, with continuous presence of subsyndromal depressive symptoms, is common and has been demonstrated to contribute to both long-term dysfunction and disability, and to an increased risk of relapse.[5] Furthermore, suicide risk is higher in the depressive phases in both type I and type II BD.[6]

There is a growing awareness that bipolar depression is a current major diagnostic and therapeutic challenge. Several factors may complicate the diagnosis of bipolar depression, including incomplete clinical history, lack of patients' insight, and the presence of high rates of psychiatric comorbidity with anxiety disorders and substance use disorders, which may worsen the illness course and increase the number of suicide attempts.[7,8] For this reason, BD is often under-diagnosed on initial presentation, and high rates of misdiagnosis as unipolar major depressive disorder, ranging between 10% and 40% of the cases, have been reported.[9] Misdiagnosis often leads to inappropriate treatment, which may compromise long-term outcome by inducing manic or mixed states, or by increasing mood cycling and affective instability.[7]

Diagnostic accuracy may be improved by clinicians' careful screening for the presence of current and past symptoms of mania or hypomania in all patients presenting with depressive symptoms. Since bipolar patients typically are very concerned about the depressive phases of the illness and have impaired insight regarding hypomania or mania-related episodes, the involvement of family members or close friends in the diagnostic process can be helpful.[10,11] Moreover, even in the absence of a clear bipolar course of the illness (lifetime occurrence of manic or hypomanic symptoms), several demographic and clinical features[12–21] have

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Table 1. *Depression and bipolar spectrum: diagnostic indicators of "bipolarity" in patients with depressive episode*[12–21]

- Family history for bipolar disorder or suicide
- Hyperthymic or cyclothymic temperament
- Early age at onset (<25 years)
- Postpartum depression
- High rate of recurrences (>3 episodes/year)
- "Atypical depression" (hypersomnia, hyperphagia, mood reactivity, and interpersonal sensitivity)
- Great severity of depressive episode (psychomotor retardation and/or psychotic features)
- Substance abuse comorbidity
- Lack of response to ≥2 adequately administered antidepressant medications
- Wearing off of antidepressant efficacy
- Antidepressant-emergent affective switch or dysphoria; affective switch induced by treatments (interferon, steroid) of autoimmune diseases

been proposed as diagnostic indicators, suggesting that a depressive episode belongs to the bipolar spectrum[22–24] (Table 1).

Furthermore, it was estimated that more than two-thirds of depressed bipolar patients present an episode of depression with at least subtle concomitant manic features.[25] By the current narrow Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR) definition of mixed bipolar states, these individuals would be classified as purely depressed rather than mixed. Subsyndromal manic symptoms during a depressive episode, however, outline a more severe and complex clinical state than pure bipolar depression, with prognostic and therapeutic implications. The treatment of these mild mixed depressive states is poorly studied and less clearly defined, but they appear to predict a lower response to standard treatments, as well as to increase the trend toward emotional destabilization following antidepressants.[11,26] In the next edition of DSM-V, the introduction of the "with mixed features" specifier has been proposed to identify these depressive episodes with subthreshold mixtures of manic symptoms.

Despite the disease burden of bipolar depression, little evidence is available to guide the treatment of this phase of the disorder in contrast to mania or hypomania. The goal of treatment of depression in BD is not only to achieve full remission of acute episodes and to prevent suicides, but also to obtain long-term stabilization by preventing relapses. Therapeutic options for bipolar depression are provided by all current treatment guidelines,[27–31] and some convergence between them has been reported.[32] However, evidence-based knowledge often derives from clinical trials conducted with strict inclusion criteria in samples that do not completely reflect the broad spectrum of bipolar depressed patients in clinical practice. Since a few studies have specifically investigated the treatment of depression in BD, many treatment options are often translated from unipolar to bipolar depression, and several other agents are used off-label in the daily clinical practice to treat depressed bipolar patients.

To date, there are still several unanswered questions about the management of bipolar depression. Among them, the major issue is the role of antidepressants and their potential risk of producing long-term mood destabilization.

This article will provide an overview of available treatment options for bipolar depression and some indications for the appropriate management of these patients in clinical practice.

Treatment Options of Bipolar Depression

Pharmacological treatment

Lithium

Although lithium has been generally considered the most effective compound for maintenance treatment of BD,[33] the evidence in bipolar depression is not as sound.[11] The EMBOLDEN (Efficacy of Monotherapy SEROQUEL in Bipolar DEpressioN) trial failed to demonstrate a significant acute antidepressant effect of lithium when compared to placebo, as to be expected because of its delayed antidepressant action.[34] While its efficacy in preventing depressive episodes was not clearly shown, the major evidence supporting an important role of lithium in the treatment of bipolar depression is its well established antisuicidal efficacy.[35,36]

Anticonvulsants

Lamotrigine. Despite the widespread notion that lamotrigine is effective on depressive symptoms of BD, as reported in different guidelines, specific trials in monotherapy yielded inconsistent findings.[37,38] Recent meta-analysis of five randomized, placebo-controlled trials, which individually failed to show a statistically significant result, concluded that the effect of lamotrigine was modest, although the advantage of this compound was evident for the most severe patients at baseline.[39,40] However, the first controlled multicenter study evaluating lamotrigine monotherapy in the treatment of bipolar I depression[41] supported its efficacy and led to its inclusion as a first-line treatment for bipolar depression in several guidelines. Lamotrigine shows benefits in bipolar depression mainly in combination with other mood stabilizers,[38] particularly when co-administered with lithium.[42]

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In addition, it was more effective than risperidone and inositol as an augmentation strategy in resistant bipolar I and II depression.[43] However, its use in acute bipolar depression is limited by the need for a slow upward dose taper to reduce the risk of skin reactions. Lamotrigine showed efficacy in the prophylaxis of BD, in particular for preventing depressive relapses.[44,45]

Divalproex. Divalproex is a widely prescribed anticonvulsant for BD, but just four randomized trials in acute bipolar depression have been conducted, and their results are controversial.[46] A recent meta-analysis provided preliminary evidence that divalproex is effective for the reduction of depressive symptoms of acute bipolar depression.[47] Moreover, some evidence suggests that divalproex presents at least a moderate prophylactic efficacy for bipolar depression.[48] The BALANCE (Bipolar Affective disorder: Lithium/ANtiConvulsant Evaluation) study suggested that divalproex was probably similar to lithium in preventing manic relapses, but less effective in preventing depressive relapses.[49]

Carbamazepine. While carbamazepine has shown efficacy in the treatment of acute manic or mixed states, the evidence for its use in acute bipolar depression is less consistent.[46] However, carbamazepine has been used in long-term prophylaxis, despite limited and uneven evidence of efficacy, particularly against recurrences of bipolar depression.[50]

Atypical Antipsychotics

Quetiapine. All second-generation antipsychotics are effective antimanic agents, but only quetiapine demonstrated a striking acute effect for depression in bipolar I and II patients.[46] It is currently recommended by all guidelines as a first-line choice for the treatment of acute bipolar depression, and even as adjunctive treatment in patients already taking antimanic medications. Its efficacy in bipolar depression has been supported consistently in several placebo-controlled trials.[34,51–54] Quetiapine has shown to produce significant and sustained reductions in the majority of core mood symptoms of depressive episodes, including suicidal thinking.[51,52] In relapse prevention studies, either as monotherapy or when added to lithium or divalproex, quetiapine significantly reduced the time to relapse of a mood event.[55,56]

Olanzapine. Olanzapine monotherapy was found to be more effective than placebo in a short-term randomized controlled trial for the treatment of bipolar I depression.[57] In comparison to olanzapine monotherapy, the combination of olanzapine with fluoxetine was superior for all measures of depressive symptoms, with higher rates and faster times of response and remission.[57] The combination of olanzapine and fluoxetine was also shown to be more effective as an acute treatment in comparison with lamotrigine.[58] To date, the long-term use of olanzapine or olanzapine plus fluoxetine in patients with bipolar depression lacks consistent research support.[11] Olanzapine monotherapy was superior to placebo in relapse prevention of subsequent mood episodes in a sample of bipolar I disorder patients who responded to open-label acute treatment with olanzapine for a manic or mixed episode.[59] In comparison trials, it was not superior to lithium or divalproex in the prevention of depressive relapse.[60,61]

Other second-generation antipsychotics. Among other common second-generation antipsychotics, aripiprazole monotherapy did not show significant benefits in the acute treatment of bipolar depression,[62] although it demonstrated efficacy as an adjunctive treatment to antidepressants in patients with major depressive disorder.[63] As a maintenance treatment, there is some evidence of efficacy in preventing manic, but not depressive, episodes.[64] There is little and generally unconvincing evidence about the effectiveness of risperidone and ziprasidone for treating bipolar depression.[11]

Antidepressants

The role of antidepressants in the treatment of bipolar depression is a controversial issue.[65] It is estimated that antidepressants are prescribed routinely to bipolar depressed patients in about 50% of cases, often as augmentation strategy for depressive episodes not responding to mood stabilizers alone.[66,67] However, the evidence of their efficacy in bipolar depression, especially as a long-term treatment strategy, is inconclusive, and their use has been associated with an increased risk of hypomanic/manic or mixed switch and cycle acceleration.[68–71] Particularly, the use of antidepressants in monotherapy is not recommended in patients with a history of manic episodes, and care should be taken also in patients with treatment-induced hypomania.[28] As a consequence, few studies have explored the efficacy of these agents in monotherapy for bipolar I depression.[3] In a randomized clinical trial, fluoxetine monotherapy was found to be as effective as olanzapine or olanzapine/fluoxetine in both type-I and type-II bipolar patients, with no evidence of increased manic symptoms.[72] On the contrary, the EMBOLDEN II study revealed no statistically significant differences between paroxetine and placebo, in both bipolar I and II patients, and the active compound did not result in

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association with high rates of manic/hypomanic switch.[54] In bipolar II patients, the risk of manic induction by antidepressant monotherapy is estimated to be lower, and beneficial effects of this drug class were reported.[37,73] One large study examining bipolar II patients treated with fluoxetine monotherapy concluded that it is a safe and effective short-term treatment for bipolar II depression, with a relatively low rate of syndromal hypomanic episodes.[74] A small placebo-controlled study gave further support to the effectiveness of escitalopram, another selective serotonin reuptake inhibitor (SSRI), in managing BD II.[75] In fact, this drug provoked significant improvement of depressive symptoms and of functional impairment of bipolar II patients over nine months, compared with placebo, with no mood destabilization in long-term use. SSRIs were therefore suggested to have a possible role as "mood stabilizers" for BD II.[75] In a short-term study, venlafaxine alone was superior to lithium monotherapy in both response and remission rates, with a low hypomanic switch rate.[76]

A meta-analysis of 12 randomized controlled trials assessing antidepressant use in the short-term treatment of bipolar depression reported that antidepressants were effective and not associated with a higher incidence of affective switch.[77] However, the studies that were reviewed had a short duration, and antidepressants were administered in combination with mood stabilizers in the majority of the patients. In contrast, a more recent meta-analysis of six trials comparing antidepressants to placebo or other standard treatments for bipolar depression failed to show a significant benefit of antidepressants over placebo or active drugs, even if they were not associated with an increased risk of switch.[78]

In several studies, antidepressants in bipolar depression were investigated when co-administered with mood stabilizers. In their meta-analysis, Gijsman *et al.*[77] showed a significant advantage in achieving response in the patients treated with antidepressants; these patients were also more likely to reach remission, as compared with the group treated with mood stabilizers plus placebo. In contrast, the long-term use of adjunctive treatment with paroxetine or bupropion did not significantly increase the rate of recovery compared with mood stabilizers alone, although it did not enhance the risk of mood destabilization.[68]

Overall, data on the risk of manic/hypomanic switch associated with the use of antidepressants in acute bipolar depression are still controversial.[79] Methodological limitations, such as the small sample size; short duration of the studies, which does not allow researchers to evaluate the possible long-term destabilization; and the criteria adopted to define an affective switch, should be taken into account.[3,71] To further complicate interpretation of data on antidepressant use in bipolar depression, there is the wide variability in the spontaneous course of BD. A higher risk of switch or treatment-emergent mixed symptoms seems to be associated with the use of tricyclic antidepressants or venlafaxine,[77,80,81] while SSRIs and bupropion are considered the safest antidepressants.[68,82] Although common, the co-treatment with a mood stabilizer does not seem to produce a major protective effect, as expected, in limiting the possible mood instability induced by antidepressants .[68,80,83]

In conclusion, the available evidence indicates a cautious use of antidepressants in bipolar patients, especially type I, and recommends that these drugs should be used for limited periods and in combination with antimanic agents in order to avoid manic switch, as suggested by almost all guidelines.[27–31] However, the duration of treatment still remains an open question, and there is no consensus among current guidelines. Some studies showed a greater risk for depressive relapses following the interruption of treatment with antidepressants, with no reports of an increased risk for manic switching when treatment was continued.[84,85] This suggests a possible role of these drugs as maintenance treatment in association with mood stabilizers, at least for a subgroup of bipolar patients.[85,86]

Further studies, carried out for longer periods in more heterogeneous samples that include the wide spectrum of bipolar conditions, are needed to fully assess the benefits of antidepressants in BD and to better define the characteristics of patients who are candidates for continuous treatment with antidepressants.

Experimental treatments

Recently, a number of novel treatments have been suggested for the treatment of bipolar depression. One of these is modafinil, an anti-narcoleptic and mild stimulant agent, although the efficacy and safety of this off-label approach is not clear. A placebo-controlled study in bipolar I depressed patients who responded inadequately to monotherapy with mood stabilizers showed higher response and remission rates in the group of patients treated with the addition of modafinil to the mood stabilizer than in the placebo-controlled group.[87]

Another novel agent proposed for bipolar depression is pramipexole, as some small studies have demonstrated its significant antidepressant effect when added to mood stabilizers in patients with bipolar depression.[88,89]

Preliminary data suggest a possible role of two N-methyl-D-aspartate (NMDA) receptor antagonists in the treatment of bipolar depression. The co-administration of i.v. ketamine with mood stabilizing drugs was found to have rapid antidepressant effect and improvement of suicidal ideation in patients with treatment-resistant bipolar depression.[90–92] Memantine

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shows neuroprotective and pro-neurogenesis effects in several neurodegenerative diseases, and there is a small amount of evidence to support its efficacy as add-on therapy in improving cognitive performance and depressive symptoms in treatment-resistant bipolar depression.[93]

There is also inconsistent evidence that the administration of omega-3 fatty acids, in particular, eicosapentanoic and docosahexaenoic acids, in addition to standard mood-stabilizing treatments in bipolar depression is associated with a significantly higher improvement of depressive symptoms over placebo.[94] Nevertheless, another trial with eicosapentanoic acid as adjunctive treatment produced negative findings.[95]

Nonpharmacological treatment

Psychotherapy

The role of psychosocial interventions should be taken into account in the management of BD patients, since life events and other stressors appear to play major roles in shaping the expression of the illness, in both onset and relapses. In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial, bipolar I or II depressed outpatients were randomly assigned to one of three intensive psychosocial treatments or to a brief psycho-educational intervention, all in conjunction with pharmacotherapy. A duration of over 1 year of intensive psychosocial treatment as an adjunct to pharmacotherapy was associated with higher rates of recovery from bipolar depression, suggesting that psychotherapy has a potential role in enhancing stabilization from bipolar depression.[96]

BD is associated with high levels of subsyndromal symptoms that provide a possible target for psychosocial interventions; consequently, most of the literature on this topic focuses on relapse prevention. Group psychoeducation appears to be an effective psychotherapeutic adjunct to standard pharmacological treatment in BD I and BD II, as it was shown to reduce significantly the number of relapsed patients and of recurrences per patient, and to increase the time to a recurrence.[97] The role of cognitive-behavioral therapy in relapse prevention remains uncertain.[46] A randomized controlled study supported the conclusion that cognitive-behavioral therapy specifically designed for relapse prevention in BD was useful in conjunction with mood stabilizers to prevent relapses and promote social functioning.[98] On the contrary, in a larger pragmatic study, no significant benefit of additional cognitive-behavioral therapy was demonstrated when compared with common treatments.[99] Combining family-focused therapy with pharmacotherapy has been examined for relapse prevention of BD, and it was shown to enhance post-episode symptomatic adjustment and to improve compliance to medications.[100] Finally, interpersonal and social rhythm therapy added to pharmacotherapy have been associated with shorter time to recovery from an episode of depression, longer survival time without a new affective episode, and an improvement of psychosocial and occupational functioning.[101,102]

Electroconvulsive therapy

Electroconvulsive therapy (ECT) should be considered an option for patients with severe and treatment-resistant bipolar depression, high suicide risk, catatonic or psychotic features.[28–31] However, it is unclear whether the response to ECT in BD might be somewhat lower than in unipolar depression.[11,103] While some studies have reported that ECT had a similar efficacy in both types of depressive patients,[104] there is some evidence of higher remission rates in unipolar patients, as compared with BD I and BD II patients.[105] A recent meta-analysis investigating the relative efficacy of ECT in both forms of depression provides evidence for the equal efficacy of ECT in unipolar and bipolar depression.[103]

Management of Bipolar Depression

A series of preliminary assessments is necessary for the proper management of different presentations of bipolar depression (Table 2). The initial evaluation

Table 2. *Variables influencing treatment choice*

Clinical features of depressive episode (pattern and severity of symptomatology):
● Psychotic features
● Psychomotor retardation/catatonia
● Suicidal ideation
● Concomitant subthreshold manic features (mild depressive mixed state)
Course of illness:
● Number and polarity of previous affective episodes
Patient-related factors:
● Age and gender
● Personality disorders and temperament
● Psychiatric comorbidity (current or lifetime)
● Somatic comorbidity and any concomitant nonpsychiatric medication
Treatment-related factors:
● Previous treatments (response and tolerability, in both patients and their relatives)
● Current treatment

Preliminary assessment of these variables may guide the therapeutic choices.

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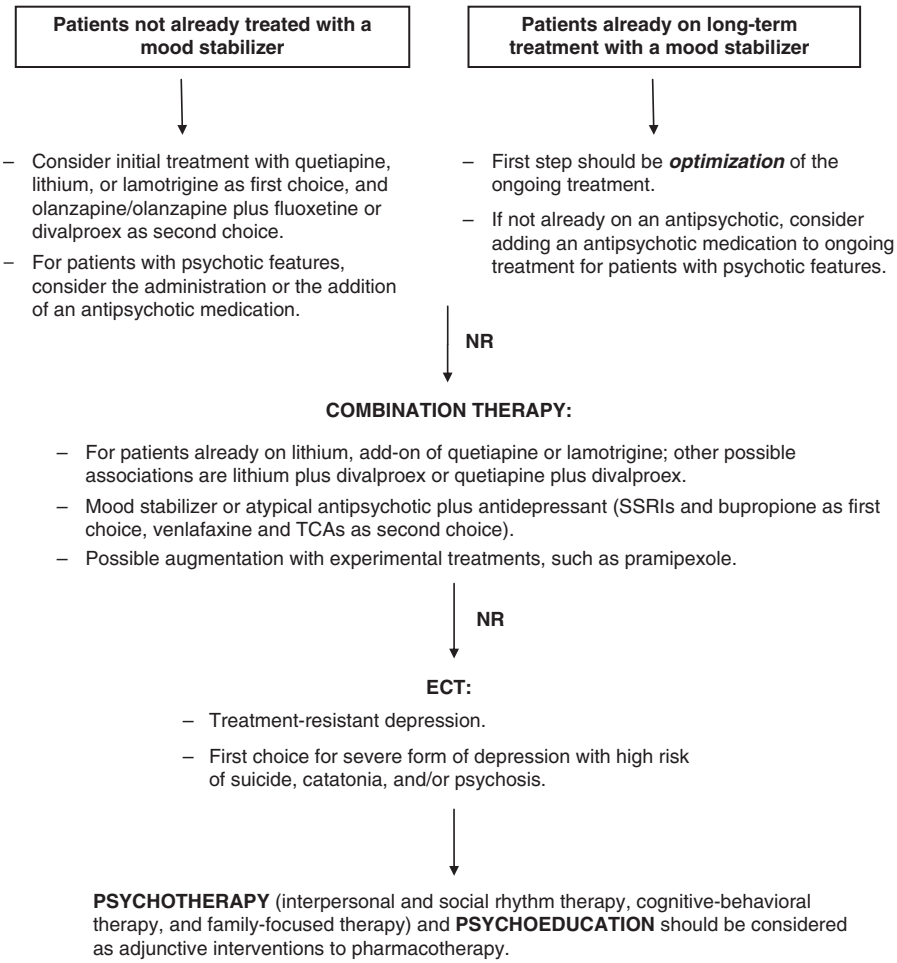


Figure 1. Management of acute bipolar depression. Abbreviations: NR = non responders, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants, ECT = electroconvulsive therapy.

should include both symptomatological characteristics of the depressive episode, such as psychotic features, severe psychomotor retardation, suicide risk, concomitant subthreshold manic/hypomanic symptoms (mild mixed depression), and the previous course of illness. The treatment of the acute episode, in fact, will be different for patients presenting with a first depressive episode or with previous relapses, and the prevalent polarity of the relapses must be taken into account. Even the presence of psychiatric comorbidity, in particular with anxiety, substance abuse, and eating disorders, or of somatic comorbidity and intake of nonpsychiatric medications must be considered. Other factors that may influence the therapeutic decisions include response to previous psychopharmacological treatments (in both the patient and his or her relatives), age, and gender (e.g., fertile women), as well as personality and temperamental characteristics that may complicate the clinical presentation and affect compliance. Finally, an important element in choosing medications for acute bipolar depression lies in the assessment of the current treatment.

If the patient under maintenance treatment with a mood stabilizer suffers from a depressive relapse, it may be appropriate to evaluate the serum concentration of the drug (e.g., lithium or anticonvulsant) and the compliance of the patient. If any of these is inappropriate, the dosage of the mood stabilizer should be adjusted (optimization). Furthermore, if reduced thyroid functioning emerges, it may be useful to begin or increase the dosage of thyroid hormone. If treatment optimization is not sufficient and the severity of the episode is not so severe as to require hospitalization, adjunctive treatment with a second mood stabilizer or antidepressant may be considered. The addition of quetiapine to the current treatment is recommended by the guidelines as a first choice, or the addition of lamotrigine for patients already on lithium. In clinical practice, antidepressants are often administered in association with mood stabilizers to

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treat the acute episode. Among the various classes of antidepressants, the majority of guidelines recommend the use of SSRIs and of bupropion, with venlafaxine or tricyclics as second choice (Figure 1).[27–31]

If the patient presents with a depressive episode and is not currently being treated with a mood stabilizer, the severity of the episode, as well as the longitudinal course of the disorder, should be assessed. For patients with a clear bipolar course of the illness, the first step may be the use of a mood stabilizer; the choice of a mood stabilizer may depend on somatic comorbidity, as well as on frequency, severity, and prevalent polarity of the relapses and history of suicidality. Lithium still represents the mood stabilizer with the best evidence of efficacy in the maintenance treatment of BD, as well as in the prevention of suicide.[33,36] Nevertheless, the use of this compound in monotherapy in acute bipolar depression is limited by the delayed onset of the therapeutic effect. For this reason, in the most severe forms of depression, the addition of a second drug to lithium should be considered. Furthermore, over the last few years, the use of lithium has often been limited, particularly in the United States, because of its potential side effects and also because of the increased availability of other therapeutic options.[106] Besides lithium, most guidelines indicate quetiapine as first choice in monotherapy, or as adjunctive therapy in combination with lithium or divalproex. Lamotrigine may be indicated, although evidence in favor of its efficacy in acute treatment is debatable. Even olanzapine may represent a therapeutic option for bipolar depression, particularly in combination with fluoxetine or other SSRIs (Figure 1).

If the patient is suffering from a depressive episode with psychotic features, the administration of antipsychotics in addition to the ongoing treatment should be considered. In the most severe forms of depression, with elevated risk of suicide or with severe psychomotor retardation, a prompt hospitalization and ECT may be necessary.

The therapeutic management of mild depressive mixed states,[107] which often occur in comorbidity with anxiety disorders, eating disorders, personality disorders, impulse control disorders, and substance abuse, is particularly complex. In fact, these conditions respond poorly to classical treatments with mood stabilizers, and the use of antidepressants is associated with a worsening of the manic/hypomanic symptomatology, in particular of psychomotor agitation, with mood destabilization in the long-term, with a trend toward chronicity and an increased suicide risk.[25,26,108] Some authors have reported a possible beneficial effect of divalproex in the treatment of depression with mixed features, as it may be indicated for the management of anxiety in comorbidity, and also of some atypical antipsychotics, in particular quetiapine and olanzapine.[107] In clinical practice, combination with mood stabilizers (lithium and anticonvulsants) and/or atypical antipsychotics (quetiapine and olanzapine) is often necessary. Even the association of psychopharmacological treatment with psychotherapy/psycho-educational interventions could be particularly useful.[109]

Conclusions

Despite the availability of several treatment options for bipolar depression, the ensuing findings from the specific literature are often controversial, and many questions remain open. Therefore, in daily clinical practice, the therapeutic choices are often empirical and guided by the personal experience of the clinician, who must assess and manage a series of variables, thus making the presentation of bipolar depression extremely heterogeneous. These include the temperamental and personality characteristics of the patient, the presence of psychiatric and somatic comorbidity, and the exposure to previous treatments, as well as the tendency of the disorder to follow also spontaneously different courses.

The main debated question in the treatment of bipolar depression remains the use of antidepressants. Given their widespread use in clinical practice, over the last few years, many studies have tried to investigate the reason for this practice,[83,110,111] and to identify clinical characteristics predictive of response to antidepressants.

Further naturalistic studies, with longer observation periods, are needed to assess whether effective treatments in the acute phase may be useful also in continuation and maintenance phases without inducing mood destabilization. Future directions should focus on better definition of response to treatment in different subtypes of bipolar depression by integrating the scientific knowledge with everyday clinical practice.

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