Review Article

Management of Bipolar Depression

Jae Seung Chang, Kyooseob Ha

ABSTRACT

Patients with bipolar disorder spend more time in a depressed than manic state, even with individualized treatment. To date, bipolar depression is often misdiagnosed and ineffectively managed both for acute episodes and residual symptoms. This review attempts to summarize the current status of available treatment strategies in the treatment of bipolar depression. For acute and prophylactic treatment, a substantial body of evidence supports the antidepressive efficacy of lithium for bipolar disorders and its antisuicidal effects. Among numerous anticonvulsants with mood-stabilizing properties, valproate and lamotrigine could be first-line options for bipolar depression. Due to receptor profile, mood-stabilizing properties of second-generation antipsychotics have been explored, and up to date, quetiapine and olanzapine appear to be a reasonable option for bipolar depression. The usefulness of antidepressants in bipolar depression is still controversial. Current guidelines generally recommend the cautious antidepressant use in combination with mood stabilizers to reduce the risk of mood elevation or cycle acceleration. Results from clinical trials on psychosocial intervention are promising, especially when integrated with pharmacotherapy. Most patients with bipolar depression need individualized and combined treatment, although the published evidence on this type of treatment strategy is limited. Future studies on the utility of currently available agents and modalities including psychosocial intervention are required.

Key words: *Anticonvulsants, antidepressants, bipolar depression, lithium, psychosocial intervention, second-generation antipsychotics*

INTRODUCTION

Bipolar disorder is a highly relapsing condition associated with psychosocial dysfunction and socioeconomic burden.[1,2] Despite clinical prominence of manic symptoms, individuals with bipolar disorders spend a larger proportion of their lives in a depressed state.[3,4] Although the number of approved therapeutic agents is continually increasing, a large proportion of patients with bipolar depression do not benefit from adequate trials.[5,6]

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The benefits and drawbacks of pharmacotherapy for bipolar depression with a specific agent need to be extensively explored for making evidence-based decisions regarding the effective management of this condition. However, even the new advances in recommendations from updated guidelines are less definitive and more controversial for bipolar depression than for mania.[7] Different compounds and therapeutic modalities may be differentially effective against specific facets of bipolar disorders. This review provides a brief summary of current treatment strategies in the acute and prophylactic treatment of bipolar depression.

MANAGEMENT OF ACUTE BIPOLAR DEPRESSION

Lithium in acute bipolar depression

Lithium is a highly cost-effective treatment for all phases of bipolar disorder including acute depression.[8] Current

Department of Psychiatry and Behavioral Neuroscience, Seoul National University College of Medicine, Seoul, South Korea

Address of correspondence: Dr. Kyooseob Ha
Department of Psychiatry and Behavioral Neuroscience, Seoul National University College of Medicine, Seoul, South Korea.
E-mail: kyooha@snu.ac.kr

guidelines recommend lithium as a first-line treatment for acute bipolar depression.[9,10] A systematic review of randomized trials also revealed the favorable effects of lithium on the prevention of suicide and self-harm in patients with bipolar disorders.[11] On the other hand, in a recent 8-week placebo-controlled trial comparing lithium and quetiapine, lithium monotherapy (N=136) did not differ from placebo (N=133) in reducing depression severity.[12] In order to strengthen the effectiveness of lithium in bipolar depression, augmenting lithium with lamotrigine, valproate, or antidepressants may be clinically plausible.[13,14]

Anticonvulsants in acute bipolar depression

Valproate

Valproate, either as divalproex or as other formulations, is widely used for treatment of bipolar disorders. Current guidelines for pharmacological options also recommend valproate monotherapy or cotherapy with other agents as a first- or second-line treatment for acute bipolar depression.[9,10,15] A recent meta-analysis demonstrated that valproate treatment is associated with the reduction of depression severity in acute bipolar depression,[16] but the small sample size of included trials may compromise the generalizability of these findings. Adequately powered studies are warranted to determine antidepressant properties of valproate.

Carbamazepine and oxcarbazepine

Both carbamazepine and oxcarbazepine are currently considered the primary medications for bipolar disorder. At least for selected subpopulations, carbamazepine and oxcarbazepine may exert a beneficial influence on mood fluctuation comparable with other mood stabilizers.[17,18] In addition, relatively lower risk of weight gain and metabolic problems compared with other mood stabilizers may lead clinicians to explore the usefulness of these agents in patients with bipolar disorders.[19] Although the results from previous trials are limited by the use of heterogeneous samples (both bipolar and unipolar), antidepressant effects of carbamazepine has been suggested.[20,21] Current guidelines recommend carbamazepine and oxcarbazepine as a second- or third-line treatment for acute bipolar depression.[10,15]

Lamotrigine

Lamotrigine is one of the most studied anticonvulsants for the treatment of bipolar depression and is currently used to manage depressive symptoms associated with bipolar disorders. Although a growing body of evidence from naturalistic data and controlled trials indicates that long-term lamotrigine therapy may be effective in alleviating symptoms of bipolar depression,[22,23] the results of placebo-controlled trials did not confirm antidepressant effects of lamotrigine on acute phase of bipolar depression.[24] A recent systematic meta-analysis was conducted on data from 1 072 patients in all five randomized trials comparing lamotrigine with placebo, and demonstrated the usefulness of lamotrigine in acute bipolar depression, especially for severely ill patients.[25] In addition, results from a recent randomized controlled trial suggested the therapeutic benefits of adding lamotrigine to lithium in patients with acute bipolar depression.[13] Therefore, current guidelines classify lamotrigine into a first-line treatment option for acute bipolar depression.[9,10,15]

Second-generation antipsychotics in acute bipolar depression

Second-generation antipsychotics (SGAs) have emerged as new treatment options for bipolar depression. Substantial data from randomized trials implicate antidepressant effects of SGAs, and current guidelines are updating the potential role of SGAs based on published materials.

Olanzapine

Numerous studies have been conducted to assess the efficacy and safety of olanzapine in the treatment of bipolar disorders, mainly focused on the treatment of mania. The olanzapine-fluoxetine combination (OFC) has been studied in the treatment of bipolar depression. In an 8-week double-blind trial comparing olanzapine (N=370), OFC (N=86), and placebo (N=377), OFC showed superior efficacy over olanzapine and placebo in treating depressive symptoms of patients with bipolar I disorder.[26] Olanzapine was also more effective in reducing depression severity than placebo. Both olanzapine and OFC also led to greater improvement of subjects' health-related quality of life compared with placebo.[27] In a 7-week double-blind trial, greater improvement of bipolar depression was associated with OFC compared with lamotrigine, but this finding could be partly attributed to the differences in titration schedule.[28] Furthermore, lamotrigine showed clear advantages in metabolic profile over OFC. Olanzapine and OFC are generally recommended as a first- or second-line treatment for acute bipolar depression.[10,15]

Quetiapine

Quetiapine is the first SGA licensed for acute treatment of bipolar depression based on the results from six double-blind, randomized placebo controlled studies.[29] Antidepressant efficacy of quetiapine at a dose of 300 or 600 mg/day was first noticed in two 8-week randomized controlled trials (BOLDER studies).[30,31] The effectiveness of quetiapine was recently replicated in acute bipolar depression through two 8-week double-blind trials conducted by multicenters throughout Europe, Canada, and Asia (EMBOLDEN studies).[12,32] Oversedation appears to be the main obstacle compromising the use of quetiapine in acute phase

of bipolar depression.[29] All updated guidelines for the treatment of acute bipolar depression recommend quetiapine as a first-line option.[9,10,15]

Antidepressants in acute bipolar depression

As for the management of bipolar depression, a tricky point is that clinical data from unipolar depression cannot be transferred and applied directly to bipolar depression. Despite phenomenological similarities, the neurobiological link between unipolar and bipolar depression still remained an unsolved problem.[33] Therefore, treating bipolar depression is the main obstacle to clinicians managing patients with bipolar disorders, since a growing body of evidence suggests that bipolar patients spend much more time depressed than manic, although mostly subsyndromal.[3,34] Because psychiatrists are highly concerned about the efficacy of antidepressant monotherapy in treating bipolar depression and the risk of polarity switch and cycle acceleration,[35] adding an antidepressant to ongoing mood stabilizers is often considered as an aggressive approach.[36] Although confirmatory evidence for antidepressant-induced hypomania/mania was not found through a meta-analysis and systematic reviews of antidepressant trials for bipolar depression,[37-39] the limitations in the designs of previous trials could make a substantial contribution toward these results. Both clinical characteristics of individuals and biochemical profile of antidepressants may be involved in affective instability led by antidepressant use.[40,41] With regards to the risk of polarity switch and overdose, selective serotonin reuptake inhibitors are generally preferable to tricyclic antidepressants.[7] Depressed patients with bipolar disorders inadequately responsive to mood stabilizers, at least in part, may be benefited from the addition of an antidepressant.[42] For instance, in combination with olanzapine, fluoxetine can be prescribed safely for bipolar depression.[26] Given the high rate of antidepressant use in treating bipolar depression in a real-world practice,[43] further controlled trials are needed to understand the potential role of antidepressants. Current guidelines generally recommend antidepressants combined with a mood stabilizer as a first- or second-line treatment for acute bipolar depression.[9,10]

Other agents and therapeutic modalities

To control sleep disturbance and anxiety symptoms of acute bipolar depression, benzodiazepines can be used as adjunctive medication regardless of antidepressant efficacy.[42] Dopamine agonists, especially pramipexole, have been tested for their possible antidepressant effects. In a 6-week randomized placebo-controlled trial, pramipexole led to a greater reduction of depression severity in patients with bipolar depression than placebo.[44] Antidepressant efficacy of pramipexole was also demonstrated in the treatment of bipolar II depression.[45] Adjunctive modafinil at doses of 100 to 200 mg/day was effective for depressive symptoms in patients with bipolar disorders inadequately responsive to a mood stabilizer.[46] Inositol augmentation of mood stabilizers can be a possible option for refractory depressive patients with bipolar disorders.[47] Electroconvulsive therapy can serve as one of the acute treatment options for bipolar depressive patients resistant to conventional mood stabilizers.[48]

MAINTENANCE THERAPY FOR BIPOLAR DEPRESSION

Because mania and depression are inseparable with regards to the maintenance therapy for bipolar disorders, long-term mood-stabilization can be a practical goal to prevent bipolar depression. Interepisode residual symptoms are now recognized as a strong predictor of recurrence in the long-term course of bipolar disorders.[49]

Pharmacological treatments for prophylaxis and maintenance

In addition to acute antidepressant effects of lithium, long-term use of lithium has been considered to provide a recurrence-prevention not only to mania but also to depression.[50,51] Discrepancies in the results between early and more recent maintenance trials may be attributable to a cohort effect, which means responders to long-term lithium use are unavailable for recent trials.[52] Again, antisuicidal effects of lithium is highly advantageous in the maintenance therapy for patients with bipolar disorders, especially those with residual depressive symptoms.[11]

A substantial body of evidence support the prophylactic efficacy of valproate and carbamazepine in the maintenance treatment of bipolar disorders.[53] In addition, valproate can be a reasonable option for bipolar patients with co-occurring alcohol dependence.[54] The prophylactic efficacy of lamotrigine appears to be comparable with lithium under clinical routine conditions.[55] In a recent 52-week naturalistic study, sustained improvement of residual depressive symptoms with adjunctive lamotrigine was found in 109 patients with bipolar II depression partially responsive to mood stabilizers.[56] Considering weak protection of lamotrigine against manic symptoms, adjunctive use of lamotrigine may be clinically meaningful.

Long-term use of olanzapine, when used as monotherapy or adjunctive therapy, appears to delay time to relapse into any mood episodes.[57,58] As for OFC, a recent 6-month double-blind trial comparing OFC with lamotrigine demonstrated a greater improvement in patients treated with OFC than those treated with

lamotrigine.[59] The prophylactic efficacy of quetiapine has been supported by the results of randomized controlled trials assessing time to recurrence of any mood event.[10] Both quetiapine monotherapy and cotherapy with a mood stabilizer can be useful in the prophylaxis of depressive episode.[60-62] Despite the lack of data on long-term use of risperidone in bipolar disorders,[10] risperidone long-acting injection, when used as monotherapy or adjunctive therapy, may exert a beneficial effect on long-term mood stabilization of bipolar disorder.[63] Although aripiprazole monotherapy failed to show the prophylactic efficacy for bipolar depression,[64,65] the long-term effectiveness of adjunctive aripiprazole for residual depressive symptoms needs to be explored. In a recent 6-month double-blind trial, adjunctive ziprasidone with a mood stabilizer was effective in delaying time to intervention for depressive episode.[66] Ziprasidone possesses a favorable tolerability profile different from other SGAs, especially with regards to metabolic effects,[67] thereby suggesting its advantage in the maintenance treatment of bipolar disorders. Clozapine, a prototype of SGA that has been widely used for treatment-resistant schizophrenia, can also serve as an augmenting agent for long-term prophylaxis of depressive episodes in refractory cases.[68]

As for the long-term use of antidepressants in bipolar disorders, the results of a 26-week large placebo-controlled trial did not confirm the superior efficacy of adjunctive antidepressant over adjunctive placebo in bipolar depressed patients receiving a mood stabilizer.[6] A systematic review of antidepressants in people with bipolar disorder concluded that they are effective and unlikely to cause mood switching in the short term.[37] Nonetheless, some have expressed concerns that these agents do increase switch rates and destabilize the long-term clinical course.[69]

Psychosocial interventions for maintenance therapy

Although pharmacotherapy is the mainstay of the management of bipolar depression, medication alone is often not enough to address residual depressive symptoms, medication adherence, and psychosocial functioning.[70] After remission of acute mood episodes, 40% of patients with bipolar disorders continue to suffer from subsyndromal symptoms, with 32% of them presenting depressive symptoms.[3,71] In addition, subsyndromal depressive symptoms negatively influence relapse and quality of life,[72] and confers substantive risk of suicide.[73] Poor adherence to medication is also a major cause of relapse in bipolar disorders.[74] Accumulated data from randomized controlled trials suggest that psychosocial interventions are valuable in improving long-term outcome of bipolar depression.[75] Group-based psychoeducation can offer practical and ongoing help to psychosocial functioning and medication adherence.[76,77] Cognitive behavior therapy appears to be helpful in improving long-term outcome of bipolar disorders.[78] Family therapy and social rhythm therapy are also promising options for adjunctive psychosocial interventions.[70] Psychosocial interventions should be utilized as a routine component of management, and as early after diagnosis as feasible. Future studies are needed to explore what type of psychosocial intervention is most beneficial for particular patients at particular stages of bipolar depression.

CONCLUSION

Bipolar depression is a complex condition which constantly poses diagnostic and therapeutic challenges. Given the differences in pathophysiology between unipolar and bipolar depression, overall treatment strategies should be tested independently. Differences in recommendations of treatment guidelines for bipolar depression stems from the debates on the possible options for the treatment of bipolar depression.[79] Nonetheless, first- or second-line options for acute bipolar depression is increasing based on newly published data from well-designed studies. Lithium, quetiapine, and lamotrigine seem to be well-established pharmacotherapeutic options for bipolar depression. The usefulness of antidepressants still needs to be explored through randomized controlled trials. Psychosocial interventions may enhance adherence to psychiatric treatment, and thus contribute to the prophylaxis of episodic recurrences. This review highlights that the management of bipolar depression should be multifaceted and individualized with aid of current guidelines.

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