Bipolar Depression: Diagnostic Dilemmas to Innovative Treatments

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This activity is intended for physicians, physician assistants, nurse practitioners, and registered nurses engaged in the care of patients with major depression.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Discuss the prevalence of bipolar disorder in different psychiatric patients.
- Describe the different symptoms that occur in children, adolescents, and adults.
- Use the evidence base, including FDA approval for different treatments, to inform therapy for bipolar depression.
- Provide details to ensure that physicians consider the potential metabolic profile of antipsychotics when choosing agents.

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Toward a Better Understanding of the Bipolar Depression Spectrum

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BOTTOM LINE: Toward a Better Understanding of the Bipolar Depression Spectrum

Depressive symptoms and episodes are the predominant presentation of bipolar disorder and account for much of the morbidity associated with the illness. Mixed features in bipolar disorder are common, associated with a more complex and severe illness presentation, linked to suicide and comorbidity (eg, obesity), and often lead to misdiagnosis.

Introduction

Bipolar disorder (BD) is a severe, lifelong disorder associated with high rates of nonrecovery, chronicity, and premature mortality.[1] The actionable opportunity for reducing the morbidity and mortality of BD is to address current unmet needs. Herein, we review the current unmet needs in BD: (1) suboptimal diagnostic accuracy/ timeliness; (2) insufficient treatments for bipolar depression, anxiety, and cognitive symptoms; (3) the management of comorbidity; and (4) treatments capable of improving functional recovery/integration (***Table 1***).

Suboptimal diagnostic accuracy and timeliness

It has been amply documented that most individuals with BD are not diagnosed accurately or in a timely manner. Individuals with BD experience observable characteristics of the disorder for approximately 8 to 10 years before the diagnosis is applied, despite contact with approximately 2 to 4 health care providers during that time.[2] Misdiagnosis and delayed diagnosis are influenced by multiple factors, including, but not limited to, the predominance of depressive and anxious symptoms at initial presentation and during the longitudinal course of the illness (***Tables 2, 3***).[3]

Screening for BD is augmented by the use of reliable, valid, sensitive, and specific screening tools. Multiple screening tools for BD are considered sufficient psychometrically and complement the detection and diagnostic process of BD.[4] However, a major limitation of screening tools for BD is their suboptimal specificity. Moreover, the psychometric performance of the screening tools is influenced by the ecosystem wherein they are administered, with better screening tool performance in specialty care settings.[5] Implementation barriers for screening tools are protean, including the length of administration decreasing patient acceptability for both patient- and clinician-administered screening tools.

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An unanswered question, however, is how do existing screening tools for BD, as well as their briefer variants, perform in detecting BD in more recently encountered clinical cohorts? For example, persons with BD with predominantly mixed presentations, which is becoming the predominant presentation of BD, are much less likely to endorse elation, as well as mood congruent psychotic features and behaviors. Instead, more persons with BD are likely to endorse dysphoric symptoms, many of which are captured in the DSM-5 polythetic list for mixed features specifier (***Table 4***).[6,7]

Replicated evidence indicates that approximately 10% of individuals with "major depressive disorder" (MDD) (ie, pseudounipolar) will declare BD across 10 years of observation.[8] Results from a recent study conducted utilizing a cross national pharmaco-epidemiological database in Taiwan indicates that the probability that an individual's diagnosis will shift from major MDD to BD increases as

TABLE 1

Unmet needs of bipolar disorder

1) Suboptimal diagnostic accuracy and timeliness
2) Insufficient treatments for bipolar depression, anxiety symptoms, and cognitive function
3) Anti-suicide treatments
4) The management of comorbidity
5) Treatments capable of improving functional recovery/ integration

a function of the number of insufficient antidepressants, with rates of approximately 25% declaring BD after 3 insufficient antidepressant trials.[8]

Insufficient treatment for bipolar depression and cognitive symptoms

Currently, only 4 treatments are US Food and Drug Administration (FDA)-approved for BD (cariprazine, quetiapine, lurasidone, and olanzapine-fluoxetine combination [OFC]). Cariprazine and quetiapine are also indicated for mania and mixed episodes, while quetiapine has an additional maintenance indication. A limitation, however, of quetiapine and OFC is significant rates of sedation/ somnolence and clinically significant weight gain/metabolic disturbance. Cariprazine is the newest FDA agent approved for BD. Cariprazine is a "D3 preferring" D3D2 partial agonist. The rationale for evaluating cariprazine in BD is provided in part by this agent's ability to engage D3 systems. D3 receptors are implicated in key dimensions of depression, including cognition, motivation, and reward.[9,10] Pharmacologic and preclinical models (eg, D3 knockout models) indicate that D3 receptors are disproportionately localized in reward substrates (such as nucleus accumbens) as well as cognitive control networks and structures (eg, hippocampus).[11] It could be conjectured that cariprazine may have salutary direct and independent effects on measures of motivation and reward, as well as reward decision making (eg, alcohol use and substance use disorders).

Other treatments that are not FDA-approved but have evidence supporting efficacy in BD are lamotrigine, lithium, and electroconvulsive therapy (ECT). Manualized-based therapies (eg, cognitive-behavioral therapy [CBT] and interpersonal rhythm therapy [IPSRT]) also demonstrate antidepressant activity, with most evidence indicating recurrence prevention effects rather than acute antidepressant effects.[12]

Conventional antidepressants have not been FDA-approved for BD, yet are frequently prescribed. Controversy exists regarding the deft and safe application of antidepressants in BD. The hazards for destabilization are well-described, with perhaps greater hazard with antidepressants that engage norepinephrine (eg, venlafaxine, desipramine) and when used in monotherapy in Bipolar I disorder (BD-I).[13] Emerging evidence indicates that select subpopulations of persons with Bipolar II disorder (BD-II) may be safely and effectively treated with antidepressant monotherapy (ie, sertraline, fluoxetine, venlafaxine).[14] No sufficient and compelling evidence supporting antidepressant monotherapy in BD-II currently exists.

Disturbances in cognitive functions in BD are prevalent, often progressive, and are pervasive in all domains of cognitive function (eg, executive function, attention, memory).[15] Additional lines of evidence indicate that cognitive dysfunction in BD is an endophenotype and worsens as a function of episode frequency.[16] Cognitive dysfunction in mood disorders, both MDD and BD, warrants attention from clinicians as it is shown to be the principle reason many patients affected by either of these conditions cannot function optimally.[17]

In MDD, the FDA recognizes only 1 antidepressant (vortioxetine) as having direct, independent, and clinically relevant effects on cognitive functions.[18] In BD, however, no existing agent has demonstrated robust and replicated efficacy in targeting cognitive functions in large, randomized, double-blind, placebo-controlled pivotal trials. Consequently, the FDA has not recognized the pro-cognitive effects of any treatment for BD. More than 2 dozen putative therapeutic agents for cognition in BD have been suggested based on results from relatively small, often single-center studies. These agents are from disparate classes of therapeutics, including but not limited to antipsychotics, stimulants, anti-inflammatory, metabolic agents, and trophic agents.[15] In the interim, clinicians are encouraged to consider screening for cognition in BD until interventional agents are discovered. Preventative efforts are encouraged, including episode frequency reduction, managing comorbidities (eg, hypothyroidism, obesity, and diabetes mellitus), removal of anti-cognitive therapeutics (eg, benzodiazepines), and the reduction of alcohol use and discontinuation of marijuana and illicit substances.[19]

TABLE 2

Factors suggestive of bipolar disorder versus major depressive disorder

Phenomenology	Atypical symptoms (eg, hyperphagia, hypersomnia), psychotic symptoms, mood reactivity, anxiety, circadian disturbance
Age of onset	Adolescent-early adult onset of illness
Family history	Positive for psychopathology; extensive family loading
Course of illness	More frequent episodes
Pattern of comorbidity	High rate of poly comorbidity (ie, 3 or more comorbid conditions, usually anxiety disorders, substance/alcohol misuse disorders, attention-deficit/hyperactivity disorder, binge eating disorders, personality disorders, migraine, obesity, diabetes, and cardiovascular)
Association with reproductive life events	Onset/recurrence during pregnancy, postpartum, and/or related to menstrual cycle
Treatment-emergent mania as a consequence of conventional antidepressants	

TABLE 3

Benchmarking kappa correlational coefficients[25]

Interclass kappa range	Reliability
0.60–0.79	Very good
0.40–0.59	Good
0.20–0.39	Questionable
<0.20	Poor

TABLE 4

The Four A's of bipolar mixed[26]

Anxiety
Agitation
Anger
Attentional problems

Management of comorbidities

Most individuals with BD meet criteria for an additional mental disorder. Commonly encountered medical disorders that disproportionately affect individuals with BD are obesity, cardiovascular disorders, diabetes mellitus, and migraine. The over representation of these non-communicable medical disorders in BD has provided the basis for hypothesizing that common neurobiological and socio-ecological factors that affect the risk for BD also contribute to medical disorders. For example, disturbances in immune inflammatory systems (ie, meta-inflammation) have been implicated in the phenomenology and treatment of BD as well as the over-representation of inflammatory-mediated comorbidities in BD.[20] Further evidence supporting disturbances in immune-inflammatory systems, metabolic homeostasis, and the stress response axis in BD is provided by replicated evidence indicating that exposure to childhood physical and sexual abuse is highly associated with medical morbidity in BD and a more complex bipolar presentation, course, and outcome.[21] Preliminary evidence suggests that individuals with histories of trauma in BD may be more likely to benefit from treatments that primarily target the immune inflammatory system.[22]

Taken together, the available data suggest that all patients with BD should be screened and clinically evaluated for the presence of psychiatric and medical comorbidities, and contemporaneous treatment must occur when present. This foregoing point is instantiated by evidence indicating that the presence of medical comorbidity (eg, obesity) interferes with cognitive function and depressive symptom recovery in BD, and may be changing the phenotype of BD. For example, it has been conjectured that obesity is changing the phenotype of BD away from a predominantly euphoric presentation toward a mixed dysphoric presentation.[23] The basis for hypothesizing such a phenomenon is supported by neuroscience evidence wherein obesity affects brain topology (ie, obesity metastasis to the brain).[23]

Treatments capable of improving functional integration

The complex and pervasive functional problems in BD provide the impetus for parsing key mediational factors. Convergent evidence indicates that disturbances in depression and cognition are key mediators of functional impairment in BD. It stands to reason that preservation and improvement in cognitive and depressive symptoms would improve overall function. Notwithstanding, a significant degree of functional impairment persists even among individuals who are euthymic and without cognitive impairment.

Available evidence indicates that functional recovery in BD, particularly in multi-stage progressed BD, is achieved best with functional remediation.[24] Functional remediation is a systematic and integrated multidisciplinary approach targeting not only psychopathology but also aspects of resiliency, well-being, and motivational dimensions. The integration of multi-disciplinary services, preferably in a single center, appears to provide for better outcome opportunities among individuals who suffer from BD. Moreover, the observation that decrements in psychosocial functioning are most pronounced early in the illness course provides additional incentive for timely diagnosis and treatment.

Conclusion

The portrait sketched of BD is one of severity, heterogeneity, multi-dimensionality, and comorbidity. The burden of illness in BD is staggering and multiple novel treatment avenues are currently being pursued. In the interim, narrowing the "knowing-doing" gap (ie, what is known in medicine versus what is done) holds promise to reduce morbidity and improve the quality of life and function in BD.

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Recent Advances in Treatment of Bipolar Depression

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BOTTOM LINE: Innovative Strategies for Treatment of Depressive Episode in Bipolar Disorder: A Brief Review of Recent Developments

Depression accounts for most of the disease burden in BD; hence, it must be treated aggressively. This article provides guidance for clinicians on current and novel strategies for management of depression in BD.

Introduction

Bipolar disorder (BD) is characterized by manic and depressive episodes. Although mania is the defining feature of BD, depression is the predominant pole of this illness. About two-thirds of patients with bipolar I disorder (BD-I) present with depression as the first mood episode. Depressive episodes lead to significant work and psychosocial impairment and are associated with a significant increased risk of suicide and dysfunction. Therefore, treatment of depression is a significant unmet need in the management of BD. Indeed, the National Institute of Mental Health longitudinal study of BD-I in clinical settings demonstrated that patients with BD-I are euthymic only about half the time; the other half the time, they experience syndromal or subsyndromal mood symptoms. Weeks with depressive symptoms/episodes outnumber manic/hypomanic symptoms/episodes by a ratio of 3 to 1. Despite the frequency and significant dysfunction associated with depressive episodes in BD-I, fewer approved treatment options exist for management of depression in this population.

This article will review current and newer pharmacological and somatic treatment options and provide guidance to clinicians for management of depression in BD-I.

Pharmacotherapy for acute bipolar I depression

Monotherapy

A total of 23 double-blind placebo-controlled randomized controlled trials (RCTs) have assessed the efficacy of various agents for treatment of acute bipolar depression (***Table 1***).[1] These include lithium, lamotrigine, aripiprazole, olanzapine, ziprasidone, quetiapine, paroxetine, lurasidone, and cariprazine. Of these 23 trials, only 11 studies have been positive, ie, the agent tested was more effective than placebo in improving depressive symptoms on the primary efficacy measure in only 11 trials (***Table 1***).

Quetiapine IR and XR have been tested in 5 large RCTs. In all 5 studies, quetiapine monotherapy was more effective than placebo in improving depressive symptoms, suggesting that quetiapine monotherapy is clearly effective in treating acute bipolar I depression, which led to US Food and Drug Administration (FDA) approval for this indication. Although olanzapine was also superior to placebo in 2 RCTs, improvements in sub-items of sleep, appetite, and inner tension but not in core symptoms of depression contributed to the efficacy of olanzapine monotherapy. This might have been why Lilly had not sought FDA approval for olanzapine monotherapy for acute bipolar depression.

Lurasidone was examined for its efficacy in a large double blind placebo controlled trial of 6 weeks duration. Lurasidone was more effective than placebo in improving depressive symptoms, as indicated by a greater reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) scores of 15.44 compared with the placebo group, which had a reduction in MADRS scores of 10.7. The separation from placebo occurred at as early as week 2. The data showed that 51% to 53% of patients in the

TABLE 1

Treatment of Acute Bipolar Depression

No. of Trials	Agent vs Placebo	Author	Primary Outcome
1	Lithium	Young et al 2010	Negative
5	Lamotrigine	Calabrese et al 2008	All 5 negative
2	Aripiprazole	Thase et al 2008	Negative
2	Olanzapine	Tohen et al 2012 Katagiri et al 2013	Positive
2	Ziprasidone	Lombardo et al 2012	Negative
5	Quetiapine	Calabrese et al 2005, Thase et al 2006, Young et al 2010, McElroy et al 2010, Suppes 2010	All 5 positive
1	Paroxetine	McElroy et al 2010	Negative
1	Lurasidone	Loebel et al 2014	Positive
4	Cariprazine	Durgam et al 2016, Earley et al 2019, Saraf et al 2019	1 Negative/ 3 Positive
Total 23			**Only 11 out of 23 positive**

Young AH, et al. *J Clin Psychiatry*. 2010;71(2):150-162.; Calabrese JR, et al. *Bipolar Disord*. 2008;10(2):323-333.; Thase ME, et al. *J Clin Psychopharmacol*. 2008;28(1):13-20.; Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.; Katagiri H, et al. *BMC Psychiatry*. 2013;13:138.;Tohen M, et al. *Br J Psychiatry*. 2012;201(5):376-382.; Lombardo I, et al. *J Clin Psychopharmacol*. 2012;23(4):470-478.; Calabrese JR, et al. *Am J Psychiatry*. 2005;162(7):1351-1360.; Thase ME, et al. *J Clin Psychopharmacol*. 2006;26(6):600-609.; McElroy SL, et al. *J Clin Psychiatry*. 2010;71(2):163-174.; Suppes T, et al. *J Affect Disord*. 2010;121(1-2):106-115.; Loebel, et al. *Am J Psychiatry*. 2014;171(2):160-168.; Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-281.; Earley W, et al. *Am J Psychiatry*. 2019;176(6):439-448; Saraf G, et al. *Expert Opinion Pharmacother*. 2019; In press.

lurasidone monotherapy groups responded compared with 30% of patients in the placebo group; these differences were statistically significant. In general, lurasidone was well-tolerated, with only akathisia, extrapyramidal symptoms, somnolence, nausea, headache, sedation, and dry mouth being more common in the lurasidone groups than placebo groups.

Cariprazine, a D2 and D3 partial agonist with preferential affinity for D3 receptors, has been examined in 4 double-blind placebo-controlled trials (RGH-MD52, RGH-MD56, RGH-MD53, and RGH-MD54).[2-4] In 3 (RGH-MD56, RGH-MD53, and RGH-MD54) of these 4 trials, cariprazine 1.5 mg per day was more effective than placebo in improving depressive symptoms, as measured by improvement in MADRS scores from baseline. The RGH-MD56 study[2] was of 8 weeks duration and included 3 different doses of cariprazine (0.75 mg, 1.5 mg, and 3 mg) as well as placebo. This study and the previous RGH-MD52 study clearly demonstrated that 0.75 mg per day was not effective; hence, this dose was dropped in the subsequent 2 studies of cariprazine. In all 3 positive studies, the primary efficacy measure was change in total MADRS score from baseline to week 6. In each study, cariprazine 1.5 mg was more effective than placebo in improving depressive symptoms at the 6-week primary endpoint. The 3 mg per day dose was more effective than placebo in the RGH-MD54 study, but not RGH-MD53 or RGH-MD56. Response rates, as defined by ≥50% reduction in total MADRS scores from baseline to week 6, were greater in RGH-MD56 and RGH-MD54, but not in RGH-MD53. Similarly, remission rates, defined as a total MADRS score of ≤10, were significantly greater than placebo in RGH-MD54 and RGH-MD56, but not RGH-MD53. Cariprazine was generally well-tolerated, with headache, akathisia, restlessness, and nausea being more common in the cariprazine groups compared with the placebo groups. The changes in weight were minimal in the cariprazine group relative to placebo. Similarly, there were no significant changes in lipid or glucose profiles in the cariprazine group relative to placebo.[3]

In summary, only atypical antipsychotic monotherapy has demonstrated efficacy in double blind RCTs for acute bipolar I depression. Of the 4 atypical antipsychotics with positive data, 3 (quetiapine, lurasidone, and cariprazine) have been approved by the FDA for treatment of acute bipolar I depression.

Combination therapy

A total of 12 double-blind RCTs have assessed combination therapy in the management of acute bipolar I depression. Of these, only 5 studies showed that the combination was more effective than placebo adjunctive therapy (***Table 2***).

Olanzapine plus fluoxetine combination (OFC) therapy was more effective than placebo plus olanzapine in improving depressive symptoms in the only RCT. Based on this, the FDA approved OFC for treatment of acute bipolar I depression. In investigator-initiated smaller RCTs, lamotrigine adjunctive therapy to lithium as well as modafinil adjunctive therapy were more effective than placebo adjunctive therapy. However, armodafinil adjunctive therapy was not effective in 2 larger RCTs.[1]

Lurasidone adjunctive therapy was approved by the FDA for treatment of acute bipolar I depression. Two studies assessed the efficacy of lurasidone adjunctive therapy; of these, lurasidone adjunctive therapy was more effective than placebo adjunctive therapy in improving bipolar depressive symptoms in only 1 study. In this study, the separation from placebo adjunctive therapy began as early as week 3 and the improvement was maintained to the primary endpoint of

TABLE 2

Augmentation Studies in Bipolar Depression

Agent	Author	Primary Outcome
Paroxetine+lithium vs imipramine+lithium vs placebo+lithium	Nemeroff et al 2001	Negative
MS+paroxetine or bupropion vs MS+placebo	Sachs et al 2007	Negative
OFC vs olanzapine vs placebo	Tohen et al 2003	Positive
Lamotrigine+lithium vs placebo+lithium	Van der Loos et al 2009	Positive
Adjunctive modafinil vs placebo; adjunctive armodafinil vs placebo	Frye et al 2007, Calabrese et al 2010, Calabrese et al 2014	Positive/Negative/Positive
Adjunctive levetiracetam vs placebo	Saricicek et al 2011	Negative
Adjunctive ziprasidone vs placebo	Sachs et al 2011	Negative
Agomelatine + MS vs placebo + MS	Yatham et al 2015	Negative
Lurasidone + MS vs placebo + MS	Loebel et al 2014 Suppes et al 2016	Positive Negative
Total 12		**5 out of 12 positive**

Abbreviations: MS, mood stabilizer.

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6 weeks. Regarding responder rates, 57% of patients in the lurasidone adjunctive therapy group met the criteria for a response compared with 42% in the placebo adjunctive therapy group. In general, lurasidone adjunctive therapy was well-tolerated with only nausea, extrapyramidal symptoms, tremor, akathisia, and insomnia greater than in the placebo group.

The role of antidepressants in the treatment of bipolar depression

There has been continued controversy about the role of antidepressants in the treatment of acute bipolar I depression. Although antidepressants are widely used as adjunctive therapy in real world clinical settings, only one RCT (fluoxetine adjunctive therapy to olanzapine) supported their efficacy. The other larger RCTs that assessed the efficacy of paroxetine, bupropion, and agomelatine adjunctive therapies failed to demonstrate their benefit on the primary efficacy measure, although a post-hoc analysis supported the efficacy of agomelatine adjunctive therapy.

A total of 4 meta-analyses have been conducted that included studies comparing the efficacy of antidepressant therapy with placebo. Of these 4 meta-analyses, 3 showed superiority of antidepressants versus placebo, with the fourth showing a trend toward superiority ($P = .06$). A more recent meta-analysis,[5] which restricted the inclusion of studies to only those that assessed second generation antidepressant adjunctive therapy, reported that modern antidepressant adjunctive therapy was more effective than placebo adjunctive therapy in improving depressive symptoms. However, the effect size for efficacy was only 0.165, suggesting that while antidepressant adjunctive therapy may be effective, the magnitude of benefit is only modest. Further, this meta-analysis examined both short-term and long-term manic switch risk and the results showed that while there was no increase in manic switch risk during the acute treatment period, there was a significant increase in manic switch in the long-term, if antidepressants were continued for 1 year, with an odds ratio of 1.774. Therefore, this meta-analysis suggests that if antidepressants are used for the treatment of acute bipolar depression, they need to be discontinued after remission of depressive symptoms as long term continuation is associated with an increased switch risk.

ECT for treatment-resistant depression

Electroconvulsive therapy (ECT) was effective for treating acute bipolar depression in previous studies. A more recent study showed that ECT was twice as effective as algorithm-based pharmacological treatment in bipolar depressed patients who were resistant to pharmacotherapy.[6] The response rates in the ECT group were close to 74% versus 35% in the algorithm-based pharmacotherapy group, indicating that ECT is twice as effective as pharmacotherapy in improving treatment-resistant bipolar depression.

Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT/ISBD) guidelines for management of bipolar depression

These guidelines provide hierarchical rankings for first- and second-line treatments based on the efficacy and tolerability of agents for various phases of bipolar disorder.[1] For acute bipolar I depression, the guidelines recommend quetiapine, lurasidone adjunctive therapy, lithium, lamotrigine, lurasidone, and lamotrigine adjunctive therapy as first-line agents, in that order. Divalproex, adjunctive antidepressant therapy, ECT, cariprazine, and

OFC are recommended as second-line agents.[1] If clinical experience supports the efficacy of cariprazine, it will likely be moved to a first-line agent in the next revision of CANMAT/ISBD guidelines.

Dosing and tolerability considerations

Quetiapine or quetiapine XR can be started at 50 mg daily, with a target dose of between 200 and 300 mg per day. There is no evidence that doses higher than 300 mg per day of quetiapine or quetiapine XR are more effective in treating acute bipolar I depression, although some patients may require higher doses. Sedation is a significant concern when quetiapine is used for treating acute bipolar I depression.[1]

Lurasidone can be started at 20 mg daily and increased to 120 mg, although the target for most patients is about 60 mg per day.[1] If significant akathisia is noted with 20 mg per day and it does not improve within 4 to 7 days, lurasidone may not be an appropriate option for that particular patient.

Cariprazine can be started at 1.5 mg as this dose was reasonably well-tolerated in clinical trials and has the best evidence for efficacy. Akathisia and nausea can occur in some patients with cariprazine. The weight gain is minimal, and it has good tolerability profile from a metabolic side effects perspective.[3]

Non-invasive brain stimulation treatments

Although transcranial magnetic stimulation (TMS) has been studied widely and approved for treatment of major depressive disorder, there is dearth of data for its efficacy in treating acute bipolar I depression. A meta-analysis that included data from various small RCTs with differing stimulation parameters reported that repetitive TMS (rTMS) was effective in treating acute bipolar I depression.[7] However, the effect size for its efficacy was modest. Larger trials with more valid methodology are needed to confirm its efficacy.

A recent study reported that transcranial direct current stimulation (tDCS) was significantly more effective than sham tDCS in improving depressive symptoms in BD-I and BD-II depression.[8] Patients in this study received 30-minute daily sessions of treatment 5 days a week for 2 weeks, followed by two more sessions at 2-week intervals. The response rates were 68% in the active group vs 30% in the sham treatment group with a number needed to treat of 5.8, suggesting that tDCS is effective in treating acute bipolar depression.[8]

Light therapy

Since the publication of a previous meta-analysis in 2016 demonstrating efficacy,[9] a few well-designed RCTs have confirmed the efficacy of light therapy in treating acute bipolar depression. Further, a more recent meta-analysis of these newer RCTs also demonstrated efficacy with no increased risk of manic switch rates (unpublished).

Anti-inflammatory agents for acute bipolar depression

There has been increasing interest in the role of inflammation in the neurobiology of BD.[10] Several small trials reported on the adjunctive efficacy of anti-inflammatory agents, although the findings have been inconsistent. For instance, one study reported that N-acetyl cysteine was effective while a more recent study failed to confirm its efficacy.[11,12] A study comparing aspirin, minocycline, and their combination reported that aspirin and minocycline combination was effective and that the efficacy of this combination was mainly attributable to aspirin.[13] A recent study that recruited patients with bipolar depression with elevated C-reactive protein levels failed to show benefits of infliximab in improving depressive symptoms.[14]

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