Lithium use in bipolar disorder: Summary of evidence for acute mania, acute depression, and maintenance treatment

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ABSTRACT

Lithium has been used for more than 50 years for the treatment of bipolar disorder. There is a substantial body of literature about use of lithium in this condition, much of it with conflicting results. Many guidelines and algorithms support the use of lithium for treatment of episodes of acute mania and depression. However, additional research exploring prevention of depressive and manic relapse, treatment of acute depression, and use of combination treatments are needed.

KEYWORDS

lithium, bipolar disorder, acute mania, acute depression, maintenance

INTRODUCTION

Lithium is a well-established, first-line treatment for bipolar disorder. Despite conflicting study results, there is a substantial body of evidence supporting the efficacy of lithium for the treatment of bipolar disorder. This article will review lithium's role in the treatment of acute mania, acute depression, and maintenance of bipolar disorder.

ACUTE MANIA

Treatment guidelines and algorithms vary significantly in their recommendations for acute mania but overall, lithium is recommended as a first-line agent (Table 1).[1-6] Lithium is widely used in the setting of acute mania, with clinical trials supporting its efficacy in the treatment of classic/euphoric mania; however, lithium may not be as effective in patients experiencing mixed states or rapid cycling.[7-10]

In one double-blind, parallel group study, acutely manic bipolar subjects were randomized to receive lithium (n = 36), valproate (n = 69), or placebo (n = 74) after a minimum 3-day washout period from psychoactive drugs. The purpose of the study was to evaluate the efficacy and safety of valproate by comparing it with two control groups, which consisted of subjects treated with lithium or placebo. The study was not powered to directly compare valproate and lithium. Subjects could take concomitant lorazepam or chloral hydrate to control agitation, irritability, restlessness, insomnia, and hostile behaviors. Lorazepam and chloral hydrate use were highest in the placebo group. Subjects received the study drugs for 21 days and then reduction in acute manic symptoms was evaluated using the Mania Rating Scale, Schedule for Affective Disorders and Schizophrenia. By day 5, the valproate group had statistically significantly greater improvement on the Mania Rating Scale than the placebo group. The effect size for the lithium group was similar to valproate on day 5 but did not reach significance due to the smaller number of subjects in that group. Both lithium and valproate were significantly better than placebo in reducing manic symptoms with 49% of lithium subjects (p=0.025), 48% of valproate subjects (p=0.004), and 25% of placebo-treated subjects experiencing an improvement of 50% or more. [8]

Trials comparing lithium to antipsychotic medications for treatment of acute mania generally found lithium to be superior in overall symptom improvement, mood, and ideation.[11-12] The antipsychotic agents are generally superior in terms of onset of activity and improving motor hyperactivity.[11-12] Studies comparing treatment with lithium alone or in combination with an antipsychotic generally found combination therapy to be superior to monotherapy.[13] However, two double-blind studies did not find combination therapy with lithium and either haloperidol or pimozide to be superior to treatment with the antipsychotic agent alone.[14-15]

ACUTE DEPRESSION

Depressive symptoms associated with bipolar disorder are often less responsive to treatment than manic symptoms and are more prevalent during the longitudinal course of the illness.[16] Individuals with bipolar disorder are also more likely to commit suicide during episodes of

depression than during mania.[17] There is evidence supporting lithium's anti-suicidal effects in patients with mood disorders but this effect is not solely limited to episodes of depression.[16,18] Lithium is the oldest agent studied for acute treatment of bipolar depression and current guidelines recommend lithium as a first-line treatment option (Table 2).[2-5, 19]

A 1993 review identified eight studies that found lithium to be more effective than placebo for the treatment of bipolar depression.[20] Many of these studies had design and methodological limitations, however. A more recent randomized, placebo-controlled study assessed the antidepressant effects of quetiapine and lithium for bipolar depression. This was an 8-week trial in which 136 subjects received lithium 600 to 1800 mg/day, 265 received quetiapine 300 mg/day, 268 received quetiapine 600 mg/day and 133 received placebo. Lithium was dosed to maintain a serum concentration between 0.6 and 1.2 mEq/L but the mean median serum concentration of lithium was 0.61 mEq/L, with 34.9% of subjects having median serum concentrations below 0.6 mEq/L. Subjects were evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS) and no statistically significant differences were found between lithium and placebo in reducing depression severity (p=0.123). Both quetiapine doses were significantly more effective than placebo (p <0.001) and the 600mg dose was significantly more effective than lithium at week 8 (p=0.013).[21]

A study by Nemeroff et al. (2001),[22] indicated the plasma level of lithium plays an important role in efficacy. This was a double-blind, placebo-controlled study in which 117 subjects with bipolar depression, stabilized on lithium, were randomized to receive paroxetine (n=35), imipramine (n=39), or placebo (n=43) for 10 weeks. Subjects were stratified according to their trough serum lithium level at baseline screening (high: >0.8 mEq/L; low: <0.8 mEq/L). They were evaluated using the Hamilton Rating Scale for Depression and the Clinical Global Impression illness severity scale. Among the total sample, paroxetine and imipramine were no more effective than placebo on continuous measures of depression. However, paroxetine and imipramine were superior to placebo among patients stratified on the basis of low lithium levels. These results indirectly suggest lithium should be dosed to attain goal plasma levels ≥0.8 mEq/L, when possible, to achieve greater antidepressant efficacy.[16] Patients able to maintain higher lithium levels may not require additional treatment with antidepressant medications. Augmentation with antidepressant therapy may be beneficial for patients who cannot tolerate higher serum lithium levels or who have refractory symptoms not responsive to the antidepressant effects of lithium.[22]

Lithium may have anti-suicide effects when treating patients with bipolar disorder.[23-25] Patients treated with lithium may be less likely to attempt suicide, require hospitalization for suicidal behavior, or complete suicide than patients treated with other mood stabilizers.[23] Treatment with lithium is associated with lower mortality rates in individuals with bipolar disorder due to a reduction in completed and attempted suicides.[24]

MAINTENANCE TREATMENT

Maintenance treatment of bipolar disorder is generally recommended after a single, acute manic episode due to a large lifetime risk of recurrence. Maintenance treatment is also recommended for patients who experience a breakthrough episode during the first year of treatment and in chronically ill patients who are not able to achieve adequate symptom remission.[11] Unfortunately, few studies have explored maintenance treatment outcomes in bipolar depression. There is more evidence for the long-term treatment of patients with mania.[11, 16] Treatment guidelines continue to recommend lithium for maintenance treatment of bipolar disorder (Table 3).[2-5, 26]

The prophylactic efficacy of lithium in bipolar disorder was confirmed in a 2001 Cochrane review. Nine studies were evaluated and lithium was found to be more effective than placebo in preventing relapse. None of the studies found a negative effect for lithium.[27] Several meta-analyses also suggest lithium is the gold standard for preventing bipolar relapse.[28-30] An 18-month study performed by Calabrese et al.(2003),[31] showed that among 463 subjects who recovered from a depressive episode with lamotrigine, lithium was superior to placebo in preventing manic or hypomanic episodes (p=0.026) and lamotrigine was superior to placebo for preventing depression (p=0.047). There was an initial 8-16 week open-label phase in which lamotrigine was added to current therapy for bipolar I depression and concomitant drugs were gradually withdrawn. Subjects were then randomized to open-label treatment with lamotrigine (n=221), lithium (n=121), or placebo (n=121) monotherapy. Lithium was not as effective as lamotrigine for preventing a relapse of bipolar depression (46% intervention-free for depression at 1 year versus 57%). Lithium can reduce depressive recurrences by approximately 50% when dosed appropriately but appears to be more effective against manic than depressive relapses.[31-32] The anti-suicidal effects of lithium remain advantageous in maintenance therapy.[18]

CONCLUSION

Lithium has been used in the treatment of bipolar disorder for over 50 years and is widely viewed as a gold-standard, first-line treatment. Many treatment guidelines continue to recommend lithium as a first-line treatment for acute mania, acute depression, and maintenance despite conflicting study results. There are many limitations in the available literature on lithium treatment for bipolar disorder, making interpretation of the results difficult. More studies exploring prevention of depressive and manic relapse, treatment of acute depression, and use of combination treatments are needed.

Table 1 Guideline recommendations for the treatment of acute mania. Adapted from reference 1.

	American Psychiatric Association, 2002	Canadian Network for Mood and Anxiety Treatments, 2009	Texas Medication Algorithm Project, 2002	British Association of Pharmacology, 2009	World Federation of Societies of Biological Psychiatry, 2009
1st choice	***Severe:*** Li or Vp+AAP ***Mild-mod:*** Li, Vp, AAP	Li, Vp, AAP	Li, Vp, Olz	***Severe:*** AP, Vp ***Mild-Mod:*** Li, AP, Vp, Cbz	Li, Vp, AP, Cbz
2nd step	Various combinations of two 1st choice agents, ECT	Various combinations of two 1st choice agents	Various combinations of two 1st choice agents	Various combinations of two 1st choice agents, clozapine, ECT,	Various combinations of two 1st choice agents, clozapine, ECT

AP = antipsychotic, AAP = atypical antipsychotic, Cbz = carbamazepine, ECT = electroconvulsive therapy, Li = lithium, Olz = olanzapine, Vp = valproic acid

Table 2 Guideline recommendations for the treatment of acute bipolar depression. Adapted from reference 1.

	American Psychiatric Association, 2002	Canadian Network for Mood and Anxiety Treatments, 2009	Texas Medication Algorithm Project, 2002	British Association of Pharmacology, 2009	World Federation of Societies of Biological Psychiatry, 2010
1st choice	Li, La, Li +AD	Li, La, Que, Olz or (Li, Vp, Olz) + SSRI	Li, Vp, Olz or (Li, Vp, Olz) + (SSRI or La)	***Severe:*** ECT ***Mild-Mod:*** Que, La or (Li, Vp, AP) + SSRI	Li, La, Vp, Cbz, Que, Olz or MS + SSRI
2nd step	Various combinations of 1st choice agents, ECT	Various combinations of 1st choice agents, adjunct modafinil	Various combinations of two or more 1st choice agents, ECT	Various combinations of 1st choice agents, augmentation strategies, TCAs	Various combinations of 1st choice agents, clozapine, ECT

AD =antidepressant, AP = antipsychotic, Cbz = carbamazepine, ECT = electroconvulsive therapy, La = lamotrigine, Li = lithium, MS = mood stabilizer, Olz = olanzapine, Que = quetiapine, SSRI = selective serotonin reuptake inhibitor, Vp = valproic acid

Table 3. Guideline recommendations for maintenance treatment of bipolar disorder. Adapted from reference 1.

	American Psychiatric Association, 2002	Canadian Network for Mood and Anxiety Treatments, 2009	Texas Medication Algorithm Project, 2002	British Association of Pharmacology, 2009	World Federation of Societies of Biological Psychiatry, 2004
1st choice	Continue treatment effective in acute stage (Li, Vp, or possibly La, Cbz, Ocbz)	Li, La, Vp, AP	Li, Vp, Olz ± AD proven effective during acute phase	***After mania:*** Li, Vp, AP ***After depression:*** La, Que	***After mania:*** Li, Vp, AP ***After depression:*** SSRIs + (Li ,La, Vp, Cbz)
2nd step	Combination of 1st choice agents, ECT, discontinue AP unless persistent psychotic symptoms	Various combinations of 1st choice agents, Cbz	Various combinations of 1st choice agents	Various combinations of 1st choice agents, Cbz	Various combinations of 1st choice agents

AD =antidepressant, AP = antipsychotic, Cbz = carbamazepine, La = lamotrigine, Li = lithium, Ocbz = oxcarbazepine, Olz = olanzapine, Que = quetiapine, SSRI = selective serotonin reuptake inhibitor, Vp = valproic acid

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