Key Treatment Studies of Lithium in Manic-Depressive Illness: Efficacy and Side Effects

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Lithium is the most extensively studied single psychopharmacologic agent. This review summarizes efficacy results of key studies in manic-depressive illness, the increasingly practical findings regarding predictors of response, and the implications of the increasingly better understood adverse effect profile of lithium. A recent well-designed study confirms earlier studies regarding the marked effectiveness of lithium in alleviation of acute mania. Early maintenance studies of marked superiority of lithium over placebo have been countered by recent open reports of lesser effectiveness. A recent randomized study provides support for the efficacy of lithium in maintenance therapy, but a satisfactory assessment of the effectiveness of lithium for maintenance and its optimal role requires further study. Many of the adverse effects of lithium can be addressed by dosage reduction, use of sustained-release lithium, or combination therapy. *(J Clin Psychiatry 1998;59[suppl 6]:13–19)*

Lithium, the world's first effective treatment for bipolar disorder, effectively revolutionized the approach to treatment, and indirectly improved the diagnosis of this major, relatively common chronic disease. In part because of the remarkably positive initial studies of lithium both in acute mania and in the prevention of new episodes of bipolar disorder, subsequent systematic studies were largely neglected for over 20 years. Several naturalistic studies during the last decade have reported less favorable results, as well as greater problems with treatment adherence and adverse effects, than had earlier been suggested. Two randomized, comparative trials of lithium have recently been published; they deal with acute mania and maintenance therapy, respectively. The purpose of this article is to review the fundamental design features of both the early and recent studies and their results and to endeavor to place the results in the context of modern diagnosis of bipolar disorder and the current understanding of the spectrum and course of this recurrent, severe disorder.

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STUDIES IN ACUTE MANIA

Comparisons With Placebo or Valproate

Commencing with the study of Schou et al. in 1954, four placebo-controlled studies of lithium were published by 1971, leading to the approval by the FDA of lithium for the treatment of acute mania in 1970.[1–4] Each of these studies was of relatively small numbers of patients, who were all treated in crossover designs, wherein patients at some point in treatment receive lithium and at some other point receive placebo. Each of the studies as well as the Bowden et al.[5] study in 1994 reported marked superiority for the response to lithium treatment to that on placebo (Table 1). The percentage of patients with moderate or greater improvement after 2 to 3 weeks of treatment ranged from 40%[1] to 80%.[2] The current DSM system was not conceived at the time of these studies. Similarly, concepts such as bipolar II disorder, secondary bipolar disorder, and rapid cycling were yet to be introduced. The concept of mixed mania had been well developed by Kraepelin, but its reintroduction into usual psychiatric practice was not to occur until the current decade.[6] Although these studies were uniformly positive, extrapolation to the psychiatric practice of the current decade has been increasingly difficult. Descriptions of patients in the publications suggest that most of these patients would meet criteria for bipolar I disorder in DSM-IV terms, and that most had classical, or elated, forms of manic episodes.

The 1994 study of Bowden et al.[5] is the only placebo-controlled, parallel-group study of lithium for patients with acute mania and the largest placebo-controlled trial

Table 1. Placebo-Controlled Studies of Lithium in Acute Mania

Study	Year	N	Procedure	Response
Schou et al[1]	1954	30	Variable duration	40% definite, 50% probable, not double-blind
Maggs[2]	1963	18	14-14-14 d	9 of 28 dropped out on lithium
Goodwin et al[3]	1969	12	3 wk	4 unequivocally, complete 4 probably, complete 1 unequivocally, partial 3 worse
Stokes et al[4]	1971	38	10–14 d	75% any improvement 7% no change 18% worse
Bowden et al[5]	1994	36	21-d, randomized	49% markedly improved

Table 2. Randomized Studies of Lithium Vs. Carbamazepine in Bipolar Disorder*

Study	Year	N	Duration (wk)	Response (%) Lithium	Response (%) Carbamazepine
Lerer et al[10]	1987	28	4	61	24
Lusznat et al[11]	1988	44	6	Not calculable	Not calculable
Okuma et al[12]	1990	101	4	59	61
Small et al[13]	1991	48	8	33	33

*All studies are parallel group vs. lithium.

Table 3. Randomized Studies of Lithium Vs. Neuroleptics in Bipolar Disorder

Study	Year	Response (%) Lithium	Response (%) Neuroleptic
Johnson et al[15]	1971	78	36
Takahaski et al[17]	1975	32	12
Shopsin et al[16]	1975	70	15
Spring and Frankel[14]	1981	88	50

conducted. Patients were diagnosed according to the Research Diagnostic Criteria by structured rating instruments, and the efficacy assessment was the Mania Rating Scale derived from the Schedule for Affective Disorders and Schizophrenia. These explicit psychometric tools were not available to the investigators who had conducted the initial placebo-controlled studies of lithium. Patients with substance abuse, drug-induced mania, and mania secondary to medical disorders were excluded. Otherwise, the patients were characteristic of the spectrum of patients hospitalized for manic episodes by practicing psychiatrists today. The results are therefore particularly important in light of changes in the presentation of patients with bipolar disorder over the past several decades and as an updated comparison with the results of studies a quarter century ago.

Marked improvement, defined as 50% improvement in the manic syndrome subscale score, occurred in 49% of the lithium-treated patients and 48% of the divalproex-treated patients, compared with only 25% of the placebo-treated patients. No significant differences in overall response occurred between lithium-treated and divalproex-treated patients. The effect size for the improvement in the lithium-treated patients was 0.79,[7] essentially a large effect size, which is defined by Cohen as 0.8 or greater.[8] The results are particularly noteworthy in that the patients were severely ill, over one third had psychotic symptoms, no neuroleptics were allowed, and the only adjunctive medication was low-dose lorazepam or chloral hydrate during the first 10 days of the 21-day study. The results provide conclusive evidence of the marked efficacy of lithium in acute mania.

One other randomized, blinded comparison of lithium versus the valproic acid form of valproate has been published.[9] Both drugs were effective, with the percentage of patients at least moderately improved nonsignificantly greater among the lithium-treated than the divalproex-treated patients (92% vs. 63%). The large majority of patients were women, which yielded a somewhat atypical sample.

Comparisons With Carbamazepine

Four randomized comparisons with carbamazepine have been published; lithium was superior in one and equal in two (Table 2).[10–13] In the larger study that reported equivalent results,[13] only 33% of patients were assessed as improved with each treatment, suggestive of the atypicality of the patients enrolled.

Lithium Versus Neuroleptics

Studies of lithium versus neuroleptics have consistently reported lithium superior to the neuroleptic (Table 3).[14–17] Some studies report neuroleptics equivalent or superior for nonspecific components of manic syndromes, particularly motor hyperactivity and agitation.[18] No systematic comparisons of lithium versus atypical neuroleptics have been published. Clozapine, risperidone, and olanzapine have been reported as effective in some acutely manic patients.[19–22] These studies are limited to case reports and small, open series, principally of schizoaffective patients.

The troublesome adverse effect profile for neuroleptic medications, particularly in the dosages used for bipolar disorder further limits their potential effectiveness in bipolar disorder.[23,24] Although lithium and valproate are not broadly effective antipsychotic medications, patients with psychotic symptoms do show some alleviation of the psychotic symptoms with monotherapy with both lithium and valproate.[5]

Lithium Versus Other Putative Antimanic Drugs

Verapamil has been reported as effective in control of mania in a small number of patients in methodologically compromised reports.[25,26] Lithium was reported superior to

Table 4. Placebo-Controlled Studies of the Prophylactic Effectiveness of Lithium in Bipolar Disorder

Study	Year	Duration (mo)	Relapse Rates (%) Lithium	Placebo
Baastrup[34]	1970	5	0	55
Melia[35]	1970	24	57	78
Cundall[33]	1972	12	33	83
Coppen[32]	1971	4–26	18	95
Stallone[36]	1973	8–22	44	93
Prien[37]	1973	24	43	80

verapamil in a recent randomized, but open trial.[27] A randomized, double-blind parallel group comparison of verapamil has recently been completed and showed negligible evidence of superiority of verapamil over placebo.[28]

Predictors of Response to Lithium

Previous response to lithium is a practical indicator of likelihood of response in an acute manic episode. Patients whose last episode was effectively treated with lithium had very good responses when in a new manic episode, whereas those patients who had failed to respond well previously had minimal improvement, despite comparable dosing in a blinded, randomized study.[5]

The quality of response to lithium may differ somewhat from the pattern of quality present with divalproex and other drugs. Inferential data in the recent lithium, divalproex, and placebo study of acutely manic patients indicate that when lithium was beneficial, the magnitude of improvement was generally marked. Among those patients who did not respond, the effect of lithium was negligible for many, or associated with some actual worsening of symptomatology. This pattern stands in contrast to divalproex, which tended to achieve a spectrum of response, ranging from mild to marked.[5] This observation from one study warrants further investigation, since the difference among bipolar disordered patients treated with lithium may serve to characterize fundamentally different subgroups of the disorder.

One important source of estimating the overall effectiveness of lithium is the reported previous response to lithium in descriptions of samples enrolled in systematic prospective studies. The reported response rate is remarkably consistent at 46% to 52%.[29,30] The effects of lithium are almost certainly greater on manic episodes than on depressive episodes. Randomized maintenance studies whose results enable answers to this question reported a greater degree of protection against new manic episodes compared with that against new depressive episodes.[30–33] For example, Denicoff et al.[30] recently reported that patients spent significantly less time manic during a year's trial with lithium or carbamazepine compared with the year prior to entry (9.6% vs. 18.1%), but actually tended to spend more time in depression during the year of randomized treatment than the comparison year before entry (27.4% vs. 23.2%). A report of results for the lithium-treated and carbamazepine-treated patients separately has not been published.

EFFECTIVENESS IN MAINTENANCE THERAPY

Lithium Versus Placebo

Early randomized parallel-group studies consistently showed lithium superior to placebo in various dimensions of efficacy (Table 4).[32–37] However, the design features of these studies result in limited applicability to current practice decisions. Both bipolar and recurrent unipolar depressed patients were included in most studies. As with studies in acute mania, diagnostic criteria were generally unspecified, and patients with schizoaffective features were often included. A particular difficulty is that patients stabilized on lithium treatment had their lithium dosage abruptly discontinued if they were randomly assigned to placebo. This increased the short-term relapse rate into mania, thus artifactually widening the apparent advantage of lithium over placebo. In fact, these early trials constitute a major component of the evidence that abrupt discontinuation of lithium is undesirable.[38,39] Additionally, these early studies generally reported patients who completed the trials, without reporting results for patients who dropped out prematurely for reasons of intolerance, treatment failure, or other factors.[40] Also, these early maintenance trials were relatively short, and extensive use of adjunctive treatments was allowed. For example, Coppen et al.[41] allowed unrestricted use of neuroleptics, antidepressants, and electroconvulsive therapy (ECT).

These problems, largely unrecognized until recently, have contributed to an unduly pessimistic interpretation of several more recent naturalistic reports of lithium's effectiveness in maintenance treatment. Aagaard and Vestergaard[42] reported that only 40% of patients did well, i.e., had no, or only one hospital admission during a 2-year follow-up period. Tohen et al.[43] reported that 4 years following a first manic episode, only 40% of patients were stable. Harrow et al.[44] reported that 40% of patients had manic recurrences over a 1.7 year follow-up period; there were no significant differences between patients taking lithium and those not taking lithium. No placebo-controlled maintenance studies of lithium have been published since 1973. A recently completed study that includes a divalproex comparison should soon be available.[45]

Lithium Versus Other Putative Mood Stabilizers

Neuroleptics have been little studied in maintenance phase treatment. Unlike the case with valproate and carbamazepine, there are few case reports of patients that show long-term benefit when neuroleptics are used as primary mood stabilizers.[46] Neuroleptics have been compared with lithium in two reports; both indicate that lithium is superior on some measures and the neuroleptic superior on none.[47,48]

Carbamazepine was comparable with lithium in two small maintenance studies, neither of which utilized a placebo group.[12,49] The one maintenance study of carbamazepine versus placebo did not find superiority of carbamazepine over placebo.[12] Additionally, the advantage of lithium over carbamazepine in reducing suicidal behavior (see below) further argues against routine employment of carbamazepine for maintenance therapy.[49]

A large randomized, open, parallel-group comparison of lithium with the valpromide form of valproate was published in 1992, although the results of the study,[50] published in French, have not been widely available in the U.S. Both drugs were generally effective over the 18-month trial. A slight superiority in terms of new episodes occurring over the course of the trial favored valpromide (0.51 vs. 0.61 episodes per patient). A greater number of patients were changed from lithium to valpromide for reasons of intolerability or poor clinical improvement than were changed from valpromide to lithium. Fewer than 5% of patients had moderate or worse adverse effects with either treatment, and there were somewhat fewer side effects in the valpromide group.

An additional source of evidence for the prophylactic efficacy of lithium is evidence that lithium reduces the likelihood of suicidal behavior.[41] These data were recently strengthened by evidence that suicidal behavior was lower in patients randomly assigned to lithium in a blinded, 2.5-year prospective trial than in patients randomly assigned to carbamazepine.[51]

Lithium Combined With Other Mood Stabilizers

Controlled psychopharmacologic studies have, with few exceptions, been of single drug therapy. The rationale for this is generally sound, but has proved to be a limiting factor in analyzing the relative efficacy of different treatment strategies. Several studies indicate that from one third to over half of patients with bipolar disorder are treated with more than one drug.[46,52] Two treatment needs drive such practices. A medication may benefit one or more aspect of bipolar disorder, but not adequately alleviate an additional dimension, i.e., depression continuing in the context of optimal lithium therapy. A second circumstance is partial response to a mood stabilizer; a second, or in some instances a third medication is added in an effort to further improve the quality of the response. Lithium has been reported successfully combined with valproate, carbamazepine, and neuroleptics.[53–55] None of these publications presents controlled data; therefore, both the indications for such combined drug therapy and the efficacy and safety remain open but important questions. Although combined drug therapy with lithium and carbamazepine, neuroleptics, and valproate is apparently well tolerated and has been reported, lithium-valproate combinations have some inherent advantages. No drug interactions occur between the two, since metabolism is not overlapping, and neither thyroid nor renal function is affected by valproate. The two are the only approved antimanic drugs for bipolar disorder. Carbamazepine may have additional effects on thyroid function when combined with lithium.[56] Several recently presented reports indicate additional benefit when valproate is added to lithium that had been ineffective or partially effective when taken alone.[55] The recent expert consensus derived guidelines for treatments of bipolar disorder are supportive of such strategies.[57]

Table 5. Factors Associated With Beneficial Lithium Response

Elated mania
Previous response to lithium
No neurologic impairment
No psychotic symptoms
No substance abuse
Relatively few episodes of illness

Reports of efficacious combination therapy have generally been of patients who have been ill for some time, rather than of those treated during an acute manic episode. Nevertheless, the rationale for combination therapy seems sound and may apply to some patients who are acutely manic. For acute mania, the combination strategy should generally be limited to patients who have been tolerating lithium, who have shown a partial response, and in whom the upper range of the tolerated dose has been tested. Combinations of lithium and carbamazepine may be more problematic due to concurrent thyroid function impairing effects of both drugs.

Efficacy in Subtypes of Bipolar Disorder

There is increasing emphasis on identification of pretreatment variables that can be used clinically to aid in prediction of response, or nonresponse to a specific treatment. Most of the reported findings for lithium are based on open, uncontrolled data obtained in post-hoc analyses that have substantial risk for capturing unintentional bias. Nevertheless, several factors, reviewed extensively elsewhere,[58,59] are reasonably well established. Relatively good antimanic response to lithium is associated with each of the illness course or symptomatic characteristics listed in Table 5. The data are firmly established for elated, or euphoric, mania, also called pure or classical mania.[60–62] Only for elated mania and mixed mania does the evidence come from a randomized, double-blind placebo-controlled study that effectively rules out alternative explanations.[59] However, there is not substantial evidence in either direction in regard to the effectiveness of lithium in the prophylaxis of elated manic episodes.

Patients with fewer lifetime episodes respond better to lithium than patients with more lifetime episodes.[63] It is plausible, but untested, that strategies that achieve earlier illness identification and treatment could yield better long-term outcomes.

Probably linked to lifetime number of episodes is rapid cycling. Rapid-cycling patients appear to constitute the most difficult-to-treat cohort of bipolar disorder patients.[64] Rapid-cycling patients have been established as less responsive to lithium in both acute manic episodes and maintenance treatment.[65,66] It is possible that some rapid cycling is contributed to by lithium-induced hypothyroidism. It is therefore important to regularly assess thyroid function and add thyroid hormone if the thyroid levels are suboptimal.

Patients with substance abuse, late-onset mania, and secondary mania appear to have relatively poor response to lithium, but complex factors make it difficult to determine whether secondary factors or the subtype per se is associated with poor response. For example, mixed mania and rapid cycling are relatively common in these subtypes. It is therefore possible that patients with, for example, substance abuse who do not have mixed mania have more favorable outcomes to lithium.

Psychiatrists have tended to dichotomize certain of the good prognosis–bad prognosis dimensions. Mixed mania is often presented as the opposite of elated mania. However, experts do not agree fully on the criteria for either variant of the disorder, and the currently applied criteria for one are not the obverse of the other.

Adverse Effects and Their Management

The first investigators of lithium's effectiveness in bipolar disorder recognized the importance of its adverse effects. Lithium is distributed throughout the body; therefore, a large number of organ systems—including skin, thyroid, kidneys, heart, gastrointestinal tract, and central nervous system—may be adversely affected. Cognitive impairment, expressed largely as impaired information processing and short-term memory deficits, contributes most to patients' discontinuing lithium or taking less than the prescribed dose. Only weight gain is a major noncognitive factor in poor compliance.[67] Authorities once tended to view noncompliance as largely driven by a patient's impaired insight and a wish to regain some of the pleasurable aspects of manic states. Indeed, these factors are operative and need to be addressed when present. However, many of the compliance difficulties with lithium reflect a partially realistic effort by patients to reduce the subjective adverse effect burden. Additionally, the availability of alternatives to lithium, such as divalproex, has heightened interest in strategies to reduce side effect burden when it is present. Three strategies have general utility, and may sometimes be fruitfully combined. For almost all adverse effects, lowered doses can be advantageous, particularly during maintenance therapy, on the basis of evidence that adequate maintenance serum lithium levels are generally lower than serum levels needed for acute episode treatment, and that serum levels rise after recovery from an acute episode unless dosage is reduced by approximately one third.[68] Studies of serum level relationships to maintenance therapy effectiveness are somewhat in conflict.[32,63] However, evidence that some patients do well at serum levels in the 0.4 to 0.8 mEq/L range has encouraged psychiatrists to adopt this strategy as an important component of optimizing lithium tolerability.

A second strategy is use of sustained-release lithium preparations rather than immediate-release lithium. The prevalence and severity of some lithium-related adverse effects is a function of the rate of increase of serum lithium levels.[69,70] Since this increase is much diminished with sustained-release preparations, an advantage is gained in regard to side effects such as tremor. Less trough-to-peak-level lithium level variation can also make once daily dosing regimens more feasible. Lithium administered once daily has the advantages that accrue generally with once daily dosage regimens. Compliance rates are better and many side effects become relatively innocuous when they occur only or largely during sleep. Use of the Lithobid sustained-release preparation was associated with better retained urinary concentrating ability than was use of immediate-release lithium.[71] Furthermore, only in patients dosed with immediate-release lithium was there evidence of a positive correlation between serum lithium level and impairment of maximum urinary concentrating ability. These advantages have resulted in near uniform use of sustained-release lithium preparations in Europe, but, perhaps as a function of minimal publicity about these advantages, relatively lower use of sustained-release lithium has occurred in the United States. The range of adverse effects that may be expected to benefit from this strategy includes tremor, upper gastrointestinal cramping and nausea, rashes, cognitive dulling, urinary frequency, and neuromuscular slowing. The only adverse effect that is sometimes worse with sustained-release lithium preparations is lower gastrointestinal effects, such as diarrhea.

The strategy of combining lithium with other mood stabilizers or neuroleptics may also have advantages in terms of adverse effects. Dosage of lithium, and thus serum lithium levels, can often be lower when the drug is utilized as a component of combined drug therapy.

One complication of lithium therapy that has received attention for years is the consequence of discontinuation of lithium. Abrupt discontinuation of lithium is associated with a short-term increase in the number of manic episodes. By contrast, abrupt discontinuation is not associated with a rebound increase in depression.[39,63] Therefore, patients should be educated on the importance of not simply stopping lithium, even for inadvertent reasons such as running out of a prescription. An additional undesirable consequence of stopping lithium is treatment refractoriness induced by lithium withdrawal. A small number of patients have been observed to have loss of control of symptoms after discontinuation of lithium that had effectively controlled the illness, but subsequent restarting of

lithium did not yield control of the episode. Recent larger scale studies have not found evidence of this refractoriness.[51,72,73] Therefore, although some small percentage of patients may be at risk for this phenomenon, at most it represents a rare occurrence.

CONCLUSION

Lithium has a somewhat different role in the management of bipolar disorder currently than it did 10 to 20 years ago. When few alternative treatments were available or had been systematically assessed, lithium was used not only as the best but the only treatment option for the many components of illness expression in this complex disorder. Present data provide useful guidelines in regard to which patients are most likely to be effectively treated with lithium, thereby increasing likelihood of treatment success and minimizing exposure to adverse effects from the drug in patients with substantially lower likelihoods of efficacious response. For some components of bipolar episodes, lithium either alone or in combination therapy provides greater efficacy than other available therapies. Finally, strategies that improve the therapeutic index of lithium further expand the range of patients who may achieve its benefits without experiencing troublesome side effects.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), divalproex (Depakote), olanzapine (Zyprexa), risperidone (Risperdal), verapamil (Calan and others).

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