

Efficacy of Lithium in Mania and Maintenance Therapy of Bipolar Disorder

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Lithium was introduced in 1949 as a treatment for mania, for which there is still the strongest evidence of its efficacy. It has consistently yielded better results in the treatment of mania than neuroleptics and carbamazepine and equivalent results to divalproex. Its efficacy in bipolar depression remains inadequately studied. Lithium also provides benefit in prophylaxis. However, the percentage of patients persistently benefited is low, because it has both low efficacy in many symptomatic and illness course presentations of the disorder and low tolerability. Converging evidence from clinical and animal studies indicates that a principal behavioral effect of lithium is reduction of motor activity. Lithium is increasingly used in combined treatment regimens, often thereby allowing lower, better tolerated dosing and complementary benefits from drugs with different profiles of action.

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MANIA

Placebo-Controlled Studies

The strongest evidence for the efficacy of lithium is in treatment of acute mania. Early placebo-controlled studies were positive.¹⁻⁴ These early studies were conducted before operationalized criteria for diagnosis or structured ratings were developed. Each had the problems of interpretation associated with carryover effects and period effects in crossover designs. The study of Bowden et al. in 1994 was therefore of particular importance in demonstrating the marked superiority of lithium over placebo in the largest placebo-controlled study in mania⁵ (Table 1) conducted to date under randomized, parallel-group, double-blind conditions. This study, which used standardized rating scales, found a statistically significant superiority of lithium compared with placebo at weeks 2 and 3. Forty-nine percent of lithium-treated patients improved at least 50% as assessed by the Mania Rating Scale derived from the Schedule for Affective Disorders and Schizophrenia, compared with 25% with placebo treatment. The study utilized DSM-IV criteria, employed stringent severity criteria, and enrolled a broader spectrum of bipolar I manic patients than were studied in the 1960s.

Efficacy vs. Other Drugs

Lithium has been compared with antipsychotics and anticonvulsants in the treatment of mania. The agent has been found consistently superior to antipsychotic drugs in randomized, double-blind trials.^{6,7} In the largest and only parallel-group, placebo-controlled study of lithium in mania, lithium was comparable to the anticonvulsant divalproex, and both drugs were significantly superior to placebo.⁵ The results are particularly noteworthy, since the patients were severely ill—with over one third having psychotic symptoms—no neuroleptics were allowed, and only adjunctive lorazepam or chloral hydrate was permitted during the first 10 days of the 21-day study. In the one other randomized, blinded comparison of lithium with valproate, the drugs were equally effective, with nonsignificantly greater moderate improvement among lithium-treated patients.⁸ In the small number of comparisons with carbamazepine, lithium was either superior to carbamazepine or equally effective. Each of the studies had methodological limitations, and none were placebo controlled.^{9,10} Lithium was reported superior to the calcium-channel blocker verapamil in the one randomized study.¹¹

Predictors of Antimanic Effectiveness

Lithium has a relatively narrow range of efficacy. The largest randomized study in mania suggests that lithium has either unequivocal benefits or lacks benefit altogether, rather than having partial benefits across the spectrum of manic states.⁵ Factors associated with a good response include a previous good response to lithium when manic,⁵ pure manic symptomatology, few lifetime episodes of illness, lack of a rapid-cycling course, lack of psychotic features, lack of substance abuse, lack of co-

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Table 1. Lithium in Mania: Placebo-Controlled Studies^a

Study	Method	Randomized	N	Marked Response, %	Comment
Schou et al., ¹ 1954	Crossover	Yes	30 typical, 8 atypical	40 25	Not double blind
Maggs, ² 1963	Crossover	Yes	18	NR	Lithium superior to placebo, 9 of 28 receiving lithium dropped out
Goodwin et al., ³ 1969	Crossover	No	12	75	67% complete, 8% partial, 24% worse on lithium
Stokes et al., ⁴ 1971	Crossover	No	34	NR	75% any improvement receiving lithium vs 40% receiving placebo
Bowden et al., ⁵ 1994	Parallel group	Yes	110	49	25% of placebo-treated patients improved

^aAbbreviation: NR = not reported.

morbid symptomatology, and lesser overall severity of the manic state.^{12,13}

EFFECTIVENESS IN MAINTENANCE THERAPY

Lithium has been extensively studied in maintenance treatment of bipolar disorder. In the aggregate, these studies indicate superiority over placebo. However, design limitations, some of which are inherent in the disease, some of which could not have been anticipated at the time of planning the studies, have led both to ambiguity and to continuing controversies regarding maintenance efficacy.^{14,15} Because of the difficulties of conducting long-term studies with a placebo arm, it is reasonable to review open-trial data as well.

Efficacy Compared With Placebo

Early placebo-controlled studies of lithium in bipolar disorder were consistently positive.^{16–20} However, diagnostic criteria were not specified except in the studies by Prien et al.,^{17,18} 1 used a crossover design,²¹ some were not blinded to raters,¹⁷ and most abruptly stopped stabilized lithium at the point of randomization.^{16–20} Investigators at that time did not know that abrupt lithium discontinuation increases early relapse into both mania and depression.^{22,23} This design flaw increased response differences between lithium and placebo.²⁴ The recent study by Bowden et al.²⁵ is the first to include a taper of the mood stabilizer—either lithium or divalproex—at the point of randomization to maintenance treatment for bipolar disorder.

Only the study of Bowden et al.²⁵ used survival analyses to determine time to relapse to a mood episode. There were no significant differences between divalproex and lithium on that analysis. There is evidence that premature withdrawal early in the course of maintenance studies owing to protocol violations and noncompliance occurs more frequently in patients receiving placebo than in those receiving an active drug.²⁴ Omission of such patients from the subset of subjects included for primary efficacy analyses may reduce reported relapse rates with placebo. Such omission may have contributed to the lack of statistical superiority on survival analysis in the Bowden et al. study.²⁵ The Bowden et al. study²⁵ also had design features that reduced the proportion of patients with more severe

bipolar disorder and was underpowered for a test of lithium. Therefore, although it is the largest placebo-controlled maintenance study to date, it is not a conclusive test of lithium compared with placebo during maintenance therapy of bipolar disorder. A detailed review of placebo-controlled studies of lithium and other drugs in maintenance treatment, with an analysis of methodological difficulties in this field, has recently been published.²⁶

Effectiveness in Comparison Studies

Neuroleptics have been compared with lithium in 2 reports.^{27,28} Each indicated that lithium was superior on some measures and the neuroleptic superior on none. In 2 comparisons with the anticonvulsant valproate, lithium was numerically slightly less effective in 1 and was associated with higher rates of discontinuation.²⁹ In the other study, valproate was associated with somewhat less sub-threshold depressive symptomatology than was lithium and with a longer average time in the study.²⁵ Carbamazepine has been compared with lithium in 2 recent large randomized studies, one a crossover design and the other a parallel-group, open design.^{30,31} In both studies, lithium was superior to carbamazepine on some measures. Carbamazepine was equivalent to lithium on a few measures, and there were no significant differences in efficacy among atypical patients, defined to include patients with other than pure manic episodes, in the Greil et al. study.³¹ Carbamazepine was equivalent to lithium in 2 small, methodologically flawed studies.^{10,32}

Longitudinal analysis also provides support for the efficacy of lithium prophylaxis. In one study, relapse rates were reduced during the period of lithium prophylaxis and increased during the period that it was stopped.³³ A portion of bipolar patients treated with lithium for long periods have full response. It has been difficult to analyze such results from naturalistic reports. For example, in some studies, long-term benefits of lithium were not evident when patients taking lithium were compared with patients not taking lithium.^{34–36} Rates of full response and good tolerability were low in other recent naturalistic studies.^{37,38} Perhaps the systematic long-term studies headed by Maj and associates^{39–41} provide the fairest presentation of results, since the percentage of initially treated patients who achieve sustained good outcomes can be calculated from

the full data presentations. Some authors have taken these results to cast doubt on any prophylactic efficacy of lithium.^{14,15} However, most authorities do not view the results in such negative terms.³

Recently, Baldessarini and Tondo⁴² reviewed published reports on long-term lithium treatment since 1970. The study included an analysis of the clinical effects of lithium monotherapy on 360 patients with bipolar disorder who started treatment after 1970. Neither reported recurrence rates nor average proportion of time ill nor patient improvement of 50% or more during lithium maintenance treatment changed significantly in this time period. The authors suggested that no other proposed treatment for bipolar disorder has such substantial research evidence of long-term efficacy and reduced mortality risk.

Given that the conduct of definitive placebo-controlled studies in maintenance therapies has numerous methodological difficulties and poses ethical issues as well, in the near term we are likely to be left with disparate data, most indicative of definite but less than complete benefits from lithium. We must therefore sort through these data to determine which patients, treated in what manner, are most likely to achieve and maintain benefit from lithium maintenance therapy.

In several ways, the general superiority of lithium over other drugs, except valproate, provides stronger and less flawed evidence of the long-term effectiveness of lithium than do current placebo-controlled data. Comparator studies do not have the serious design flaw of abrupt discontinuation of lithium and assignment to placebo. Furthermore, such studies can justify enrollment of a more severely ill sample of patients. Also, showing superiority over medications that have some benefits in bipolar disorder is a substantial accomplishment. Finally, the methodologies of published active comparator studies appear to be free of bias.

Factors Associated With Responsiveness to Lithium During Maintenance Treatment

Only a small number of factors have been studied in relationship to prediction of prophylactic benefit from lithium. Patients with a rapid-cycling course are less likely to benefit than those without rapid cycling.^{30,43} Patients without psychotic features are more likely to benefit from lithium prophylaxis.⁴⁴ Patients with more lifetime episodes or more frequent episodes of illness are less likely to respond to lithium prophylaxis.^{33,45} As in mania, serum levels of 0.8 mEq/L or greater in bipolar disorder are associated with better efficacy than lower levels. However, tolerability and, relatedly, adherence to the treatment regimen are better with lower serum levels of lithium.^{38,45,46}

Effects on Risk of Suicide

There are consistent suggestions that lithium reduces the established high risk of suicide and suicide attempts in

bipolar disorder. Most evidence is naturalistic, comparing rates with historical controls.⁴⁷⁻⁴⁹ While acknowledging the methodological problems that can arise from pooling data across diagnostically and otherwise heterogeneous studies, Baldessarini et al.⁵⁰ found that comparisons of risks with and without lithium maintenance treatment could still be made in many studies involving matched conditions of diagnosis, follow-up, and assessment of patients with and without lithium treatment. Examining a number of such reports, they found that the mean \pm SD overall rate of suicide attempts or deaths with lithium treatment was $0.255\% \pm 0.403\%$ of subjects per year during lithium treatment in 22 studies, compared with $1.778\% \pm 1.444\%$ per year without lithium treatment in 13 of the reports. This 7-fold difference in crude rates was highly statistically significant ($t = 3.73$, $df = 34$, $p < .0017$). Each of the 13 reports involving direct comparison within the same study found annual rates of suicidal behavior to be substantially lower in patients during maintenance treatment with lithium than in comparison groups of patients with severe affective illnesses who were not so treated.

One comparative, randomized open trial⁵¹ compared lithium with carbamazepine and found substantially higher rates of suicidal behavior among patients treated with carbamazepine than those treated with lithium. Earlier studies indicated reduction of suicidal risk when lithium therapy is conducted with supportive care⁴⁶ but not when lithium is provided without an associated educational and psychological treatment program; these findings suggest that an important component in reducing suicidal behavior is maintaining the patient in a psychosocially supportive treatment relationship.³⁸

Tolerability

Lithium has a therapeutic dose to toxic dose ratio among the narrowest of any medication. Distributed throughout body water, it is present in relatively similar concentrations in all body organs. These factors contribute to its difficulties in use. Early discontinuation rates for lithium have been higher than for divalproex in randomized comparisons.^{25,29} Open trials also report high rates of early discontinuation.^{38,52,53} A large, naturalistic study reported that bipolar disorder patients averaged only 65 days of initial, continuous lithium use in maintenance therapy despite standard psychiatric care.⁵⁴ A substantial factor in early discontinuation of any mood stabilizer may be inadequate control of manic symptomatology, with resultant impaired judgment, impulsivity, and consequent discontinuation. When such circumstances present, a primary approach to intervention is recognizing that the issue is less the tolerability of the medication than the insufficient effectiveness of the medication and related therapeutic program. However, psychomotor slowing, cognitive impairment, weight gain, tremor, and gastrointestinal irritability

clearly interfere with comfortable, satisfactory function and contribute to patients' either taking less lithium than prescribed or discontinuing it altogether. In some instances, change to an alternative regimen, with particular consideration for use of divalproex, given its indication for use in mania and its broad range of efficacy, is a reasonable strategy. In others, particularly where benefits are unequivocal with the lithium, efforts to alter the regimen to achieve a well-tolerated schedule are preferable. Such efforts should emphasize testing over a period of several months to determine whether lower serum levels provide better tolerability while still providing effective symptom control.⁷ Sustained-release lithium preparations provide less exacerbation of adverse effects associated with peak serum levels, allow once-daily or at most twice-daily regimens, and are to be preferred for nearly all patients. If lithium is discontinued, the action should be a gradual taper rather than abrupt discontinuation.^{22,55} Some worsening of illness course in crossover-designed studies of lithium, and in circumstances such as abrupt discontinuation at the time of pregnancy, is probably a consequence of rebound-induced worsening of short-term illness course.

An additional important strategy is combining lithium with one or more other medications effective in some phase of bipolar disorder care: case report data support almost all conceivable combinations. In the few randomized studies, the combination of lithium and valproate has been reported effective in patients unresponsive to lithium alone.⁵⁶⁻⁵⁸ Lithium plus carbamazepine was effective in controlling manic symptomatology in rapid-cycling patients in 1 crossover study, whereas either drug alone was ineffective.³⁰ However, in the same study, the combination was as ineffective as either drug alone in reducing percentage of time spent depressed. It is plausible that lithium is beneficial in combination therapy at serum levels lower than those characteristically used during monotherapy, although few data provide clinically useful evidence on the question. Prospective studies suggest that patients discontinued from lithium and later restarted have approximately the same likelihood of response as during the first treatment period.²³ However, the suggestions that some patients may have lithium withdrawal-induced treatment refractoriness take on new currency in light of the recent report that the variable of more than 8 lifetime affective episodes was associated with negligible rates of responsiveness to lithium during mania compared with good response in patients with 8 or fewer lifetime episodes. This report strengthens the rationale for early diagnosis and sustained intervention from the first episode.^{12,59}

Efficacy on Components of Mania

Increased and now well-established evidence suggests that a range of illness course and subsyndromal factors is associated with favorable or unfavorable response to lithium both acutely and during maintenance therapy. It is sur-

Table 2. Changes in Manic Symptoms Significantly Different Between Lithium or Divalproex and Placebo^a

Behavioral Measure	Drug	Change, Mean \pm SD	p, Placebo vs Drug	Effect Size
Elevated mood	Lithium	1.20 \pm 1.92	.18	0.64
	Placebo	0.69 \pm 1.51		0.40
	Divalproex	1.27 \pm 1.95	.04	0.83
Increased activity	Lithium	1.34 \pm 1.89	.01	0.82
	Placebo	0.33 \pm 1.86		0.22
	Divalproex	1.09 \pm 1.57	.01	0.82
Motor hyperactivity	Lithium	0.94 \pm 1.64	.03	0.61
	Placebo	0.19 \pm 1.60		0.14
	Divalproex	0.82 \pm 1.56	.02	0.66
Less need for sleep	Lithium	0.97 \pm 2.50	.069	0.50
	Placebo	0.10 \pm 1.91		0.07
	Divalproex	1.46 \pm 1.65	< .001	0.93

^aData from Bowden et al.⁶⁰

prising, then, that little attention has been given to component behaviors most specifically affected by lithium. Statistically analyzed data are available from 3 published studies^{5,12,60} and 1 unpublished study (Swann AC, 2000). In a randomized, double-blind study of lithium compared with placebo and divalproex, 4 dimensions of behavior that differed significantly between treatments and from baseline to final assessment were analyzed for effect size.⁶⁰ As shown in Table 2, lithium significantly improved increased activity and motor hyperactivity compared with placebo. The effect size was large (≥ 0.8) vs. placebo for increased activity and moderate (≥ 0.5) for motor hyperactivity. For both of these behavioral items, the effect size was comparable for lithium and divalproex. By contrast, neither elevated mood nor less need for sleep improved significantly compared with placebo, and the effect size of improvement was less for both items than that associated with divalproex treatment. This apparent primary effect on activity levels elevated above normal is consistent with the description of the first patient treated with lithium, who was described as "settled down" after 3 weeks of therapy with lithium from a "state of chronic manic excitement for 5 years, restless, dirty, destructive, mischievous and interfering. The most troublesome patient in the ward."⁶¹ Swann studied dimensions of behavioral change among mixed manic patients who responded to lithium. Whereas a factor that included excessive energy and activity improved significantly from baseline, factors for anxiety/depression, psychosis, and irritability neither improved significantly nor differed from change in patients randomly assigned to placebo. There is also some evidence that lithium results not only in reduction toward normal in increased activity levels but also in a reduction to levels of activity substantially below those observed in normal controls (Bowden CL, Katz MM, Swann AC, unpublished data, 2000). Impairment in motor speed is greater at serum lithium levels of 0.8 mEq/L or greater than at lower levels.⁶² Reduction in psychomotor activity is one of the most consistently reported adverse effects from lithium.⁶³ Fur-

thermore, an animal model to test for manic-like behavior in animals utilizes drug-induced hyperactivity, which is significantly reduced by acute lithium administration.⁶⁴ In the aggregate, this evidence suggests that a fundamental property of lithium is reduction of motor activity and that the effect may extend to reduction of normal as well as elevated activity levels.

Two studies suggest that lithium may increase sub-threshold depressive symptomatology or be less effective in preventing its occurrence than the recurrence of hypomanic symptoms during long-term lithium treatment of bipolar disorder.^{25,65}

CONCLUSION

Lithium is a drug that revolutionized both treatment and phenomenological study of bipolar disorder. It remains a valuable treatment for bipolar disorder. The use of lithium is more limited than was the case in the decade following its regulatory introduction, as a consequence of a better understanding of its spectrum of efficacy and poor tolerability. It is increasingly utilized in combination therapy in bipolar disorder. The availability of valproate as a second drug with established efficacy now makes it possible to utilize lithium and valproate to assess pharmacodynamic mechanisms and behavioral effects of the drugs. Previously, it was not possible to disentangle illness course features intrinsic to the disease from those linked to a specific drug mechanism. Thus, in addition to a continued role in the treatment of bipolar disorder, in the next decade, lithium may contribute to important advances in knowledge about mechanisms of mood-stabilizing effects and the pathophysiology of bipolar disorder.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), lorazepam (Ativan and others), verapamil (Calan and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine has not been approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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