The Psychopharmacologic Specificity of the Lithium Ion: Origins and Trajectory

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This article examines the development of lithium therapy since its dramatic introduction into psychiatry in 1949. Since that time, lithium has been examined in the treatment of a variety of neuropsychiatric conditions, but it is in the treatment of bipolar disorder that it is most effective. This suggests that it has specificity in the treatment of this disorder. These findings are very relevant as they suggest that understanding the mechanism of action of lithium in bipolar disorder may hold keys to elucidating its pathophysiology and to developing newer and more effective treatments. We review the published data on the effectiveness of lithium in bipolar disorder and various neuropsychiatric conditions and also the available data on anticonvulsants and newer therapeutic agents in the treatment of this condition. *(J Clin Psychiatry 2000;61[suppl 9]:16–22)*

The time course of the development of lithium since its introduction in 1949 spans the professional career of one of us (S.G.).[1–3] My role here is thus of a historian and participant in the evolution of these events. Cade's paper published in 1949 was entitled, "Lithium Salts in the Treatment of Psychotic Excitement."[4] This report published in the *Medical Journal of Australia* did not engender much excitement or interest outside Australia. This report, however, heralded a number of dramatic events. Lithium has a unique and pivotal position in psychopharmacology. It preceded the introduction of chlorpromazine into psychiatry and in fact fired the first barrage that initiated the modern era of psychopharmacology. With lithium, however, there was a phenomenal lag between its discovery and acceptance in usage in the United States. The time interval is remarkable. It was not approved by the Food and Drug Administration until 1970. Even after this, there was little commercial interest or marketing devoted to it.

Looking closely at the first accounts by Cade[4] on the evolution of his work that led to his clinical report, we see that serendipity was a major contributor to these momentous events. The story unfolds along a fortuitous path. The short version starts with an interest in pursuing a possible toxin present in urine as a cause of psychosis. The basis of these ideas lay in Cade's feeling that mania might represent a state of intoxication arising as a result of an excess of some normal metabolites, while depression represented the effects of abnormally low levels of the same metabolites. Urine samples were collected from manic, depressive, and schizophrenic patients as well as from normal controls. The urine was then injected intraperitoneally into guinea pigs. That from manic patients proved to be more toxic than urine from the other groups, although all the samples led to deaths among the animals. Cade reported his observations on the guinea pigs thus: "That after an injection of a solution of lithium they could be turned on their backs and that, instead of their usual frantic fighting behavior, they merely lay there and gazed placidly back at him."[4]

This experience sets a pattern for many subsequent discoveries in pschopharmacology. Even with serendipity, the next major contribution was made by the clinical investigator himself. In the case of Cade, whatever inclarity existed in his preclinical work, once he observed the effects of the treatment on patients, he was uncannily prescient. On the basis of his observations that lithium had a calming effect in guinea pigs, the Australian psychiatrist administered lithium to 6 manic patients and found remarkable benefits in all of them. In 3 of 6 patients with dementia praecox, there was only a quieting effect, and no effects in the others, and in 3 chronic depressive psychotic patients, there was no effect at all. These findings led Cade to comment: "The effect on patients with pure psychotic excitement—that is, true manic attacks—is so specific that it leads to speculations as to the possible etiologic significance of a deficiency of lithium ions in the genesis of the disorder."[4] The role of lithium deficiency in the pathogenesis of the disorder, of course, has not been supported by subsequent work. Yet, another observation about his clini-

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cal report should be highlighted—the original therapeutic dose fortuitously proved to be the usual optimum dose, that is, 1200 mg of lithium citrate or 600 mg of lithium carbonate thrice daily.

In regard to his clinical findings with lithium, Cade presented some quite dramatic constructs:

1. The concept of lithium specificity, that is, the therapeutic target being "true manic attacks."
2. His follow-up observation with his small patient sample of the potential of prophylaxis. He raised the possibility for the first time in psychopharmacology that continued treatment may prevent a recurrence of the disease, viz., mania.
3. The concept (the most remarkable within the therapeutic context of the time) that an agent might treat manic excitement without secondary behavioral effects, such as drowsiness, sedation, hypotension, or other neurologic side effects. This profile is still a goal that we would like to attain with our current and yet to be discovered agents, i.e., (a) specificity, (b) predictability, (c) freedom from side effects, (d) potency and efficacy in the majority of cases of the disorder.

Lithium has recently been suggested again to be a specific treatment for bipolar disorder.[5,6] In this article we briefly review the findings of lithium trials in various neuropsychiatric disorders that gave subsequent confirmation to the notion of lithium's specificity, and we review emerging concepts with the new agents that have become available for the treatment of bipolar disorder.

The first clinical paper on lithium in the world literature following Cade's report on the treatment of 6 manic cases was published by Noack and Trautner in the *Medical Journal of Australia* in 1951.[7] When they reported the results of lithium treatment of 100 patients with various psychiatric disorders, including 30 patients with mania, all but one improved, again supporting the idea of specificity. Noack and Trautner[7] introduced the use and stressed the importance of measuring plasma lithium levels for safety monitoring and proposed the concept of therapeutic plasma levels. Cade did not utilize such a monitoring procedure, and other studies in Australia reported cases of lithium poisoning without monitoring. It is also of interest that the methodology for electrolyte assays was developed by Dr. Victor Wynn[8] in the same department (Physiology) as Dr. Trautner at the University of Melbourne.

I will digress to mention another study carried out by Trautner and colleagues entitled "The Excretion and Retention of Ingested Lithium and Its Effect on the Ionic Balance of Man."[9] This study raised an interesting concept of the differential pattern of retention and excretion of the lithium ion in manic versus nonmanic subjects. These findings also furthered the suggestion of therapeutic specificity of lithium in "mania," i.e., "typical" mania.

Following these Australian reports, publication activity was limited to several French reports using lithium in states of agitation as well as manic disorders, and in 1953, a single report in the Italian literature. Over the subsequent 5-year period there were a few more French reports,[10,11] 2 Italian,[12,13] 2 Czech,[14] and one English.[15] Thus, there was no storming of the barricades for publication on lithium usage.

Then, a report in 1960 in the United States suggested that lithium had little or no effect on a variety of psychiatric disorders, including schizophrenia, epilepsy, premenstrual tension, and sociopathy but that it was highly efficacious in manic patients.[16] There were 2 early contributions from Canada, Kingstone in 1960[17] and Nassr in 1966.[18] Both reported specific activity in mania. In the United States, reports appeared in the 1960s by Wharton and Fieve[19] and Schlagenhauf and others.[20]

CLINICAL TRIALS OF LITHIUM

Bipolar Mania

Lithium is in general the most effective medication for acute mania, producing improvement in about 70% to 80% of cases.[5,6,21–24] Two studies found neuroleptics to be superior.[25,26] Lithium has been shown to be at least as effective or superior to neuroleptics in various controlled trials.[27–32] In these studies, lithium was more specific for the core manic symptoms (affective symptoms, ideational symptoms), whereas neuroleptics were generally as good or more effective for hyperactivity and psychomotor agitation, suggesting that the main effects of neuroleptics would involve nonspecific sedation, rather than a true antimanic action.

Response rates have varied in different samples of bipolar patients. In typical "pure" manic states, lithium seems to be the most effective, while in mixed states, atypical, or secondary mania, the response rates tend to be lower, with reports of response rates as low as 29% to 42%.[33–37] In conclusion, lithium is most effective in "typical" cases of bipolar disorder, suggesting specificity for its action in this condition.

Bipolar Prophylaxis

Cade's original report mentioned a preventive effect on recurrent mania in some of his patients. Since then, many studies, both open and controlled, have documented the effectiveness of lithium treatment for prophylaxis of the manic and depressive phases of bipolar disorder.[38–47] Generally, the typical bipolar patients are the ones who appear to respond better. Data from naturalistic studies show lower response rates, with failure rates of up to 70% in some studies.[48,49] This change in response rates has occurred over time. Early studies reported failure rates of 20% to 30%.[16] Then, reports in the 1960s and 1970s reported failure rates on average of 33%,[50] and some studies

presented failure rates of over 55%.[51] In particular, patients with mixed states or atypical features appear to have low response rates to lithium treatment.[6,24,52] The higher response rates found in lithium's early trials have been disputed,[53] but the prevailing view is still that lithium is the most effective agent in the treatment of bipolar disorder, with effectiveness demonstrated in several controlled studies.[5,54] This superior efficacy in bipolar disorder is consistent with the hypothesis of lithium's specificity in the treatment of this disorder.

The Characteristics of Lithium Responders

Classic manic states and mania followed sequentially by euthymia and depression predict good prognosis on lithium prophylaxis.[55–57] Mania with mixed or dysphoric features, rapid cycling, and mania secondary to medical conditions respond poorly to lithium.[30,50,58–60] Patients with high frequency of previous episodes[61,62] and comorbid substance abuse or personality disorders are also less responsive.[62–66] Family history of mood disorders is related to better response to lithium prophylaxis.[62,66] In another study,[67] family history of bipolar disorder, but not unipolar depression, was shown to be related to positive lithium response. These family data, if confirmed, also point to a specificity of lithium for bipolar disorder. Grof et al.[68] recently readdressed this question and found that a primary diagnosis of affective disorder, episodic course, and family history of bipolar illness were the best predictors of lithium response in the maintenance treatment and remission with *restitutio ad integrum*. In the bipolar II population, lithium is also an effective prophylactic treatment.[41,69] It is effective in the prophylaxis of hypomanic episodes but may not reduce the frequency of depressive episodes. However, the depressive episodes may be less severe.[41] Thus, lithium is highly effective in the prophylaxis of bipolar disorder, types I and II. It is not as effective in atypical bipolar patients, rapid cyclers, and patients with organic mania, dysphoric mania, and comorbid psychiatric disorders. These studies of predictors of lithium response also give strong support for the idea of lithium's specificity, with typical features predicting response.

Bipolar Depression

Lithium has significant effects in the acute treatment of depression, in particular, depression associated with bipolar disorder.[70–73] However, it is generally not as effective as antidepressants. This superior effectiveness for bipolar in comparison with unipolar depression is also consistent with the hypothesis of its specificity in bipolar disorder.

Unipolar Depression

Lithium was demonstrated to have therapeutic effects in unipolar depression in the acute treatment and in prophylaxis.[69,74–77] In some countries, it is a popular and even favorite treatment for prophylaxis of recurrent unipolar depression. The role of lithium as an augmentation agent in refractory depression has been well studied and documented,[78,79] with findings that it has a clear role for this indication. In conclusion, lithium has acute antidepressant effects in unipolar depression and also some prophylactic action, but it is generally not as effective as antidepressants for acute treatment or prophylaxis of unipolar conditions.[51] Its effects in unipolar depression are apparently smaller than the effects in bipolar depression, once again suggesting specificity for bipolar disorder.

Schizoaffective Disorder

Johnson et al.[28,80] found a substantially better response rate to lithium treatment in bipolar as compared with schizoaffective patients. These studies found that there were no significant benefits with lithium, with some patients exhibiting worsening of thought disorder. Chlorpromazine on the other hand produced significant improvement. Other reports found lithium to have some beneficial effects for cases of schizoaffective disorder.[55,81–84] Generally, the more prominent the affective component, the more effective lithium is. In particular, if manic symptoms are prominent, lithium has been shown in these studies to have significant therapeutic effects. However, in most cases, the successful pharmacologic management of schizoaffective disorders requires associated antipsychotic treatment, which often is the mainstay of treatment.

A prophylactic treatment trial[45] found lithium to be substantially more effective in bipolar than in schizoaffective patients. Thus, there are 2 distinct points of view: one proposes a continuum diagnostic concept and the other, separate and discreet diagnostic entities.

Schizophrenia

Lithium has been administered to schizophrenic patients in various uncontrolled and controlled studies,[6,16,85–87] with marginal or no therapeutic effects. The overall results of these studies allow us to say that there is no demonstrated effectiveness of lithium for schizophrenic symptoms. In some studies, there were suggestions of therapeutic effects, which were most often due to an affective component associated with the condition.[83,88,89] In a review of the literature,[85] it was concluded that lithium might benefit those cases with "psychomotor acceleration and periodicity." Therefore, the results of these studies strongly suggest that lithium has specificity in its actions for bipolar disorder.

Aggressiveness

Lithium has been demonstrated to have therapeutic effects in some cases of aggressiveness,[90–95] in particular, cyclic aggressiveness. A placebo-controlled, crossover discontinuation study showed that lithium had significant effects on cyclic aggressiveness, violent explosive behavior, and mood swings in children.[91] This study demon-

strates that the pharmacologic spectrum of lithium may include these key components.

Substance Abuse

Lithium has been examined as a potential treatment for alcohol and cocaine abuse or dependence. The claims for alcoholism date back to a 1974 double-blind controlled study[96] reporting efficacy. Several subsequent studies supported this. The Dorus et al.[97] study involved 457 depressed and nondepressed alcoholics. No significant effects of lithium were found in either patient group. Most of the studies in alcoholics demonstrated that lithium has no significant therapeutic effects,[97–99] even though there may be effects in associated affective symptoms.[100] In cocaine addicts, it was suggested to potentially have therapeutic effects in some,[101] but not all[102] open trials; no controlled evidence supports any therapeutic effects of lithium in these conditions.

Other Conditions

Lithium has also been examined in obsessive-compulsive disorder[103] and premenstrual syndrome[104,105] and generally does not seem to be helpful in these conditions. In compulsive gambling, eating disorders, and hypersomnia states, it has been suggested to have positive effects in anecdotal reports,[106–109] but no controlled evidence to date supports any therapeutic effects of lithium in these conditions.

OTHER THERAPEUTIC AGENTS

Carbamazepine

Carbamazepine was initially used in bipolar disorder patients in studies conducted in Japan, which suggested its therapeutic potential.[110] To date, several double-blind controlled studies demonstrate its effectiveness in the treatment of mania and also suggest its prophylactic effects.[111–116] However, its effectiveness in prophylactic treatment in comparison with lithium is not clearly determined.[117] These studies also suggest that, for patients with mixed states, rapid cycling, treatment refractoriness, or neurologic abnormalities, carbamazepine may be more effective than lithium.[118–122]

Valproate

Valproate, an anticonvulsant introduced in the United States in 1996, has been shown in controlled studies to have effectiveness for treatment of bipolar mania.[57,123–125] There is also a suggestion of effectiveness superior to lithium for patients with mixed states, rapid cyclers, and refractory patients.[58,126–128] However, the results of a multicenter study, which examined the effectiveness of valproate in prophylaxis in comparison with lithium, are not yet fully published. Thus, its comparative effectiveness to lithium for this indication has still to be demonstrated.[127]

New Anticonvulsants

Lamotrigine. Lamotrigine is an effective antiepileptic medication that has been suggested to be effective in the treatment of bipolar disorder. Initial open reports and more recent controlled trials suggested its effectiveness in the treatment of mania and also in the treatment of bipolar depression.[127,129–131] It was also suggested to be effective in rapid cyclers[132] and in refractory cases.[131,133] The potential role of lamotrigine in the prophylactic treatment of bipolar disorder remains to be examined.

Gabapentin. Gabapentin is another effective antiepileptic medication whose potential as a mood stabilizer has recently emerged. Retrospective reports and open trials suggest its effectiveness in bipolar disorder.[134–137] It was also suggested to be effective in bipolar depression in one open trial.[138] However, its potential remains to be further examined in double-blind, placebo-controlled studies. Such a study has recently been conducted.[139] Bipolar patients experiencing mania, hypomania, or mixed state and with ongoing lithium, valproate, or lithium and valproate combination therapy were enrolled. One hundred seventeen patients entered the study. Both the gabapentin and placebo groups had a decrease in total Young Mania Rating Scale from baseline to endpoint, but the decrease was statistically significantly greater in the placebo group than in the gabapentin group ($p < .05$). No difference between treatments on the Hamilton Rating Scale for Depression was observed.

Calcium Channel Blockers

Verapamil. Initial open trials and preliminary controlled trials suggested that verapamil would be effective in the treatment of bipolar disorder.[140–143] However, a recent double-blind, controlled study failed to demonstrate its effectiveness in this condition.[144]

Nimodipine. There are anecdotal reports, open studies, and preliminary controlled trials suggesting that nimodipine would be an effective treatment for bipolar disorder.[122,145–150] Double-blind, placebo-controlled studies are needed to examine its efficacy further.

Combination Therapy

Current reports suggest that lithium, even when augmented by antidepressants, benzodiazepines, and neuroleptics, is inadequate for more than half the bipolar patients. Denicoff et al.[151] reported that response to random-assignment monotherapy for 1 year and crossover in the second year was 33.3% for lithium and 31.4% for carbamazepine, and for combination treatment during the third year was 55.2% with a larger differential effect in rapid cyclers. However, the sample size of 18 was small and subsamples were 6 or 7 patients. Still, 30% to 40% were inadequately responsive. The definition of response in this study is complex. A strong belief has developed that combination therapy may be necessary and beneficial in

some cases. However, the data available on combination therapy are not adequate to reach firm treatment recommendations. More systematic clinical trials are essential before proposals can be developed for rational combination pharmacotherapy.

CONCLUSIONS

The research findings over the past 50 years support Cade's original proposition that lithium is most effective in bipolar disorder.[4] It is particularly beneficial for the acute treatment of mania and its prophylaxis and also has positive effects in the treatment of depression in bipolar patients. Thus, several authors have proposed that the unique targets with lithium are the specific features of recurrence, cyclicity, episodicity with affective features, and intervals of remission that optimally return to normality. This paradigm of specificity in psychopharmacology may prove to be very useful for elucidating the pathophysiology of the disorder. A better understanding of lithium's mechanism of action in this condition may result in elucidating the basic mechanisms involved in causation of this condition and guide future drug development efforts in this field.

New agents have appeared for the treatment of bipolar disorders. However, based on the evidence reviewed here, lithium is still the most effective agent, and if a patient can tolerate it relatively well and responds to it, lithium can be the treatment of first choice. The comparative study of lithium's effects with the effects of other medications shown to be effective in bipolar disorder is an important psychopharmacologic strategy that should lead to a better understanding of its pathophysiology and ultimately to further drug development in this field. Future studies examining the actions of lithium, anticonvulsants, and calcium channel blockers in various membrane, neurotransmitter, and signal transduction processes may provide the path to achieve these goals.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), gabapentin (Neurontin), lamotrigine (Lamictal), nimodipine (Nimotop), verapamil (Calan and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, the following agents are not approved by the U.S. Food and Drug Administation for the treatment of bipolar disorder: carbamazepine, gabapentin, lamotrigine, nimodipine, verapamil.

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