Historical Perspectives and Current Highlights on Lithium Treatment in Manic-Depressive Illness

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This article reviews the use of lithium from Roman times, when physicians first recommended alkaline springs in the treatment of mania, to the present. Serious interest in lithium began in 1949, with a report of improvement of mania in 10 of 10 patients. Since then, lithium has become increasingly popular both for treating acute mania and as a prophylactic agent. Its use in depression is also described. Finally, lithium's clinical spectrum is discussed, noting that its use extends far beyond the treatment of mania.

THE HISTORICAL aspects of the use of lithium in psychiatry are quite fascinating and date far beyond Cade's first report in 1949. The first therapeutic application of lithium in mania was prescribed in Rome in the second century AD by the Greek physician Seranus Ephesios (from Asia Minor) who, in his section on the treatment of mania, writes: "Utendum quoque naturalibus aquis, ut sunt nitrosae...," which means: "use should also be made of natural waters, such as alkaline springs."

The 5th century AD Roman physician Caelius Aurelianus recommended specific alkaline springs, many of which contained lithium, to treat certain physical and mental ailments. The tradition of natural spring water for the treatment of emotional illness was widely accepted throughout the centuries, and several European wells in England, Ireland, France, Germany, Scotland, Italy, and Greece had developed a more than local reputation.

Around 1818, J. A. Arfwedson, working in the laboratory of Berzelius, discovered a silvery white substance which he called lithium, from the Greek lithos, which means stone. It constitutes about 20 parts per million of the igneous rock of the earth's crust, so it is sparsely, but widely distributed. Its chemical individuality was the key to its discovery as the unaccounted for percentage component of the newly found mineral petalite. Arfwedson demonstrated that the mysterious element resembled sodium and potassium in some reactions but not in others. Bunsen disclosed the presence of lithium in tobacco, sugar cane, and seaweed which belied the exclusive occurrence of this element in minerals. Its salts were later detected in the spa waters of England and Germany, and thus lithium was launched on its medical and therapeutic career. It was believed that the reputed effects of these spas on rheumatoid arthritis and gout were due to the presence of lithium. The mineral waters contain about 1 mEq/liter of lithium.¹,²

Its distribution in nature is extensive and diverse. It has been detected in trace amounts in plants, marine life, milk from several animals, and various animal and human tissues, but not human bone. It is not known whether these traces of lithium naturally present in the organism play any physiological role.

Lithium salts seem to have been first introduced into medicine by Sir Alfred Garrod³ about 1859 for the cure of gout, rheumatic gout, and urinary calculi. They were introduced on the assumption that, since lithium salts were excellent solvents for uric acid and the urates in experiments in vitro, they would dispose of the deposits in the joints when given orally. These high therapeutic hopes were dispelled by subsequent clinical and biochemical work,⁴,⁵ and lithium salts are no longer used in these disorders. Next, lithium bromide was advocated both as a mild tonic by Gibb⁶ in 1864 and as a sedative by Levy⁷ in 1874. Mitchell⁸ reported that it was as efficient as sodium or potassium bromide in treating epilepsy and that its influence over insomnia was greater. Other medicinal properties for the various lithium salts were recorded by Squire⁹ in 1916, including the diuretic, hypnotic, and anticonvulsant.

Lithium again attracted wide attention and a notorious reputation during the late 1940's when its chloride salt was introduced as a salt substitute for cardiac and hypertensive patients. Its use was quickly discontinued when reports linked it to numerous instances of severe poisoning and several deaths.
Ironically, at the same time lithium carbonate was withdrawn from the market as a salt substitute, the first report of its efficacy in treating episodes of mania appeared. In 1949 in Australia, a report by Cade\textsuperscript{10} stated that lithium salts given to 10 manic patients resulted in improvement in the condition of all. There are several aspects of this first report of the use of lithium in mania that demand special consideration.

First, the introduction of lithium in 1949 makes it the first agent in the modern era of psychopharmacology in that it preceded the introduction of chlorpromazine and reserpine. Second, this report by a clinician set a pattern which was to be followed for the other major groups of psychoactive drugs. Therefore, the details of Cade’s report should be looked at carefully and in detail. Third, serendipity seems to have been the midwife for lithium, as was the case later with the phenothiazines and the tricyclic antidepressants. Fourth, no reliable predictions based on preclinical pharmacological studies could have been made about the profile of clinical activity of lithium. This problem of clinical predictability based on current preclinical pharmacological studies is also the case with many new psychoactive drugs.

In looking at the details of the first report on the use of lithium in mania, we find that the study suggests a remarkable order of drug effectiveness in that clear and marked improvement occurred in every one of the 10 cases. The report includes the trial of lithium in six patients suffering from dementia praecox. No fundamental improvement was noted in any of them, but there was some decrease in restlessness in three. Three patients suffering from chronic depressive psychosis were given lithium for several weeks and no improvement or aggravation of depression was noted.

Lithium carbonate and lithium citrate were both used in doses of about 50 mEq/day. Remission was observed in all of the manic cases approximately 7 days after starting medication. Thus, this report represents an open uncontrolled study by an astute clinician, and it is these observations that have been explored over the past 30 years. In large part, these original observations still stand.

The pattern of discovery of lithium was to be repeated with many of the major psychoactive drugs subsequently introduced. Cade presents the fascinating story of how he came to use lithium in mania. This material is presented in two papers by Cade\textsuperscript{10} in 1947 and 1949. He observed in the course of some experiments on the toxicity of urea injected intraperitoneally into guinea pigs that the animals became extremely lethargic and unresponsive to stimuli for 1 or 2 hours before becoming normally active and timid. He goes on to say: “It may seem a long distance from lethargy in guinea pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.” In examining the link between the effects observed in animals and their use for predicting clinical activity, we find that the lethargic effect observed here was more likely due to lithium toxicity.\textsuperscript{11} But the lithium story does not fulfill the requirements of currently established animal screens for activity as a major tranquilizer.

Further developments following Cade’s discovery are that, a year later, the next report to appear was of a death resulting from lithium used for psychiatric purposes, followed shortly by a letter to the editor describing successful use in more than 50 patients without fatalities, and a year after that by the first formal confirmatory paper. Meantime, the French, beginning with Despinoy, started using lithium for all types of excitement states (including manic ones).

Of all these, only one states that its administration was ineffective. Guistino\textsuperscript{12} failed to find improvement in the two patients he studied. The literature includes trials in manic patients, schizophrenic patients, and those in other diagnostic entities. Even in those studies on manic subjects, it is difficult to assess the specific therapeutic activity of lithium because no rating scales were employed, diagnostic problems are considerable, and other medications were used concomitantly. Since no rating scales were used in these studies, the term “improvement” may vary greatly in significance. The large variation in reports of incidence of the disease tends to suggest large variation in diagnostic criteria, which alone could account for significant differences in the results in studies of mania.

Unfortunately, the full input of Cade’s original work was not fully realized at the beginning, and for the first 5 years following his discovery, relatively little work with lithium was undertaken. Several factors could be attributed to this lag between discovery and application. Prominent among these have been: (1) the acknowledged toxic potential of lithium based on the fact that lithium salts, used in the 1940’s as NaCl substitutes in salt-restricted diets, had become discredited because of their toxicity; at the time of Cade’s discovery, they had just been taken off the market and the climate was therefore unfavorable for their reintroduction; (2) the relatively low price of lithium salts which influenced drug manufacturers not to pursue the investigation of such a substance; and (3) the coincidental discovery of a wide variety of antipsychotic medications, including neuroleptics and the Rauwolfia alkaloids. Cade himself suggested that the primary investigation “made by an unknown psychiatrist, working alone in a small chronic hospital with no research training, primitive techniques and negligible equipment, was hardly likely to be compellingly persuasive, especially in the United States.”
The major turning point in the history of lithium came in 1954 when Schou and co-workers in Aarhus State Hospital, Risskov, Denmark, resumed this line of investigation which they have continued quite successfully to date. They confirmed Cade’s initial observation and found that lithium has a prophylactic effect in manic depressive conditions. In more detail, in 1954 Schou and associates reported the first controlled study in lithium research where lithium was shown to have a significant antimanic potential quite promising for clinical as well as research applications.

This was followed by Magg’s controlled evaluation of lithium against placebo in 1963, and up-to-date lithium’s effectiveness in the treatment of acute mania has been well established by 12 controlled studies. However, there is still some question regarding lithium’s comparative efficacy to other treatments, especially neuroleptics, and the commonly encountered 20–40% therapeutic failures in most of the studies remain a controversial issue requiring further investigation.

In the United States the first clinical reports on lithium trials did not appear until 1960 when Gershon and Yewiler first reported about the prophylactic properties of lithium. Subsequent trials by Schlegenhauf et al. and Wharton and Fieve, as well as the personal insistence of Gershon and Fieve, hastened acceptance of lithium in this country. Since the mid-1960’s, the major clinical work on lithium has been conducted in the United States and Scandinavia. Finally, in 1970, the United States Food and Drug Administration permitted the reintroduction of lithium in the United States in a strictly limited way, specifically for the treatment of mania.

**Maintenance Treatment**

The task in establishing the prophylactic efficacy of lithium in recurrent mania has been considerably more difficult. Furthermore, no controlled studies have been carried out on the problem of prophylactic activity of any other form of chemotherapy in recurrent affective disorders. The claim for prophylactic activity emerges from some of the earlier longitudinal studies. Such references appear in reports of Noack and Trautner and Schou et al., which suggest primarily activity in the manic phase and the prophylaxis for recurrent mania. In a report by Gershon and Yewiler, a similar suggestion of prophylactic activity for recurrent mania is presented. Then, in 1963, Hartigan concluded that a prophylactic action of lithium against recurrent mania occurs and added a claim for its prophylaxis against recurrent depressive cycles. It is important to note that Hartigan adds the reservation that “atypical” cases, in which there was diagnostic doubt because of conspicuous schizophrenic or paranoid features, did not do as well as the pure classical forms of mania. It appeared in some of these studies that the medication led not only to diminution of the manic episodes, but also to attenuation of the depressive symptoms. This seems to indicate that lithium might exert a prophylactic action in depression as well as in mania.

Independently, Bastrup and Schou also reported that this continued medication of patients seemed to produce a beneficial effect on the prevention of recurrences of both the manic and depressive episodes.

Among the first to claim prophylactic effects of lithium in bipolar manic-depressive illness were Hartigan and Bastrup and Schou. The latter study indicated that lithium reduced the frequency of hospitalization and length of psychotic episodes. This study was followed by an extraordinarily forceful paper by Blackwell and Shephard who labelled the claims for this aspect of lithium’s therapeutic effectiveness as a “therapeutic myth,” drawing a fierce rebuttal from Bastrup and Schou.

Since the late 1960’s, considerable evidence has accumulated indicating that the effectiveness of lithium in long term or maintenance treatment consists in diminishing the frequency and severity of recurrent attacks of mania and depression in bipolar manic-depressive illness. This effect, far from being “preventive or prophylactic” in the true medical sense (i.e., vaccinations in infectious diseases), can be compared with the effectiveness of insulin or antihypertensive agents in medicine and allows patients to live productive lives without serious limitations in their functioning.

Most of these studies were of high quality and they tried to overcome several methodological problems encountered in previous studies except some unresolved ones like the preservation of “blindness,” which still remains a problem in lithium research due to easily recognizable side effects. These studies have shown quite consistently the effectiveness of lithium in maintenance treatment, justifying the claims originally made from retrospective studies. Although lithium has been shown to be effective against both manic and depressive recurrences in bipolar illness, it exerts a higher order of control against manic recurrences than depressive ones.

**Lithium in Depression**

Another area of significant research has been the exploration of the possible effects of lithium in a current manifest depressive illness as well as the prophylaxis of recurrent depression. The first attempt to evaluate the effectiveness of lithium in the treatment of depression was included in Cade’s original report. Three patients suffering from chronic depressive psychosis were given lithium for several weeks and neither improvement nor aggravation of depression was noted. A similar conclusion was reached after a trial in several depressed patients in the report by Noack and Trautner. Similar conclusions
were reported by Gershon and Trautner and Gershon and Yuwiler. Lithium has also been found significantly, but not conclusively, effective in acute depressions in at least seven studies. Also, Mendels has suggested the possibility of a particular subgroup of depressed patients with lithium-responsive illness. The most well-defined characteristics of Mendels' subgroup are: the diagnosis of bipolar illness, family history of bipolar illness, and endogenous symptom patterns. Less likely traits are failure to respond to other somatic therapies and certain personality traits such as lability in mood, increased eating in response to stress, and increased or unchanged sleep patterns under stress.

**Lithium Specificity**

The claim as to lithium's specificity for mania, although scientifically sound at the time, needs to be re-examined in view of the currently accumulated evidence for lithium's wider range of usefulness.

In addition to its antimanic effect, several other therapeutic claims have been made, especially for recurring cyclical and episodic disorders. Thus, lithium has been found effective in certain depressions, in schizoaffective or cycloid illness, periodic psychosis, children with chronic maladaptive behavior patterns combined with mood swings not reactive to environment stimuli (emotionally unstable character disorder), recurring aggression, epilepsy, schizophrenia (combined with neuroleptics), and chronic cluster headaches, just to mention some of the most extensively studied clinical applications. Despite methodological limitations, most of these studies have shown lithium's effectiveness at a statistically significant level.

In addition, several other therapeutic applications of lithium have been reported but could not be replicated in subsequent well-designed studies. Thus, lithium has been used in the treatment of premenstrual tension, phobias, and anxiety.

This accumulated evidence strengthens the idea of lithium's multiple clinical actions and has intriguing theoretical and clinical implications. If we accept this as a fact, it seems likely that lithium's effectiveness is not restricted to a particular nosological entity but to a broader cluster of different nosological syndromes of a recurrent episodic nature alternating with intervals free of evident psychopathology.

To what extent this cluster of syndromes represents a separate clinical entity with different phenotypical expressions must be further investigated using appropriate diagnostic criteria centered around a multiaxial approach.

**References**

6. Gibb GD. Note on the action of bromides of lithium, zinc, and lead. Report, 34th Meeting of British Association for the Advancement of Science, September 1864.