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The history of lithium therapy

Edward Shorter
History of Medicine Program, Faculty of Medicine, University of Toronto, Toronto, Canada

Abstract

The use of lithium in psychiatry goes back to the mid-19th century. Early work, however, was soon forgotten, and John Cade is credited with reintroducing lithium to psychiatry for mania in 1949. Mogens Schou undertook a randomly controlled trial for mania in 1954, and in the course of that study became curious about lithium as a prophylactic for depressive illness. In 1970, the United States became the 50th country to admit lithium to the marketplace. Meanwhile, interest in lithium for the prophylaxis of depression was growing apace and today the agent is widely prescribed for that indication, even though it has not been accepted by the Food and Drug Administration. Lithium was almost derailed by a small group of opponents from the Maudsley Hospital and its status today is threatened by the "mood stabilizers."

Keywords

depressive illness; drug treatment; history; lithium; mania; prophylaxis; randomized controlled trials

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At a meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration (FDA) in the early 1970s, opinion was divided on the use of lithium for "the prevention of recurrent mania." Gerald Klerman, professor of psychiatry at Harvard, was strongly in favor. But the FDA believed the indication ill justified because of a lack of studies.

Klerman complained at another forum about the bureaucrats' obduracy. He said he had objected to them that the literature wasn't always perfect. "What about the first physician who used [lithium] and therefore couldn't call upon a reasonably good body of evidence in the literature …?" he asked them.

John Jennings (from the FDA): "He's like the man who ate the first oyster" (1).

The history of lithium is a little bit like that of the man who ate the first oyster. Lithium has been in medical use—including psychiatric use—for many years (2). Many mineral springs contain lithium, among other elements, and some of them, such as Mineral Wells in Texas, have age-old reputations as "crazy waters" (3). In 1847, London internist Alfred Baring Garrod discovered uric acid in the blood of gouty patients. Garrod made the lithium

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Corresponding author: Edward Shorter, Ph.D., FRSC, History of Medicine Program, Faculty of Medicine, University of Toronto, 88 College Street, Room 207, Toronto, Ontario M5G 1L4, Canada, Fax: 416-971-2160, history.medicine@utoronto.ca.

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treatment of gout—including "brain gout" —widely known in his 1859 work, *The Nature and Treatment of Gout and Rheumatic Gout*, and subsequent editions (4). Amdi Amdisen and F. N. Johnson have recently reviewed lithium's early history (5, 6). By the 1930s, a number of lithium-containing products were on the market, mostly indicated for the control of renal calculi and the "uric acid diathesis." For example, in 1939, the German pharmaceutical index, *The Red List* (*Die Rote Liste*), featured "Lithosanol Bauer," a combination product of lithium citrate and several other components for kidney, bladder, and gallstones (7, 8).

In an early psychiatric reference to lithium in 1870, Philadelphia neurologist Silas Weir Mitchell recommended lithium bromide as an anticonvulsant and a hypnotic (9). Mitchell later came out for the bromides, preferably lithium bromide, for "general nervousness" (10). In 1871, William Hammond, professor of Diseases of the Mind and Nervous System at the Bellevue Hospital Medical College in New York, became the first physician to prescribe lithium for mania: "Latterly I have used the bromide of lithium in cases of acute mania, and have more reason to be satisfied with it than with any other medicine calculated to diminish the amount of blood in the cerebral vessels, and to calm any nervous excitement that may be present" (11).

It was, however, Denmark that became the flagship land in using lithium for the treatment and prophylaxis of depression. In 1894, Danish psychiatrist Frederik Lange made explicit reference to lithium in the treatment of melancholic depression, ultimately treating 35 patients with lithium carbonate (12; see reference to F. Lange). (Frederik's older brother Carl, Professor of Pathology in Copenhagen, is often associated with the introduction of lithium in Denmark in the mid-1880s, yet Carl wrote little about it).

This early Danish literature was then forgotten. In the first half of the 20th century there are virtually no references to lithium in the psychiatric literature, although a tradition of lithium treatment does seems to have persisted. French physician Roger Reyss-Brion recalled that a preparation called "Dr. Gustin's Lithium" had been popular in the south of France; "It's quite simply for that reason that you don't have a lot of manic-depressives in Marseilles" (13).

The modern revival of lithium began in 1949 in the Bundoora Repatriation Hospital, a veterans' hospital in a suburb of Melbourne, Australia, when John Cade, aware of Garrod's success in using lithium a century previously in the treatment of gout, hypothesized that some condition involving uric acid might lie behind his manic patients' "psychotic excitement"; Cade began treating 10 of them with lithium citrate and lithium carbonate. Some responded remarkably well, becoming essentially normal and capable of discharge after years of illness (14). Unfortunately, 1949 was precisely the wrong time for such an article to appear—after a recent failed experiment with lithium chloride as a substitute for sodium chloride in patients with congestive heart failure (15)—and moreover, in such a then-obscure journal. Cade's discovery was significant not just because it added an important new agent to the psychopharmacologic armamentarium but because it illustrated the triumph of the scientific method, at a time when psychiatry was in danger of losing sight of science. As Cade's son Jack, himself an intensive-care specialist in Melbourne, and

Sydney psychiatry professor Gin Malhi noted in 2007: “John Cade’s discovery demonstrates the importance of clinical observation, the significance of reporting case findings, the value of being patient centered and the scientific benefit of an open and inquiring mind” (16).

The Cade article did not go entirely unnoticed, prompting isolated studies of lithium. In 1951, C. H. Noack at the Mont Park Mental Hospital in Melbourne and E. M. Trautner in the Department of Physiology at the University of Melbourne found in an open trial of over 100 patients that the therapeutic benefits outweighed the side effects, judging lithium “very beneficial” for mania (17). In France in 1951, two physicians at the Saint-Albain mental hospital administered lithium citrate to ten patients with “chronic mania,” concluding, “The use of lithium in the manic phases of manic-depressive psychoses seems particularly effective” (18). Yet the echo was faint.

The breakthrough in lithium treatment for mania and the prophylaxis of manic-depressive illness began in 1952, when Erik Strömgren, head of the Aarhus University psychiatric clinic in Risskov, Denmark—who had read the Cade article—suggested to a staff psychiatrist at the hospital, Mogens Schou, that he might undertake a randomly controlled trial of lithium in mania. Random controls were just being introduced in psychiatric drug trials in those years. Schou randomized the mania patients with a flip of a coin to lithium or placebo, and in 1954 he published the results in a British journal. Schou concluded, “The lithium therapy appears to offer a useful alternative [to electroconvulsive therapy (ECT)] since many patients can be kept in a normal state by administration of a maintenance dose” (19).

The Schou article had a large impact and awakened the possibility of lithium treatment for an illness that previously had been governed mainly with barbiturates (but was in fact highly responsive to ECT, introduced in 1938). A number of important international trials occurred, ably reviewed by F. Neil Johnson in his *History of Lithium Therapy* (2).

Yet lithium was tricky to administer, and blood levels a matter of guesswork. The introduction of the Coleman flame photometer in 1958 (20) changed the situation, making it possible to ascertain more precisely than with the old Beckman photometer how much lithium a patient actually had on board. This opened the way for lithium’s widespread therapeutic use in clinical medicine.

In the international history of lithium, the United States was more or less the last in, first out, in the sense that “the United States is one of the few countries—perhaps the only one—where other drugs, such as valproate and antidepressants, are given to bipolar patients much more often than lithium” (personal communication, anonymous referee). At a time when lithium was firmly established elsewhere, in the United States interest in lithium only began to build in the 1960s. The seminal event was probably Samuel Gershon’s arrival in 1960 at the Schizophrenia and Psycho-pharmacology Joint Research Project of the University of Michigan at the mental hospital in Ypsilanti, Michigan. Gershon, familiar with lithium from working with a group at the University of Melbourne that included Edward M. Trautner, Douglas Coats, and Everton R. Trethewie, introduced lithium to the hospital. In a program financed by Jonathan Cole at the National Institute of Mental Health (NIMH) and directed by Ralph W. Gerard, the investigators at Ypsilanti bought lithium by the kilo from a

chemical supply store, then had the local pharmacy put it into capsules. In 1960, Gershon and Arthur Yuwiler, also at Ypsilanti, brought out the first North American publication on lithium (21). [Actually, they tied with Edward Kingstone, a resident of Ewen Cameron's at the Allan Memorial Institute in Montreal, for that honor (22)]. It was evidently Gershon's Michigan experiences that caused the Rowell Laboratories in Minnesota to acquire an early interest in commercializing lithium (23). In 1963, Gershon moved to the University of Missouri in St. Louis, then to New York Medical School, where he became prominent among American investigators of lithium.

In 1962, George Winokur introduced lithium to Washington University in St. Louis, having the Barnes Hospital pharmacy make up the pills and achieving an "amazing remission" in a patient who had failed on chlorpromazine treatment and 18 sessions of convulsive therapy. "After that experience," recalled Paula Clayton, "lithium was the mainstay in the treatment of mania at Barnes Hospital" (24).

Following the leadership of Gershon, in the 1960s numerous investigators began lithium studies: Nathan Kline at Rockland State Hospital in New York, Stanley Platman in Buffalo, Paul Blachly in Portland, and Eugene Ziskind in Los Angeles (25). A number of these were supported by the NIMH. Ronald Fieve began in the mid-1960s to make the New York State Psychiatric Institute an epicenter of research in lithium, and published in 1966 an influential open-label study (26).

As well, a number of controlled lithium trials in mania contributed to assuaging the doubts of the few naysayers, mainly from the Maudsley Hospital. In 1963, Ronald Maggs, at Hellingly Hospital in Hailsham, Sussex, organized the first controlled trial of lithium versus placebo, concluding, "The drug is found to be of value during the acute manic illness" (27). Under the leadership of William Bunney and Frederick Goodwin, the NIMH became actively involved in lithium studies in the mid-1960s. In 1966, at the fourth World Congress of Psychiatry, Bunney reported a double-blind study of two manic patients treated with lithium (28). By 1969, the study had grown to 30 patients with depression and mania: "Therapeutic results in mania were dramatic," the investigators said (29). In 1971, in a double-blind study led by Peter Stokes and the Psychobiology Study Unit at the Payne Whitney Clinic of New York Hospital–Cornell University Medical College, lithium "demonstrated a significant advantage … over placebo in mania" (30). In these four controlled studies of 116 patients, the average response rate was 78% (31), an impressive plus for lithium in mania.

By the late 1960s, a kind of "lithium underground" had formed in the United States, many physicians prescribing it without bothering to seek "INDs," or a permit to use an investigational new drug from the FDA (32). Meanwhile, lithium had long become registered elsewhere: lithium gluconate in 1961 in France, lithium carbonate in 1966 in the United Kingdom, lithium acetate in 1967 in Germany, and lithium glutamate in 1970 in Italy (33, 34). Surely it was now time for the FDA to act? (And in fact when, later in 1970, the FDA did approve lithium, the United States became the 50th country to do so.) At the FDA, it was Merle Gibson, director of the Neuropharmacology Division, who finally overcame internal agency apprehensions and pushed for approval of lithium for acute mania. It is

possible that this decision was also motivated by Paul Blachly's public declaration that he would prescribe it even without FDA approval (35). Gibson is said to have held back the Rowell company's lithium New Drug Application to give Smith Kline and Pfizer a chance to bring their own products to market (J. O. Cole, telephone interview, 17 July 2002).

How about lithium in the prophylaxis of depression, as opposed to the treatment of mania? Even today, the FDA does not accept an indication for lithium prophylaxis in depression (though it accepted, in 1975, the lithium prophylaxis of mania). Yet considerable evidence speaks on behalf of lithium maintenance in depression.

The idea of lithium maintenance originated with Schou at the time of his 1954 study. He had a bipolar patient that, "When we gave him continuous lithium treatment to keep away the highs, we saw that also the lows disappeared. … However, at the time we did not pay much attention to this observation." Then in 1959, Geoffrey P. Hartigan in England and Poul Baastrup in Denmark independently wrote Schou to ask "whether long-term lithium treatment might perhaps keep away also depressive recurrences, because this was what they had seen in a dozen patients" (36, see p. 265). That was the beginning of several open-label trials in the 1960s. The study that Baastrup and Schou conducted in 1967 of 88 patients at Glostrup Psychiatric Hospital who had been admitted between 1960 and 1966—known as "a medical landmark" —did show lithium's ability to reduce the frequency of hospitalization in depression (37). Three years later, in 1970, Schou and Jules Angst in Zurich, using Angst's model of bipolar disorder, demonstrated that lithium had in fact a preventive effect in mood disorders (38), that, in Per Bech's terms, it was "not simply for maintenance" (39).

Fieve conducted the first controlled trial of lithium in acute endogenous depression in 1968, finding "only a weak to mild antidepressant effect" (40). But how about prophylaxis in long-term depressive illness? In 1970, Baastrup and Schou led a placebo-controlled discontinuance study of 84 patients with manic-depressive and endogenous depressive illness. "During the whole trial, which lasted five months, twenty-one placebo patients relapsed and none of the lithium patients" (41).

In 1971, Alec Coppen at West Park Hospital in Epsom, together with collaborators at three other mental hospitals, randomly assigned 65 patients with "recurrent affective disorders" to lithium or placebo: "Patients receiving lithium had very significantly less affective illness than patients receiving placebo tablets. No patient on lithium required convulsive treatment while almost half of the placebo group did" (42). Coppen later described the results of this study as "absolutely staggering." "After that we decided to set up a lithium clinic because this obviously was a service we should offer our patients." Later, Coppen followed up a group of such patients, using as a measure the number of deaths by suicide, "Instead of having a suicide rate of seven per thousand, which is the norm, we had a suicide rate of less than one per thousand" (43, see pp. 272–273).

This round of studies in the early 1970s provided convincing evidence of lithium's efficacy in preventing relapse in depressive illness. The subsequent literature, ably reviewed in Goodwin and Jamison, will not be considered here (44). In a meta-analysis in 1999, Davis et al. concluded that relapse rates on placebo average 74%, on lithium, 29% (45).

In retrospect, “the miracle of lithium was not its treatment of acute mania,” as Dennis Charney at Yale University put it at a 1995 meeting of the Psychopharmacologic Drugs Advisory Committee of the FDA. “Neuroleptics, and even high-dose benzodiazepines, are quite effective for the treatment of acute mania. … The issue is prevention of relapse” (46). Indeed, this is the issue, and the mystery is why the FDA has not accepted the prophylaxis of depressive disorder—“bipolar illness,” if one will—as an indication.

With the exception of ECT, lithium is the single most effective treatment in psychiatry. Its side effects are easily manageable, and many patients stay on low-dose lithium for decades. Its benefits, in terms of the relief of mania and the prophylaxis of depression, are incalculable. In assessing the history of lithium, therefore, two questions present themselves:

First, why a small group from the Maudsley Hospital in the 1960s could, in an almost malicious manner, have sown scholarly confusion about the true effectiveness of lithium. Aubrey Lewis, professor of psychiatry and head of the Maudsley, considered lithium treatment “dangerous nonsense” (47). Lewis’s colleague at the Maudsley, Michael Shepherd, one of the pioneers of British psychopharmacology, agreed that lithium was a dubious choice. In his 1968 monograph, *Clinical Psychopharmacology*, Shepherd said that lithium was toxic in mania and that claims of efficacy for it in preventing depression rested on “dubious scientific methodology” (48). Shepherd also scorned “prophylactic lithium” in an article with Barry Blackwell (49). Moreover, Shepherd was publicly contemptuous of Schou. He told interviewer David Healy that Schou had put his own brother on it, and that Schou was such a “believer” in lithium that he seemed to think “really there ought to be a national policy in which everybody could get lithium” (50, see p. 249). [In a separate interview with Healy, Schou confirmed that the family member was his brother (36, see p. 267)]. Lewis and Shepherd were major figures in the field, and their poorly grounded objections to lithium doubtless steered many practitioners away from a beneficial agent. [Years later, when questioned about this mad campaign against lithium, Shepherd said that English psychiatry did not distinguish between psychogenic and endogenous depression, and if lithium were accepted, “all doctors in England would use it against all types of depression, with the result that many patients not in need of it would only suffer damage from it—therefore lithium must be ravaged with fire and sword” (51)].

Second, the lithium story raises the question: why in psychopharmacology, scientific evidence—in this case about lithium—often has difficulty in prevailing over commercial messages that run counter to established knowledge (52). When Abbott gained FDA approval to market valproate (Depakote) for mania in 1995, a great shift toward the “mood stabilizers” and away from lithium commenced. As David Healy points out, the use of valproate off-label for mania had been growing in the late 1980s, and it was in 1995 that Columbia University closed its lithium clinic. Increasingly, trainees from psychiatry training programs became untutored in lithium use, and would be uncomfortable about prescribing it in practice (53). Is lithium about to be eclipsed by less effective but widely advertised mood stabilizers? We cannot definitively answer the question at this time. But it becomes increasingly insistent.

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