A Brief History of Lithium Treatment in Psychiatry

Mark L. Ruffalo, LCSW[a,b,c,*]

ABSTRACT

The history of lithium as a psychiatric medication is marked by its serendipitous discovery, its lengthy path to US Food and Drug Administration approval, and controversy surrounding its current status in bipolar disorder treatment. Without doubt, the discovery of lithium as a psychotropic agent forever changed the course of psychiatry. The drug's fascinating, and sometimes contentious, history is reviewed here.

Prim Care Companion CNS Disord
2017;19(5):17br02140
https://doi.org/10.4088/PCC.17br02140

[a]Department of Psychiatry, University of South Florida, Tampa, Florida
[b]Department of Psychiatry, Centerstone Hospital, Bradenton, Florida
[c]Psychoanalyst in private practice, Tampa, Florida
**Corresponding author:* Mark L. Ruffalo, LCSW, 10335 Cross Creek Blvd, Ste 15, Tampa, FL 33647 (mlruffalo@gmail.com).

Lithium occupies a unique position among the psychotropic agents. A naturally occurring salt, lithium has been dubbed both a miracle drug and the gold standard in the treatment of bipolar disorder, alternatively—and perhaps more descriptively—known as manic-depressive disorder. While its use in psychiatry dates to the mid-19th century, the widespread discovery of lithium is usually credited to Australian psychiatrist John Cade who introduced it for mania in 1949. The drug was not approved by the US Food and Drug Administration (FDA) in the United States until 21 years later in 1970, and although lithium remains the single most effective treatment for bipolar illness, its status has been threatened in recent years by the newer and more profitable "mood stabilizers." This report provides a brief sketch of the rich and sometimes controversial history of lithium therapy in psychiatry.

Lithium's early medical use was in the treatment of gout. After London internist Alfred Baring Garrod discovered uric acid in the blood of his patients with gout in 1847, he investigated lithium as an antigout agent and subsequently published *The Nature and Treatment of Gout and Rheumatic Gout* in 1859,[1] which led to its widespread use. By the 1930s, various lithium-containing products were being marketed for the control of kidney stones and "uric acid diathesis."[2]

Perhaps the earliest psychiatric reference to lithium was made in 1870 by Philadelphia neurologist Silas Weir Mitchell, who recommended lithium bromide as an anticonvulsant and hypnotic and later promoted lithium bromide for treatment of "general nervousness."[2,3] In 1871, William Hammond, professor of diseases of the mind and nervous system at Bellevue Hospital Medical College in New York, became the first physician to recommend lithium for treatment of 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."[4(p381)]

Around the same time in Denmark, psychiatrist Frederik Lange began using lithium in the prophylaxis of melancholic depression, ultimately treating 35 patients with lithium carbonate.[5] His brother Carl, professor of pathology in Copenhagen, is credited with introducing lithium to Denmark in the mid-1800s, yet he wrote little about it. The early Danish and American work on lithium was soon forgotten, and in the first half of the 20th century, there are virtually no references to lithium in the psychiatric literature.[2]

John Cade holds the distinction of being the modern discoverer of lithium as a psychiatric medication, and, indeed, it was his research at a small hospital in rural Australia that forever changed the treatment of manic depression and mental illness more generally. Aware of Garrod's success in using lithium as a gout medication nearly 100 years earlier, Cade hypothesized that some condition involving uric acid might cause the "psychotic excitement" that so characterized his manic patients. He chose lithium as an investigatory drug and treated 10 of his patients at the Bundoora Repatriation Hospital with lithium citrate and lithium carbonate. Some patients responded incredibly well, essentially returning

Clinical Points

- Lithium remains the single most effective psychotropic agent in all of psychiatry and has applications in the treatment of bipolar disorder and major depressive disorder.
- Referral to a psychopharmacologist trained in the use of lithium may be warranted for patients with bipolar disorder and severe depressive disease.
- The use of lithium in the United States is declining despite its clear effectiveness.

to normal functioning after years of hospitalization. Cade's original article appeared in an obscure Australian medical journal in 1949,[6] and although the article has become one of the most widely cited in the entire history of psychiatry, it went largely unnoticed at the time due in part to a recent failed experiment with lithium chloride as a substitute for sodium chloride in patients with heart failure.[2,3]

Despite the generally muted response to Cade's original article, a few researchers in Australia and France investigated further with lithium and determined it to be remarkably effective in the management of acute mania. The real breakthrough in lithium therapy came in 1952, when Erik Stömgren, a Danish psychiatrist and head of the Aarhus University psychiatric clinic in Risskov who had read Cade's article, suggested to a staff psychiatrist at the hospital, Mogens Schou, that he undertake a randomly controlled study of lithium for mania. Random controls were just being introduced to psychiatric drug trials at that time, and Schou randomly assigned patients to lithium or placebo by the flip of a coin. His results were published in a British journal with the article concluding, "The lithium therapy appears to offer a useful alternative to [electroconvulsive therapy] since many patients can be kept in a normal state by administration of a maintenance dose."[7(p255)]

Following publication of Schou's article,[7] a number of international drug trials were initiated, ably reviewed by F. Neil Johnson in his *History of Lithium Therapy*.[8] Despite lithium's demonstrated effectiveness in treating manic depression, the drug remained difficult to administer and attainment of blood levels was impossible. This all changed with the introduction of the Coleman photometer in 1958, which made it possible to ascertain precisely the amount of lithium present in a patient's blood. This advancement opened the door for the widespread introduction of lithium in clinical psychiatry.

Shorter[2] perceptively notes that the United States was more or less the "last in, first out"[(p6)] when it comes to lithium therapy. At a time when the drug was in widespread use elsewhere, American interest in lithium only began in the 1960s. And, currently, the United States is one of the few countries in which other drugs—such as valproate and antidepressants—are given to "manic-depressive" patients much more often than lithium. Samuel Gershon and Arthur Yuwiler,[9] both of the University of Michigan working at the Ypsilanti State Hospital, published the first North American article on lithium in 1960 after Gershon's arrival in the United States from the University of Melbourne in Australia. Reportedly, it was Gershon's work at the University of Michigan that piqued the interest of Rowell Laboratories in Minnesota in the commercialization of lithium. In 1963, Gershon moved to the University of Missouri and then to the New York Medical School, where he became a well-known researcher of lithium.

Following Gershon's introduction of lithium to the United States, several prominent psychiatrists began lithium studies in the 1960s: Nathan S. Kline of the Rockland State Hospital in New York, Stanley Platman in Buffalo, Paul Blachly in Portland, and Eugene Ziskind in Los Angeles.[9] Under the leadership of William Bunney and Frederick Goodwin, the National Institute of Mental Health supported many of these studies. Perhaps the best-known American researcher on lithium is Ronald Fieve, who in the mid-1960s made the New York State Psychiatric Institute an epicenter of research on lithium and in 1966 published an influential open-label study.[10] Fieve remains in clinical practice in New York City to this day. Incidentally, it is also Fieve who introduced the "bipolar II disorder" concept to psychiatry.

The few naysayers on lithium, mainly of Maudsley Hospital, were assuaged by the growing number of controlled trials, and in 1963, Ronald Maggs, at Hellingly Hospital in Sussex, England, conducted the first controlled trial of lithium versus placebo, concluding, "The drug is of value during the acute manic illness."[11(p56)] Further studies[2] carried out around this time at Rockland State Hospital and New York Hospital–Cornell University Medical College, among other centers, demonstrated the effectiveness of lithium in the acute and prophylactic treatment of mania.

While researchers were making use of lithium in standardized drug trials, a kind of "lithium underground" developed among clinical psychiatrists in the United States with many physicians prescribing it without bothering to seek FDA permits to use an investigational new drug.[3] The drug had long become registered by government authorities elsewhere: lithium gluconate in 1961 in France, lithium carbonate in 1966 in England, lithium acetate in 1967 in Germany, and lithium glutamate in 1970 in Italy. When the FDA did approve lithium later in 1970, the United States became the 50th country to do so. It was Merle Gibson, head of the FDA's neuropsychopharmacology division, who finally pushed for approval of the drug over internal agency apprehensions. The FDA's decision was also very likely motivated by psychiatrist Paul Blachly's public declaration that he would prescribe it even without FDA approval.[12] Gibson allegedly stalled the Rowell Laboratories' lithium new drug application to give GlaxoSmithKline and Pfizer a chance to bring their own products to market.[2]

Following initial FDA approval, additional studies were conducted on lithium's utility in the prophylaxis of depression, and although the FDA does not accept this indication, considerable evidence speaks on behalf of lithium management of depression.[13–15] In 1975, after further investigation, the FDA approved lithium in the

prophylactic treatment of mania. Speaking in 1995 at the Psychopharmacologic Advisory Committee of the FDA, Dennis Charney of Yale University noted that "The miracle of lithium was not its treatment of acute mania. Neuroleptics, and even high-dose benzodiazepines, are quite effective for the treatment of acute mania. The issue is the prevention of relapse."[2(p135)]

With the exception of electroconvulsive therapy, lithium remains the single most effective treatment in all of psychiatry. Its side effects can be well-managed, and many patients stay on low-dose lithium for decades. The benefits of lithium, in terms of relief from mania and the long-term treatment of depression, cannot be understated. Why, then, is lithium prescribed less frequently than other psychotropics for bipolar disorder in the United States? When Abbott Laboratories gained FDA approval in 1995 to market valproate (Depakote) for mania, a great shift away from lithium and toward the so-called mood stabilizers commenced. The off-label use of valproate for mania had been growing since the late 1980s, and it was in 1995 that Columbia University closed its lithium clinic. Psychiatry trainees have become increasingly unskilled in lithium use, and many feel uncomfortable prescribing it in practice. One is left wondering if the shift away from lithium in American psychiatry has occurred primarily for economic reasons. Clearly, it is not due to the discovery of a more effective treatment.

Submitted: March 21, 2017; accepted May 19, 2017.
Published online: October 12, 2017.
Potential conflicts of interest: None.
Funding/support: None.

REFERENCES

1. Garrod AB. *The Nature and Treatment of Gout and Rheumatic Gout*. London, UK: Walton; 1859.
2. Shorter E. The history of lithium therapy. *Bipolar Disord*. 2009;11(suppl 2):4–9.
3. Lieberman JA, Ogas O. *Shrinks: The Untold Story of Psychiatry*. New York, NY: Back Bay Books; 2015.
4. Hammond WA. *A Treatise on Diseases of the Nervous System*. New York, NY: Appleton; 1871.
5. Schioldann JA. *The Lange Theory of "Periodical Depressions."* Adelaide, Australia: Adelaide Academic Press; 2001.
6. Cade JF. Lithium salts in the treatment of psychotic excitement. *Med J Aust*. 1949;2(10):349–352.
7. Schou M, Juel-Nielsen N, Stromgren E, et al. The treatment of manic psychoses by the administration of lithium salts. *J Neurol Neurosurg Psychiatry*. 1954;17(4):250–260.
8. Johnson FN. *The History of Lithium Therapy*. New York, NY: Macmillan; 1984.
9. Gershon S, Yuwiler A. Lithium ion: a specific psychopharmacological approach to the treatment of mania. *J Neuropsychiatry*. 1960;1:229–241.
10. Ayd FJ Jr. Invited ACNP Lecture: the early history of modern psychopharmacology. *Neuropsychopharmacology*. 1991;5(2):71–84.
11. Maggs R. Treatment of manic illness with lithium carbonate. *Br J Psychiatry*. 1963;109:56–65.
12. Wardell WM, Lasagna L. *Regulation and Drug Development*. Washington, DC: American Enterprise Institute for Public Policy Research; 1975.
13. Zivanovic O. Lithium: a classic drug-frequently discussed, but, sadly, seldom prescribed! *Aust N Z J Psychiatry*. 2017;51(9):886–896.
14. Geier M. Lithium as augmentation for major depressive disorder. *Mental Health Clinician*. 2012;2(1):15–17.
15. Bschor T. Lithium in the treatment of major depressive disorder. *Drugs*. 2014;74(8):855–862.