Lithium

Lithium compounds have been used in medicine for a range of physical and psychological conditions beginning in the mid-19th century. They fell out of favor by the early 20th century, and by midcentury, they were rediscovered and began a contested rise to prominence as a psychiatric medication. Today, lithium is known as a mood stabilizer and is mainly used in the treatment of bipolar disorder (formerly manic-depressive illness). Its effectiveness in treating bipolar disorder, despite its mechanism of action remaining unknown, makes it one of modern psychiatry's success stories. The history and continuing use of lithium is important to our understanding of bipolar disorder, the concept of the mood stabilizer, and personal implications of psychiatric medication use, as well as the political economy of psychopharmaceuticals.

In the 19th century, physicians used lithium for a variety of disorders based upon the theory of uric acid diathesis, a belief that uric acid, a breakdown product of urea, led not only to gout but also to a number of other ills ranging from cardiac disease to mania. The finding that lithium dissolves urate stones led to the logical notion that lithium might effectively treat those illnesses believed to be due to precipitates of uric acid. Between 1859 and 1876, the English physician Alfred Baring Garrod described the use of lithium for gouty conditions that included mania and other forms of psychological distress. In 1870 in the United States, Silas Weir Mitchell advocated its use as a hypnotic and, in 1877, for general nervousness. In 1871, William Hammond prescribed it for acute mania. In Denmark in 1886, Federik Lange identified periodic depression, a melancholia without psychotic features, and suggested lithium carbonate to prevent symptoms from recurring over time. Although lithium was still available in patent medicine in the United States into the early 20th century, it fell out of favor in medical practice as the theory that underpinned its use became discredited.

Lithium as a psychotropic drug reappeared in 1949 in Australia with John Cade, who was aware of Garrod's work and curious if uric acid could lie behind mania. Of Cade's 10 patients, those with mania who remained on lithium showed remarkable improvement. Mogens Schou, in Denmark in 1952, learned of Cade's work and began an early double blind trial in which patients were switched between lithium and a placebo. Schou's study found lithium effective, and he recommended using it with a maintenance dose; in later work with Paul Baastrup in the 1960s, he advocated for prophylactic use and defended the methods of his earlier studies (Cade, too, faced criticism for his methods). Lithium was accepted sooner in western Europe, with governments granting approval for its use in 1961 in France, 1966 in the United Kingdom, 1967 in Germany, and 1970 in Italy.

In the United States, the acceptance of lithium was significantly hindered by the Food and Drug Administration's (FDA's) decision to ban it in 1949 after a few cardiac patients died when they used it as a salt substitute. The dominance of psychodynamic approaches to psychiatric illness also slowed the acceptance of lithium by American psychiatrists. However, by the early 1970s, lithium was developing a reputation as a prophylactic treatment for bipolar disorder, and in the United States, where work by Samuel Gershona and Baron Shopsin helped bring it to the fore, its use was already gaining momentum without government approval. The United States was the 50th country to formally approve its use, in 1970, for treatment of acute mania and, in 1975, for mania prophylaxis (although never for depression prophylaxis). The United States was also a country in which alternate, but not necessarily more effective, therapies were put forward by pharmaceutical firms to challenge lithium's preferred status in the treatment of bipolar disorder.

Unique Bipolar Treatment

Lithium is unique among medications used for bipolar disorder, in that popular preparations such as lithium carbonate cannot be patented, and as a result, lithium was never aggressively promoted by pharmaceutical firms. Furthermore, when more profitable, patented medications appeared, they were immediately marketed as superior alternatives to lithium, regardless of clinical evidence for these claims. This occurred first with anticonvulsant medications (carbamazepine, valproate, and lamotrigine) described as mood stabilizers and, since the late 1990s and 2000s,

with the new generation of atypical antipsychotics. Abbot's anticonvulsant medication Depakote (valproate) gained traction as an off-label alternative to lithium for mania in the late 1980s, as did Novartis's Tegretol (carbamazepine). (A similar link between anticonvulsant properties and positive psychological outcomes was observed for lithium in the 19th century.) In 1985, Abbott received FDA approval for the treatment of bipolar disorder (manic episodes) with valproate, which was followed by GlaxoSmithKline's 2003 FDA approval for Lamictal (lamotrigine) for bipolar disorder (type I) in 2003.

Clinical demonstrations of lithium's ability to treat bipolar mania and depression, combined with its comparative ineffectiveness with both schizophrenia and unipolar depression, contributed to the perception that bipolar disorder was unique from both conditions. By the 1970s in the United States, lithium's effectiveness was beginning to influence diagnostic practices for bipolar disorder (types I and II), with favorable response to the drug counting toward a diagnosis for the condition.

From the mid-1990s until the turn of the century, there began a decline, led by the United States, in the prescription rates of lithium for bipolar disorder, just as Depakote (and then Lamictal) prescriptions increased. This decline was linked to intense marketing for these alternatives to lithium; a study in the *American Journal of Psychiatry* noted that, while lithium was the most common mood stabilizer in 1995, prescriptions dropped 40 percent by 1999, a change that cannot be said to result from the clinical characteristics of patients. At this time, research on lithium moved toward studies comparing it to these and other (atypical antipsychotic) potentially mood-stabilizing compounds. Questions remain about the extent of its effectiveness, owing at least in part to the ethics of entering severely ill patients in placebo groups in the long-term trials that could help establish this effectiveness and the consequent lack of clinical guidelines.

Lithium is held up both as a major success of psychiatry for its ability to relieve suffering and prolong life and as a symbol of the potential trade-offs associated with the use of psychiatric drugs. The long-standing association of bipolar disorder with both elevated periods of creativity and decidedly less creative periods of hopelessness and depression is accompanied by the question of the potential side effects from drugs such as lithium. Lithium illustrates contradictions within the pharmaceutical industry, as its effectiveness has not been matched with equal amounts of medical interest or commercial promotion, especially in the United States. There is concern, for example, that many psychiatrists are comparatively undertrained in the administration of lithium, thereby reducing the drug's effectiveness. Nonetheless, it remains a front-line treatment for bipolar disorder.

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See Also: Bipolar Disorder; Mania; Mood Disorders; Pharmaceutical Industry; Suicide.

Further Readings

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Lobotomy

As early as 1888, Swiss psychiatrist Gottlieb Burckhardt initiated the first psychosurgery, excising portions of the cerebral cortex in six