Lithium in Psychiatry.

Litio en Psiquiatría.

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SUMMARY

Background: Lithium is a light, metallic element and minerals containing it are most abundant in the Andes. John Cade introduced lithium carbonate for the treatment of mania in 1949, opening the era of modern clinical psychopharmacology. Lithium remains the most extensively studied mood-stabilizing agent. It has had a revolutionary impact in supporting bipolar manic-depressive disorder as a discrete diagnosis, and on psychiatric therapeutics. ***Methods***: We survey the development of lithium treatment in psychiatry, including findings concerning effects on suicide. ***Results:*** Lithium is the most extensively studied treatment for bipolar disorder and the prototypical mood-stabilizing agent, despite emergence of anticonvulsants and modern antipsychotics. In addition to limiting recurrences of mania, and some reduction of recurrences of bipolar depression, lithium has demonstrated protective effects against suicide. All treatments for bipolar disorder have notable limitations, including sometimes serious adverse effects, incomplete prevention of recurrences of mania and limited prevention of depression, which accounts for three-quarters of the approximately 50% time-ill in long-term follow-up with standard treatments. Lithium can be toxic in untreated overdoses; safe dosing requires monitoring of serum concentrations. Lithium also may have mild teratogenic effects, but far less than those of anticonvulsants used for bipolar disorder. ***Conclusions****:* Lithium opened the era of modern psychopharmacology and continues as the best-established mood-stabilizing treatment for bipolar disorder as well as having strong evidence of suicide-preventing effects.

KEY-WORDS: bipolar disorder, depression, lithium, mania, mood disorders, suicide.

RESUMEN

Antecedentes: Litio es un elemento metálico ligero y los minerales que lo contienen abundan predominantemente en la región andina. John Cade introdujo el uso de carbonato de litio para el tratamiento de manía en 1949, iniciando con ello la era de la moderna psicofarmacología clínica. Litio se mantiene como el más extensamente estudiando agente estabilizador del ánimo. Ha tenido un impacto revolucionario en la preservación del trastorno maniaco-depresivo o bipolar como un diagnóstico discreto y en el campo de la terapéutica psiquiátrica. ***Métodos:*** Se examina el desarrollo histórico del tratamiento con litio en psiquiatría, incluyendo hallazgos en relación a su efecto sobre conducta suicida. ***Hallazgos:*** Litio es el tipo de tratamiento más extensamente estudiado en el manejo de trastorno bipolar disorder, constituido como el prototipo de agente estabilizador del ánimo, a pesar de la emergencia de agentes anticonvulsivantes y de los antipsicóticos modernos. Además de limitar la recurrencia de episodios maniacos y reducir en algo las recurrencias de depresión bipolar, litio ha demostrado efectos protectores en relación a suicidio y conducta suicida. Todos los tipos de tratamiento de trastorno bipolar tienen limitaciones notables, incluyendo algunas veces serios efectos adversos, prevención incompleta de recurrencias de manía y prevención limitada de depresión, todo lo cual constituye las tres cuartas partes de aproximadamente el 50 % de tiempo con enfermedad en estudios de seguimiento a largo plazo con tratamientos estándar. Litio puede ser tóxico en casos no tratados de sobredosis; una dosis segura requiere monitorización de concentraciones séricas. Litio puede también tener efectos

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teratogénicos leves pero, en todo caso mucho menos severos que los producidos por anticonvulsivantes usados en el tratamiento de trastorno bipolar. ***Conclusiones:*** Litio inició la era de la psicofarmacología moderna y continua siendo el mejor establecido tratamiento estabilizador del ánimo en casos de trastorno bipolar, habiendo demostrado también fuerte evidencia de efectos preventivos de suicidio y conducta suicida.

PALABRAS CLAVE: Trastorno bipolar, depresión, litio, manía, trastornos del ánimo, suicidio.

BACKGROUND

Early history of lithium

This history has been reviewed extensively elsewhere (1–9). A new mineral, petalite ($LiAl(Si_2O_5)_2$), was discovered in 1800 on Utö island, off the coast of Sweden, by Brazilian chemist-statesman José Bonifácio de Andrada e Silva (1763–1838). In initial chemical analyses, about 5% of the material in petalite could not be identified. In 1817, Swedish chemist, Johan Arfwedson (1792–1841), determined that the unknown fraction was an alkaline substance. His laboratory director, Professor Jons Berzelius (1779–1848), initially named the material lithion (from the Greek λιθοσ [lithos] or stone); the sodium- and potassium-like alkali metal element contained in the salt complex was later called lithium. Lithium occurs in other minerals well as in brines and clays. Its natural abundance is highest in the Andes, where more than half of known terrestrial sources occur. Lithium is found in traces in animal tissues but does not serve any identified physiological role (9). Pure lithium was isolated in 1821, by English chemist William Brande (1788–1866), by electrolysis of lithium oxide, and more efficiently by electrolysis of lithium chloride in 1855 by chemists Robert Bunsen (1811–1899) of Germany and Augustus Matthiessen (1831–1870) of England. The atomic weight of lithium is 6.94, and it occurs in two common isotopes, ^6Li and far more abundant (92.5%) ^7Li, which can be identified in body tissues including brain by magnetic resonance spectroscopy (MRS) (10,11). This very light, monovalent element has been prepared as a variety of pure, water-soluble salts, including the most commonly clinically used carbonate (Li_2CO_3) as well as the citrate ($Li_3C_3H_5O[COO]_3$) for liquid preparations.

Initial medical uses of lithium

Lithium salts may inadvertently have been used for the treatment of states of excitation in ancient and medieval times in recommendations for drinking and bathing in alkaline mineral waters by Greek and Arabic physicians, including Avicenna, Galen, and Soranus (1). Its later medicinal applications have been reviewed elsewhere (1,5–7). In the 19th century, Scottish surgeon Alexander Ure (1853–1928) proposed using lithium carbonate to treat renal stones in 1843, based on observing a reduction in weight of such a stone in a solution of lithium carbonate. He experimented with infusions of the lithium salt into the urinary bladder in 1860, but without clinical success.

London physician, Sir Alfred B. Garrod (1819–1907) discovered elevated concentrations of uric acid in the blood of patients with gout in 1843. He later attempted to treat gout by soaking the feet in a solution of lithium carbonate, based on his belief that gout results from deposits of excess uric acid in the joints that might better be dissolved and eliminated with lithium. Neither this external treatment nor orally administered lithium carbonate was successful (1). However, oral administration of lithium carbonate led Garrod to discover typical adverse effects of ingested lithium carbonate, including tremor, polyuria, nausea and vomiting. Garrod also proposed that effects of excessive uric acid on the central nervous system might produce “gouty mania” (12). The theory of excesses of uric acid in both rheumatic and mood disorders spread throughout Europe and appeared in major medical textbooks. Physician Alexander Haig (1853–1924) of London also considered excesses of uric acid to contribute to a wide range of rheumatic, renal, metabolic, and neuropsychiatric disorders, and supported the potential value of lithium salts in treating such conditions (13).

In 1871, William A. Hammond (1828–1900), of New York, one of the first professors of neurology in the United States, and Surgeon General of the Union Army during the American Civil War, recommended lithium bromide as superior to other bromides as a sedative, including for treating manic excitement (14). His recommended doses were comparable to modern doses of lithium carbonate for mania. However, in a later edition of his textbook, he expressed doubt the lithium bromide was superior to other bromides, and so probably did not recognize the specific therapeutic potential of lithium (7).

Danish psychiatrist, Carl G. Lange (1834–1900) resisted broad inclusion of all mood-disorders in a broad manic-depressive illness category being promoted by his German contemporary Emil Kraepelin (1856–1926), and instead proposed that there was a specific group of patients with recurrent depressive illness (15,16). He and his physician-brother Frederick ("Fritz") proposed that lithium carbonate may have a therapeutic effect in depression. Carl also reported that some depressed patients treated with lithium carbonate had increased levels of urinary sediment that he attributed to liberated uric acid (16).

The mineral waters fad

The uric acid hypothesis and its broad application to various general medical and neuropsychiatric conditions, along with initial efforts at using lithium salts therapeutically, were paralleled by the popularity of mineral waters containing low concentrations of lithium for a wide variety of ailments (1). Even respected medical journals touted the value of lithium waters for a remarkably broad range of maladies. It became fashionable in the late 1800s and early 1900s to use such waters for both bathing and drinking in search of cures. In response to this belief, for example, the *Lithia Springs Sanitarium* was founded in Georgia in 1890 for the treatment of alcoholism, opioid dipendence, and other compulsive behaviors. Those who could not afford a holiday "cure" at a famous spa could at least buy bottled mineral water, such as that marketed as *Bear* and *Buffalo Lithia Waters* from Virginia and the District of Columbia, *White Rock Spring* water from upstate New York, and *Lithia Beer* from Wisconsin. Such products were promoted as cures for conditions as varied as kidney and bladder disorders, elevated uric acid levels, gout, rheumatism, phosphate deposits, inflammation, dyspepsia, stomach pain, flatulence, constipation, obesity, acute and chronic "hepatic torpor," albuminuria of pregnancy, urinary incontinence, cystitis, urogenital disorders, asthma, headache, neuralgia, back pain, and others. In the early 1900s, over 40 products touting the presence of lithium salts made medicinal claims in the US. Some of them eventually were found to contain very little lithium. A lingering influence of the faddish use of mineral waters containing lithium is found in the popular non-alcoholic beverage *Seven-Up*, which was developed in St. Louis in the 1920s, and initially contained some lithium (until 1950); there remains considerable uncertainty of the origin of the name, which may or may not be related to the atomic weight of lithium. In the early 1900s, the Supreme Court of District of Columbia declared that "in order to achieve a therapeutic dose of lithium by drinking *Buffalo Lithia Water*, a person should drink from 150,000–225,000 gallons of water a day." And yet, the public remained fond of lithium, despite its status as a form of medical quackery (17).

Uncontrolled use of lithium salts came to a crisis in the late 1940s, when lithium chloride appeared in concentrated solution as a substitute of sodium chloride for use by patients with cardiovascular and other medical illnesses. Reports of severe intoxications and several deaths soon led to its withdrawal from the market (18,19). This notoriety stimulated very negative impressions of lithium salts by many American physicians. These impressions continued for years and threatened to slow or prevent introduction of lithium carbonate in controlled doses into psychiatry (20).

Lithium as a treatment for severe psychiatric illness

Reintroduction of lithium carbonate into modern psychiatry

At about the same time as the appearance of reports of lithium intoxication, John J.F. Cade (1929–1996), a psychiatrist working in a small hospital in Melbourne, Australia, serendipitously initiated a revolution in psychiatric therapeutics. Following an ancient tradition of humoral theories of medical illnesses (15), Cade theorized that major mental illnesses might be associated with deficiencies or excesses of unidentified chemical substances in the body. In addition to his clinical responsibilities on an inpatient unit, he devoted some time to laboratory research. Initially, he injected the urine of manic patients into guinea pigs, and found that the animals were more likely to die than those given urine of patients diagnosed with schizophrenia or melancholic depression. For uncertain reasons, he suspected the nitrogen-containing metabolic products urea and uric acid found in urine as contributing to the effects he observed. Evidently in response to still-prevalent ideas about the role of uric acid in some metabolic disorders including gout, Cade injected lithium urate in the animals, evidently expecting increased circulating concentrations of urate and increased toxicity, but instead found a protective effect against responses to injections of the urine of manic patients that was sustained by pretreatment with lithium carbonate. He also treated control animals with lithium carbonate. Unexpectedly, the animals soon became lethargic and unresponsive to stimuli,

but slowly recovered over several hours. A plausible interpretation now would be that he had induced well-known cerebral toxic effects of lithium rather than a potentially useful psychotropic effect. Nevertheless, based on his observations of selectively toxic effects of urine from manic patients and their reduction by giving lithium carbonate, he decided, in an act of serendipity, to carry out a small, cautious trial of lithium carbonate to treat mania. This decision was made feasible since Austrialian medicine at the time still considered this salt to be a plausible treatment for gout, at least (1,7,21).

The first of the initial ten manic patients treated with lithium carbonate was described by Cade (22) as:

"a small man of 51 years who had been in a chronic state of manic excitement for five years ... always in motion, dirty, destructive, bad and intrusive." The patient had caused many problems where he had been hospitalized, but it was feared that he could never be discharged. He was started on treatment with lithium carbonate on March 29, 1948. On April 1, Cade described an improvement in the patient that was beyond his imagination. Indeed, after a few more days, the patient was clearly "quieter, orderly, less uninhibited and less distractible" and began to improve enough to resume working. Cade described results "equally satisfying" with the other nine patients.

Cade's initial report (22) described not only the typical time-course of antimanic action of lithium carbonate, but also observations that discontinuing the treatment soon led to relapse into mania. Indeed, Cade initiated prolonged continuation of lithium treatment, in anticipation of the long-term effects later termed "mood-stabilizing" and considered characteristic of lithium. The concept has also been used to promote other newer agents including certain anticonvulsants and modern antipsychotic drugs used to treat bipolar disorder—usually based on inadequate evidence (7). Cade acknowledged that specific diagnosis was difficult in psychiatry and, after noting that lithium had limited benefit in schizophrenia patients, proposed that it may be more important to know whether an illness is responsive to particular treatments or not [23]. This view was revolutionary in encouraging more precise diagnosis, if only to guide treatment of psychiatric disorders.

A revolution of the treatment of mood disorders would seem to have begun. However, when later he was asked why lithium was not immediately adopted by psychiatry, Cade noted in 1999 (21) that:
"a discovery by an unknown psychiatrist without research training, working in a small hospital for the chronically mentally ill, with primitive techniques and negligible equipment, could not attract much attention."

In addition to a need for additional research support for the new treatment, simultaneously emerging concerns about the potentially lethal toxicity of lithium salts in high, unregulated doses, initially had a chilling effect on any medicinal use of lithium (1,7,24).

Establishing the efficacy and safety of lithium for mania

In 1954, Professor Erik Strömgren, MD, PhD (1909–1993), a prominent academic psychiatrist, read of Cade's experience with lithium for mania and asked his junior colleague Mogens Schou, MD (1918–2005) to replicate the Australian study at the University of Aarhus medical center at Risskov, Denmark. Schou not only did so, but pursued the study of lithium to contribute in a major way to establishing its safe and effective clinical use for the treatment of manic-depressive illness. Personal factors may be relevant to Schou's life-long crusade in favor of lithium: he had a younger brother with manic-depressive illness whom he treated highly successfully with lithium carbonate, and a daughter with the same illness. Of further note, his father, Hans Jacob Schou (1886–1952), a psychiatrist, had advised against the use of lithium for mood disorders in the 1930s, and was particularly critical of the work of the Lange brothers [25]. Mogens Schou was born and educated in Copenhagen, grew up in the psychiatric hospital where his father worked, specialized in clinical chemistry, and worked in a laboratory associated with the psychiatric hospital in Aarhus, when Professor Strömgren proposed that he attempt to replicate Cade's research.

In 1964, another Danish psychiatrist, Poul Christian Baastrup (1918–2001), developed additional observational data to support the most important effect of lithium—its efficacy in preventing recurrences of manic-depressive illness (26). A few years later the two Danish researchers, Baastrup and Schou, combined efforts and released a landmark study on the prevention of depressive and manic recurrences (27). However, their studies lacked now-expected design characteristics of randomization, adequate controls, "blinding," and prospective assessment. They were severely criticized by the English psychiatrists, Barry

Blackwell (living) and Michael Shepherd (1923–1995), who spoke of lithium as another "therapeutic myth" (28,29). In the United States, however, the prominent research psychiatrist Nathan S. Kline (1916–1983) considered lithium, as "the Cinderella of psychopharmacology" (30). In Zurich, psychiatric investigator and expert on bipolar manic-depressive disorder, Jules Angst (living) confirmed the findings of prophylactic benefits of lithium treatment (31). In addition Angst and Paul Grof (living) and their colleagues proposed methods of trial design that would be suitable for testing for long-term, prophylactic effects of a treatment such as lithium (32).

Gradually lithium began to be used in clinical practice around the world, receiving regulatory approval by the US Food and Drug Administration (FDA) in 1970 for the treatment of acute mania and in 1974, as the first—and the only treatment for many years—for prevention of recurrences in bipolar disorder. Early commercial preparations included Eskalith®, Lithonate®, and Lithane®. Regulatory approval was made possible by the support of the manufacturers of these products (Smith Kline and French, Roeric-Pfizer, and Rowell pharmaceutical corporations) and strong endorsement by Nathan Kline, Jonathan O. Cole (1925–2009), and other early leaders of the American College of Neuropsychopharmacology (ACNP), as well as inundation of the FDA by individual clinician-investigators eager to use lithium [1]. Such support was needed since lithium carbonate had the status of an unpatentable mineral, and was a classic "orphan" treatment of little commercial value.

Clinical applications of lithium were made possible by introduction of sensitive, reliable, quantitative methods of assay of lithium concentrations in serum, initially with flame spectrophotometry and later with atomic absorbtion, electrochemical, and other methods. Such assays were required to establish the timing and concentrations of lithium ion required to provide effective and safe clinical applications, in view of the narrow "therapeutic index" (ratio of median toxic to therapeutically effective doses, of approximately 3) or margin of safety of lithium salts (7) Indeed, lithium remains unique in not being dosed adequately by mg of drug to be given per day, but instead by achieving serum concentrations at their daily nadir (most stable range) on the order of 0.6–1.0 mEq/L, knowing that earlier, daily peak concentrations can be as much as 2–3-times higher and potentially toxic for some patients (7,33).

Current clinical status of lithium in psychiatry

Lithium treatment is still considered the "gold standard" of treatment for bipolar manic-depressive illness. However, it has gradually become underutilized, for several probable reasons. Its reputation arising in the late 1940s as a toxic substance has not entirely disappeared, despite long-established standards for its safe use with monitoring of serum concentrations of lithium. Fears of intoxication currently are more often directed to putative renal toxicity with long-term use of lithium, although such effects are uncommon and can usually be anticipated by rising serum concentrations of creatinine or declining efficiency of creatinine clearance (7,34). There may also be a "stigmatizing" effect of the use of lithium for some patients and families, in contrast to the use of seemingly less threatening antidepressants, anticonvulsants, and other psychotropics (7). An important additional factor is that lithium salts, as unpatentable minerals of little commercial interest, have received little support for research and development or for assertive marketing. In some countries, particularly in the US, vigorous promotion of alternative, patentable, and highly profitable treatments have led to substantial displacement of lithium, although it continues to hold a major position among treatments for bipolar disorder internationally and tends to be used for longer times than most alternatives (7,35,36).

Promotion of alternatives has sometimes led to unwarranted implications that lithium is inferior in efficacy, or has been losing effectiveness over the years as the concept of bipolar disorder has become less "classical." Such allegations have been particularly directed at relatively complicated forms of bipolar disorder, such as with rapid-cycling, psychotic features, co-occurring anxiety syndromes or substance-abuse. However, most of such claims appear to be unwarranted, and implications that alternatives to lithium are more effective or safer remain inadequately tested and unproved (7,37). For example, lithium has been found to be at least as effective in rapid-cycling bipolar disorder as any of the commonly employed anticonvulsants with antimanic or putative "mood-stabilizing" effects, and possibly more effective (37). Marketing efforts critical of lithium have also emphasized the claim that it is of value virtually only for preventing recurrences of mania but not of other aspects of bipolar disorder. However, no available long-term treatment for bipolar disorder has proved to be highly clinically successful

in preventing recurrences of depressive components of bipolar disorder (38–40), nor to be consistently more effective than lithium overall (41–45).

Efficacy of lithium in the treatment of bipolar disorder

Lithium was introduced into modern medical therapeutics specifically to treat mania [22] and its use was gradually extended to seek prophylactic benefits in reducing risks of recurrences of mania (or hypomania) and of bipolar depression (or dysphoric-agitated, "mixed"-states). In acute mania, lithium has performed well in short term, controlled trials (typically of three weeks duration). Recent meta-analyses found little difference between the efficacy of lithium in randomized, placebo-controlled trials and various older and modern antipsychotic agents and several anticonvulsants, although antipsychotics as a group appear to be more rapidly quieting (7,45–47). Nevertheless, for the current era of managed care and efforts to limit hospital-level treatment, lithium is relatively slow in exerting antimanic effects, particularly with the need to dose lithium slowly to avoid potential toxic effects. Given in monotherapy, lithium may require more than a week to yield appreciable beneficial effects. For this reason, current treatment of acute mania usually employs antipsychotic or anticonvulsant agents, often supplemented with potent benzodiazepine sedatives such as lorazepam or clonazepam (7). Lithium is more likely to be employed for aftercare or long-term treatment, sometimes in combination with alternative treatments, at relatively low, well-tolerated circulating concentrations.

Indeed, the primary value of lithium is as a "mood-stabilizing" agent, aiming at long-term prevention of recurrences of acute illness-episodes in bipolar disorder patients (7). An earlier meta-analysis of the few available (five) placebo-controlled, long-term trials of lithium, benefits versus recurrences of mania were clearly superior to those for bipolar depression (41). Whereas the pooled, overall superiority of lithium over placebo treatment averaged 21%, this difference was only 5% for depression (not significant) and twice-greater for mania. More recent meta-analytic reviews further considered the benefits of various putative mood-stabilizing treatments on risks of recurrence of mania and depression in bipolar disorder patients, in more than a dozen placebo-controlled, long-term trials carried out for approximately 1.5 years (48–50). Again, lithium reduced recurrences of mania or mixed-states more than depression: respectively, by 59% versus 14% more than placebo. Moreover, lithium was clearly more effective than valproate in a recent comparison trial lasting 1.8 years (42).

Based on the preceding reviews, the performance of long-term treatment with lithium has compared favorably with other options (48–50). Modern antipsychotic drugs were similar or superior to lithium versus recurrent mania, and varied in their observed efficacy against recurrences of bipolar depression (from 4% inferior, to an average of 36% superior to lithium), and quite consistently superior against mania than bipolar depression. An exception was quetiapine, which was 79% more effective against recurrences of depression than mania. In addition, the anticonvulsants lamotrigine and valproate were quite effective against depression (43%–50% superior to placebo), with relatively weak effects against recurrences of mania (4%–27% over placebo-effects). These findings are consistent with the general impression that available treatments for bipolar disorder, including lithium, are notably limited in their effectiveness against recurrences or acute episodes of bipolar depression (7,39,43,44,51).

We found consistently in six studies that the response to lithium or other mood-stabilizing treatments was significantly inferior among patients who typically presented in bipolar depressions and then shifted into mania, followed a euthymic interval ("DMI" pattern) compared to the opposite ("MDI") pattern. The pooled difference favored the MDI pattern by 29% (CI: 18%–40%) (52). This finding again suggests that depression-prone bipolar disorder patients may be more difficult to treat. Of interest, both the tendency toward the DMI or MDI recurrence pattern, as well as the tendency to a long-term excess of mania versus bipolar depression appear to be identifiable very early in the course of bipolar disorder, posssibly from the first-lifetime episode or cycle (6,52,53).

We also addressed the question of whether the effectiveness of long-term treatment of bipolar disorder patients has waned as a secular effect over the past decades by reviewing 26 trials of various designs reported between 1967 and 2001 (54). The overall, meta-analytically computed difference between outcomes with versus without lithium treaetment highly significantly favored lithium-treatment by 3.2-fold [confidence interval [CI]: 2.7–3.8]. Moreover, the relative benefit of lithium over the decades declined very little (by approximately 0.88 [CI: 0.06–1.68] %/year, p=0.04).

We also found, unexpectedly, that neither the delay of long-term treatment of bipolar disorder with lithium or other apparently mood-stabilizing treatments (which typically averages 5–10 years from illness-onset) nor the number of recurrences before treatment had a measurable impact on the likelihood of responding once treatment was initiated (7,55,56). This optimistic finding seems to be inconsistent with expectations arising from the view of bipolar disorder as a progressive illness, with shortening wellness intervals or recurrence-cycles as the episode count rises (57). However, that view is not consistently supported by available data and, to some extent, may reflect selection biases, such that patients in a finite sample become fewer and fewer as recurrence count rises, leading to the erroneous impression that cycles become shorter with more recurrences. This error has been found repeatedly since it was first identified by Eliot Slater in findings reported by Kraepelin, and can be avoided by comparing cycle-lengths among individuals matched for recurrence counts (7,58,59).

We have reported that discontinuing long-term treatment with lithium leads, as expected, to a substantial risk of recurrences of illness, as well as of suicidal behavior, in bipolar disorder patients (60). Importantly, these risks appear to include an iatrogenic component that may reflect the putative "pharmacological stress" associated with treatment-discontinuation itself, in that rates of recurrence and their latency are much more adverse than with previous illnesses without treatment in the same bipolar disorder patients (60). Support for the concept of treatment-dicontinuation stress is provided by repeated findings with various types of psychotropic drugs (antipsychotics and antidepressants as well as lithium) that the rate of discontinuation of long-term treatments has a marked impact on the risk and rapidity of recurrences, encouraging slow reduction of doses whenever possible (61–66).

Treatment-discontinuation associated recurrence risk appears to be a general phenomenon, and is likely to confound many experimental treatment trials in both psychiatry and in general medicine that involve re-randomizing partially recovered patients to continued treatment with an effective drug versus discontinuation to placebo (62,64,65). Circumstances in which rapid or abrupt treatment-discontinuation is particularly likely currently is in anticipation of, or the presence of, pregnancy, in which concern about potential teratogenic effects on the developing fetus (and associated liability claims) are typically not appropriately balanced against risks to the psychiatrically vulnerable mother (67).

There has been disagreement about whether lithium is as effective after restarting it after discontinuation, but the balance of the available evidence suggests that second or even third trials yield similar benefits as initial trials in the same bipolar disorder patients (68,69).

The potential value of long-term lithium treatment to reduce risks of recurrences in unipolar major depressive disorder is not adequately studied. However, lithium may have value to supplement antidepressant treatment during episodes of unipolar major depression when antidepressant monotherapy is yielding unsatisfactory results. Most studies supporting this application have involved older, tricyclic antidepressants, but similar effects may occur with modern antidepressants as well (7,70–72).

Lithium and suicide

Suicidal risk in bipolar disorder

Bipolar disorder and severe, recurrent major depression (especially involving psychiatric hospitalization) have the highest standardized mortality ratio (SMR) of any psychiatric disorders, averaging 20-times above the international general population rate of approximately 15/100,000/year (0.015%/year) (73,74). Suicide is far more likely in depressive, and especially dysphoric-agitated or mixed, phases of bipolar disorder than manic periods, and is rare in hypomania (75,76).

We found an annual risk of *suicide* among 843 bipolar I and II disorder patients in Sardinia of 150/100,000, or more than 15-times higher than in the Italian general population, and three-times greater than among 1,983 patients diagnosed with recurrent major depressive disorder, most of whom were moderately ill outpatients (77). The annual rate of *suicide attempts* was 1.26% among bipolar disorder patients versus 0.48% in unipolar depressive cases. In a review of the medical records of nearly 3,000 outpatients diagnosed with DSM-IV major mood disorders, we found the risk of suicide to be similarly high in both types I and II bipolar disorder (77), as has been confirmed in subsequent studies (78,79). These suicide rates with bipolar disorders were somewhat higher than among patients diagnosed with unipolar major depressive disorder, overall, but similar among

bipolar or unipolar disorder patients who ever required psychiatric hospitalization (77).

In a synthesis of findings from 28 studies, we found a suicide rate of 0.39%/year (823 suicides/21,484 patients/9.93 years) among bipolar disorder patients with varying states of treatment (73). This rate was more than 20-times higher than the international suicide rate in the general population, of approximately 0.015%/year.

We also proposed an *index of lethality* of suicidal behavior as the ratio of attempts/suicides (A/S) (79). This ratio was 8.6 in bipolar disorder patients (similar in types I and II bipolar disorder cases), and 9.6 in unipolar depression patients, compared to an estimated risk-ratio of 20–30 in the general population (80). These observations indicated relatively high lethality of suicide attempts among mood disorder patients generally, and particularly among bipolar disorder patients—presumably reflecting both intent and methods.

Early indications of a possible suicide risk-reducing effect of lithium treatment

Initial proposals that lithium treatment might contribute to suicide prevention date to the early 1970s (81). A controlled, two-year, treatment trial in that era involving over 300 mood-disorder patients encountered suicides at a rate of 1.28%/year with placebo-treatment and none with lithium or imipramine treatment (82). A *mirror* study of 100 mood-disorder patients during five years without, versus five years with treatment, found half as many suicide attempts during treatment (83). A similar study found a six-fold lower annual rate of suicide attempts among 95 patients with recurrent major affective disorders, during versus before 5.1 years of lithium treatment (84). In another mirror study of 33 unipolar depressive disorder patients, the rate of suicides before versus during 8.3 years of lithium maintenance treatment fell from 2.55%/year to zero (85).

In the 1990s, Coppen and his colleagues (86) also found no suicides among 103 major affective-disorder patients attending a lithium clinic for 11 years (<0.09%/year). A later extension of this study identified one suicide in a total of 1,519 patient-years (0.07%/year) of lithium maintenance treatment for major affective disorders (87). Moreover, a 13.8-fold higher rate (0.91%/year) was found in 27 untreated unipolar depressed patients, suggesting a possibly broad protective action of lithium not limited to bipolar disorder patients (87).

An early case-control study of suicidal risk in 68 patients with various major affective disorder diagnoses and at least one suicide attempt, found a rate of suicides or attempts during 8.0 years of lithium treatment of 1.1%/year, and a highly significant increase to 2.0%/year following discontinuation of lithium treatment (88). A later clinical study found a significant, 4.8-times higher rate of suicides among patients who discontinued lithium (89).

We studied suicidal behaviors in 360 type I or II bipolar disorder patients before, during, and following discontinuation of long-term lithium monotherapy (90). Rates of suicide and life-threatening attempts were 6.4-times lower during lithium-treatment than either before or long after treatment. Notably, the risk of suicidal acts increased by 20-fold within several months after discontinuing lithium maintenance treatment, but later fell back to the same level encountered before lithium treatment had started. Moreover, this early suicidal risk following discontinuation of long-term treatment with lithium was twice-higher following abrupt or rapid (less than 2 weeks) versus more gradual discontinuation of lithium. Also of interest, the ratio of attempts/suicides (A/S) was twice greater during treatment with lithium, suggesting reduced lethality of suicidal behavior with this treatment (79). In our initial meta-analytic review of 12 early studies, the pooled rate of suicides and attempts without lithium was 1.02%/year, and 8.85-times [CI: 4.14–19.1] lower with lithium treatment ($p<0.0001$) (91). In addition, a meta-analysis of 8 studies on unipolar recurrent depression patients found that long-term lithium treatment was again associated with a substantial reduction of risk of suicides and attempts (by approximately 76%) among patients treated with lithium compared to other alternatives, mainly antidepressants and anticonvulsants (92).

There is little research that directly compares suicidal risks during treatment with mood stabilizing agents other than lithium, and available findings have usually favored lithium (93). Two studies found nearly three-fold average lower suicidal risks with lithium than with either carbamazepine or valproate among bipolar or schizoaffective disorder patients (94,95). A study based on retrospective data from 161 bipolar disorder patients found that rates of nonlethal suicide-related events were lower during long-term lithium treatment than with other mood-stabilizers given alone

or with first- or second-generation antipsychotic drugs (96).

Despite recent questions about suicidal risks among epileptic patients (97,98), anticonvulsants as used to treat bipolar disorder may have some beneficial effects on suicidal behavior (99–101). We carried out a meta-analysis comparing the protective effects against suicidal behavior of lithium versus several proved or putative mood-stabilizing anticonvulsants (including carbamazepine, lamotrigine, and valproate) in six studies with more than 30,000 patients treated with lithium or an anticonvulsant (for 1.6–2.6 years). Lithium was associated with significantly lower rates of suicide-related behaviors and interventions, uncorrected for exposure times, but involving randomized treatment-assignment in half of the trials (92). The observed rate of suicide-related acts or interventions averaged 0.3%/year during treatment with lithium versus 0.9%/year with anticonvulsants, to yield meta-analytically pooled risk ratio of 2.86 (CI: 2.29–3.57; $p<0.0001$), favoring lithium by nearly three-fold over the few anticonvulsants that have been tested in this way.

A Danish national pharmacoepidemiological cohort study of over 16,600 persons sampled for six years found significantly fewer suicides among patients filling prescriptions for lithium or valproate in addition to an antipsychotic drug, compared to antipsychotic-treatment alone (102). Another controlled and randomized, but small (statistically under-powered) trial found no difference in rates of suicidal behavior among 35 potentially suicidal bipolar disorder patients randomized to lithium versus valproate (without or without other uncontrolled treatments) for up to 30 months (103). A recent study from the US Veteran Administration on more than 1000 bipolar disorder patients found reduced incidence rates for attempted suicide ranking: lithium plus divalproex < divalproex alone < lithium alone (104). It is unclear whether these studies support the hypothesis that both valproate and lithium exert similar antisuicidal effects, or are simply inconclusive.

Current status of studies of lithium and suicide

To date, an association of reduced suicidal risk during long-term treatment with lithium in bipolar disorder patients is supported consistently by nearly three-dozen original studies, meta-analyses, and reviews (37,91,105–111).

Our meta-analysis of 31 studies included eight trials randomized versus placebo or active-alternative treatments (79). Averaged crude rates of suicidal acts in these studies were 0.56%/year (or per 100 person-years) with lithium and 2.64%/year without it, indicating a major overall, crude reduction of suicidal risk of about five-fold. Apparent reductions were similar for both suicides and attempts, and among purely bipolar disorder patients and samples including various recurrent major mood disorders. Meta-analysis of the available studies found an overall reduction of risk by approximately 80% (risk ratio [RR] = 4.91, CI: 3.82–6.31; $p<0.0001$) (79), a result that was sustained when this analysis was expanded to include 34 studies (112).

Since these meta-analyses, additional studies have provided more data. One was a rare randomized, controlled trial (113) which found a substantial but statistically nonsignificant difference in rates of suicidal acts between patients treated for 12 months with lithium versus those randomized to placebo (adjusted hazard ratio [HR]: 0.52, CI: 0.18–1.43, favoring lithium). However, all three completed suicides occurred in the placebo-treated group. In another randomized comparison of lithium versus placebo added to citalopram treatment for four weeks, suicidal behavior and ideation were rated explicitly with several validated rating scales. No suicides or attempts occurred in either group in this brief trial, but all of the rating scale scores related to suicidal risks decreased significantly more with the combination of citalopram and lithium than with citalopram plus placebo (114). This effect may represent an added antidepressant effect of combining lithium with an antidepressant (115) and not specifically indicate an antisuicidal action of lithium.

A more recent meta-analysis considered randomized, controlled trials comparing long-term with lithium versus placebo or other active drugs in mood disorder patients [116]. The 48 trials (with 6674 subjects) included indicated that lithium in bipolar disorder patients was far more effective than placebo in reducing the number of suicides (odds ratio [OR] = 0.13, CI: 0.03–0.66), and in decreasing deaths from any cause (OR=0.38, CI: 0.15–0.95). Similar effects also were found in patients with unipolar depression, and lithium generally tended to be more effective than other active comparators.

Overall, the findings summarized here, appear to provide strong and quite consistent support for the

hypothesis that lithium treatment may have a special role in reduction of suicidal risks. Although these findings are as encouraging as they are unusual, it must be emphasized that such a role of lithium treatment is not securely demonstrated and has not been accepted by the FDA as an explicit indication for lithium treatment.

Design of trials to evaluate potential antisuicidal effects

Of note, the results of our meta-analyses (79,112) remained highly significant when eight randomized, controlled trials, involving more than 110,000 person-years of risk, were considered separately (RR=1.76, CI: 1.65–1.88; p=0.001) (79). Moreover, the recent meta-analysis by Cipriani et al. [107] involved comparisons of suicidal risks between treatment groups randomized to lithium versus placebo. Nevertheless, even in these randomized, placebo-controlled trials, suicidal behavior usually was ascertained along with other adverse outcomes in an informal and incidental manner, as have adverse events in most randomized, controlled treatment trials for any purpose. A notable exception was the randomized, prospective InterSePT trial supporting superior antisuicidal effects of clozapine versus olanzapine in suicidal schizophrenia patients, leading to the unique status of clozapine as only treatment with an FDA-approved indication of reducing suicidal risk (116). There is emerging interest by both investigators and regulatory bodies to address adverse events in trials by more probing assessment methods, although the benefits, limitations, ethics, and costs of such approaches remain to be clarified (117). In general, scientifically and ethically appropriate methods to test for antisuicidal effects remain at a very early state of development, and such trials remain very challenging.

Potential lethality of lithium overdoses versus effects on suicidal risk

The evident beneficial effects of lithium in reducing mortality as well as morbidity associated with suicidal behaviors are even more remarkable given the potentially lethal toxicity of lithium in acute overdoses. However, recent analyses of outcomes of ingestions of potentially toxic substances reported by the US Centers for Disease Control and Prevention (CDCP) indicate that mortality from overdoses of lithium is similar to that associated with modern antidepressant or antipsychotic agents, or less than expected—possibly owing to protection from lethal effects by vomiting as well as timely treatment by hemodialysis (7,118). Despite lithium's potential lethality, suicide attempts with lithium during long-term treatment have been reported to be uncommon (119), none was found among more than 700 patients with major mood disorders treated with lithium for several years at the Lucio Bini Mood Disorders Center in Sardinia (Tondo L, unpublished observations, 2013). It is possible that suicide attempts using this agent are limited by its major antisuicidal effects or that the unpleasant effects of lithium overdoses are now widely known.

Mechanisms of proposed antisuicidal actions of lithium

Potential mechanisms by which lithium might reduce suicidal risk are not clear. They may involve preventing recurrences of high-risk mood-states (mixed-states, dysphoria, depression) or represent a distinct action on suicidal and perhaps other aggressive or impulsive behaviors. Some investigators have supported an association of antisuicidal with mood-stabilizing actions of lithium (81,87). Others have found an imprecise correlation of mood-stabilizing and antisuicidal effects, or have emphasized clinical observations of increased suicidal behavior after stopping lithium, independent of the previous responsiveness of mood symptoms to lithium therapy, and suggested that lithium may have distinct antisuicidal or anti-aggressive actions (88,109,111,120,121). It is also possible that the unusually close medical monitoring required for safe treatment with lithium may improve support of suicidal patients and so contribute to antisuicidal effects.

CONCLUSIONS

The preceding overview indicates that the introduction of lithium for the treatment of mania in 1949 has exerted broad and powerful effects on modern psychiatry—far beyond proving to be a highly effective and selective treatment for bipolar disorder (Table 1).

Its introduction greatly supported the emergence of bipolar disorder as a distinct syndrome in the 1960s and 1970s, and has since encouraged studies of the nature of the disorder, its epidemiology, clinical course, and responses to treatments in general. Notably, lithium opened the modern era of clinical psychopharmacology as the first of a series of serendipitous discoveries that provided at least one example of every class of

Table 1. Impact of lithium treatment on modern psychiatry

- First effective treatment for acute mania
- Prime example of the value of serendipity
- First selective treatment for mania versus psychotic disorders
- Encouraged broad acceptance of the concept of bipolar disorder
- Opened the era of modern psychopharmacology since 1950
- First treatment with long-term prophylactic efficacy in any major psychiatric disorder
- Encouraged critical assessment of methods to test prophylactic effects of psychiatric treatments
- First treatment with substantial evidence of suicide-preventing effects
- First psychiatric treatment with clinically useful drug monitoring by serum assays
- Stimulated extensive studies of molecular pharmacodynamics

currently available psychotropic drugs in the decade preceding 1960. Lithium has value in the treatment of acute mania, but its clinical importance lies in its well-demonstrated ability to prevent recurrences in bipolar disorder, more against mania than bipolar depression. Nevertheless, its effects against bipolar depression are not insignificant, as bipolar depression continues to be one of the most challenging psychiatric conditions for which no available treatment is highly effective. Lithium is especially noteworthy in having the most abundant evidence of suicide risk-reducing effects of any known treatment. Long-term treatment with lithium has provoked much-needed consideration of the many pitfalls and shortcomings of efforts to test for prophylactic effects of all psychotropic drug treatments, particularly for a complex and protean illness like bipolar disorder. Lithium has led the way to the concept that specific treatments may be of particular value for certain disorders, thus indirectly supporting efforts to advance descriptive and biologically based psychiatric nosology aiming at improved diagnosis, prognosis, treatment-selection, and research.

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