Thomas A. Ban: Lithium in psychiarry in historical perspective

Edward Shorter's commentary: Introduction to Lithium in psychiatry in historical perspective

The story of lithium is really the story of everything that's wrong with psychopharmacology. It was difficult to get lithium accepted. It has been difficult to keep lithium on the radar. Yet it is the most powerful form of pharmacoptherapy that psychiatry has on offer. Possibly the most effective drug treatment for mood disorders ever introduced, lithium was systematically shoved aside in graduate training and marginalized in clinical use, so that more profitable – but less effective – "mood stabilizers" carried the day and lithium found itself in the rear of the van. The whole story documents the inadequacy of psychiatry's efforts to become a clinical neuroscience.

Preamble: Lithium had a long "folkloric" existence

At some point, Senator Tom Connally of Texas asked Morris Fishbein, longsttanding editor of the *Journal of the American Medical Association* and a leader in the campaign against quackery of the 1920s and '30s, if Fishbein couldn't possibly interest the FDA in the "Crazy Crystals" of Texas, evidently containing lithium. Fishbein dismissed the notion.[1] But there is some evidence that the lithium springs had an impact on mental illness and in 2014, on the basis of these lithium-water stories, the *New York Times* headlined, "Should We All Take a Bit of Lithium?" (Sept 13). The effectiveness of lithium in spring water holds up in a statistical analysis: The 27 Texas counties where lithium in the water ranges from 70-170 micrograms/L have significantly lower levels of suicide, homicide and rape than do the low-or no-lithium-counties.[2]

Lithium inserted itself rather insidiously in American culture in the 1930s and '40s. The soft drink "7-Up" was advertised as "lithiated lemon soda" from its launch in 1929 until 1950[3]';

ads featured happy babies consuming bottles of it.[4] So the notion that lithium was somehow beneficial infiltrated popular culture before medical culture. Various medical efforts in the 19th century to use lithium therapeutically in psychiatry may be noted.[5] All remained curiosities of the literature and had no impact. John Cade, in any event, had probably never heard of any of it and deserved, as Carroll puts it, "a pass, in recognition of the distractions of WWII and the concentration camp. Then after the war, he was a man in a hurry to make up for lost time."[6]

Rise

As is well known, in the mid-1940s Cade discovered the efficacy of lithium in mania and published in 1949 one of the most famous articles about it in the history of psychiatry.[7] In today's lingo Cade's patients, in Carroll's view, were probably "rapid cycling bipolar" rather than "chronic mania" and very lithium-responsive.[8] There have been several recent histories of this epochal discovery, including Walter Brown's *Lithium: A Doctor, A Drug, and a Breakthriough* (2019). Yet Cade's initial patient died of a lithium overdose; Cade turned his back on the treatment and, as Sam Gershon points out, it was the 1951 paper of Charles Noak and Edward Trautner at the University of Melbourne[9] that, as Gershon put it, "did much to stem the flight from interest in exploring lithium in psychiatry."[10]

This Noak-Trautner study was the first in the world to monitor lithium levels with the newly developed flame photometer. And it was in fact this photometer that made possible the expansion of lithium therapy because the ion was otherwise too tricky to use.[11] It was impossible to obtain blood levels and overdoses could easily be fatal.

At the instigation of his chief Erik Strömgren at the University of Aarhus, in 1954 Mogens Schou published the first of a series of papers on lithium based on randomly controlled trials. These were among the first RCTs in psychiatry.[12] The story was so good it could not possibly be true! A group at the Maudsley Hospital led by psychopharmacologist Michael Shepherd sought to diminish Schou's contribution and to downplay the importance of lithium. Healy writes, "This controversy dragged lithium out of obscurity and made it one of the stars in the psychotropic firmament."[13]

Yet it has been a controversial star. Among authorities on "bipolar disorder," the lack of enthusiasm for lithium has been palpable. In 2007, Guy Goodwin at Oxford and others, in an ECNP "consensus meeting on bipolar disorder," essentially give lithium the back of their hand and concluded that "positive findings seem to many authorities to... support the addition of lamotrigine during or after the resolution of a depressive or manic episode to prevent further depressive relapse."[14] A patent-protected remedy of indifferent clinical application – What a recommendation!

What could explain such foot-dragging in the presence of unquestionable data on the efficacy of lithium in treating and forestalling mood disorders and in suicide prevention? First, there was the Zeitgeist argument. Psychiatry was just emerging from its emtombment in psychoanalysis.

Then, Sam Gershon ventured the "complexity" explanation: "The clinical monitoring for lithium usage is too complicated for psychiatrists and [they are] better off using antipsychotics or anticonvulsants. The other attraction is that for the latter drugs you do not need to carefully make a diagnosis, which may take a couple of visits. So educational instiutions are actively contributing to these decisions because it's quicker and cheaper for the instiution, but does lifelong harm to the patient."[15]

Other explanations spring readily to mind: clinicians drowning in the torrent of Pharma literature praising patent-protected "mood stabilizers" and so forth. But the phenomen of lithium-aversion remains puzzling; the ion gave clinicians the means of actually saving lives – 70% of suicides are caused by serious depressive illness, which responds readily to lithium. Why would doctors not rush to take advantage of it?

Schou coined the term "mood stabilizer" in 1963,[16] by which time he had become the most enthusiastic academic authority on lithium and, to be sure, on lithium in all mood disorders, not just acute mania. So at the beginning, the concept of "mood stabilization" was a portmanteau term for any agent affecting mood.

Prophylaxis

The notion that lithium could be prophylatic rather than merely therapeutic had been in the air yet without garnering much support. Jules Angst later said, "I remember one CINP meeting in Munich in 1962, at which Mogens Schou stood up in a discussion dominated by talk of neuroleptics and antidepressant drugs and spoke about the prophylactic properties of lithium and was greeted with loud laughter. People simply didn't believe that lithium was active."[17]

Then in 1963, with anecdotal data, Geoffrey Hartigan at Queen Square observed that lithium "has repeatedly shown its worth in the prophylaxis of manic-depressive and manic states," and the few cases that he presented suggested that once again.[18]

In 1967 Schou and fellow psychiartrist Poul Baastrup reported lithium prophylaxis in an open trial of 88 female patients at the Glostrup Psychiatric Hospital. The authors concluded, "Lithium is the first drug for which a clear-cut prophylactic action against one of the major psychoses has been demonstrated... Lithium seems to be of unusual potential value for reserarch on manic-depressive psychosis." (The authors meant manic-depressive illness in the Kraepelinian sense of all mood disiorders, not in the DSM sense of "bipolar disorder.")[19]

The demonstration of lithium prophylaxis of mania and depression was eye-opening. Heinz Lehmann, chief of the Douglas Hospital in Montreal, said in 1978, "Perhaps the most important new development during the last decade has been contributed by Baastrup and Schou with the lithium maintenance treatment of affective disorders. A number of studies in several countries have demonstrated reliably that continuous lithium treatment, carried on over the years, can prevent many recurrences in patients who previously were periodically disabled and endangered by frequent arttacks of depression or mania."[20]

Lehmann was prescient: Lithium became significant only when Baastrup and Schou found it useful in "preventing *recurrences* of affective disorders," as Linford Rees, who virtually initiated controlled trials in psychiatry, put it.[21] In a discussion at an FDA approvals committee in 1995, Dennis Charney, then at Yale University, seconded this point, "The miracle of lithium was not its trteatment of acute mania. Neuroleptics, even high-dose benzodiazepines, are quite effective for the treatment of acute mania. And neuroleptics may even be superior to lithium in the treatment of acute mania. The issue is prevention of relapse."[22]

In 1971 Alec Coppen at West Park Hospital in Epsom and colleagues published in *The Lancet* an RCT of 65 patients with recurrent depression. The results were striking: "Patients

receiving lithium had very significantly less affective illness than patients receiving placebo tablets... No patient on lithium was given electroconvulsive therapy (E.C.T.), whereas 43 percent of the placebo group received one or more courses of E.C.T." Coppen said that his research affirmed Schou's conclusion "that lithium has a definite prophylactic action in recurrent affective disorders."[23] (Coppen remembered, at a meeting of the "Denghausen Group" on some Caribbean island, "Ted [Edward] Hare coming along with his colleague Ramon Gardner and he said that this can't be right. He and Gardner went through the results but they couldn't find any fault with them."[24]). Coppen strengthened doubts about bipolar and unipolar depression as constituting two separate diseases when, at a symposium in St. Moritz in 1972, he said that his group could detect no difference in the lithium prophylaxis of depressions of either polarity.[25] (With time, belief in the separateness of unipolar depression ["major depression"] and "bipolar disorder" became an article of faith.)

International Spread

The global progress of lithium following its introduction in Australia was swift.

In France there had been a long history of using lithinated spa waters, including such venerable remedies as "Les Lithinés du Docteur Gustin," in the treatment of gout.[26] In 1951, two French investigators reported on 12 psychiatric cases treated with lithium citrate, of whom three had "chronic mania." All three did well and the authors concluded, "The use of lithium in the manic phases of manic-depressive psychosis seems particularly effective."[27] French clinicians used lithium citrate, which enjoyed a momentary vogue until the introduction of chlorpromazine 1953.[28] By 1958 the firm Laboratoire T.E. in the Rue Ste Anne was indicating lithium benzoate for "the biological treatment of anxiety and anxious insomnias."[29] Not quite mania yet, but getting close.

In Britain, in 1966 the *Drug and Therapeutics Bulletin* praised the use of lithium in the treatment of mania and said it could be prophylactic against recurrent depression and mania: "Because there is a delay of two or three days in onset, a major transquilliser should be given parenterally at the start."[30] Yet it was unhelpful that Aubrey Lewis, professor of psychiatry at

the Institute of Psychiatry at the Maudsley Hospital – the primary training center in England – thought lithium "dangerous nonsense."[31]

In 1968 Curt Rossman at the Women's Clinic of the Uppsala Academic Hospital in Sweden reported good results with lithium in the treatment of premenstrual syndrome. The eight women were said to have "severe premenstrual conditions with aggressiveness, irritability, emotional lability and listlessness as well as marked water retention." At serum levels between 0.4 and 0.7 mg/Eql "in all cases the result has been good or very good and the patients have all been satisfied. All mental symptoms have been alleviated."[32]

The US story

It was a trainee of John Cade, Sam Gershon, who brought lithium to the United States in 1959 when he accepted a post in the "Schizophrenia and Psychopharmacology Joint Research Project" of the University of Michigan. One of the program's clinical arms was at Ypsilanti State Hospital – financed by a program grant from John Cole's Psychopharmacology Service Center at NIMH – and there Gershon would, according to Cole, buy lithium "by the kilo from a chemical supply store and then get a drug store pharmacist to put it into capsules."[33]

Barry Blackwell writes of Gershon's migration, "He would have more to do with lithium there [in the US], and became an evangelist, preaching its virtues to the non-believers until the Americans eventually re-entered the fray – like their entry into both world wars – late."[34]

Gershon and Arthur Yuwiler reported in 1960 – in anecdotal form – the results of their lithium trials at Ypsilanti State.[35] At the same time, Edward Kingstone – or "Eddie" as he styled himself in the title – reported an open trial that he had conducted, under the supervision of D. Ewen Cameron, the directior of the Allan Memorial Institute in Montreal.[36] (Kingstone said he was first to write. Yet publication was delayed when the *American Journal of Psychiatry*, under the editorship of Clarence Farrar, turned it down.). Both trials included patients with a variety of diagnoses and highlighted lithium for investigation in North America.

In 1962 George Winokur initiated the use of lithium at Washington University in St. Louis. Paula Clayton, then a resident, recalled their early use: "We had a manic minister, kind of like Elmer Gantry [figure in a novel by Sinclair Lewis]. He'd written bad checks. George

[Winokur] read about lithium in *The Lancet* and after the patient was given multiple ECTs and trifluoperazine, but was still not well, George had the pharmacy make up lithium pills because nobody produced them. We gave lithium to the manic minister and he got better. So we began using lithium for mania in 1962 even though it wasn't marketed and approved by the FDA."[37]

By 1971 four RCTs of lithium had been conducted for acute mania. The average response rate was 71%.[38] These results could not be overlooked. In 1970 the FDA approved simultaneously all three New Drug Applications for lithium carbonate: Pfizer for Lithane, Rowell for Lithionate and Smith Kline and French for Eskalith – all were for "acute manic states."[39] Thus, the US became the 50th country to adopt lithium, a testimonial to the foot-dragging of the FDA in this area.

Yet already in the 1960s a network of US practitioners who prescribed lithium was forming, some of whom had permits to study Investigational New Drugs (INDs) from FDA. (And some didn't, just ordering their lithium from abroad or getting the corner pharmacist to buy some from a chemical supply house and put it in capsules[40]). In 1968 an Ohio physician wrote to an FDA administator saying that he had "a few patients who could definitely benefit from this treatment." But the Ohio doctor knew only of Dr. Arthur Sugerman at the Carrier Clinic in Belle Mead, New Jersey, who administered lithium; yet Ohio patients would need to have their levels checked monthly and New Jersey was a long drive. Were there no Ohio physicians, this doctor asked, who had been approved by FDA?[41]

A member of this network was Paul Blachly at the University of Oregon. And it was partly owing to a campaign organized by Blachly that FDA was finally induced to approve lithium for "acute manic states in manic-depressive psychosis" in 1970[42] (and for "the maintenance" of manic-depressive psychosis in 1974). "The FDA has had no good reason for holding this drug up," Blachly told the press.[43] In 1971 Blachly and his resident Barry Maletzky wrote the first textbook, *The Use of Lithium in Psychiatry*.[44]

Lithium clinics began opening. Ronald Fieve at the New York State Psychiatric Institute, alerted to the European literature by director Larry Kolb, established in 1966 the first lithium clinic in the US.[45] David Dunner, who was a junior associate of Fieve's in the clinic, said later, "Ron Fieve's major effort was to get wider acceptance of lithium. When patients from our clinic went on vacation, it was difficult to find psysicians they couuld consult who knew about the

drug."[46] Fieve said at a conference in 1973 that there was no doubt as to lithium's effectiveness in the prophylaxis of bipolar illness. As well, "Studies to date strongly suggest that lithium alone or lithium plus tricyclics may likewise be the future choice for maintaining unipolar depressives in a lithium clinic."[47]

Further lithium clinics saw the light of day: in 1968 William ("Dutch") Dyson founded one at the Coaldale Mental Hospital in the Delaware Valley; in 1973 Bernard Carroll at the University of Michigan established another. Donald Klein imported lithium to Hillside Hospital, Nathan Kline to Rockland State Hospital. These were the pioneers. By the early 1980s, lithium had been generally accepted as the therapy of choice in mania (except for highly active episodes) and for forestalling the recurrence of depression.

Lithium in depression

Schou had suggested in 1954 that lithium might have antidepressant action but this was not widely taken up. Then, as noted, in 1967 Baastrup and Schou reported that lithium was effective in the prophylaxis of depression as well as in manic-depressive illness.

Lithium changed the diagnostic picture considerably in the 1970s in the US. Under the influence of psychoanalysis, "schizophrenia" had been the favorite diagnosis of analytically-influenced clinicians for patients not suitable for psychotherapy. But once mania and manic-depressive illness became treatable with lithium, much of the previous "schizophrenia" turned into mood disorder. At Mt. Sinai Hospital in New York, in the years 1947 to 1957, 15% of the patients were diagnosed as schizophrenic, only 4% as manic-depressive. This then reversed once lihium was included in the hospital pharmacopeia. At the Payne Whitney Psychiatric Clinic, as staffer Stuart Asch said in 1987, "Every year, as previous schizophrenic patients were readmitted... we have had to repeatedly correct the old diagnosis of schizophrenia to manic-depressive illness."[48]

A substantial literature arose on the use of lithium in the treatment of depression.[49] (See the level-headed assessment in the respected *Drug and Therapeutics Bulletin* in 1981.[50]) In 1969 Fred Goodwin and colleagues at NIMH became first to document in an RCT that lithium had antidepressant effects outside of the framework of bipolar disorder. There were only five

patients in the "noncyclic group" and the study was scarcely definitive.[51] The antidepressive effect of lithium was confirmed in 1972 by Joseph Mendels and William ("Dutch") Dyson at the University of Pennsylvania; the authors said their finding "raises the question of whether lithium carbonate might be effective in the treatment of selected depressed patients."[52] (The University of Pennsylvania became a fortress of the study in lithium in bipolar illness, led by Dyson's successor Jay Amsterdam at the Depression Research Unit.[53])

Paul Janssen, who founded Janssen Pharmaceutica and counts as one of the epoch's great drughunters, advocated lithium in depression rather than one of his own drugs. He described disagreements within his lab: "In our laboratory I have always fought the idea of some of the old pharmacologists who claimed to be interested in making antidepressants – my question has always been: What is an antidepressant? Because the best treatments that I know of for endogenous depression are electroconvulsive therapy and lithium. For me these two modes of treatment are clinically far more obviously effective than imipramine-like tricyclics."[54] The use of lithium in depression has been a turning point at which the conventional wisdom failed to turn, for even today lithium is considered a bit experimental in the treatment of unipolar depression.

Resistance

Things got off to a bad start. In 1955 the second edition of *Goodman and Gilman*, the stanard guide to pharmacology, said, "The lithium ion has no therapeutic application."[55] The third edition in 1965 was scarcely more enthusiastic but did note without comment Schou's work.[56]

In the 1960s there was a whole scientific climate of opinion that pushed back against lithium. After the discovery of amine neurotransmitter reuptake at the National Institutes of Health in the late 1950s, the field focused laserlike upon drugs with differing reuptake profiles. It was clear that serotonin and norepinephrine were the key to some kind of antidepressant effect. But a drug that was simultaneously antimanic and antidepressant? That did not fit well within the theoretical framework and so, as a a result, it didn't exist. Goodwin, then at NIH, later recalled, "One of my patients was on lithium and I felt both the patient's depression and mania

was getting better, which was counter to the prevailing wisdom of the time; the amine hypotheses were dominant and it was incomprehensible to have a substance that combined antimanic and antidepressant effects."[57]

Lithium treatment is not innocuous. From the beginning it was known that lithium, excreted in the kidneys, could cause renal damage. This was nailed in 1977 by a team of pathologists and clinicians at the University of Aarhus who, in renal biopsies of fourteen patients on long-term lithium treatment who had been admitted for acute lithium intoxication, found twice the amount of damage in interstitial renal connective tissue as in controls. As well, "The number of sclerotic glomeruli was five times as great as in controls."[58]

Bernard Carroll later commented, "Australians are very pragmatic and all through the 1950s, lithium was widely used in Australia and was picked up in England through Mogens Schou in Scandinavia and later in Europe in the 1950s and the 1960s. The resistance to lithium as a clinical agent was centered mostly in the United States."[59] Why so much resistance in the US?

It was a mixture of commercial rivalry and psyhchoanalysis. The spirit of the times in psychiatry in the 1950s and -60s was psychoanalysis. Alec Coppen, the very image of a bioloical psychiatrist, said "A lot of people who are in psychiatry are not really interested in the medical model. They went into psychiatry to get away from it."[60] Clearly, those who sought the origin of illness in "the unconscious" would be skeptical of lithium.

As for commerce, there is a fine line between documenting side effects and counter-detailing on the part of commercial competitors. As one psychiatrist in a small town in Wisconsin told his listmates in 2008, "Under Abbot Labs coaching, I switched many lithium patients to valproate starting in the 1980s, and well, yes, it was better for several years. And now it is not in way too many patients . . . [Valproate] has at least as many cognitive difficulties as lithium, and is unacceptable in women aged 16 to 50."[61]

A whole subculture arose around the supposedly severe side effects of lithium treatment. Goodwin and Kay Redfield Jamison described in 1990, "The antagonism towards lithium . . . on the part of some mental health workers, who may subtly or overtly sabotage drug compliance."[62]

At the request of Abbott, Charles Bowden, at the SanAntonio campus of the University of Texas, led in 1994 the first RCT of valproate versus lithium and placebo in the treatment of mania (48% of the divalproex [Depakote] patients improved, 49% of the lithium patients; 25%

of the placebo patients).[63] Bowden's lack of enthusiasm for lithium was palpable. He told an interviewer in 2003, "Lithium is a very poorly tolerated medication. I think the evidence increasingly is that it worsens depression more often than it helps depression (sic)." He added a bit later in the interview, "Valproate has its own side effects but was generally much more tolerable [than carbamazepine or lithium]. It also seemed to have a broader spectrum of efficacy."[64] Bowden continued to work closely with Abbott. (Valproate was not universally admired. George Simpson, a longtime clinician with Nate Kline at the Rockland State asylum in New York State, said, "When valproate came they sold it to everybody saying it was the most efficacious treatment for bipolar patients, which is clearly untrue. It's never ben proven; the more serious studies suggest lithium is still the drug to beat and I would agree with that. I also think that the side effects of lithium are somewhat exaggerated."[65])

It was Abbott's promotion of valproate that led to the concept of "mood stabilizer," given that few knew of Schou's earlier usage.[66] Carroll was scathing on the subject of Abbott's promotion of valproate (Depakote). He called Pharma influencing medical practice "a familiar story – look at how Abbott badmouthed lithium to promote Depakote (aided and abetted by venal KOLs [key opinion leaders], of course."[67]

Ads for the mood stabilizers made no secret of the superiority of their products to lithium. Abbott Labs trumpeted in 1995, apropos its drug Depakote (divalproex sodium), "Significantly superior to placebo in patients intolerant or not responsive to lithium."[68]

Lithium was not driven entirely out. DSM-III in 1980 abolished Kraepelin's "manic-depressive illness," a basin that included all mood disorders, and replaced it with unipolar depression ("major depression") and "bipolar disorder," a quite separate illness, said the Manual. Yet such was the purchase that manic-depression had in psychiatric practice, that companies manufacturing lithium continued to promote it for "manic-depressive illness" long after 1980.[69] (Other companies did, however, switch their lithium indications over to "bipolar patients" – SmithKlineBecham 1993). Manic-depression was thus a trailing edge rather than a leading one. But it was a powerful edge.

The contagion spread. American drug companies producing "mood stabilizers" had no interest in promoting lithium and, just as with electroconvulsive therapy, it was hoped this was a treatment that would die in silence. Mogens Schou said in retrospect, "The industry was never

really interested in lithium because of the lack of opportunity to make money from it... Students and young physicians [in the United States] hear exclusively about the anticonvulsants and nothing about lithium, and that of course gives a bias."[70]

Much was made of the "triad of toxicity": tremor, desequilibrium and confusion. Of course all drugs have side effects. Important is the balancing of the risk/benefit ratio and increasingly this ratio was made to move to lithium's disfavor. The alternative "mood stabiliozers," such as lamotrigine and valproic acid, were presented as much more appealing. So successful was this campaign that many trainees and younger clinicians removed lithium from their personal pharmacopeias. And even among lithium fans, there was a lively awareness that supposedly subtherapeutic doses of lithium could have toxic effects. In 1994 Jonathan Himmelhoch, at the University of Pittsburgh (who had trained at Yale in the 1960s), cautioned against "the failure to recongize lithium failure."[71]

Experienced old hands pushed back, pooh-poohing the renal toxicity alarm. Ivan Goldberg in New York City had been treating patients with lithium since 1962.[72] He had been on staff at Columbia-Presbyterian Medical Center and by 2008, as a very experienced senior figure, told colleagues on a list-serve, "I'd estimate the percent with renal impairment sufficient to require the discontinuation of lithium being in the 5-10 percent range."[73] This was not a forbidding number. He continued in another note, "Over the years I have treated about 400 patients with lithium. I know of four patients who required dialysis... While I suspect there are people who progress to total renal failure with no risk factors other than long-term lithium treatment, I have not seen such a patient as yet."[74]

Senior clinicians, generally speaking, were lithium fans. Said one, "For you young ones on the list whose pharma-company-sponsored teachers brainwashed you against Li, I have not seen any other medication than Li fully normalize the mental status of a severely disturbed patient."[75]

But the battle was largely lost. In 2017, Olga Zivanovic at the Univeresity of Novi Sad in Serbia reached the discouraging conclusion, "Despite abundant evidence regarding the efficacy of lithium in the treatment of bipolar disorders, its use is declining at the beginning of the 21st century." It was, she said, necessary to remind the field of this again and agin, so that lithium "should once again become the first-line treatment for bipolar disorders." Jay Amsterdam, who

led the Mood Disorders Unit of the University of Pennsylvania, asked rhetorically in 2017, "Who do you know in the US since 2008, who actually applies lithium as a first-line therapy for bipolar disorder (whether manic or depressed), when the *de jour treatment-of-choice* in the US is 'anything but lithium.'"[76]

The indictment of the nay-sayers by Bernard Carroll in 2017 is interesting. He told Sam Gershon, "I remain deeply wary of the anticonvulsant Mafia. What they did to lithium use and education was terrible. Full disclosure: John Cade was one of my teachers in Melbourne."[77] As indeed Cade had taught Gershon.

Pushback

A page was turning. Paul Grof at the University of Ottawa said in 2014, "Voices have now arisen suggesting that lithium may actually be the only true mood stabilizer, as it demonstrably acts against both polarities of manic-depressive disorders." [78] He himself helped lead the comeback.[79]

The pushback against the patented mood stabilizers in favor of lithium commenced around 2000. It was precisely in 2000 that a group of investigators at the Free University in Berlin conducted a "withdrawal" study to assess the effectiveness of lithium in the continuation phase of a trial for depression. The technique: in phase I a group of 75 depression patients were placed in an open trial of lithium + antidepressant. In phase II, the 29 responders from phase I were randomly assigned to antidepressant + placebo or antidepressant + lithium for four months; in the placebo group, the lithium was then tapered early. The results were significant. In the lithium-taper group one of the patients committed suicde; several other experienced severe relapses. Evidently, it was the lithium, not the "antidepressant," that had kept everyone well in phase I. The authors concluded, "Substitution of placebo for lithium medication resulted in a rapid return of severe symptoms in a significant number of patients who were euthymic during the week lithium was withdrdawn. One-third of the patients suffered a depressive relapse after they had entered the placebo phase of the study but none of the patients who were randomly assigned to receive active lithium medication did so." [80]

Then it was discovered that lithium responsiveness may cluster in families – and thus have a genetic basis. This goes back to the work of Paul Grof and colleagues in 2002. Finding a genetic basis for anything is rare enough in psychiatry and the discovery that 67% of the relatives of bipolar lithium-responders – as opposed to 35% of contrrols – had an "unequivocal" prophylactic lithium response was an important advance.[81]

As for looking at lithium versus the on-patent mood stabilizers, in 2003 a study led by Frederick Goodwin at George Washington University comparing the prevention of suicide and suicide attempts in *bipolar disorder* at treatment centers in Washington DC and California, concluded that lithium had a superior efficacy to divalproex. The authors commented rather ironically, "This evidence of lower suicide risk during lithium treatment should be viewed in light of the declining use of lithium by psychiatrists in the Unites States, particularly among recently trained psychiatrists."[82]

In a meta-analysis of eight studies, Francesca Guzzetta at the University of Bologna, and Ross Baldessarini at McLean Hospital and colleagues confirmed this finding in 2007 for *unipolar depression*: "Antisuicidal effects of lithium in recurrent major depressive disorder [are] similar in magnitude to that found in bipolar disorders."[83]

There was a continuous string of findings. A large trial in 2010 known as BALANCE and led by John Geddes at 41 centers in the UK, France, Italy and the US, found lithium more effective than valproate in preventing relapse in bipolar disorder. Most effective was a lithium-valproate combination.[84]

A nationwide registry-based prospective study in Finland in 2015 of suicide in bipolar patients found that, among mood stabilizers, lithium was the only one associated with a significant reduction in suicide mortality. The authors concluded, "Maintenance therapy with lithium, but not with other medications, is linked to decreased suicide and all-cause mortality in high-risk bipolar patients."[85]

These were powerful moments in the lithium comeback, conducted by seasoned investigators at leading institutions. They were seen essentially as a poke in the eye to antipharmacotherapy groups such as the Critical Psychiatry Network in the UK that denied that pharmacotherapy had any disease-specific action.

In sum, lithium responsiveness opens the question of what Donald Klein called a "pharmacological torch" in the area of bipolar disorder. There is a small group of these patients who respond beautifully to lithium. As Martin Alda at Dalhousie University in Halifax puts it, "Compared to other psychiatric conditions, lithium-responsive bipolar disorder appears to be a narrower, more homogeneous and highly heritable phenomenon... The excellent responders are a reminder that there is a group of patients for whom lithium is not only the best but perhaps the only treatment option." [86] That would make lithium-responsive bipolar disorder, or even better, lithium-responsive mood disorder, a separate disease.

In historical perspective, it is difficult to disagree with Gershon: "Lithium was the first unlikely salvo in the revolution of psychopharmacology in psychiatry."[87]

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