LITHIUM IN NEUROPSYCHIATRY

The Comprehensive Guide

Editors
Michael Bauer
Paul Grof
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CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20141208

International Standard Book Number-13: 978-0-203-00705-1 (eBook - PDF)

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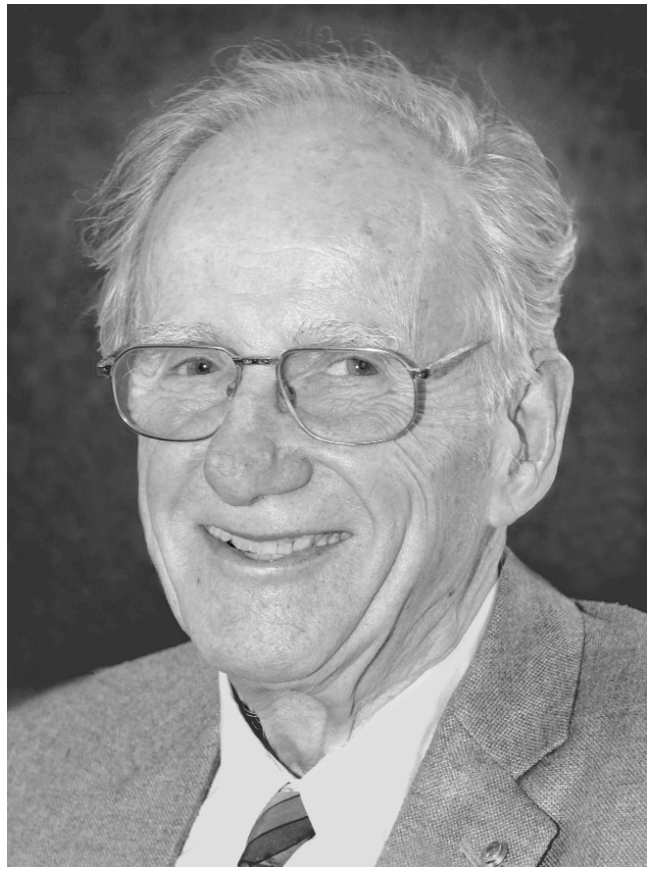

Prof Dr Dr hon MOGENS SCHOU (1918–2005)

This book is dedicated to MOGENS SCHOU who taught all of us how to use lithium in neuropsychiatry. Once he discovered lithium's prophylactic action in mood disorders, he researched tirelessly all its aspects and did not spare any effort to make the treatment available to all those in need, the millions of patients with recurrent mood disorders.

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Foreword

Lithium is nothing if not fascinating. Created in the first minutes after the Big Bang, it was discovered nearly 15 billion years later, in 1817, by a chemist analyzing minerals excavated from an island cave off the coast of Sweden. Within the year, lithium had been isolated by English chemists William Thomas Brande and Sir Humphry Davy. Because it was not found free in nature – existing instead in igneous rocks and mineral springs – it was given the Greek name *lithos*, for stone.

Within 75 years of its discovery, lithium had been utilized to treat a variety of medical conditions, including periodic depression and mania. Its therapeutic uses in these disorders of mood is the primary focus of *Lithium in Neuropsychiatry: The Comprehensive Guide*. This excellent book gives an outstanding and comprehensive overview of the history of lithium's use in the treatment of affective illness, including early controversies and the increasingly sophisticated experimental paradigms developed to test both its efficacy and its safety. Leading clinical researchers give the evidence for lithium's effectiveness in acute mania, depression, mixed states and rapid cycling, as well as in prophylaxis. The use of lithium in special clinical populations, such as children, the elderly and pregnant women, is covered in detail, as is its singularly important role in the prevention of suicide. Lithium's demonstrated ability to decrease the mortality rate in high-risk patients makes the book's emphasis upon lithium – still the gold standard of care for bipolar disorder, despite disturbingly effective promotional campaigns on behalf of medications that have demonstrated much less efficacy – all the more important. The role of lithium in non-psychiatric illnesses such as leukopenia, viral infections and thyrotoxicosis is also discussed, as are the potential therapeutic implications of recent research into lithium-induced neurogenesis. The effects of lithium on kidney, cardiovascular, metabolic and thyroid functioning are covered at length, in addition to findings from more basic research fields such as pharmacokinetics, studies of cellular signal transduction pathways, brain imaging and immunology. The last section of the book deals with highly practical issues involved in clinical practice, namely, drug interactions, medication adherence and toxicity.

I cannot pretend to be entirely objective about lithium. I have taken it, except for an initial period of intermittent, and quite damaging non-compliance, for the better part of 30 years. I owe my life to lithium, as do many hundreds of thousands of patients with manic-depressive illness. I also owe my life to the research done by several of those who contributed to this book. Lithium is not an easy drug, but neither are mania and depression easy illnesses to have, or to treat. This book gives to lithium the seriousness and importance it deserves.

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Preface

Lithium in Neuropsychiatry offers a comprehensive outline of the many uses of lithium in neuropsychiatric disorders as well as indications for its use in internal medicine. We intended it primarily for use by clinicians – physicians and other health-care workers who use lithium to treat patients suffering from these disorders. Thus, it addresses various aspects of effective and safe use of lithium in clinical practice. But, because the book also provides an up-to-date description of basic neuroscience relevant for the use of lithium and of the variety of lithium's effects in the brain and human body, it will also serve interested researchers. The contributors to this book are all experts in their fields and internationally recognized for their significant contributions to lithium research.

Lithium was discovered almost 200 years ago and has been used in medicine in one form or another for almost 150 years. Since its introduction into psychiatry in 1949, many new aspects of its use in psychiatry and the neurosciences have been discovered in basic and clinical research.

Lithium is intriguing for several reasons. It is a simple element easily found in the periodic table, yet it has demonstrated a unique, striking efficacy in many patients with bipolar and unipolar mood disorders. Although its value has now been established for several decades, its clinical use varies markedly among different countries. Its value as a suicide-preventing agent is being increasingly recognized and has spurred new interest in lithium's use. The ability of lithium to significantly reduce suicidal risk distinguishes it from other mood-stabilizing agents that are available today. Furthermore, basic research has recently revealed that lithium may possess demonstrable neuroprotective properties. These new data suggest that lithium may become useful in the prevention and treatment of dementia and other neurodegenerative disorders.

We are very grateful to the authors, who with their contributions to this book have provided clinicians and patients with a rich source of knowledge and experience. We would also like to thank Catherine Aubel, Arlene Fox and Anke Schlicht for their general and editorial assistance.

THE INTERNATIONAL GROUP FOR THE STUDY OF LITHIUM-TREATED PATIENTS (IGSLI)

Over the past 17 years IGSLI has worked in, and significantly contributed to, the core areas of lithium research. This book was therefore written in close collaboration with IGSLI. The group was founded in 1988 by Mogens Schou (Risskov/Aarhus, Denmark), Bruno Müller-Oerlinghausen (Berlin, Germany) and Paul Grof (Ottawa, Canada). The main goal of this

cooperation has been to conduct systematic work on those important problems of lithium treatment that can be resolved only in an international joint effort. Unified designs have been created and scientific data from the IGSLI member centers linked for the purpose of shared analyses. This approach allowed us to work with large numbers of prospectively followed patients – something that could be accomplished only within a multicenter approach. Centers in Vienna, Prague, Zürich and Dresden quickly joined the group. All these centers had longstanding experience in the long-term lithium treatment of patients with mood disorders. Overall, the research is based on shared, standardized, computer-based documentation of the diagnosis, family history, course of illness before and during treatment, and on modalities of treatment that are comparable. The group meets regularly at research conferences to plan and discuss joint projects and to prepare publications. In 2002, the group converted to a registered association and launched its own homepage (www.igsli.org).

The most recent 19th IGSLI meeting took place in Poznan, Poland, in September 2005. At this gathering Mogens Schou presented a new project testing the efficacy of lithium in unipolar patients with unrecognized bipolar propensity ('hidden bipolars'). He passed away 3 days after this meeting, a few weeks short of his 87th anniversary. The picture of him on the dedication page was taken just before the IGSLI meeting in September 2005.

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Part A

INTRODUCTION AND HISTORY

1 Lithium: a fascinating element in neuropsychiatry

Philip H Cogen, Peter C Whybrow

'Everything Old is New Again'

What accounts for the fascination with lithium in neuropsychiatry? The role of the guinea pig in its serendipitous discovery as an antimanic agent, the subsequent establishment of lithium as the 'gold standard' of treatment in bipolar disorder in humans and the protean neuroendocrine manifestations of treatment are well supported by the breadth of material in this monograph. Perhaps more than any of these, however, it is the fact that a naturally occurring element rather than an engineered biopharmaceutical remains the first-line treatment for patients with bipolar disorder. This is truly remarkable in this age of 'designer drugs'.

Indeed, that lithium is derived from a natural source and continues to play a pivotal role in psychiatry many years after its discovery invites a comparison with digitalis, which for many decades was considered the most valuable drug for the treatment of cardiac failure[1]. As with digitalis, lithium therapy mandates determination of the appropriate balance between insufficient dosing with suboptimal efficacy and overdosing with considerable toxicity. Both medications are titrated by combining clinical status with blood level determinations. Thus, in many ways, although digitalis has now lost its primacy, that it once had for the heart, lithium now has it for the brain.

As with digitalis, first identified by William Withering in 1741 from the foxglove plant[1], attention has been given to treatments containing lithium since ancient times. Mineral springs, recognized as having therapeutic value as early as the 5th century, have subsequently been found to contain lithium[2]. Although in most instances the content of lithium in such therapeutic waters was later found to be meager, a fashion for mineral spas and bottled lithium water was initiated that has continued into modern times.

A brief review of the identification and subsequent medical use of lithium serves to highlight this fascinating history. The element now called lithium was first obtained from the mineral petalite that was discovered in 1800 by Jorge Bonifacio de Andrada e Silva, a Brazilian scientist and nobleman, on Uto, an island off the Swedish coast[2]. The initial chemical analysis of petalite by the Reverend Edward Clarke revealed that 1.75% of the sample was unaccounted for by previously identified elements[2]. In 1818 additional studies by Arfwedson, a Swede working in the laboratory of Berzelius, successfully isolated the new element, which he

named lithion as it came from a mineral sample[2] (Figure 1.1).

The name was later changed to lithium. As early as 1843 Alexander Ure proposed that lithium carbonate could be used to dissolve urinary calculi, owing to its affinity for uric acid[3]. Similarly, gout being known to be the result of an increase in uric acid, Alfred Garrod in 1859 proposed that lithium could be dissolved in water to treat gouty phalanges by topical application. It was around this time that a 'uric acid diathesis' was proposed as the root cause of certain mood disorders[4]. Professor A. Trousseau thus believed that 'folie' – specifically mania – was the result of excessive uric acid when 'gout retroceded to the head'[2].

In 1870 the pioneer neurosurgeon S. Weir Mitchell published a paper in the *American Journal of Medicine* proposing the use of lithium bromide as an antiepileptic medication[2]. In 1884 Alexander Haig proposed that the 'uric acid diathesis' accounted for gout, headache, digestive diseases and depression, and in 1888 supported his thesis by demonstrating that oral lithium citrate decreased uric acid excretion[5]. Haig suggested that this offered a new therapy for the various maladies then attributed to an excess of uric acid[5].

Figure 1.1 Lithium-containing lepidolite

Such an attempt to describe a unifying therapeutic concept for a myriad of maladies, including those of the brain, strongly parallels the history of digitalis. Following the initial use of preparations of digitalis designed to treat dropsy (edema), it was proposed that similar treatment might be useful for maladies as variable as epilepsy, hydrocephalus and even insanity[1]. In the late 1880s foxglove was widely used as a remedy for psychiatric disease, and the artist Vincent Van Gogh, who famously suffered with bipolar disorder, was treated with a preparation containing foxglove by Dr Gachet, his personal physician and friend[6]. Van Gogh immortalized Gachet in two well-known portraits in which the doctor is shown holding the foxglove plant as a representation of his 'melancholy nature'[6]. That Van Gogh was prescribed foxglove rather than lithium is especially ironic, given the medical history of the times. In 1889, as Van Gogh lay dying in Auvers from his self-inflicted wounds, he was only a few hundred miles from Munich, where Emil Kraepelin was busily developing the modern classification of manic-depressive illness, and contemporaneously the physician Karl Lange had begun to explore the use of lithium as a treatment for affective illness.

It was Karl Lange, indeed, who first showed the value of lithium in the treatment of depression. A Danish internist, he found that patients with depression and gout treated with lithium showed an improvement in their mood. He published these results in a monograph[2]. His brother Fritz Lange, also a physician, subsequently published a monograph in 1894 entitled *The Most Important Groups of Insanity* in which he listed lithium carbonate as an antidepressant[2].

The late 19th century also saw the rise of mineral spas as a fashionable health-promoting activity in both Europe and North America. As

early as 1824 Berzelius described the mineral springs in Bohemia as a source of lithium[2]. In concert with the times Willard Morse, a physician, proposed in 1887 that these mineral waters could be used to treat gout and rheumatism because of lithium's action on uric acid[2]. By 1889, however, analysis of the mineral springs showed that these waters actually contained very little lithium. For example, the commercially sold Londonderry Lithium Water had only 4 ppm of lithium[2]. Thus, to achieve a physiologic lithium effect, one would have to drink 150 000–200 000 gallons! In fact, water from the Potomoc River was shown to have a content of lithium five times that of these bottled waters (one wonders what the content is today). As the results of these analyses became better known, the uric acid hypothesis fell into disrepute and a waning of popularity for lithium ensued.

Half a century later, the first experimentally based use for lithium in medicine arose from the work of the Australian psychiatrist John Cade. In 1946 Cade obtained urine samples from patients with mania, depression and schizophrenia, and injected them intraperitoneally into guinea pigs, looking for the elusive substance causing these mental disorders. The urine from the manic patients killed the animals most easily, and Cade once again entertained the old idea that urea might have an important role in triggering this increased mortality. He added lithium to the preparation to render the urea more soluble. In the experiments that followed, Cade observed that the guinea pigs treated with this urea–lithium solution became docile and lethargic approximately 2 hours after injection for a period of approximately 1–2 hours. This behavioral change suggested to Cade that patients exhibiting manic symptoms might benefit from lithium treatment. On 3 September 1949, in his classic article in *The Medical Journal of Australia*, Cade reported the treatment of ten patients who suffered chronic mania; all received a beneficial effect from either 1200 mg of lithium citrate or 600 mg of lithium carbonate[7]. It is of interest that six patients with mania and schizophrenia were also treated, and each showed improvement in their mood with no change in their psychotic symptoms[7]. While the first patient treated later died from toxicity, the last patient died in 1980, some 31 years later, at age 76, of a myocardial infarction[2].

In the USA, the widespread use of lithium as a treatment for mania was hampered initially by an earlier effort to replace sodium with lithium salts in hypertension. Lithium had been shown to have a salty taste as early as 1936, and it was marketed as a salt substitute in 1948, only to be withdrawn in 1949 after several deaths from toxicity[2]. Physicians were therefore reluctant to recommend lithium treatment, and patients similarly were reluctant to try it. Outside the USA, however, after careful scrutiny, lithium was shown to be an effective agent in mania and in the prophylaxis of manic-depressive illness. Work by Ron Young in England demonstrated positive results in the treatment of mania, albeit with little effect on depression[2]. Safety further increased with the advent of the spectrophotometer, when lithium levels could be monitored to avoid toxicity. Samuel Gershon worked on lithium in Australia, and subsequently had a major role in bringing lithium treatment to the USA[8]. The widespread clinical use of lithium, however, is mostly associated with the pioneering work of the Danish physician Mogens Schou. (Remarkably, Dr Schou's father, also a physician, had previously written a negative critique of the Lange brothers' work on lithium and its effect on mood disorders[2].) Mogens Schou's first reported trial, in 1953, consisted of 35 manic patients treated with both lithium citrate and lithium carbonate. All these patients showed improvement in their manic states[9]. Flow spectrophotometry was used to obtain lithium levels, which were targeted to the 0.5–2.0 mmol/l range. There was one patient

death, due to a pontine infarction, which was attributed to vascular disease, although the patient had a serum lithium level of 4.5 mmol/l. In a subsequent study in 1955, of 48 patients, 81% showed improvement in their illness, and demonstrated lithium's potential as a prophylactic agent[9].

In subsequent years, lithium use was expanded, particularly in France and England. GP Hartigan showed a positive treatment effect of lithium for both mania and depression, suggested routine monitoring of serum lithium levels and published treatment guidelines in the *British Journal of Psychiatry* 1954[10]. Despite the growing evidence of the effect of lithium on patients with mood disorders, there remained skeptics. Perhaps most notable was Barry Blackwell, who wrote a paper entitled 'Prophylactic lithium – another therapeutic myth?'[11]. He suggested that prior studies had targeted inappropriate patients such as those who had received electroconvulsive therapy, and that follow-up was insufficient. Additional studies proved this to be untrue. In 1968, Nathan Kline, one of the main proponents of the use of lithium in the USA, wrote an opposing monograph entitled 'Lithium comes into its own'[2]. Baastrup and Schou, who in 1969 reported the outcome of a double-blinded study of the effect of lithium treatment on mood disorders showing clearly positive results, provided further evidence of efficacy[12]. However, in the USA, widespread acceptance of lithium came only after a Veterans Administration–National Institute of Mental Health (VA-NIMH) study run by Samuel Gershon showed positive results for lithium treatment of patients with acute bipolar disorder. In 1974 lithium was also shown to be effective in the prophylaxis of patients with bipolar disorder in another combined VA-NIMH study, and the Food and Drug Administration (FDA) released it for widespread use, some 21 years after its initial proposal as an effective antimanic agent[2].

Lithium has an effect on multiple systems, and metabolic balance is paramount in the successful use of lithium in the treatment of bipolar disorder. Common side-effects of lithium treatment include renal, endocrine, digestive and nervous system components[13]. Maintaining the balance between lithium use and thyroid function is particularly critical. As early as 1970 goiters were identified in up to 60% of patients treated with lithium[14], and subsequently both clinical and chemical hypothyroidism were reported[15]. The direct effect of lithium on the thyroid is multi-faceted: there is both a decreased uptake of iodine into the gland and possibly an increase in antithyroid antibodies[13]. Thyroid biopsy specimens from some patients treated with lithium assume the pathologic appearance of Hashimoto's thyroiditis[13]. This alteration of thyroid function by lithium use creates a paradoxical situation. As hypothyroidism is associated with an increase in the severity of bipolar disorder, lithium treatment thus both improves and potentially worsens the condition of patients with this illness, should the thyroid axis prove vulnerable to lithium's antithyroid action. In a similar fashion, the improvement in nervous system function brought on by the control of the bipolar diathesis contrasts with the side-effects including tremor, distractibility, disorientation, and poor memory and judgment. The occurrence of these effects rests in part on the variation in distribution of lithium in different bodily organs. Thus, a serum lithium level of 1.0 mmol/l (the goal for optimal treatment) in nuclear magnetic resonance spectroscopic studies has been shown to result in brain lithium levels of only 0.2–0.3 mmol/l in the occipital pole[16].

Recently, lithium's role in modulating nervous system function has expanded with studies revealing its neuroprotective properties, specifically in the retardation of viral infection and against degenerative illness including Alzheimer's disease. There is evidence that

lithium protects against *N*-methyl-d-aspartate receptor-mediated excitotoxic damage to rat cerebellar granule and cortical neurons in culture[17]. Such glutamate-mediated excitotoxicity has been linked to cellular damage in stroke, amyotrophic lateral sclerosis, and possibly neurodegerative diseases such as Alzheimer's dementia[17]. Pre-treatment with lithium has reduced quinolinic acid damage to striatal neurons in a model of cortical ischemia[17]. Lithium has also been shown to induce neurogenesis *in vivo* in rat hippocampal progenitor cells[18]. These observations further illustrate the myriad of functions attributed to this single element.

Hence, the story of lithium use in psychiatry is one of serendipity, international collaboration, miscommunication and finally vindication of a unique therapeutic role, now with established widespread use. This is not only a humanitarian triumph but also a remarkable economic achievement. It has been estimated that the use of lithium carbonate to treat bipolar disorder in the USA has reduced the costs of mental health care by 2.9 billion dollars over a 10-year period[19]. In combination with an additional estimate of savings of 1.3 billion dollars resulting from the return of patients to their functional productive lives, that results in cumulative savings of over 4 billion dollars[19]. Not a bad record for a simple salt!

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2 History of lithium treatment

Mogens Schou, Paul Grof

INTRODUCTION

The history of the introduction of lithium into psychiatry is intriguing. It offers insights both into the way in which new ideas originate and develop in medicine and into the social and historical forces that help to mold them and to promote or oppose their acceptance.

This cursory account of the history deals only with the main points and tells only part of the story. For more details the reader must turn to publications where the history has been outlined more fully[1–5].

The acceptance in the 1970s of lithium as an effective prophylactic agent prompted a sudden increase of interest in its past. Many fascinating links to its early use in medicine and psychiatry were uncovered. A checkered history emerged.

EARLY USES IN MEDICINE

Lithium salts were observed to dissolve urate deposits on cartilage in a test tube, and this gave rise to the assumption that they might remove gouty deposits *in vivo* as well. In 1859 Garrod[6] introduced lithium salts for the treatment of gout and urinary calculi. Lithium was thereafter given as a treatment of rheumatism, uremia, renal calculi and a large variety of related disorders, but without confirmation of effect in these diseases.

Several other uses were proposed, for example lithium as a stimulant, as a sedative, for the treatment of diabetes and infectious diseases, or as a caries-preventive additive to toothpaste. Lithium was also thought to be an active ingredient of spring waters used medicinally, even though they contained only minimal amounts. For decades lithium continued to be utilized for such varied purposes without scientific verification.

EARLY USES IN PSYCHIATRY

Nineteenth century physicians used lithium salts for what they called 'folia', 'mania', 'gouty mania' and 'mental derangement', but apparently their clinical descriptions had only transitory effects on lithium usage. In 1886 the Danish

neurologist and physiologist Carl Lange published a monograph entitled 'On Periodical Depressions and their Pathogenesis'[7]. It was published in Danish and German, and it has lately been translated into English and supplemented with a biographical portrait of the author[8]. In this publication Lange gave the first report of his and his brother's use of a lithium-containing mixture for the prevention of recurrences of periodic depressions. Lithium was given in accordance with Lange's belief in 'the uric acid diathesis' – a chimera that nevertheless had an extraordinary resilience.

This hypothesis was eventually given up, and lithium treatment was abandoned. The evidence of its effect had been based on clinical impressions and not on systematic trials.

JOHN CADE'S CONTRIBUTION

In the late 1940s the Australian psychiatrist John Cade was searching for a treatment of 'psychotic excitement', i.e. manic-depressive illness. He suspected that a normal metabolite circulating in excess in the body was the cause of the illness. On the basis of a reasoning that is not easy to follow, Cade injected lithium urate intraperitoneally into guinea pigs and saw that they became calmer and less responsive to stimuli but without becoming drowsy.

He further found that lithium carbonate had the same effect on the guinea pigs. The lithium ion, not uric acid, must accordingly have been what produced an effect. The idea then dawned on Cade that lithium might be used in the treatment of agitated psychiatric patients.

Before Cade used lithium carbonate on his patients he tried it on himself for a few weeks. He observed no ill effects and embarked on a clinical trial in groups of psychiatric patients. The ten manic patients responded, their symptoms disappeared and the symptoms returned on discontinuation of lithium. This dramatic finding was reported in the September 1949 issue of *The Medical Journal of Australia*[9]. Cade later experimented with the therapeutic potential of elements resembling lithium such as rubidium, cesium and strontium, but, although some of his observations seemed promising, they were not followed up.

Unexpected obstacle: toxicity panic

An obstacle that delayed the introduction of lithium treatment in psychiatry was a panic that erupted in the late 1949s in the USA. Within that context the timing of Cade's discovery was inopportune. A solution of lithium chloride has a salty taste and was sprinkled on the almost tasteless low-salt diet of cardiac and hypertensive patients. When lithium was given in this uncontrolled way, it produced a number of intoxications, some of them lethal. Although Talbott[10] showed that lithium intoxication could be avoided by monitoring the serum lithium concentration, this unfortunate incident left many physicians leery of any medical use of lithium.

Confirmation of the antimanic effect

Cade's discovery should eventually lay the foundation of modern lithium therapy, but Cade did not extend his observations beyond the ten patients described in his paper. The torch was fortunately carried on, and his findings were soon supported by Noack and Trautner[11] and by clinical reports from France. Names such as Despinois, Reyss-Brion, Deschamps, Duc, Lafon, Passouant and Carrère could be mentioned. In these studies there were no control groups.

It was in 1952 that professor Erik Strömgren in Risskov, Denmark, drew the attention of Mogens Schou to the Australian reports, and Schou designed a protocol for a partly open and

partly double-blind trial, which he carried out in collaboration with Strömgren and two other clinicians. Serum lithium levels were monitored systematically throughout the trial. The study was published in 1954[12], and it confirmed Cade's clinical findings of a therapeutic effect of lithium in mania. During the following years observations similar to those from Risskov were made elsewhere in Denmark and in England, France and Australia. The vast majority of the patients improved when they were treated with lithium.

GROUNDWORK FOR PROPHYLAXIS

In the following decades lithium was used to treat manic episodes, but an effect on depressive episodes was also noted[13]. The possibility of a long-term, stabilizing treatment in bipolar and depressive disorder was nevertheless not explicitly considered, and the concept of any maintenance treatment emerged only against much opposition.

In 1956 Schou[14] had noted that a patient stopped having manic and depressive recurrences when he was given lithium also during the intervals between episodes. Some years later Hartigan in England[15] and Baastrup in Denmark[16], similarly observed that manic patients continued on lithium showed a marked reduction of the frequency of both manic and depressive recurrences. These parallel observations encouraged Baastrup and Schou to undertake a longitudinal study of patients with many recurrences. Baastrup selected and treated the patients in Glostrup, and Schou, working in Risskov some distance from Glostrup, collected and analyzed the data and wrote the final paper. The findings were published 1967[17] and showed that recurrences were significantly less frequent and severe during long-term lithium treatment than before such treatment, or they remitted fully.

Schou and Baastrup then joined forces with Angst and Grof and published their prospective observations of 250 lithium-treated patients. Their study led to the same result[18]. By the end of the 1960s there was a sizeable body of observations demonstrating lithium as a useful drug in both acute and long-term treatment of mood disorders. The potential importance of lithium in psychiatry finally dawned for the psychiatric profession.

OPPOSITION: THE THERAPEUTIC MYTH

While the data supporting a prophylactic effect of lithium were accumulating, so was criticism of the evidence. Psychiatrists who had never tried to treat patients with lithium were skeptical of such novelty.

Blackwell and Shepherd[19] felt that the evidence did not support the notion of a prophylactic effect. They claimed that some of the patients had had a 'fragmented' rather than a recurrent course of illness, that the follow-up period had been too short, that the statistical method chosen weighted the facts in favor of the hypothesis, and finally that the non-blind evaluation of recurrences was biased. In a subsequent letter to the editor, Lader[20] argued that patients selected for having had frequent episodes for some years must be expected to have fewer episodes during the following years. Baastrup and Schou refuted these criticisms[21,22].

Views about the evidence and about the prophylactic usefulness of lithium became sharply divided. Based on their own clinical observations many psychiatrists came out strongly in favor of prophylaxis, but there were several aspects to this controversy. The underlying difficulty was that a generally accepted

methodology of prophylactic trials had not been available before 1970, and it is in fact still being perfected[23]. Systematic research on the natural history and course of mood disorders was still at an early stage. The historical development of lithium treatment has served to illustrate the methodological and ethical issues involved in the testing and documentation of drug effects, particularly during long-term treatment.

IRREFUTABLE PROOF

The controversy created uncertainty among British and American psychiatrists, who hesitated to start prophylactic lithium treatment, and it became clear that more than verbal refutation was needed. What was required was new evidence entirely free of methodological weaknesses.

However, a painful ethical problem was involved, namely that of switching some patients from lithium to placebo in order to place them in a control group. Since Baastrup and Schou's data strongly indicated that lithium is effective against recurrent depressions, giving patients placebo might expose them to further suffering and perhaps suicide.

Schou therefore designed a trial protocol that took the special ethical problems into consideration. It was blind to the observers, but a non-blind outsider could transfer a patient to lithium if she or he relapsed during the trial, and he did not tell the blind observers whether that patient had been on lithium or on placebo. The trial accordingly remained double-blind.

A sequential analysis terminated the trial as soon as the difference between lithium- and placebo-treated patients had reached statistical significance ($p < 0.01$). In this way as few patients as possible were exposed as briefly as possible to placebo. The trial lasted less than 6 months[24], and the final analysis showed high significances, namely in the group of patients with depressive disorder ($p < 0.001$) and in the group with bipolar disorder ($p < 0.00001$).

The Danes had proved their point, and psychiatrists in other countries such as Ireland, England, Scotland and the USA thereafter validated the findings in a series of double-blind studies. It became clear that lithium does have a prophylactic effect against both manias and depressions, and that it acts in both bipolar and depressive disorder.

ACCEPTANCE AND WIDESPREAD USE OF LITHIUM

Now psychiatrists had an effective tool to stave off recurrences of manic-depressive illness in most patients. At long last a useful remedy had been found for a protracted, devastating and potentially fatal disease.

Psychiatrists in many countries gratefully accepted these important advances, but there were marked geographic differences. In Scandinavia the acceptance of prophylactic lithium was relatively rapid and with limited dissent. Lithium also continued to spread in Australia and in most of continental Europe, for example in Germany, Switzerland, Czechoslovakia, Italy and Greece. In Canada, Kingstone[25] published the first North American paper.

In England and the USA the spread of lithium treatment was more uneven. In the early days the introduction of lithium treatment in England was associated with the names of Rice, Maggs and Coppen. Particularly convincing and elegant was a double-blind lithium trial performed by Alec Coppen and his co-workers[26]. In the USA there was initially much enthusiasm and much opposition. Kline[27] and Gershon and Shopsin[28] played particularly important roles in the expansion of lithium treatment and the acceptance of lithium as a prophylactic drug. Lithium was also

increasingly used in Third World countries. It should have helped that it is inexpensive in comparison with other psychotropic drugs, but its use was hampered by the marked lack of psychiatric services.

In addition to manic-depressive illness the use of lithium expanded to other indications: schizoaffective conditions, cycloid psychoses, aggressive states, alcoholism, potentiation of antidepressants and several others. In some of these conditions lithium had an effect, in others not.

FURTHER PROBLEMS

Problems did not stop with criticism from the Maudsley hospital. In 1995 Moncrieff[29] claimed that a prophylactic effect of lithium had not been proved, but she mixed data of different kinds and from different eras, and careful analyses showed that lithium remains effective in those patients and those types of mood disorder for which it was proved to work in the first place.

Repeated challenges came particularly from those who evaluated the treatment in naturalistic studies, from a broadening of the diagnostic criteria for bipolar disorder, and from concern about side-effects.

The efficacy of treatment is always less in naturalistic studies than the efficacy in research studies. Naturalistic studies involve a broader patient selection and may be conducted without sufficient attention being paid to compliance and monitoring.

Broadening of diagnostic criteria beyond those that originally constituted indications for prophylactic lithium treatment[30,31] led to introduction of competing drugs from the pharmaceutical industry. Lithium is produced from the mineral spodumene in North Carolina or extracted from brine pumped up from a salt desert in Chile. As a product found in nature it cannot be patented and is therefore relatively inexpensive. While this could be seen as an advantage, it became a problem when lithium had to compete with manufactured, patented medications after 1990. Probably the best example of this paradox was the case of advertising divalproex. Without solid evidence of a prophylactic effect, divalproex became the most dispensed drug for the treatment of bipolar patients in the USA. This was also the case in Canada, but is no longer.

Side-effects of long-term treatment led, at times, to warnings against lithium. In 1977 the observation of morphological changes in the kidneys of lithium-treated patients generated serious concern among psychiatrists. Many asked themselves whether the patients' mental health was bought at the expense of their kidney function, and whether patients given lithium treatment would eventually develop uremia and require dialysis or kidney transplant. The number of patients who started lithium treatment dropped drastically, ongoing treatments were interrupted, patients had recurrences and suicides are known to have occurred. Some patients objected violently to being deprived of the treatment that had changed their lives, but protests were overruled, and the patients were left in a miserable state[32]. Chapter 21 deals in detail with lithium and the kidneys. As with any long-term treatment, our profession is only gradually learning to assess the degree of such adverse effects and to balance pros and cons of prophylactic lithium treatment for each patient.

IS THERE A RENAISSANCE OF LITHIUM TREATMENT?

Despite overwhelming evidence of the efficacy of prophylactic lithium, continuing debates are likely to occur and are perhaps unavoidable between opponents who incorrectly believe that they are discussing the same issue. The correct

evaluation of the outcome of stabilizing treatment in recurrent mood disorders is much more challenging than one would assume. Capricious course, fluctuating compliance, differently responding subtypes of bipolar disorder and in some cases only gradual improvement all make it difficult to evaluate the relationship between medication and a change in the course of illness in any individual patient.

However, there has recently been a trend to return to evidence-based medicine; interest in and use of lithium have revived. We owe this change to the demonstration of lithium's unique antisuicidal properties in affective disorders[33], to laboratory indications of a neuroprotective action of lithium[34] and to its special value as a research tool in neurobiology.

It has also been important that Canadian observations showed different indications for prophylactic treatment with lithium and for long-term treatment with competing drugs[35,36]. In patients with typical bipolar disorder, those with fully remitting, episodic bipolar disorder, lithium is clearly the best prophylactic agent. In patients with atypical bipolar disorder such as 'bipolar spectrum disorder' many patients with mood-incongruent symptoms and co-morbidity are included. Lithium may be of partial help, but then one can see rebound and low or unstable effects. In such patients anticonvulsant drugs and atypical neuroleptics are better.

IMPACT OF LITHIUM TREATMENT ON PSYCHIATRY

Until 1967 no medication had seemed capable of averting recurrences of bipolar disorder. The introduction of prophylactic treatment with lithium changed things radically. Lithium probably provides the most interesting and cogent example of the effect drugs have had upon the practice and research in psychiatry.

In practice it has primarily been lithium's ability to prevent recurrences that changed treatment fashions. In research the introduction of lithium has been a major stimulus for neurobiology, demonstrating that a simple element can produce major neurobiological changes. Lithium became the focus of attention of psychiatrists, psychologists, pharmacologists, biochemists, geneticists and many others. It was probably the advent of lithium treatment that made psychiatric research truly interdisciplinary. Research on all aspects of the affective disorders has been greatly stimulated by demonstration of the efficacy of lithium treatment. Lithium may well become one of the clues to our understanding of mood disorders.

In academic psychiatry the acceptance of lithium treatment led to the important recognition that mood disorders are much more common than was previously presumed. The existing classification systems had to be reconsidered. As the past four decades have shown, prophylactic lithium treatment has made a significant contribution to modern psychiatry, both because of its specific use in alleviating recurrent affective disorders and because of its stimulation of psychiatric research and conceptual thinking.

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3 The lithium story: a journey from obscurity to popular use in North America

Samuel Gershon, Chad Daversa

INTRODUCTION

Lithium entered into significant therapeutic usage in the USA in the late 1940s. Lithium chloride became a popular salt substitute for patients on sodium-free diets. It was being taken by patients with heart and kidney disease, and some fatalities and serious poisonings resulted[1]. These events and the history of lithium in 'therapeutic' spa waters for the treatment of a multitude of disorders would not appear to be auspicious for its re-entry into modern therapeutics.

In this chapter we present a historical travelog of some dramatic medical events leading to the therapeutic investigation of lithium in North America circa 1960. This episode began in a remote location in times distant from those of our new century. These clinical events occurred in Australia, which at that time was geographically and scientifically distant from the main stage of activities in this field. The time was also different in many regards, as my* colleague, Dr Mark Bauer, has recently referred to this aspect of scientific communication as a Third Force for the New Millennium – our current e-savvy culture and electronic discourse having a tremendous impact on every aspect of our research communications. In order to present the story of lithium's re-entry into the USA, I propose to set the picture in the frame of my own experiences and work with it, in Australia prior to my first visit to the USA in 1959.

EARLY INVESTIGATIONS AND BACKGROUND

The setting was Melbourne, Australia: a remote and isolated part of the world. It was here that John Cade published his finding of the dramatic efficacy of lithium in an open trial in 10 hospitalized manic patients in 1949[2]. Cade was not a well-known scientific figure and did not fol-

*All first person references in this text refer to the first author, Samuel Gershon.

low up with any further clinical studies on lithium at all; nevertheless, this report suggested a remarkable effectiveness in that clear and marked improvement occurred in every one of the cases studied. Notably, the prior scientific work with lithium in animals did not really establish the underpinnings for this clinical report and also could hardly establish an appropriate clinically effective dose. It is also interesting to note that Cade's report appeared in *The Medical Journal of Australia*, a journal not at everybody's fingertips in 1949. Thus, it was these uncontrolled observations by an astute clinician on just ten manic patients that produced the platform for the launch of this new era.

The same year that Cade published his report, physicians in the USA learned mainly that lithium was a toxic and lethal substance. These cardiac patients were the ideal cases for lithium toxicity, as would be clearly demonstrated in later studies[3].

Cade also became concerned and insecure of its safe usage in his own cases reported in 1949. These observations on toxicity are reported in *The History of Lithium Therapy* by Neil Johnson[4], who had access to Cade's unpublished clinical notes. In fact, Cade's first case, WB, actually died of lithium toxicity. Toxicity also led to lithium discontinuation in some of his other cases and often treatment was started and then discontinued because of toxicity.

Toxicity presented other difficulties as no formal proposals for its treatment had been evaluated and presented. Thus, lithium toxicity had the potential for changing safe usage into a hazard and carried a potential risk of patient non-compliance. Toxicity and death continued to be reported in psychiatric patients in Australia and elsewhere, and the lithium poisonings in the USA created an inopportune backdrop for its reintroduction as a therapy in North America.

To comprehend how lithium survived the toxicity scare and to appreciate fully the impact of this story, one has to introduce the modern reader to the therapeutic void and nihilism that existed in psychiatry before 1950. With lithium, we suddenly had the possibility of successfully treating a major psychiatric disorder manic-depressive disease; initially, treatment centered on the manic episode. Furthermore, this claim was made for a non-sedative agent of very low cost; sedatives, electroconvulsive therapy and extensive use of restraints were the main alternatives in 1949–50. The therapeutic scope was expanded over the years to lay claim to prophylaxis for both the manic and the depressive phases of the disorder. The era of psychopharmacology had now begun, and the landscape of psychiatry slowly evolved into the profession that it is today. This was a very different picture from our current expectation that, if the patient has psychological distress, there is a medication that is expected to address it. It was in this environment that my experience with lithium began.

AUSTRALIAN WORK

I graduated from the University of Sydney medical school in 1950 and then continued with a medical internship in 1951. During this year I had the opportunity of trying lithium with manic in-patients in a setting essentially free of concomitant medication. In 1952 I moved to Melbourne to start my psychiatric residency at the Royal Park Receiving Hospital where John Cade was the superintendent. During this period, our contacts were simply those of resident and senior staff member. My research interests and activities were all associated with my teachers, mentors and colleagues at the University of Melbourne. My main supports there were in the Departments of Physiology and Pharmacology under the chairmanship of Professor RD

Wright and F Shaw, respectively. The most important and valuable relationship at a personal and professional level was with Dr EM Trautner. These relationships and my formal association with these departments, as well as my subsequent appointment in the Department of Pharmacology, gave me the opportunity to start a number of research endeavors. Here I will mention only those related to lithium.

The publications on lithium in Australia at the time were few. In 1950, Ashburner[5] reported on two cases of toxicity and Roberts[6] on 19 clinical cases. Then, in 1951, in what 'was probably as influential as Cade's original report in promoting lithium therapy more widely'[7], Noack and Trautner presented the largest clinical experience with lithium in over 100 mixed psychiatric subjects in a paper entitled 'the lithium treatment of maniacal psychosis', which appeared in *The Medical Journal of Australia*. This paper made a case for a high success rate in manic patients with little benefit in other psychiatric diagnoses and raised the issue of a specificity of therapeutic activity for lithium[8]. Another Australian report came in 1954 from Glesinger[9], who was located in the remote region of Western Australia. I was able to meet all these people and their efforts were, in retrospect, remarkable. They took some very daring steps and none (with the exception of Trautner) had the safety net of lithium assays.

It was during my first year at the University of Melbourne that I had the good fortune to seek out Trautner. Together, we published several other papers on lithium. One paper that presented a number of interesting issues was entitled 'The excretion and retention of ingested lithium and its effect on the ionic balance of man' (1955). It raised the proposition of a differential pattern of retention and excretion of lithium ion in manic and non-manic subjects[10]. The data showed an increased retention of lithium in the manic patients during the manic phase and flushing out of more lithium in the urine when the mania resolved. These observations tended to point in the direction of pharmacological specificity for lithium in so-called 'typical' manic cases. This paper also presented the details of the use of the spectrophotometric assay of lithium.

Unfortunately, the spectrophotometer was not used for plasma monitoring in the Australian studies until Trautner's extensive work was carried out on it. Even after this technology became available, and despite the deaths experienced by Cade and reported by Roberts in 1950, some clinicians felt that careful clinical observation was an adequate safeguard. My comments in Johnson's book[4] were 'It was Dr Trautner who first used plasma lithium assays in his studies. Altogether, Dr Trautner's exceedingly important role in the early studies on lithium has sadly been completely neglected.' This was echoed by Professor R Douglas Wright, Trautner's departmental chairman, who stated 'I believe that his [Trautner's] part in the lithium story has been overshadowed'[4]. It was Professor Wright who enabled Trautner and me to set up the first spectrophotometer for lithium assays in a mental hospital in Victoria. Its use was still ignored by many clinicians. Trautner was considered by many psychiatrists in Melbourne as a biochemist, with interests limited to this domain. However, he definitely was not looking for the limelight. He was not one to press his views in public, so much so that he never made a public presentation at any scientific or psychiatric meetings. Still, I worked with him for over 10 years, and he was directly involved with our patients and followed their clinical progress throughout our entire relationship.

Over the course of these 10 years, our continued collaboration produced several other reports. Notable among these was a report that touched on the prophylactic potential of lithium in bipolar disorder entitled 'The treatment of shock-dependency by pharmacological agents'[11], though its title gives no clue to this aspect of the

issue. We also reported on the issues involved in lithium poisoning and presented a treatment plan for these cases[12]. In 1958 we attempted to address the issue of the teratology of lithium in a rat study[12]. That was my last lithium study in Australia, and the next was during my first stay in the USA in 1959–60[13].

In all, there were a total of eight papers published on lithium treatment worldwide in the first 5 years after Cade's publication in 1949. In the second 5 years there were a total of 19 clinical papers worldwide, including those of Schou and Gershon, and this number fell to 16 in the third 5 years. It is evident that during this 15-year period following the first report there was clearly no big bang. Thus, Cade's paper in 1949[2] produced only a tiny splash and a small ripple.

LITHIUM OUTSIDE AUSTRALIA

The first reports on the use of lithium in psychiatry, outside Australia, were purported to have been French publications in 1951 and 1952, after which sporadic reports appeared over the next 5 years, including a few other French articles, two Italian and two Czech articles and one English article[7]. The historical ties between Australia and Great Britain may account for the publication of the seminal reports coming out of Australia that would ultimately influence investigators such as David Rice, a British psychiatrist running his own study and whose work resulted in the first British report in 1956 on the antimanic effects of lithium[4].

Perhaps one of the most well-recognized figures to be influenced by the Australian reports was Mogens Schou, a Danish psychiatrist whose connection with the Australian work was via a fairly straight line. Schou's professor, Eric Strömgren, brought the Australian lithium work to Schou's attention. Further, it was specifically the paper by Noack and Trautner that first alerted Strömgren to lithium, which in turn led to a review of the Cade article. The Noack and Trautner article was much more detailed than that of Cade and was the more effective stimulus for Strömgren and Schou's lithium usage. Schou then engaged in a correspondence with Trautner on the use of serum lithium evaluations. Thus, Schou used routine electrolyte estimations in his studies and consequently handled toxicity very successfully.

Although the body of evidence supported the initial reports of lithium's efficacy, these early investigators experienced varying degrees of opposition to the use and claimed efficacy of lithium. Baastrup, a close colleague of Schou in Denmark, wrote to N Johnson of 'considerable opposition to lithium, not least from academics, although this opposition was not supported by criticism of our work'. Trautner wrote to Schou that 'we were experiencing similar problems in Australia'. However, in our case we had the support of the chairmen of the Departments of Physiology and Pharmacology at the University of Melbourne, without which we would not have been able to continue. Fortunately, we could continue to conduct studies and report our work primarily with the participation of the faculty at the University. Nevertheless, we were never asked to present our findings anywhere in Australia other than at the University of Melbourne.

SPREAD INTO NORTH AMERICA

While the first published report of an open study on lithium in 17 manic patients came from Edward Kingstone in Montreal in 1960[4], the significant body of data came to the USA principally from knowledge transmitted from Mogens Schou and myself. Dr Heinrich Waelsch, the Chief Biochemist at the New York State Psychiatric Institute, had worked directly with Mogens Schou and communicated his interest in 1958 to Ronald Fieve, then a resident under Waelsch[4].

When I first came to the USA in 1959, an opportunity afforded by a Research Award, the climate was quite different at the University of Michigan. I spent the year at the recently established Schizophrenia and Psychopharmacology Research Project at the University of Michigan, a group that welcomed innovative studies. With my colleague there, Arthur Yuwiler, our first study was undertaken in 1959 and published in 1960. Our report was the first published in a US journal. This paper made a case for a special therapeutic effect of lithium in 'typical' mania and a marked decrease in activity in more atypical cases[13]. A differential effect was demonstrated and later studied with my colleagues at New York University[14]. These electroencephalogram (EEG) findings demonstrated lithium toxicity with brain changes seen in the EEG, and this correlated with associated side-effects and elevated blood plasma levels[14]. Another study demonstrated a poor effect of lithium in a schizophrenic population and demonstrated a clear differential effect between chlorpromazine (CPZ) and lithium in schizophrenic patients[15].

Although many people were uninterested and some justifiably skeptical, during this year between 1959 and 1960, much interest was demonstrated around the country. During this year, Arthur and I also met on several occasions with the remarkable Jonathan Cole, who was then the head of the Psychopharmacology Research Branch at the National Institute of Mental Health (NIMH). Even though I was a most junior fellow, I had the opportunity to present our material at the NIMH, a presentation facilitated by Dr Seymour Kety, the head of the NIMH Research Program. The climate for this presentation was fundamentally receptive, and whatever criticism was presented was directed towards moving research forward and not impeding a resolution of the issues raised. Thus, a very valuable link was developed with the US community in psychopharmacology and an important link in the chain of transmission of information about lithium was afforded me. This transmission of information was rapid and resulted in the generation of many foci of contagion.

Nathan Kline was another powerful force in demanding attention to new ideas in psychiatry at this time, mainly because of his previous work with the introduction of reserpine and a monoamine oxidase inhibitor into psychiatry. He now took up the cause for studies with lithium and was responsible for helping create a responsive climate.

In 1963 I moved to the USA permanently and after a short but very active sojourn at the recently established Missouri Institute of Psychiatry in St Louis (here we had superb clinical and laboratory research facilities and with my colleagues carried out a number of studies on lithium), moved to New York University and there began an exceptionally productive period as head of the Neuropsychopharmacology Research Unit. Much of the work conducted at the New York University – Bellevue Hospital was translational, with colleagues involved in both the pre-clinical and clinical components of the project. A major contribution from this period was the significant work conducted with Baron Shopsin that explored the effect of synthesis inhibitors on the response of patients to antidepressant drugs. These studies led to the wide use of synthesis inhibitors in dissecting the role of serotonin in depression.

At this stage, it could be adduced that two pathways of transmission appear: one in the reports of Cade, Noack and Trautner transmitted to Mogens Schou via Strömgren and the other related to my contacts and travels in the USA. Both of these pathways were intersecting, and I came to know Mogens Schou very well after my stay in the USA. We maintained close contact on many occasions. The other set of contacts was with Gordon Johnson, another colleague from Australia, and Andrew Ho.

Both joined us at New York University and both contributed significantly to different aspects of work on lithium. Ho focused on animal studies of the anatomic distribution of lithium in the brain, as well as on studies of the effects of lithium on neurotransmitters.

MOUNTING EVIDENCE

In 1966, over 100 articles on the topic of lithium were published in a single year[16]. Savings related to direct costs such as lowered health-care costs and to indirect costs from increased productivity 'have led to the startling claim that about $4 billion was saved by lithium in the US economy in the decade 1969–79'[17]. Very limited information on lithium appeared until the 121st meeting of the American Psychiatric Association (APA) in New York in 1966, at which information on the use of lithium in the treatment of hypomania was presented. In this presentation by Jacobson he coined the term 'hypomanic alert'. Both this terminology and his application as an intervention strategy were ahead of the times and this early work contributed significantly to thinking about early intervention and the concept of prophylaxis.

Dr Joe Tupin and colleagues also presented a paper at this APA meeting on their experience in treating ten patients with mania. Tupin and his colleagues, Schlagenhauf and White, had earlier recommended a manic patient from Texas to Ronald Fieve, who successfully treated the patient with lithium and sent him back to Texas[4]. Tupin had been in touch with Ron Fieve and myself prior to this report and he was enthusiastic in trying the treatment and in collecting all the information he could get before going ahead. The patients in this trial had not responded well to previous intensive phenothiazine treatment, but all responded favorably to lithium with improvement noted by 4–5 days and always before the 10th day. Their clinical description is in fact the classic response pattern seen in typical manic cases. The following year Wharton and Fieve reported a good response for 19 patients treated with lithium.

FDA APPROVAL

After gaining wider acceptance in the scientific community, a well-documented flood of applications to conduct further research on the therapeutic effects of lithium carbonate began to arrive at the doorstep of the Food and Drug Administration (FDA), creating an administrative burden for the US regulatory agency[18]. However, pharmaceutical companies were loath to become involved with the marketing of a 'money-losing drug' and it quickly became apparent that some sort of intervention would be necessary to accommodate the demand, prompting the American College of Neuropsychopharmacology (ACNP) to file its own new drug application (NDA) with the FDA to bring the disowned product to market[18].

In fact, it would not be until 1970 that the FDA would approve the use of lithium[19]; however, this was limited to treatment of acute mania only. The therapeutic use of lithium in North America, and more specifically in the USA, was slow to catch on; this can be to a large degree attributed to the poisonings that occurred there, but it may also have been a result of the fact that lithium was not available for patent and that there was an initially cautious stance from both investigators and regulatory bodies in the USA. This delayed development clearly defines a phenomenal lag time between discovery and usage and acceptance in the USA. Even after this there was little widespread clinical usage and very little commercial interest in it.

The dissemination of information and usage was formalized in the USA in a report

commissioned by the National Institute of Mental Health (NIMH) on the status of lithium therapy, based on personal interviews and a review of work in both the USA and Europe in 1970[20]. All of these activities and contacts led me to publish the first textbook, entitled *Lithium: Its role in Psychiatric Research and Treatment* together with my colleague Baron Shopsin in 1973. It is our belief that this aided the distribution of information on lithium and supported the comfort of physicians in its more widespread usage.

VA–NIMH STUDY

Ultimately, in 1974 a decision to expand lithium's indication to cover prophylaxis was made by the FDA, although 'approval for unipolar recurrent depression was . . . still . . . withheld,[4]. This was due in no small measure to the Prien *et al*. Veterans Administration–NIMH Study.

Prior to the popular use of lithium, phenthiazines such as chlorpromazine were typically considered a staple in the psychiatrists' armamentarium; thus, it was not surprising that, after lithium was shown to be clearly efficacious for the treatment of mania, a large-scale, multicenter study comparing these two agents at 18 different sites was co-sponsored by the National Institute of Mental Health and the Veterans Administration, now known to posterity as the VA-NIMH study. I was fortunate to be associated with this study as a consultant. This study, which included 255 manic-depressive patients, would ultimately show chlorpromazine to be more effective than lithium in a group dubbed 'highly active'. The findings of this study also revealed that highly active patients responded more quickly to chlorpromazine than to lithium. This is inherent in lithium's rate of onset and it affected the outcome of these studies as well, resulting in early terminations in the lithium group because of behavioral overactivity. However, when viewed in the context of the existing body of data on lithium in manic patients, some were inclined to believe that the nature of the multicenter site opened the study up to criticism on the basis of diagnostic imprecision. As the study was open to patients presenting with schizoaffective disorder, it was hypothesized by the study's detractors that many in the 'highly active' group may have displayed symptoms that were more readily aligned with the atypical forms of the affective illness and would therefore predictably show a poorer response to lithium[7].

LITHIUM IN NORTH AMERICA TODAY

Although it is still considered first-line treatment for bipolar disorder in the USA today, the legacy of lithium is a mixed bag. With little interest from corporate entities, and newer, profitable drugs entering the research pipeline, it is likely that lithium's role in the landscape of pharmacotherapy for affective illness will continue to evolve. Pharmaceutical industry involvement at all levels of research, including sponsorship of drug trials run at major research universities, has raised the question of bias in study design and reporting, as well as in the publication of new drug research. Even regulatory agencies such as the FDA, once inclined to take a cautious stance on new drugs, have been accused of 'sleeping on the job'. As a result of this environment, many young clinicians now view lithium as outdated 'older generation' pharmacotherapy.

CONCLUSION

Lithium sparked a psychopharmacological revolution in psychiatry, or could be considered to

be the breeder core. It dramatically and clearly wrought much good, but, like all revolutions, also created adverse effects. These have involved a wide swathe of clinical, medical, social and economic issues, and we will have to attain a larger perspective to evaluate the total effects of these events. I enjoyed traveling this road of discovery and have been privileged to meet many fellow travelers on the way. The most rewarding aspect of the journey was the opportunity to have new colleagues join the caravan. This caravan has traveled a long and tortuous course but in the end has traversed the world and changed the face of psychiatry.

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4 Different views on the use of lithium across continents

Daniel Z Lieberman, Jaclyn Saggese, Frederick K Goodwin

Contents Introduction • History • Economics • Prescribing • Advantages

INTRODUCTION

Comprehensive management of bipolar disorder requires treatment of acute mania and depression, as well as the prevention of mania and depression during the maintenance phase. The most stringent definition of a mood stabilizer would require efficacy in all phases; however, these conditions are not easily met. A review undertaken by Bauer and Mitchner designed to evaluate how well specific agents met more or less stringent definitions of mood stabilizer concluded that only lithium, which has some degree of efficacy in all phases, is a true mood stabilizer based on the most restrictive definition[1]. Despite the fact that there is more evidence available on the use of lithium than any other drug in maintenance treatment of bipolar disorder[2], there has been a fairly marked shift away from the prescription of lithium in the USA compared to Europe and the rest of the world.

HISTORY

As discussed in Chapter 2, lithium's efficacy in the treatment of mania was first reported in Australia by Cade in 1949. Controlled trials carried out by Schou and colleagues in Denmark in the 1950s were the beginning of a broader recognition of lithium as an effective treatment for bipolar disorder. In the USA, however, there was more concern about the safety of lithium. Around the same time that Cade was observing therapeutic effects of lithium in Australia, physicians in the USA were reporting several deaths caused by unrestricted use of lithium as a salt substitute for cardiac patients, giving it a reputation as a dangerous and toxic substance. As a result of these experiences, lithium was virtually neglected in the USA until the early 1960s.

ECONOMICS

Another reason for the slow acceptance of lithium in the USA was economic. Drugs typically are introduced by pharmaceutical companies, which invest in the studies necessary for US Food and Drug Administration (FDA) approval. A pharmaceutical company receives a patent on a new drug (15 years of exclusivity at that time), which allows it to recoup its investment. Lithium salts, of course, could not be patented, and therefore lacked a pharmaceutical company as an advocate for FDA approval. It was not until 1970, when the National Institute of Mental Health and the Lithium Task Force of America (William Bunney, Irvin Cohen, Jonathan Cole, Ronald Fieve, Samuel Gershon, Robert Prien and Joseph Tupin) worked with Smith Kline and the FDA to facilitate the approval of lithium for the treatment of mania, that it became available to doctors and patients in the USA[3].

Although lithium subsequently became the first-line treatment for bipolar disorder in the USA, its use began declining relative to Europe and the rest of the world in the early to mid-1990s. A 5-year naturalistic study found that between 1989 and 1994 the portion of hospitalized patients receiving lithium monotherapy for bipolar disorder in the USA declined from 84% to 43%. During this same period the use of valproate (alone or in combination with lithium) increased from 0% to 38% of antimanic treatment regimens, while carbamazepine was decreasing from 24% to 18%[4]. More recently, Goodwin and his colleagues in two large research-oriented health maintenance organizations found that this trend continued after 1994[5]. Pharmacy data from a sample of 20 638 health plan members revealed that the distribution of first mood stabilizing drugs prescribed, based on the year of initial diagnosis, changed substantially over time. The ratio of initial filled prescriptions for lithium to that of divalproex shifted from 6:1 in 1994 to 1:2 in 2001, while there was little change in the use of carbamazepine (Figure 4.1).

PRESCRIBING

There are multiple factors that contribute to prescribing decisions made by physicians. Some, such as the inherent efficacy and safety of a medication, are the same regardless of where the physician practices. Other factors, however, are dependent on social, cultural, economic and political characteristics that vary across countries. These factors include the perceived efficacy of the agent, education and training, regulatory agency decisions, medical-legal environment and marketing activity. These different variables are described in more detail below.

In recent years, an increase in the number of lithium-resistant cases has been seen in clinical practice in the USA, and reported in the academic literature[6]. Kukopulos *et al.* reported that, among rapid cyclers, bipolar patients who had previously been exposed to an antidepressant did not respond as well to lithium[7]. When the serotonin-specific reuptake inhibitors were introduced, they were believed to be safe and easy to use, and antidepressant prescriptions increased dramatically. Now the majority of antidepressant prescriptions are written by primary care physicians who do not have the necessary expertise to distinguish bipolar depression from major depressive disorder. Increasing rates of substance abuse in the 1970s and the cocaine epidemic that started in the 1980s have also become factors in lithium refractoriness in the USA.

Long-term prescribing habits are established during medical education and specialty training, and since an increasing proportion of this comes from industry-supported educational programs, lithium is covered briefly at best. Another key component of clinical education

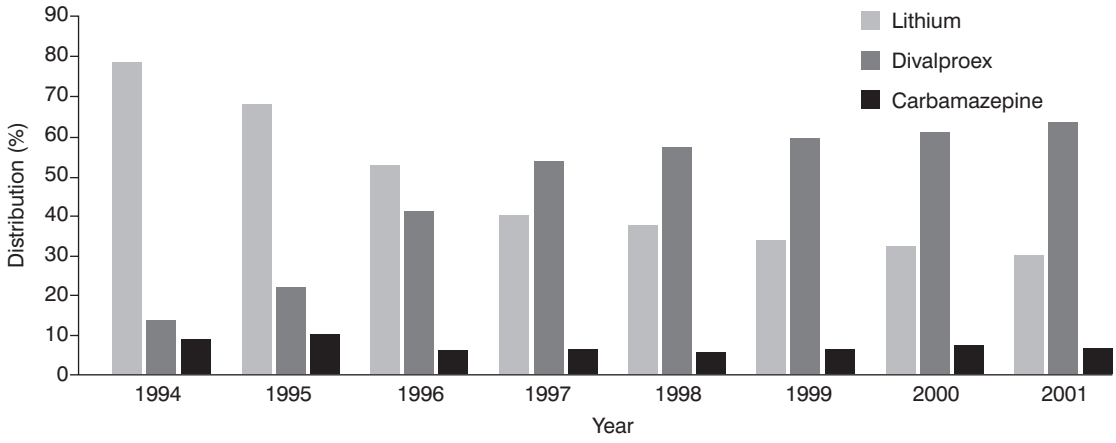

Figure 4.1 Distribution of initial mood stabilizer prescriptions according to year of initial bipolar disorder diagnosis

comes from individuals modeling themselves after mentors, teachers and supervisors. Thus new physicians who work with supervisors who have extensive experience with lithium will be more likely to develop their own expertise with this drug. This kind of education is all the more important for a generic drug like lithium, because it will never be adequately covered in the dominant industry-supported educational programs. However, if lithium use continues to diminish in the USA, it will gradually fade in this mentor-driven educational experience as psychiatrists trained since the early 1990s become tomorrow's mentors. Recommendations for training residents in the use of lithium include experience with large numbers of patients receiving lithium as monotherapy, and with long-term follow-up of at least 8–12 months[3]. Many US residencies no longer provide this type of training. Thus a vicious cycle is set in motion as lithium's increasing unfamiliarity feeds the misperception that it is too difficult to use, and has been replaced by newer agents.

The role of lithium in Europe has evolved in a way that has been very different from that in the USA. This is not to imply a monolithic approach to psychopharmacology in the European community. For example, a recent survey of psychotropic drug prescriptions given to patients with a variety of diagnoses in ten European countries found that patients in Spain were on the most drugs, and patients in Germany were on the fewest. Larger doses of antipsychotic medications were seen in Denmark, England, Germany and Spain, while higher doses of benzodiazepines were seen in Denmark, England, The Netherlands and Norway[8].

In spite of these differences, there exists a remarkable consensus on the use of lithium as the first-line agent in the treatment of bipolar disorder. A survey of 1041 patients with bipolar disorder in 11 European countries gathered information on demographics, history of illness and type of treatment received. The authors reported that the problems encountered by bipolar patients were similar throughout the European countries studied, regardless of cultural differences[9]. The most frequently prescribed medication for these bipolar patients was lithium in 9 of 11 countries consisting of Austria, France, Holland, Hungary, Italy,

Portugal, Spain, Sweden and the UK. In Finland typical neuroleptics were reported most frequently, and lithium was second. In Russia typical neuroleptics were also the most frequent, followed by amitriptyline, and then lithium[10].

Specialized lithium clinics are more common in Europe than in the USA, and they encourage lithium use in a number of different ways. The treatment environment in a lithium clinic is an intermediate step between the highly controlled setting of a clinical trial and routine clinical practice in which lithium treatment may not always be properly implemented. Because they are staffed by experienced clinicians who are sophisticated in the use of lithium, treatment is handled more skillfully, and better outcomes are possible. Furthermore, educational opportunities exist in these settings that would be hard to duplicate elsewhere.

Licht and colleagues described the treatment of the first 148 patients seen at the Aarhus University Psychiatric Hospital lithium clinic[11]. Although some patients in this clinic were treated with carbamazepine, oxcarbazepine, or valproate, 89% received lithium monotherapy. The authors stated that this was not unique to the lithium clinic environment, but reflective of the fact that lithium is the drug of first choice for maintenance treatment in Denmark[12]. The mean serum lithium level of patients in this study was 0.63 mEq/l. This level is lower than is typically seen in the USA. A consensus panel of US experts in bipolar disorder recommended a range of 0.7–1.2 mEq/l for acute mania, and 0.6–1.1 mEq/l for maintenance treatment[13]. Because many of lithium's adverse effects are related to the serum level, the common belief in the USA that lithium is associated with more severe side-effects than other mood stabilizers may be influenced by the use of higher doses.

Specialists who work in lithium clinics check levels more frequently, and are more likely to avoid levels that are too high. A lithium clinic in Somerset, UK, compared elevated lithium levels among their patients to two other groups: patients treated as psychiatric hospital outpatients, and patients treated by general practitioners (GPs)[14]. During the 3-month investigation period 1.2% of lithium clinic attendees had serum levels above 1.0 mEq/l, compared to 6.0% of the hospital outpatients, and 13.2% of the patients seen by a GP. Additionally, the mean serum lithium level was significantly lower in lithium clinic attendees (0.58 mEq/l) compared to psychiatric outpatients (0.67 mEq/l) and GP patients (0.69 mEq/l).

A hostile legal climate characterized by widespread medical malpractice litigation and increasing costs of malpractice insurance can influence prescribing patterns by forcing doctors to practice defensive medicine. The costs of medical malpractice premiums have risen rapidly in Europe, but even more in the USA. In the UK, for example, premiums have risen by 8% per year over the past 3 years, while in the USA premium increases have been approximately 30% per year[15]. An untoward fear of litigation can lead a physician to focus on the risks of a medication, while neglecting the benefits. The perception of lithium as a drug with greater risks than other mood stabilizers is a significant liability in this environment

Differing regulatory climates affect the way medications are used. Regulatory agencies grant permission for medications to be labeled for specific indications, and may require particular safety issues to be highlighted. In the USA, there are eight drugs that have been approved for the treatment of bipolar mania (lithium, aripiprazole, carbamazepine, olanzapine, quetiapine, risperidone, valproate and ziprasidone), and four drugs approved for maintenance (lithium, lamotrigine, olanzapine and aripiprazole, the last based on 6-month data). In other countries, there are fewer competitors that have regulatory approval. Although medications are routinely prescribed 'off label', regulatory approval confers important benefits. Relevant to

the medical-legal issue discussed above, off label use of a medication carries greater malpractice risk in the case of a poor outcome. Third-party payers may deny reimbursement for medications when they are prescribed off label, and pharmaceutical companies can legally market a drug for a specific indication only if that indication has received formal approval.

Marketing efforts on behalf of a drug are directly related to its potential profitability. Unlike alternative mood stabilizers, lithium cannot be patented, and therefore generates a tiny amount of money compared to any of its 'competitors'. A part of the high earnings from a mood stabilizer that is proprietary is used to finance educational programs that increase physicians' confidence in using the medication, and consequently support sales of the product.

The disparity in profitability between lithium and patented medications is larger in the USA because of a lack of price controls on pharmaceuticals (which, incidentally, the authors believe are not desirable because they can discourage innovation). For example, a 500 mg tablet of divalproex generates 71% more revenue in the USA than in Canada (US dollars (USD) 2.00 vs. USD 1.17). By comparison, a 300-mg tablet of immediate release lithium sells for USD 0.19 in the USA and USD 0.12 in Canada. Olanzapine, another widely used mood stabilizer, costs 37% more for a 10-mg tablet in the USA compared to the UK, which represents a difference of USD 2.42 per pill for this medication (USD 9.00 vs. USD 6.58). As the top-selling drug of Eli Lilly & Co., sales of olanzapine reached USD 4.4 billion-a-year in 2005, and accounted for one-third of Lilly's total earnings[16].

Many of the educational programs funded by pharmaceutical companies provide useful information that increases psychiatrists' knowledge base, and familiarizes them with new developments in the field. One drawback, however, is that most presentations focus almost exclusively on the drug being promoted. In the USA this exclusive focus is ironically due to restrictions placed on pharmaceutical companies by the FDA. The FDA prohibits speakers at promotional programs from providing comparison data or other information about alternative pharmacologic agents.

In addition to promotional programs, pharmaceutical companies also sponsor a large number of continuing medical educational (CME) courses via unrestricted educational grants. CME speakers are free to present any material that they feel is appropriate, and there is an expectation that the programs be fair and balanced by including information on all relevant compounds. Even in these settings, however, the use of lithium is rarely the focus. Instead, there is generally an emphasis on new developments in the field related to research on recently introduced drugs. The net effect of these various industry-supported programs is that substantial resources are available to teach physicians about brand name drugs, while very little is available for programs on lithium.

Direct to consumer advertising (DTCA) of prescription drugs is currently allowed in only two countries: the USA and New Zealand. DTCA (which includes increasing use of the Web for this purpose) can help increase public awareness of health problems, and when certain illnesses, such as depression and bipolar disorder, are poorly recognized and undertreated, DTCA can help encourage a useful dialog between a doctor and a patient. In other circumstances, however, DTCA can lead to pressure on doctors to prescribe a drug that they do not believe is indicated, or is not the best choice for a patient's needs. In the USA all of the currently approved mood stabilizers, except lithium, have active DTCA campaigns.

Fewer data are available regarding the use of lithium outside the USA and Europe. In Japan lithium is identified as the first choice for the treatment of mania in a published algorithm for

the treatment of bipolar disorder[17], and general agreement with this recommendation is seen among practicing psychiatrists. A survey of 298 Japanese psychiatrists found a broad consensus for the use of lithium as the first-line treatment of mania, though there was less agreement on the treatment of bipolar depression[18].

Mania was once believed to be rare in China compared to Western countries, and as a result lithium use was uncommon. A 1980 survey found that only about half of Chinese psychiatric hospitals were using lithium, and that prophylactic use of lithium was limited[19]. The author of this study speculated that the factors responsible for this limited use included the infrequency of the diagnosis of mania, fear of toxicity and lack of laboratory facilities for monitoring levels.

A similar survey in China, carried out 6 years later, found that significant gains had been made in the use of lithium[20]. The percentage of psychiatric hospitals using lithium had risen to 87%. Of those hospitals that continued to avoid lithium, many were located in rural areas. Typical neuroleptics were readily available in these areas, but patients had to travel hundreds of kilometers to obtain even small amounts of lithium, and the drug was more costly than neuroleptics.

None of the trends described above have yet shown clear signs of abating, and it is unlikely in the USA that the use of lithium will substantially increase relative to other mood stabilizers. The extent of this secular shift in prescribing practices is unfortunate, because for many patients the combination of a modest dose of lithium with an anticonvulsant is superior to the anticonvulsant alone, and for some patients, no alternative mood stabilizer is as effective as lithium monotherapy. Additionally, lithium is the only mood stabilizer shown to reduce the likelihood of suicide and this means that, on the whole, psychiatrists who do not know how to use it are exposing their patients and themselves to greater risk. For all of these reasons a psychiatrist who does not know how to use lithium should not be considered competent to treat bipolar patients, and training programs responsible for this deficiency should not be accredited.

ADVANTAGES

Finally, new research suggests that lithium has neuroprotective effects that can reverse long-term loss of neuronal viability that can occur in patients with bipolar disorder[21]. While the clinical significance of this neuroprotective effect has not yet been determined, a better understanding of the ways in which lithium exerts its therapeutic effects via interaction with intracellular signaling mechanisms may nevertheless spur the development of new mood-stabilizing compounds. Even the most fervent advocates of lithium express disappointment that no alternative has become available that exceeds the efficacy of lithium in a way that other mood stabilizers fail to achieve[22]. Restoring the benefits of lithium to patients in the USA may paradoxically require the development of a completely new medication that duplicates and goes beyond the specific therapeutic effects of this unique element that launched the psychopharmacology revolution, a revolution that not only transformed our field but has allowed millions of patients around the world to lead essentially normal lives.

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5 The position of lithium in international and national guidelines for the treatment of mood disorders

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INTRODUCTION

In an effort to improve quality and cost-effectiveness, many insurance companies and medical associations promote the implementation into everyday practice of prescribing guidelines for both general practitioners and specialists. Guidelines should assist the practitioner with routine decision-making and be based on the best available evidence. Well-known experts or professional associations usually write these guidelines. Recently, many guidelines have been issued by specialists' associations (e.g. the American Psychiatric Association (APA), Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN)), national institutions (e.g. the National Institute for Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ)) and international organizations (e.g. the World Federation of Societies of Biological Psychiatry (WFSBP)).

Fifty years ago, lithium was the only drug available for the treatment of bipolar disorder, and lithium was also widely used for episode prevention in unipolar depression. Both the introduction of many new pharmacological agents and the evolving understanding of the classification of mood disorders have transformed treatment, as is reflected in recent guidelines. In this chapter, the recommendations for the use of lithium for bipolar disorder

and unipolar depression in a sampling of well-known guidelines are compared. This chapter does not provide a systematic review of available international guidelines for mood disorders, nor does it consider how extensively treatment guidelines are implemented into routine practice.

REVIEW OF GUIDELINES

Table 5.1 contains recommendations from 11 major international and national guidelines that have been published since 2000 for both bipolar disorder and unipolar depression[1–17]. The guidelines are from Australia, New Zealand, Canada, England, Germany, Scotland, the USA and the WFSBP. Nine of these guidelines cover acute mania, ten cover acute bipolar depression, ten cover prophylaxis of bipolar disorder and seven cover unipolar depression.

LITHIUM AND ACUTE MANIA

As shown in Table 5.1, there is widespread agreement in the guidelines for the role of lithium in the treatment of acute mania. Lithium monotherapy has a primary role in the management of the 'classical' euphoric type of mania in all nine guidelines. Valproate (divalproate) and atypical antipsychotics are also noted as a treatment for euphoric mania in all nine guidelines, especially when the mania is severe. One benefit of valproate is that it can be used intravenously at a loading dose for a faster response[18]. There is also general agreement that lithium is less effective in mixed mania or rapid cycling. Eight guidelines provide a specific recommendation for mixed or dysphoric mania and all agree that lithium monotherapy is not a first-line treatment for dysphoric or mixed mania. Valproate, atypical antipsychotics and carbamazepine are considered first-line choices. A specific recommendation for mania with rapid cycling is included in five guidelines and all mention lithium in combination with valproate or an antipsychotic as either a first- or a second-line choice, while one includes lithium monotherapy as a first-line choice (APA)[4]. None of the guidelines give specific recommendations for the treatment of hypomania.

Many recommendations for the treatment of acute mania have been derived from studies of patients with classical euphoric mania or from older studies with less rigorous standards than are found in modern clinical trials. As the concept of bipolar disorder is evolving from categorical to dimensional, new studies are required to delineate the treatments most suited for the subtypes of mania and hypomania. Thus, this lack of clear evidence for the treatment of specific subtypes of bipolar disorder makes it difficult to make firm recommendations for the treatment of subtypes of mania, and is reflected in the diverging recommendations.

LITHIUM IN ACUTE BIPOLAR DEPRESSION

There is also widespread agreement among the guidelines regarding the role of lithium in acute bipolar depression. Of the ten guidelines, eight recommend lithium in combination with an antidepressant (usually specifying a selective serotonin reuptake inhibitor (SSRI)) and five also suggest lithium monotherapy as an alternative monotherapy. Eight guidelines also state that lamotrigine can be used instead of lithium. Most guidelines recommend tailoring the treatment for each patient, balancing the stronger antidepressant potential of the combination therapy (mood stabilizer plus antidepressant) with the higher risk of switching into mania. The APA was particularly cautious about the

use of antidepressants in bipolar depression, even in combination with a mood stabilizer, because of the lack of evidence of safety and efficacy at the time the guidelines were published[19]. A meta-analysis addressing this issue was available only after the APA guideline was published[20].

LITHIUM IN THE PROPHYLAXIS OF BIPOLAR DISORDER

All ten guidelines include lithium as a first-line choice of a prophylactic agent for bipolar disorder. There is a consensus that lithium is the drug with the best available evidence for efficacy in the prophylaxis of bipolar disorder and for the prevention of suicide. There is some variance, however, in the drugs recommended as alternatives to lithium, most of them including valproate, lamotrigine, carbamazepine or olanzapine (Table 5.1).

Although all guidelines include lithium as a first-line choice for the prophylaxis of bipolar disorder, it is expected that a patient survey would find considerable variability in the agents prescribed over the long term due to many factors, as described below.

Rationale for selection of the prophylactic agent

The guidelines provide different rationales for selection of the prophylactic agent. For example, the APA guidelines recommend continuing the drug that was successful in the acute manic period as the prophylactic agent[4]. In contrast, both the Danish[10] and German[11] guidelines propose that the preferred prophylactic agent for the patient determine the treatment selection for the acute manic episode.

Importance of the anti-suicide potential of the prophylactic agent

There is a different emphasis among the guidelines on the importance of the anti-suicidal potential of the prophylactic agent. With surprisingly homogeneous evidence available, lithium is undoubtedly the drug that has the greatest evidence supporting an anti-suicidal and thus mortality-reducing effect (see Chapter 15). According to a meta-analysis by Baldessarini *et al*.[21], one would need to treat only 125 patients with lithium over 1 year to save one patient per year. Yet, of the ten guidelines, only the two German guidelines recommend considering the suicidal risk when selecting an appropriate prophylactic treatment[11,15].

While the low frequency of suicidal events makes it methodologically difficult to use the reduction of suicidality as an outcome criterion in psychiatric drug trials, it is certainly an important factor to consider, especially when recommending treatments for mood disorders. To weight its epidemiological importance, one could consider that in Germany in the year 2000, suicide killed more people than did traffic accidents, drugs and violent acts together, and around 60% of these suicides were related to a depressive episode (Statistisches Bundesamt 2002, from reference 11). Long-term prophylactic treatment for bipolar disorder is certainly one of the areas in which these data should have the greatest impact.

Expanding the bipolar spectrum

With the expansion of the bipolar spectrum to include non-classical bipolar disorder, there is less evidence available as to which prophylactic agent is most efficacious. As more evidence is gathered in future studies, drugs other than lithium may be superior prophylactic agents for specific subtypes of bipolar disorder. It is particularly difficult to obtain a level of evidence that