

Archives

(Lithium Collection)

June 30, 2016

Discoveries & Their Trajectory

Psychopharmacological Specificity of the

Lithium Ion

By

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(text and slides)

I want to thank the John Curtin School of Medical Research for this prestigious award. I also want to thank them on behalf of my Australian teachers and mentors and also on behalf of my American colleagues and friends.

This presentation is about a history of the first major step in psychopharmacology. The time course of the development of lithium since its introduction in 1949 is concomitant with the span of my professional career...my role is thus of a historian and participant in the evolution of these events. Cade's report published in the *Medical Journal of Australia* did not engender much excitement, initially, outside Australia. This report, however, heralded a number of dramatic events. It preceded

the introduction of chlorpromazine into psychiatry and, in fact, fired the first salvo that initiated the modern era of psychopharmacology.

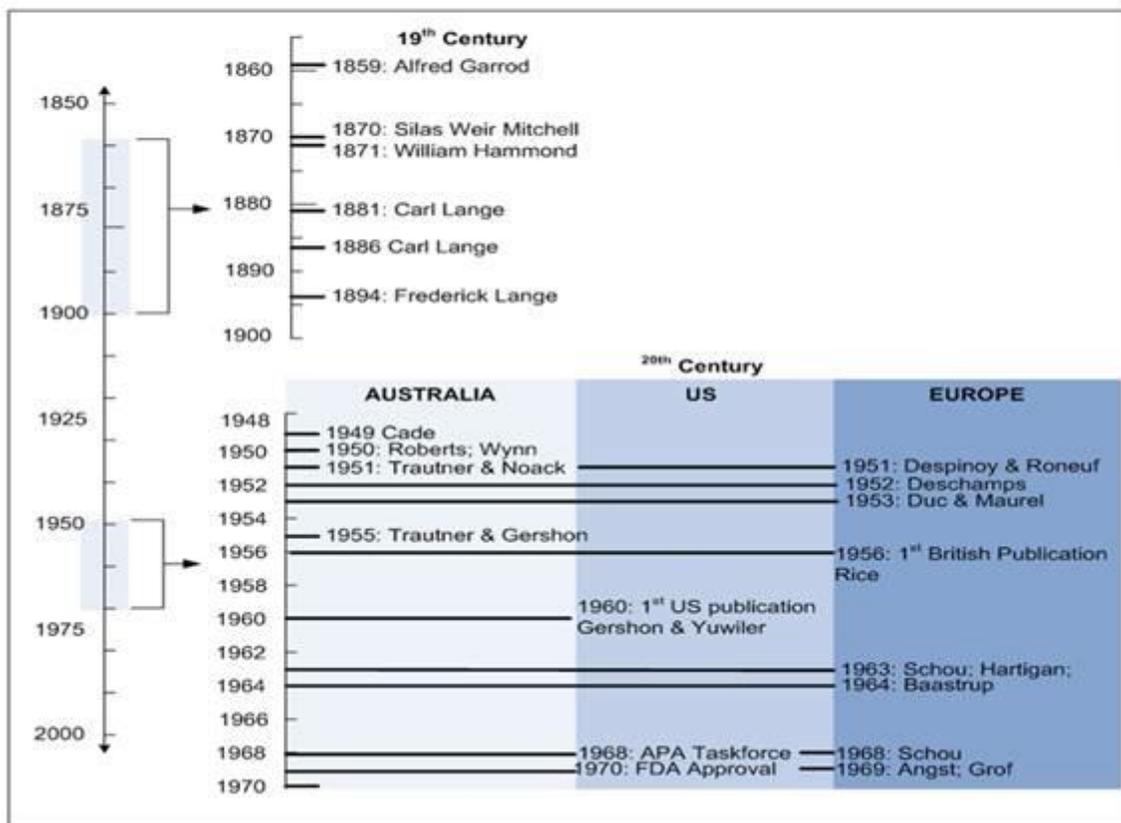
Here we have to try and answer the question – When is a “discovery” a discovery and what identifies this designation and what determines its future trajectory in science?

Serendipity is one of the many factors that may contribute to drug discovery. It played a major role in the discovery of prototypic drugs in psychiatry and lithium may well have traveled this road.

Timeline of key figures in relation to lithium

From: Malhi GS & Gershon S,
ANZJPsych, Dec 2009

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(1819-1907)

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Sir Alfred Baring Garrod

Here in our discussion of lithium we encounter a compound that has appeared in the medical literature at least since 1859 in a textbook by Alfred Garrod. He discovered uric acid in the blood of gouty patients. The use of lithium was prescribed on the basis that it would treat the “uric acid

diathesis” associated with gout. Also the notion that recurrent gout could cause both mania and melancholy was carried over into the nineteenth century. Garrod reported that “within the last two years I have made many trials of carbonate of Lithia as an “internal remedy” in cases of uric acid diathesis.”

Garrod claimed that “the Lithia salts can scarcely be said to

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have been employed therapeutically until recently (in 1858) by

myself.” Many lithium compounds were listed in Merck’s Index

from its first edition in 1889 until 1940. Then, in 1941, the

Extra Pharmacopoeia denounced them, stating that “their

introduction into medicine was due to misconception... there

is no rational foundation for the use of these salts”, (Johnson, 1984).

Thus this “discovery” phase really only became a background story among the vast array of claims and uses for lithium during this period.

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(1828 – 1900)



William Hammond 1871

However we move onto some more specific uses and claims for lithium in psychiatry by Hammond (1871) in New York and the Lange brothers in Denmark.

Hammond had a remarkable career, Surgeon General of the United States Army and later Professor of Diseases of the Mind and Nervous System.

William Hammond an alienist at the Bellevue Hospital in New York was possibly the first to have reported in 1871, the use of lithium as the bromide in the treatment of acute mania. According to his *Treatise on Diseases of the Nervous System (1871)*, translated into French and Italian, he describes the condition as acute mania with exaltation or acute mania with depression. Very much like the later classical descriptions of manic-depressive disorder. He also emphasized that “the doses should be large” namely as high as 45 mmol of lithium

or even more and repeated every 2 to 3 (a loading dose) hours and later reduced.

As Hammond did not mention the use of lithium in his later works 1882, 1883 and 1890 one could speculate as to whether he had ceased using lithium (bromide) due to toxicities from the high doses he administered.

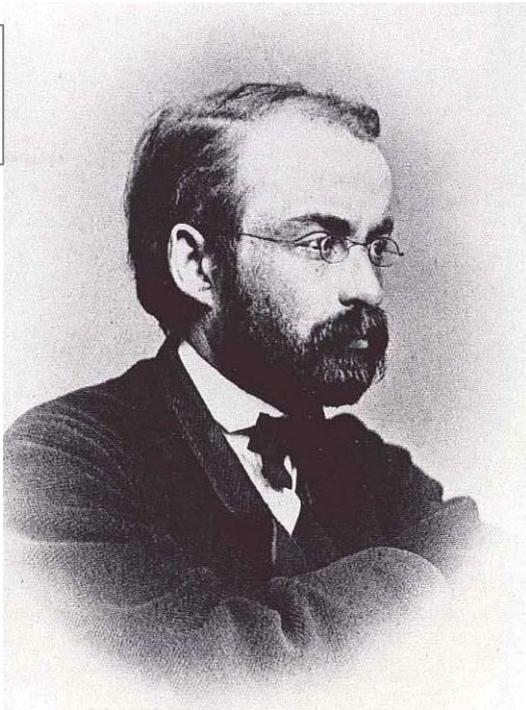
From his clinical descriptions it might appear that he was reporting some specificity for the treatment in manic states.

For whatever reasons, lithium departed the scene and was “forgotten”.

(1834 - 1900)

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(1842 - 1907)

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The Lange brothers, Carl and Fritz Lange

This Danish aspect of the story has been meticulously researched by Dr Johan Schioldann, M.D. who was born in Denmark and is now Emeritus Professor of Psychiatry at the University of Adelaide.

Carl Lange (1834-1900) a neurologist was famous for his contribution to the James-Lange Theory of Emotions published in 1885. Frederick (Fritz) Lange (1842-1907) his

brother was a psychiatrist. In 1886 Carl Lange delivered a paper to the Danish Medical Society "On periodical depressions and their pathogenesis". Both brothers treated periodical depression with lithium (carbonate). Their thinking was that these periodic depressions occurred within the constructs of the still prevalent "uric acid diathesis". Within their thinking was a belief that autointoxication was involved in the etiology of the illness.

In summary, the Lange brothers must be credited for a clinical description of periodic depression, which was recurrent, remitting and long lasting. Further that it may have a heritable or familial relationship and was of an organic

origin. They employed lithium carbonate and used dosages, which are comparable to those currently employed. They strongly maintained that the treatment should be continued beyond the current episode and fundamentally proposed its therapeutic value as maintenance treatment. Thus prophylactic pharmacotherapy was first envisaged in psychiatry.

However like many good stories, this story did not end well. The Lange's of course presented this work in Danish and thus it was open to a limited audience, but with some translations into German.

A number of Danish psychiatrists questioned the clinical concepts of periodic depression proposed by Lange. Kraepelin also joined this discussion with his own critical view of this disorder. Kraepelin presented these negative views of the Lange Theory of Depression in the 1904 and 1927 editions of his textbooks. Kraepelin was perhaps the most important psychiatrist in Europe at the time. Lastly, criticisms of the whole concept of the “uric acid diathesis” were offered at a meeting of the medical society in Copenhagen in 1911. Thus these events removed lithium therapy from the arena for about 50 years and it was again dismissed and “forgotten”.

From our current perspective, I think we can conclude that on their work on “periodic depressions they made a significant clinical contribution to later constructs of mood disorders. Their use of lithium as a treatment for “mood disorders” could be characterized as serendipitous as it was based on the false assumptions of the “uric acid diathesis” theories.

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(1912 – 1980)

John Cade 1949

John Cade was the superintendent of Royal Park receiving hospital in Melbourne when I came there as a first year resident in psychiatry in 1952.

Lithium was introduced in 1949 and one must understand the climate in psychiatry at that time. It may be difficult for many younger colleagues to even comprehend this picture which was much the same in the U.S. and Australia. My experience in Australia at 2 large chronic state facilities was about 500 patients with myself, one other resident and one superintendent. The treatment armamentarium was sedatives, ECT and insulin.

Cade's clinical paper in 1949 was preceded in 1947 by some animal studies in guinea pigs and his assumption, that manic-depressive illness is analogous to thyrotoxicosis and myxedema. He hypothesized that mania is a state of

intoxication by a normal product of the body in excess, and melancholia is a state of deficiency of the same substance.

To test his hypotheses he compared the effects of I.P. injected concentrated manic urine with urine from normal subjects in guinea pigs and found the former more toxic in killing the animals than the latter. There have been similar beliefs in more recent times, with adrenochrome by Hoffer et al, the Pink spot in Urine by Friedhoff, Taraxein by Heath in N. Orleans and Lafayette Clinic studies in schizophrenia and Akerfeld's ceruloplasmin in schizophrenia.

Cade decided to determine the toxicity enhancing effects of uric acid and used lithium urate as the most soluble of the

urates. To assess whether lithium salts alone have any effects, Cade injected large doses of 0.5% aqueous solution of lithium carbonate (poorly soluble) I.P. into guinea pigs and found that after a latent period the animals became extremely lethargic and unresponsive to stimuli for about 2 hours. It is possible that this lethargic state was due to lithium toxicity.

It may seem a long way from the lethargy of guinea pigs to the control of manic excitement. He then moved directly to a clinical trial of lithium in 10 manic, 6 schizophrenic and 5 depressed patients. He concluded that lithium was effective in all 10 manic patients and reduced over activity in the schizophrenics and no effect in the depressives. The dosages

employed were essentially like those used in current therapy. Thus once he undertook the clinical use his observations were remarkably accurate. One case subsequently died of lithium poisoning. Cade did not have available the monitoring of blood lithium levels.

It is interesting that Cade never again undertook any studies with lithium. He published a number of review articles but never pursued the many interesting possibilities his work opened up.

However, he did attempt to offer explanations of the therapeutic actions of lithium. His views appear to have been modified over time.

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In a 1970 paper Cade stated:

“It may seem a long way from lethargy in guinea pigs to the control of manic excitement, but as these investigations had commenced to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.”

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“Another proposal was that lithium “may well be an essential trace element” and leads to the speculation as to the

possible etiological significance of a deficiency in the body of lithium ions in the genesis of this disorder.”

However the conclusion must be that whatever unclarity existed in Cade’s preclinical work, once he observed the effects of treatment on patients, he was uncannily prescient.

He felt that it exhibited a remarkable specificity for the manic features, that it was not sedating to patients and that the treatment could be continued with a possible prophylactic benefit.

This clinical report by Cade heralded the Third Revolution in Psychiatry – Psychopharmacology. Following the previous era’s initiated by Pinel and then Freud with the

enormous impact of psychoanalysis. Psychoanalysis impacted all aspects of society as well as being dominant in most major medical centers.

Again there was an interruption to any widespread replication to these findings because lithium-induced fatalities were reported in Australia, e.g. Roberts, Ashburner and others including one case of Cade's. Furthermore, according to colleagues, Cawte and others, Cade was so concerned about the possibility of serious lithium poisoning that he discontinued lithium therapy. This was compounded by the reports in the USA of lithium's potential fatal toxicity reported from the use of lithium salt-substitutes for sodium chloride in

hypertension. In February 1949, the F.D.A. took urgent action and instituted a recall of all lithium containing salt substitutes from the market and this ban remained in place until 1970.

Again, if I may, I would like to digress on this issue of lithium toxicity. It would seem surprising that with the multitude of reports in the old literature on lithium, that the FDA approved lithium chloride as a salt substitute in the first place. Its usage in these cardiac cases was the group at perhaps the highest potential risk. So there was a pall over the future use of lithium in psychiatry altogether.

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To address this issue my colleagues at the University of

Melbourne led by Dr E.M. Trautner with Drs D. Coats, V.

Wynn and Charles Noack carried out a number of studies to understand the problems presented and develop treatments and safeguards. These studies made it possible to resuscitate lithium studies and offer a safe way of monitoring long-term maintenance therapy.

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DR E.M. Trautner 1951

Department of Physiology at

University of Melbourne

Chair Professor R.D. Wright

I really need to introduce Trautner into this historiography as well as the name of the chair RD Wright.

Trautner et al studied Cade's findings in close detail including the deaths that had occurred since Cade's paper. Then they studied 100 psychiatric inpatients with a variety of diagnoses.

The important aspect of the study was their introduction of the assessment of blood lithium levels in all their patients. This was done with the assistance of the recent development of

flame spectrophotometric assays by Dr V. Wynn in Physiology. Noack and Trautner published their paper in 1951 in the *Medical Journal of Australia*, “Lithium Treatment of Maniacal Psychosis”.

Dr Trautner was my mentor and friend for the whole period I worked in Australia. We went on to publish a paper with Coats on “The Treatment of Lithium Toxicity” and with others on animal teratology. A study of “The Differential Retention and Excretion of the Lithium Ion”, presented some interesting aspects of the handling of the lithium ion in the manic phase compared with the return to euthymia. – cf Hammond – reduce dose. – Lange’s

Noack and Trautner's 1951 paper did much to stem the flight from interest in exploring lithium in psychiatry and they confirmed Cade's therapeutic findings. Importantly, these authors did not encounter any serious lithium intoxication cases and concluded that "The very beneficial effect of the drug in cases of mania did not justify the abandonment of lithium treatments." Thus the work of this group established safe procedures for lithium use and noted it had a narrow therapeutic safety range and suggested the value of a "therapeutic window" and routine blood assays. This paper, as was Cade's, was among the ten most-cited articles of the *Medical Journal of Australia*. Also, this safety monitoring was

adopted by Schou and in other subsequent studies in the literature. Schou wrote to Trautner in 1974 saying that “it is my firm conviction that the studies you contributed concerning lithium toxicity and the monitoring of lithium treatment through serum lithium determinations were of primary importance for the development of this treatment into a safe and efficient procedure”.

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Our 1955 paper on the differential retention and excretion on the ionic balance in normal and manic patients offered suggestion of lithium specificity with a retention of lithium in the manic phase and increased elimination after mania broke. This report also demonstrated a relationship between plasma

lithium level and toxicity and the construct of a therapeutic window. In a 1956 paper, we offered the suggestion of a prophylactic effect on recurrent manic episodes.

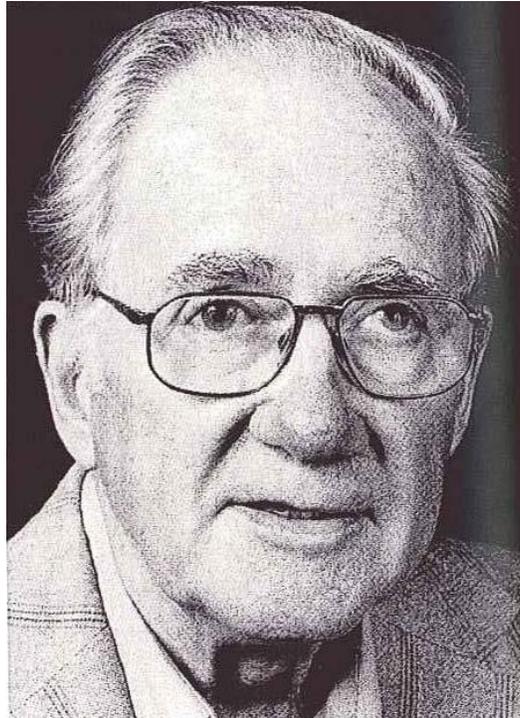
In 1954, Trautner wrote to Schou: “We are very glad to see that you were able to confirm our results, particularly in view of a lot of opposition we meet. As to the mania, we find with careful treatment we can practically get 100% under control.”

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In conclusion, I need to say that the importance of Trautner’s role in both the clinical and basic research done on lithium treatment has been almost completely neglected by history and also by psychiatrists. At the time of his

publications, e.g. Ashburner stated that “From the point of view of the practicing clinician away from the University scene, Trautner’s work meant practically nothing”, Schioldann 2009.

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(1918 – 2005)

Mogens Schou 1954

Schou was a good friend and colleague and committed his career to clearly establishing the efficacy of lithium treatment and was a worldwide crusader on educating psychiatrists about the safe and effective use of lithium.

It was Dr Stromgren of Risskov, Schou's chief, who in 1951 had drawn the attention of Mogens Schou to Trautner and Noack's paper of that year. All the papers in the literature up to this time had been uncontrolled studies and thus were open to criticism on those grounds. Schou had started to use open lithium clinically and correctly became concerned that what was needed was a placebo controlled study.

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This trial (1954) fully confirmed the anti-manic effect of lithium and was the beginning of Schou's lifelong commitment to this work.

A number of investigators had observed from their continued observation of lithium treatment in manic and

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depressive patients that prolonged treatment with lithium might ameliorate or prevent not only manic, but also depressive recurrences. In 1967 Baastrup and Schou

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published a paper "Lithium as a Prophylactic Agent: Its effect against recurrent depressions and manic depressive psychosis".

The findings were very impressive; lithium treatment caused a decrease of 87% in frequency of both manic and depressive recurrences.

Before I leave this period, I would like to briefly outline some of our studies in Australia and the U.S.

All of our Australian studies involved Trautner and colleagues at the University of Melbourne. The study in 1951 by Noack and Trautner was the largest clinical study, although open design, could essentially establish Cade's findings in his small sample.

These two open studies presented a case for a selective efficacy in mood disorders. Now we had to look at the problem that was a serious limitation to general utilization of the treatment – TOXICITY.

The 1955, study on differential retention and excretion of lithium showed a pattern of retention in the manic phase and increased excretion when the mania broke.

Thus a reduction in dose may be required and this change in the handling of lithium could account for previous investigations e.g. Hammond and others encountering toxicity even after therapeutic response was achieved. These studies also established the basis for a therapeutic window with lithium and possible need for individualization of dosage. The range of this window has been set between 0.4 – 1.2 m Eq/L.

In 1960, we published the first U.S. report presenting a case for the psychopharmacological specificity of the Lithium Ion. In 1973, my colleague Dr Shopsin and I published the first textbook entitled, "Lithium: Its Role in Psychiatric Research and Treatment". In 1968, my colleagues at NYU

and I initiated a number of controlled clinical studies of lithium and several typical anti-psychotic agents as well as findings on thyroid function and WBC proliferation and other effects related to lithium usage. A key finding from these controlled studies was the superiority of the anti-psychotics to lithium in schizophrenia and schizo-affective patients. Also, the increased neurotoxicity in patients with various forms of brain damage. Well here we came to a very positive phase in the development of lithium therapy and all's well. But now we come to another **Battle of Lithium – Britain 1968.**

Psychiatrists from the Maudsley Hospital, Blackwell and Sheppard, expressed their skepticism forcibly in the *Lancet* (1968).

This debate continued during which the Maudsley psychiatrists did not use lithium treatment. I met with Schou during this period and he took these arguments as a personal attack on his honesty, naiveté and his attitude as an advocate. He was deeply upset by these attacks. This battle continued with other salvos from Joanna Moncrieff in 1997-98.

Although, in the meantime, Baastrup and Schou in 1970 had published a double blinded discontinuation study of 100 patients with recurrent mood disorders. The results were

dramatically clear in support of prophylactic efficacy. FDA approval for lithium in acute mania did not occur until 1970 and this only after much lobbying and discussion. The U.S. then became the 50th country to do so.

In 1975, the FDA accepted a claim for lithium prophylaxis in mania....as of today (2010); it has not accepted a claim for prophylaxis for depression.

Summary of evidence for lithium in mood disorders and schizophrenia using NHMRC levels of evidence.

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From: Malhi et al. ANZJPsych. Dec 2009

	Lithium	Adjunctive lithium
Bipolar Disorder		
Acute Mania	I	II
Acute Bipolar Depression	II	II
Maintenance and Prophylaxis	I	II [†]
Rapid-cycling	III	III
Major (unipolar) Depression[‡]		
Acute Depression	I [§]	I
Maintenance	I [§]	II
Schizophrenia / Schizoaffective disorder	-	-

[†] Preliminary data is promising suggesting that a combination of lithium and valproate is better than either agent alone. However, only abstract data is available at present.

[‡] Data is best for highly recurrent depression

[§] Efficacy from family history of bipolarity

It seems that the Battle of Britain was just a skirmish and peace has been restored. We are now into the most current phase of this story:

The Balance Study:

John Geddes and Guy Goodwin 2010

This is a blind randomized multi-center controlled study of 330 bipolar I patients assigned to 3 groups, lithium plus valproate versus monotherapy of each. The very important outcome was that both combination therapy of lithium plus valproate and lithium monotherapy are more likely to prevent

relapse than is valproate monotherapy. This is irrespective of baseline severity of illness and is maintained for up to 2 years.

These findings demonstrate a number of key factors that affect the adoption of different treatments over a 60-year period.

1. Despite the scarcity of good comparative evidence, major shifts away from prescription of lithium have occurred, especially in North America. Prescription of lithium has halved between 1992 to 1999, whereas the rate of prescription of valproate tripled.
2. The tendency that the newer marketed product is better than the old.

3. Intense marketing of a patented product can significantly affect usage of a non-patentable non-commercially marketed product.
4. Commercial aspects:
 - a. Lithium is not patentable.
 - i. cost
 - b. No commercial promotion
 - c. Commercial interests against lithium
 - d. Shift to valproate when approved for market in 1995.

For over half a century, lithium has been the gold standard in the pharmacological armamentarium to treat

bipolar disorder. Also, it has been considered to be the archetypal “mood stabilizer”.

In addressing these issues, we must concede that the diagnosis of the illness has been ever changing and broadening and makes comparison of clinical findings over time more difficult. With the broader diagnostic concepts of BP, therapeutic efficacy of lithium appeared to decline and the usage of typical and atypical antipsychotics increased.

Given the claimed specificity of lithium, this outcome is logical and to be expected. That raises a major set of concerns for DSM V diagnostic criteria and appropriate targeted pharmacotherapy.

However, within these constraints the overwhelming body of evidence permits these conclusions:

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CONCLUSIONS

1. Efficacy of lithium in Acute Episodes of Mania.
2. It is the benchmark treatment for mania and the gold standard comparator.
3. Unique in exerting anti-psychotic activity without drowsiness, sedation or hypotension.
4. Efficacy in acute bipolar depression also in unipolar with family history of bipolar disorder > placebo = tricyclics.

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5. Prophylaxis in Bipolar Disorder. Lithium is the unanimous first line choice for the maintenance treatment of bipolar disorder. Effective in both manic and depressive phases. Maintenance therapy is the most important aspect of managing bipolar disorder.

6. Augmentation of lithium in treatment-resistant Major Depression for SSRI, MAO and tricyclics.

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7. Lithium effective for classic BP disorder lacks efficacy in atypical forms of Schizophrenia and Schizo-Affective Disorder, Cade, Gershon et al., claimed no major therapeutic effect. Cochrane review failed to support value of lithium in Schizophrenia – NYU studies.

8. Identify the subgroup of specific lithium responders – classical bipolar patients – positive family histories.

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UNIQUE PROPERTIES:

ANTI SUICIDAL

The risk of suicide is significantly elevated in Bipolar Disorder, with a lifetime risk 15 fold the general population.

Untreated, 20% Bipolars commit suicide. Lithium is unique, that long-term use reduces risk of suicide and suicidal behavior in BP up to 80%.

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NEUROPROTECTION

BD entails mood episodes as well as considerable structural impairment over time potentially secondary to



changes in cellular plasticity and resilience. Recent analysis of structural studies in BD showed a robust change in brain structure as well as evidence that lithium increases grey matter volume.

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Neuroprotection is the most consistent biological outcome associated with lithium treatment in both preclinical and clinical models. In this regard, neuroprotective properties of lithium are thought to relate to its mechanism of action and may be responsible for its mood-stabilizing effects.

IN SUMMARY

Lithium possesses a specific clinical therapeutic profile across the phases of bipolar disorder, with demonstrable efficacy particularly in prophylaxis. In addition, it has unique anti-suicidal properties and is the most effective augmenting agent in the treatment of major depression. These findings underscore the specificity of lithium's action in Bipolar Disorder.

Lithium was the first unlikely salvo in the revolution of psychopharmacology in psychiatry. The neuroscience findings over the past 20 years are now giving us an insight into some aspects of its mode of action and offer the

possibility of new therapeutic approaches. This allows the conclusion that lithium is a well-established therapy that has withstood the test of time and can be classified as a major discovery in psychiatry.

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