Lithium, A Slow Burner

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The Treatment of Manic Psychoses by the Administration of Lithium Salts
By Schou.M, Juel-Nielsen, N.Strömgren. E and Voldby.H (JNNP. 1954; 17; 250-260).

Background

In 1949 Cade reported that lithium could quieten patients with acute manic excitement without causing drowsiness. The rationale for his pilot trial stemmed from a series of experiments he had carried out single handedly in a disused kitchen in a psychiatric hospital where he demonstrated lithium salts reduced seizures and deaths in guinea pigs injected with toxic doses of urea. He had also noted that the animals became docile and immobile. Before proceeding to testing lithium salts on patients he then took lithium carbonate himself in increasing doses to evaluate its safety (Cade 1949).

Stimulated by Cade's paper Noack and Trautner then gave lithium salts to 100 psychiatric patients and confirmed its selective efficacy for the treatment of mania. They also demonstrated that the clinical measurement of serum lithium levels was feasible and might be a useful addition to careful clinical evaluation in detecting toxicity (Noack and Trautner 1951). Cade's findings published in the Medical Journal of Australia had appeared at a time when reports of toxic reactions caused by excessive intake of a lithium based salt substitute by cardiac patients were in the headlines in the United States of America One or two other Australian psychiatrists also then confirmed lithium's potential as a better treatment for mania than the current practice of repeated electroshock therapy and high dose barbiturates but also drew attention to its risks. The dose required to see benefit was close to the toxic range and a fatality that occurred in one of Cade's own patients led him to temporarily ban lithium's use following his appointment as the new Medical Superintendent at the Royal Park Mental Hospital in Melbourne.

Lithium therapy was teetering on the brink of oblivion when Cade's and Noack and Trautner's papers came to the attention of Mogens Schou, an academic Danish psychiatrist

who found it astonishing that the positive reports from Australia had not aroused greater international interest and determined to carry out his own investigations.

The Highly Cited 1954 JNNP paper

Schou reasoned that the lack of enthusiasm for lithium related in part to the fact that the pilot trials had not ruled out some common sources of error and he determined to carry out a more rigorous study.

Together with several colleagues he gave lithium salts to 38 patients (21 females and 17 males) with mania who had been admitted to Sindssygehospitalet Risskov Denmark. 8 of the patients had additional symptoms that the authors considered to be atypical for bipolar disorder including auditory hallucinations and thought disorder.

After a period of baseline evaluation lithium was administered in an open label fashion to some of the patients and in others double blind randomisation using a placebo was used, switching the treatment at 14 day intervals. Most of the patients received lithium carbonate (0.9-1.8 grams a day) but a few were treated with lithium citrate and lithium chloride. Electro convulsive therapy was curtailed and whenever possible sedatives avoided during the trial period. Serum lithium levels were measured routinely and, in a few cases, cerebrospinal lithium values were also obtained.

A daily 3 point scale was used to assess the severity of mania and the results reported as unequivocally positive improvement, possible improvement and no improvement. 14 patients, 11 of whom were women improved unequivocally, usually within two to three weeks of starting lithium. Graphic charts of 14 representative patient responses are included at the end of the paper showing the effects of treatment on both mood and motor activity. A further 18 patients had a ‘possible effect’. In some of this group lithium induced a distinct improvement but spontaneous remission could not be excluded, whereas in the remainder modest benefit was seen. 6 patients did not improve despite what were considered therapeutic doses of lithium and in another 5 a transition into a depressive phase occurred requiring lithium withdrawal. Discontinuation of lithium led to prompt recurrence of mania in all the responders.

Serum lithium levels which ranged from 0.5-2.0 mEq/L were considered to be an unreliable measure of lithium in the tissues and certainly no substitute for careful clinical observation. The average serum level in women was somewhat higher than that in men possibly explaining their better therapeutic response. The doses needed to see improvement

were close to mildly toxic levels and 24meq of lithium a day were recommended. Toxic symptoms included nausea, vomiting diarrhoea, postural tremor of the hands and a flattening of affect with fatigue .The authors concluded that lithium was efficacious in the treatment of mania provided the treatment was monitored closely by regular clinical evaluation serum lithium levels and electrocardiographic recordings . They also corroborated Cade's observations that lithium salts did not lead to disabling sedation. (Schou, Juel-Nielsen et al. 1954)

The paper is notable not only for its confirmatory findings but because it represented the first attempt to carry out a randomised controlled trial in psychiatry. Nevertheless the paper was rejected by The Journal of Medical Science (now the British Journal of Psychiatry) after the eminent British psychiatrist Eliot Slater had reviewed it and given it a low score. Although further support for lithium's efficacy soon came from two French authors Schou's paper had little immediate impact in part because the Journal of Neurology, Neurosurgery and Psychiatry was considered an 'out of the way' journal by most psychiatrists.

Aftermath

Further evidence gradually accumulated to support lithium's efficacy in the treatment of acute mania but much to Schou's chagrin it remained the Cinderella of the psychotropics, an unpatentable and unprofitable orphan. In contrast the company backed major tranquilisers, monoamine oxidase inhibitors and tricyclics were all rapidly approved by the regulators and entered psychiatric practice.

In the nineteen sixties Hartigan in England and Baastrup in Denmark reported that lithium could reduce the frequency of relapses in manic-depressive psychosis (Hartigan 1963) (Baastrup and Schou 1967). The possibility that a trace element might also be a mood normaliser was considered by many eminent opinion leaders to be an outlandish suggestion but the drug had finally become established as a recognised treatment for manic excitement in Continental Europe. Acceptance in the United Kingdom was hampered by a rancorous clash between Schou and Michael Shepherd, then a rising star at the Maudsley Hospital and advocate of rigorous trial methodology to psychiatry research. Schou accepted the methodological limitations of his studies but found inexcusable Shepherd's insinuations that he had personal motives for studying lithium. In some acrimonious correspondence published in The Lancet, Shepherd and his colleague Blackwell wrote that Schou's methods

were shoddy and unconvincing and that he was an enthusiastic advocate rather than an objective investigator (Baastrup and Schou 1968, Blackwell and Shepherd 1968). Baastrup and Schou in their riposte wrote,

> Our study on lithium prophylaxis was the first of its kind. It could have been a different design and possibly a better one. But even a design that is short of the ideal may, in addition to the advantage of being practically feasible, constitute useful information if the study succeeds in proving its point beyond a reasonable doubt.

Partly as a result of this criticism lithium remained underused by psychiatrists in the United Kingdom until the mid-seventies (Schou 1992).(Healy 2000). By the late sixties a few mavericks had started to use lithium in the United States of America and despite continuing regulatory anxieties the US Food and Drug Administration (FDA) were eventually pressured to grant lithium a licence for the treatment of mania in 1970 but not before many thousands of patients had been unnecessarily denied effective treatment for many years.

Schou continued his research into lithium for the rest of his professional career. In 1979 he treated twenty-four artists (a mixture of writers, composers and painters) with disabling episodes of mania . By measuring productivity levels and the quality of their art, he showed that in those who had very severe bipolar disorder (of the type that had affected the poet Robert Lowell throughout his life), lithium could improve creative output (Schou 1979).

The 1954 Journal of Neurology, Neurosurgery and Psychiatry paper eventually came to be regarded as an important landmark in the long drawn-out acceptance of lithium . When Cade and Schou spoke at a meeting in Denmark in 1970 Schou introduced his Australian colleague as 'the man who introduced lithium into psychiatry and described its antimanic effect'. Cade then stood up and acknowledged the Dane's contribution by saying, 'I feel rather like a woman who as a girl had an illegitimate child and had it adopted out. And now, 20 years later I am visiting the adoptive parents and finding out what a big fine boy he has grown into, but knowing far less about him than his adoptive parents.' (Schou 1983)

In the opinion of most practising psychiatrists lithium carbonate tablets starting with a dose of 400mg and aiming for serum levels between 0.6 and 1.0 mmol/l remains the most effective therapy for the prevention of mania in Bipolar Affective Disorder-1 Alternatives

that are particularly popular in the United States of America include the anticonvulsants, sodium valproate, carbamazepine and lamotrigine but there is less evidence for their efficacy in preventing relapse (Post 2018) and in contrast to lithium no evidence that they reduce suicide rates (Muller-Oerlinghausen, Ahrens et al. 1992).

Lithium's mode of action remains uncertain but it is known to reduce excitatory neurotransmission through effects on dopamine, glutamate and second messenger systems and also increase GABA mediated inhibition It has been shown to be effective in refractory early morning and off period dystonia in Parkinson's disease (Quinn and Marsden 1986) and has been proposed as a treatment for neurodegenerative disorders with pathological overaccumulation of phosphorylated tau protein (Matsunaga, Kishi et al. 2015).

The handful of short reports published by the Journal of Neurology Neurosurgery and Psychiatry since the classic 1954 paper all relate to lithium's neurotoxicity (Kellett, Metcalfe et al. 1975, Jacome 1987) . In contrast the British Journal of Psychiatry that rejected the paper has in the interim published more than two hundred papers on the use of lithium in bipolar disorder but none with comparable impact.

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