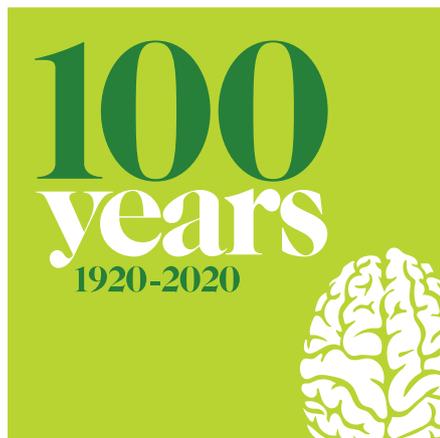


# Lithium: a slow burner

Andrew J Lees



**It took Mogens Schou and his collaborators two decades to get lithium accepted for the prevention of mania. Along the way he was vilified and his scientific objectivity questioned. These regrettable delays led to many unnecessary suicides. More profitable rebranded anticonvulsants with less efficacy now threaten lithium's primacy as the gold standard treatment for bipolar 1 disorder**

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 that 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 test lithium salts on patients, he then took lithium carbonate himself in increasing doses to evaluate its safety.<sup>1</sup>

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

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The treatment of manic psychoses by the administration of lithium salts

**Authors:** Schou M, Juel-Nielsen N, Stromgren E, and Voldby H

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feasible and might be a useful addition to careful clinical evaluation in detecting toxicity.<sup>2</sup> 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 USA. 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 women and 17 men) with mania who had been admitted to Sindssygehospitalet Risskov Denmark. Eight 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 g/day) but a few were treated with lithium citrate and lithium chloride. Electroconvulsive 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. Of the 14 patients who improved unequivocally usually within 2–3 weeks of starting lithium 11 were women. 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. Six patients did not improve despite what were considered therapeutic doses of lithium and in another five, 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 to 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 24 mEq of lithium a day were recommended. Toxic symptoms included nausea, vomiting diarrhoea, postural tremor of the hands and a flattening of effect 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.<sup>3</sup>

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 1960s, Hartigan in England and Bastrup and Schou in Denmark reported that lithium could reduce the frequency of relapses in manic-depressive psychosis.<sup>4 5</sup> 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 UK was hampered by a rancorous clash between Bastrup and Schou and Blackwell and Shepherd, the latter 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*, Blackwell and Shepherd wrote that Schou's methods were shoddy and unconvincing and that he was an enthusiastic advocate rather than an objective investigator.<sup>6 7</sup> Bastrup 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 UK until the mid-70s.<sup>8 9</sup> By the late 60s, a few mavericks had started to use lithium in the USA and despite continuing regulatory anxieties the US Food and Drug Administration 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 24 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.<sup>10</sup>

The 1954 *Journal of Neurology, Neurosurgery and Psychiatry* paper eventually came to be regarded as an important landmark in the longdrawn-out acceptance of lithium. When Cade and Schou spoke at a meeting in Denmark in 1970, Schou presented 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'.<sup>11</sup>

In the opinion of most practising psychiatrists, lithium carbonate should be started at a dose of 400 mg 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 and should be started at a dose of 400 mg aiming for serum levels between 0.6 and 1.0 mmol/L. Alternatives that are particularly popular in the USA include the anticonvulsants, sodium valproate, carbamazepine and lamotrigine but there is less evidence for their efficacy in preventing relapse<sup>12</sup> and in contrast to lithium no evidence that they reduce suicide rates.<sup>13</sup>

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 gamma-aminobutyric acid-mediated inhibition. It has been shown to be effective in refractory early morning and off-period dystonia in Parkinson's disease<sup>14</sup> and has been proposed as a treatment for neurodegenerative disorders with pathological overaccumulation of phosphorylated tau protein.<sup>15</sup>

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.<sup>16 17</sup> In contrast, the *British Journal of Psychiatry* that rejected the paper has in the interim published >200 papers on the use of lithium in bipolar disorder but none with comparable impact.

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## REFERENCES

- Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Med J Aust* 1949;2:349–52.
- Noack CH, Trautner EM. The lithium treatment of maniacal psychosis. *Med J Aust* 1951;2:219–22.
- Schou M, Juel-Nielsen N, Stromgren E, et al. The treatment of manic psychoses by the administration of lithium salts. *J Neurol Neurosurg Psychiatry* 1954;17:250–60.
- Hartigan GP. The use of lithium salts in affective disorders. *Br J Psychiatry* 1963;109:810–4.
- Baastrop PC, Schou M. Lithium as a prophylactic agents. Its effect against recurrent depressions and manic-depressive psychosis. *Arch Gen Psychiatry* 1967;16:162–72.
- Baastrop PC, Schou M. Prophylactic lithium? *Lancet* 1968;2:349–50.
- Blackwell B, Shepherd M. Prophylactic lithium: another therapeutic myth? an examination of the evidence to date. *Lancet* 1968;1:968–71.
- Schou M. The first psychiatric use of lithium. *Br J Psychiatry* 1992;161:279–80.
- Healy D. Pioneers in psychopharmacology II. *Int J Neuropsychopharmacol* 2000;3:351–4.

- 10 Schou M. Artistic productivity and lithium prophylaxis in manic-depressive illness. *Br J Psychiatry* 1979;135:97–103.
- 11 Schou M. Lithium perspectives. *Neuropsychobiology* 1983;10:7–12.
- 12 Post RM. The new news about lithium: an underutilized treatment in the United States. *Neuropsychopharmacology* 2018;43:1174–9.
- 13 Müller-Oerlinghausen B, Ahrens B, Grof E, *et al.* The effect of long-term lithium treatment on the mortality of patients with manic-depressive and schizoaffective illness. *Acta Psychiatr Scand* 1992;86:218–22.
- 14 Quinn N, Marsden CD. Lithium for painful dystonia in Parkinson's disease. *Lancet* 1986;1:1377.
- 15 Matsunaga S, Kishi T, Annas P, *et al.* Lithium as a treatment for Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 2015;48:403–10.
- 16 Jacome DE. Cerebellar syndrome in lithium poisoning. *J Neurol Neurosurg Psychiatry* 1987;50:1722.
- 17 Kellett JM, Metcalfe M, Bailey J, *et al.* Beta blockade in lithium tremor. *J Neurol Neurosurg Psychiatry* 1975;38:719–21.