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BJPsych Editorial

British contributions to the therapeutic use of John Cade's lithium

Gin S. Malhi and Erica Bell

Summary

Coinciding with the 75th anniversary of John Cade's seminal publication that first reported lithium's antimanic efficacy, we briefly recount the salient findings of the historic paper and draw attention to the important psychiatric research in Britain that reinforced its findings and the critical British opinions that likely impeded its clinical use.

Keywords

Mood stabliser; history; bipolar disorder; treatment; medication.

Britain's historical contributions to the promotion of lithium as a treatment for bipolar disorder have occurred episodically, somewhat like the illness it best treats. At different times over the past century and a half, British research into the effects of lithium and the opinions of leading figures in psychiatry and psychopharmacology on its clinical efficacy have both promoted and hindered its use. For instance, key publications on lithium research, some of which was conducted in Britain, have appeared in British journals and proven beyond doubt its antimanic properties. However, pulling in the opposite direction, influential figures have at times been extraordinarily critical, to the point of disadvantaging its clinical uptake. This *BJPsych* Editorial, the publication of which coincides with the 75th anniversary of John Cade's insightful publication,[1] traces the vicissitudes of lithium's fortune by selectively examining the contributions made by British researchers and how these have contributed to its ups and downs before ultimately ensuring its triumphant return.

Excitement

Three-quarters of a century ago, in a land referred to simply as 'down under', a modest paper quietly materialised in what Edward Shorter, a University of Toronto psychiatry professor, described as 'a then-obscure journal'.[2] The article,[1] a mere three pages long and with only seven references, details the findings from experiments conducted by the Australian psychiatrist John Cade on patients in his care. The paper is extremely modest by today's standards, as it involved a relatively small heterogeneous group of only male patients (owing to convenience sampling, as Cade was based at a psychiatric hospital for male war veterans), and there was no control or placebo. Instead, Cade administered lithium to ten patients with mania, three of whom had been in a chronic manic state for several years. He commenced with lithium citrate, most commonly at a dose of '20 grains three times a day', as this salt formulation was soluble and better absorbed than its carbonate cousin, but in nearly half of the cases the treatment had to be switched to lithium carbonate, as this was better tolerated. In two of the ten cases there seems to have been only partial and transient response to lithium, with a reduction in 'excitement' (agitation, irritability, heightened activity), but in one of these cases the patient could not tolerate lithium and so treatment had to be discontinued, and in the other, the patient developed a psychotic delusional state, prompting doubt as to whether he had 'true mania' in the first place. The remaining eight patients all seemed to benefit considerably to the extent that they remained well and were able to return to work: 'functional recovery' in today's language. Cade describes several of them as 'practically normal', with some showing signs of improvement in a matter of days. However, being an astute scientist, Cade also administered lithium citrate to six patients suffering from dementia praecox (schizophrenia) to determine the extent to which the beneficial effect is phenotype-specific. In these patients there was no 'fundamental improvement', but again in half of them their excitement was quelled, and this allowed them to forgo their regular hypnotic treatment – proving that this benefit had been brought about by lithium, an inference that was further reinforced when lithium was withdrawn and there was a recrudescence of symptoms.

In an exemplary display of the scientific method, Cade then went a step further.

Having observed an antimanic effect (diminished excitement) he wanted to know whether lithium was actually a depressant that 'might precipitate a depressive episode in predisposed persons'. Therefore, he administered lithium citrate to patients with chronic depressive psychoses in the same dosage and manner as for patients with mania. Having done this, Cade noted that there was no change in the depressive symptoms the patients were experiencing – neither improvement nor worsening – suggesting that lithium counters the symptoms of mania but does not depress mood towards the opposite pole of the illness. Thus, in a few pages, Cade manages to describe how, using several simple but elegant experiments, he had elucidated the clinical effect of lithium.

Podean contributions

The legendary antipodean John Cade begins his seminal article with reference to a British physician called Alfred Garrod, to whom Cade attributes the introduction of lithium salts into clinical practice (Fig. 1). In the latter half of the 19th century, salts such as lithium carbonate were 'vaunted as curative in gout, and […] a multitude of other so-called gouty manifestations'.[1] Garrod describes the use of such medicaments as not having 'any injurious consequences', although he also states that 'it produces no direct physiological symptom'. With the advantage of hindsight, Cade is more judicious and takes note of warnings regarding potential side-effects such as cardiac depression. Indeed, the opening column of his paper mainly comprises cautious allusions to the potential toxicity of lithium, and it is not until the beginning of the second column that we read some positive declarations wherein he pens 'it looked as if the lithium ion might have been exerting a protective effect'.

Several forerunners of this insightful line of thought can be traced back to a handful of American and Danish physicians. For instance, more than two decades after Garrod's initial observations,

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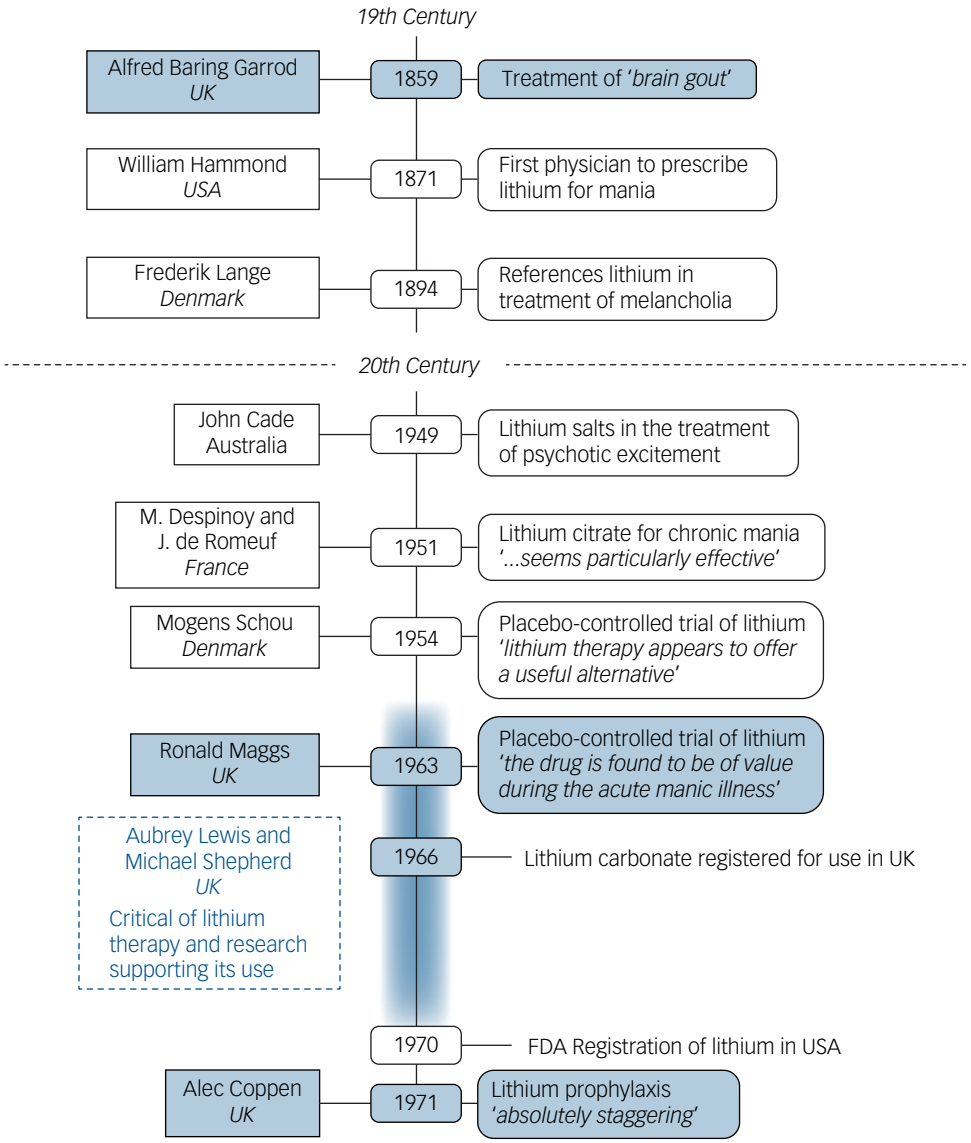

Fig. 1 Timeline of scientific contributions to the use of lithium. FDA, United States Food and Drug Administration.
This schematic illustrates the key developments that led to lithium's success as a mood stabiliser and highlights the positive contributions made by British researchers (black text on blue background). The negative influence of some British researchers is shown in blue text on a white background and by the blue shading on the central timeline. Note, the schematic is not exhaustive. For further details see Shorter.

William Hammond, a professor at Bellevue Hospital Medical College in New York, became the first to administer lithium to treat mania; a further two decades later, Danish brothers Carl and Frederick Lange did the same in patients with melancholia.[2] However, despite such prescience, the use of lithium fell almost inexplicably into abeyance for an extraordinarily lengthy period of time. It is unclear exactly why this occurred, but it may be because the Lange brothers published their findings in Danish, and the lithium findings were linked with other novel concepts introduced simultaneously (such as depression being a periodic disorder) and this led to lithium being dismissed and forgotten.[3]

Desuetude

Following the publication of Cade's paper, interest in lithium grew and its potential role in the management of manic–depressive illness seemed increasingly likely. However, not everyone was convinced, and quite correctly further research was needed to make sure the effect of lithium was indeed genuine. Inspired by Cade's observations, many British researchers viewed lithium in a positive light, but others were less enthusiastic, and a few prominent detractors began to emerge. Among these were Sir Aubrey Lewis and Michael Shepherd. Lewis was the first Professor of Psychiatry at the Institute of Psychiatry in London, and his comments were particularly critical of John Cade's seminal discovery. For example, Lewis referred to treatment with lithium as 'dangerous nonsense',[2] while Michael Shepherd, a colleague of Lewis at the Maudsley Hospital and another highly influential professor in the field of psychiatry, raised concerns about the potential prophylactic properties of lithium, specifically its use for the prevention of depression. Shepherd went as far as questioning the scientific methodology of early lithium studies that alluded to its potential benefit. Expressing puzzlement, Shorter states that 'in an almost malicious manner [Lewis and Shepherd seem to] have sown scholarly confusion about the true effectiveness of lithium'.[2]

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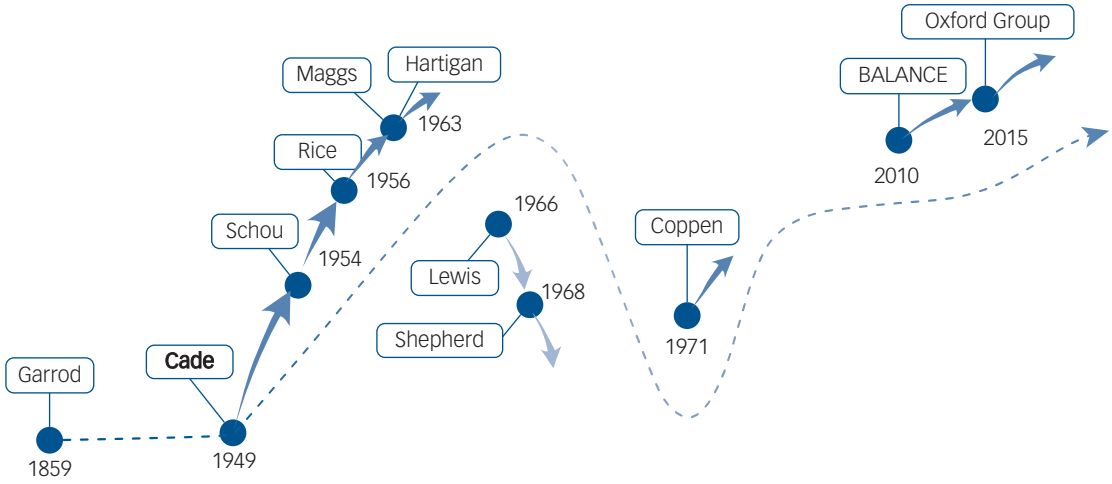

Fig. 2 The ups and downs of British contributions to John Cade's lithium.
Inquiry into the properties of lithium began with Alfred Garrod in 1859, who ignited interest, but ultimately made a largely neutral contribution. Enthusiasm for lithium was rekindled by John Cade's 1949 article, which reported the antimanic effect of lithium. The findings were corroborated and strengthened by the work of Mogens Schou (1954) and David Rice (1956), the first British author to document the antimanic effect of lithium. The benefits of lithium were further underscored by Ronald Maggs' placebo-controlled trial in mania and the work of G.P. Hartigan, which identified the prophylactic properties of the element that were later verified in a controlled trial conducted by Coppen and Maggs (1971). The 'downs' came in the form of both Aubrey Lewis and Michael Shepherd's detractions of lithium's use in clinical practice. Nevertheless, subsequently, lithium gradually became inculcated into clinical practice, before it experienced a lull in clinical uptake. Finally, in recent decades, both the Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) study and the meta-analysis by the Oxford Group restored confidence in the clinical use of lithium and fuelled a resurgence of research interest in its therapeutic properties.

Fortunately, these negative sentiments did not deter everyone in the UK, and in 1963 Ronald Maggs, a doctor at Hellingly Hospital in Hailsham, published the first properly conducted placebo-controlled trial of lithium.[4] However, the idea was not completely new, as a decade earlier, in 1954, a Danish team led by Mogens Schou had published a study comparing lithium with placebo and commented on both its antimanic effects and its ability to keep patients in a 'normal state by administration of a maintenance dose'.[5] Both articles were published in British journals, the *British Journal of Psychiatry* and the *Journal of Neurology, Neurosurgery and Psychiatry* respectively.

Thus, partly because of British research during the last quarter of the 20th century, lithium was increasingly employed in the treatment of bipolar disorder, the new name for manic–depressive illness, and it soon became the gold standard comparator in clinical trials for novel antimanic agents. Clinical experience because of widespread use, along with further research, began to reveal that lithium was perhaps the ideal medication for people with 'classic' bipolar disorder – namely, those with clear-cut recurrence of manic and depressive episodes with discernible remission in between. But in practice, only a third of patients with bipolar disorder had this phenotype and the prescription of lithium had expanded beyond bipolar disorder, with increasing use in the augmentation of antidepressants when treating clinical depression. Additional properties of the element also came to light, such as its ability to reduce suicidal thinking and protect the brain, further promoting its use.

However, at the same time, concerns regarding its harmful impact on renal and thyroid function and the need for constant monitoring of plasma levels to avoid toxicity increasingly curbed its use – especially as other agents adopted the mood stabiliser label and claimed to provide equal benefit to people with bipolar disorder. Nevertheless, lithium remained the mainstay recommendation for the treatment of bipolar disorder across international guidelines and the only uncertainty that remained concerned whether it had an antidepressant effect – both acutely and in prophylaxis.

As more and more agents entered the bipolar therapeutic field, the prescription of lithium declined. But then, as long-term data began to emerge, it became clear that none of the newer agents seemed to confer the prophylaxis that lithium provided, at least not without significant sedation and, as was later discovered, cardiometabolic harm. Thus, lithium managed to remain relevant and reasonably widely used despite lacking sponsorship and consistently facing criticism – both clinically and in research circles. Nevertheless, an injection of confidence was still needed to boost the use of lithium in the face of increasing competition, and it is here that a key study turned the tide (Fig. 2).

The BALANCE trial

The Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) study, conducted by a large European consortium of researchers led by a British group from Oxford, was a 7-year trial comparing lithium against valproate across 41 centres.

The open-label study[6] looked at patients over the age of 16 who met criteria for bipolar I disorder. They were recruited from sites across the UK, as well as France, Italy and the USA, and allocated randomly to lithium monotherapy, valproate monotherapy or both agents in combination with an active run-in period of 1–2 months when patients were on the combination of lithium and valproate. The idea behind the study was to test a common clinical practice, wherein valproate was increasingly used alongside lithium or vice versa, partly because of concerns of withdrawing either of the agents where there had been a partial response or where some mood stability had been gained, and partly because it was thought the add-on agent perhaps had additional benefits. The study was thus geared to see whether the combination strategy was better than either molecule alone.

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The findings showed that first, the combination of the two agents was an effective prophylactic strategy for the prevention of relapse. Specifically, the study found that 54% on combination therapy versus 59% on lithium alone and 69% on valproate alone had a relapse. Most noticeable, however, was the fact that combination therapy and lithium alone were effective and more so than valproate monotherapy. Further, the benefit was maintained over 2 years and seemed to occur regardless of the severity of illness at baseline. Interestingly, the study could not sufficiently separate the efficacy of combination therapy from lithium monotherapy, suggesting that the benefit is mainly attributable to lithium. Thus, BALANCE found lithium to be more effective, and this not only handed victory to lithium, but also reinvigorated research interest in the molecule using the new tools that the 21st century afforded, such as imaging, genetics and psychoimmunology.

However, despite the efficacy of lithium as the nonpareil mood stabiliser having been proven, questions remained regarding its safety profile and adverse effects. An increasing number of clinicians stopped prescribing lithium because of concerns regarding its impact on renal and thyroid function, coupled with the emergence of alternative medications that were perceived to be superior with respect to safety profile. To address this gap in understanding, once again Oxford researchers, led by Rebecca McKnight, published a seminal systematic review and meta-analysis in 2012,[7] wherein they drew together almost 400 studies from 60 years of research to systematically profile the risks of adverse effects from lithium. Overall, their meta-analysis showed that the risk of renal toxicity and end-stage renal failure are low, with risks of hypothyroidism and hyperparathyroidism being significant. The authors advocated for a balanced consideration of the risks of not prescribing lithium (i.e. missed opportunity for effective treatment) versus the potential adverse effects. Importantly, the article also drew attention to the low quality of the primary literature on lithium, appraising most studies as methodologically weak and varying significantly in design. This points to the fact that synthesising the available evidence to create meaningful clinical guidance remains difficult, and that there is much that remains to be understood regarding the mood stabilising properties of lithium.

Conclusion

It has been 75 years since John Cade's astute observations ignited interest in the use of lithium for the treatment of manic–depressive illness. Many papers and even books have been written recounting the discovery of lithium and its use in the treatment of psychiatric disorders, and although the provenance of its discovery as an antimanic agent and mood stabiliser remains disputed,[8] no one can question the importance of Cade's seminal paper[1] and the immense impact it has exerted on the field. In the years before and since Cade's paper, British research and academics have played a unique, almost 'bipolar', role by way of providing a platform for the publication of important papers, but at the same time criticising its clinical use. However, more latterly, much needed balance has been restored by British research that has once again instilled confidence in its clinical application.

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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

G.S.M. and E.B. both contributed to the initial research, drafting and editing of this manuscript. E.B. developed the figures. Both authors have read and approved of the final manuscript.

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