COMMENTARY

The rebirth of lithium as the archetypal mood stabilizer

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The serendipitous discovery of lithium’s efficacy for the treatment of manic excitement dates back to initial observations by the Danish psychologist Carl Lange in 1886 who theorised that patients with manic-depressive illness had “cerebral gout” for which he suggested lithium salts because lithium could dissolve urate stones. Modern use was triggered by Cade in Melbourne in 1949, while its efficacy for the management of manic episodes and for the prophylaxis of both manic and bipolar depressive episodes was empirically confirmed by Mogens Schou in Denmark.¹ The prophylaxis of mood episodes is the principal goal in the management of bipolar spectrum disorders. In fact, high recurrence rates instead of polarity appears to be the main clinical feature distinguishing unipolar form bipolar affective disorders. Furthermore, most international guidelines and a network meta-analysis confirm that lithium is the first-line, archetypal, mood stabilizer.² It is also noteworthy that the superior effectiveness of lithium as maintenance treatment of bipolar disorder has been repeatedly reported despite the fact that the vast majority of randomised controlled trials (RCTs) of newer mood stabilizing agents have employed so-called enrichment designs (i.e., participants who achieved acute therapeutic response to a specific mood stabilizing medication are followed-up until the emergence of a recurring mood episode). This design is aimed at assessing relapse prevention under a given treatment but does not allow to
generalize the prophylactic efficacy of the drug being tested. This methodological quirk may artificially inflate the magnitude of the effect sizes of these drugs, disadvantaging the comparator. In marked contrast, most RCTs that examined lithium’s efficacy as a long-term mood stabilizer have not followed such a design. Furthermore, evidence indicates that lithium treatment may have the best cost-effectiveness among interventions to prevent relapse in people with bipolar disorder.

Despite this large body of convincing evidence, lithium is nowadays not only markedly underutilized in clinical practice, but its use is declining. Indeed, this is part of a broader concerning trend that clinical care in bipolar disorder worldwide is markedly discordant from the evidence base and guidelines. This might be due at least partly to aforementioned competitor marketing, concerns regarding its safety and tolerability as well as the need to frequently monitor its possible side effects as well as its serum levels. Treatment with lithium has been associated with renal failure, hypothyroidism, hyperthyroidism, polyuria, tremors, as well as parathyroid disturbances. However, the possibility to measure its serum levels may enhance the clinician’s ability to routinely verify and monitor compliance. Furthermore, with proper monitoring and clinical precautions, the incidence of more serious adverse effects related to lithium therapy may be much lower than once thought. Moreover, lithium may be underused due to the absence of any promotion from pharma, which can be very influential with patent-protected products.

Lithium has several other unique and specific benefits for the long-term management of bipolar disorders. First, a large body of evidence indicates that lithium even in micro-doses prevents suicide in populations with mood disorders. Second, the recurrence of major affective episodes may activate several pathways that may drive neuroprogression in a meaningful subset of patients with bipolar disorder. Neuroprogression may be clinically reflected by refractoriness, as well as cognitive and functional decline in patients with bipolar disorders. Moreover, data from observational studies indicate that people with bipolar disorder are at a higher risk of developing dementia compared to people without bipolar disorder, while lithium seems to mitigate this risk. Nevertheless, the causality of the association between bipolar disorder and dementia awaits further scrutiny to be established. However, further high-quality evidence is needed to establish that lithium may prevent dementia in people with bipolar disorder above and beyond its superior effectiveness as a mood stabilizer.
We believe that a renewed clinical and research interest on the use of lithium in the management of bipolar disorder is warranted. This may be achieved by continuous medical education initiatives across psychiatry residency curricula worldwide. From a research perspective, although lithium response may comprise a bipolar disorder endophenotype, it is noteworthy that lithium’s precise mechanisms of action remain to be established. However, lithium’s possible neuroprotective effect may have a pleiotropic mechanism of action influencing several intracellular pathways namely, sodium/potassium ATPase pathways, GSK-3-related pathways as well as the expression of neurotrophic factors. Arguably, the identification of additional putative pharmacodynamic mechanisms underpinning lithium’s efficacy as a mood stabilizer may shed light on the underlying pathophysiology of bipolar disorder and may also inform putative novel neurotherapeutic targets for this complex illness.

References
