

DR. ANDRE F CARVALHO (Orcid ID : 0000-0002-2500-5671)

PROF. EDUARD VIETA (Orcid ID : 0000-0003-1673-8248)

Article type : Commentary

COMMENTARY

The rebirth of lithium as the archetypal mood stabilizer

Andre F. Carvalho^{1,2,3,#}, Marco Solmi⁴, M. Ishrat Husain^{1,2}, Michael Berk^{3,5}, Eduard Vieta⁶

¹Department of Psychiatry, University of Toronto, Toronto, ON, Canada;

²Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada;

³Deakin University, Institute for Mental and Physical Health and Clinical Translation, Barwon Health, School of Medicine, Geelong, Australia;

⁴Department of Neurosciences, University of Padova, Padova, Italy;

⁵Orygen, The National Centre of Excellence in Youth Mental Health, Department of Psychiatry, Florey Institute for Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia;

⁶Barcelona Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain.

#Corresponding author:

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BDI.13031](https://doi.org/10.1111/BDI.13031)

This article is protected by copyright. All rights reserved

Andre F. Carvalho, M.D., Ph.D.

Centre for Addiction and Mental Health (CAMH)

Bell Gateway Building

100 Stokes St. 4th floor, Toronto, ON, Canada, M6J 1H4

E-mail: andrefc7@hotmail.com

Disclosures:

AFC and MS have nothing to disclose. MIH is a PI for a trial sponsored by COMPASS Pathways Limited for which he receives salary support. MIH receives research support from the Brain and Behavior Research Foundation, CAMH Discovery Seed Fund, PSI Foundation, Stanley Medical Research Institute and University of Toronto. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work. MB is supported by a NHMRC Senior Principal Research Fellowship 1156072. EV has received research support from or served as consultant, adviser or speaker for AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage pharmaceuticals, Sanofi-Aventis, Shire, Sunovion, Takeda, and reports no financial or other relationship relevant to the subject of this article.

Running head: Lithium as the archetypal mood stabilizer

Keywords: Lithium; Bipolar disorder; Treatment

This article is protected by copyright. All rights reserved

Authors' contributions

AFC has written the initial draft of the manuscript. MS, MIH, MB and EV have provided relevant intellectual contribution to the manuscripts. All authors have read and approved the final version of the manuscript prior to submission.

Data availability statement

N/A

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 from 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.³ 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.³ Treatment with lithium has been associated with renal failure, hypothyroidism, hyperthyroidism, polyuria, tremors, as well as parathyroid disturbances.³ 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.³ 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.⁴ 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.⁵ 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

1. Baldessarini RJ, Tondo L, Vázquez GH. Lithium Treatment for Bipolar Disorder. *Bipolar Disord.* 2020.
2. Miura T, Noma H, Furukawa TA, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry.* 2014;1(5):351-359.
3. Carvalho AF, Firth J, Vieta E. Bipolar Disorder. *N Engl J Med.* 2020;383(1):58-66.
4. Del Matto L, Muscas M, Murru A, et al. Lithium and suicide prevention in mood disorders and in the general population: A systematic review. *Neurosci Biobehav Rev.* 2020;116:142-153.
5. Velosa J, Delgado A, Finger E, Berk M, Kapczinski F, de Azevedo Cardoso T. Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. *Acta Psychiatr Scand.* 2020;141(6):510-521.