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Author/s:

Malhi, GS;Bell, E;Boyce, P;Hazell, P;Murray, G;Bassett, D;Bryant, RA;Hopwood, M;Lyndon, B;Mulder, R;Porter, RJ;Singh, A;Gershon, S

Title:

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Date:

2020-06-01

Citation:

Malhi, G. S., Bell, E., Boyce, P., Hazell, P., Murray, G., Bassett, D., Bryant, R. A., Hopwood, M., Lyndon, B., Mulder, R., Porter, R. J., Singh, A. & Gershon, S. (2020). Make lithium great again!. *Bipolar Disorders*, 22 (4), pp.325-327. <https://doi.org/10.1111/bdi.12942>.

Persistent Link:

<https://hdl.handle.net/11343/275811>

Title: Make Lithium Great Again!

Gin S. Malhi^{1, 2, 3}

Erica Bell^{1, 2, 3}

Philip Boyce⁴

Philip Hazell⁵

Greg Murray⁶

Darryl Bassett⁷

Richard A. Bryant⁸

Malcolm Hopwood⁹

Bill Lyndon¹⁰

Roger Mulder¹¹

Richard J. Porter¹¹

Ajeet Singh¹²

Samuel Gershon^{13, 14}

¹ The University of Sydney, Faculty of Medicine and Health, Northern Clinical School, Department of Psychiatry, Sydney, New South Wales, Australia.

² Academic Department of Psychiatry, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, NSW 2065 Australia.

³ CADE Clinic, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, NSW 2065 Australia.

⁴ Discipline of Psychiatry, Sydney Medical School, Westmead Clinical School, University of Sydney, Sydney, NSW, Australia

⁵ The University of Sydney, School of Medicine

⁶ Centre for Mental Health, Swinburne University of Technology, Hawthorn, VIC 3122 Australia

⁷ University of Western Australian Medical School, Faculty of Health and Medical Science, University of Western Australia, Perth, WA, Australia

⁸ School of Psychology, University of New South Wales, Sydney, NSW, 2052 Australia

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.12942](https://doi.org/10.1111/BDI.12942)

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⁹ Department of Psychiatry, University of Melbourne and Professorial Psychiatry Unit, Albert Road Clinic

¹⁰ Clinical Senior Lecturer, Department of Psychiatry, The University of Sydney

¹¹ Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

¹² School of Medicine, Deakin University, Victoria, Australia.

¹³ Emeritus Professor Psychiatry, University of Pittsburgh, School of Medicine, Pittsburgh, USA

¹⁴ Mind and Brain Theme, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia

Gin S Malhi ORCID: 0000-0002-4524-9091

Erica Bell ORCID: 0000-0002-8483-8497

Philip Boyce ORCID: 0000-0002-9816-7356

Philip Hazell ORCID: 0000-0002-8085-2996

Richard A Bryant ORCID: 0000-0002-9607-819X

Malcolm Hopwood ORCID: 0000-0001-6004-4521

Roger Mulder ORCID: 0000-0002-8147-5838

Richard J. Porter ORCID: 0000-0002-8695-3966

Ajeet Singh ORCID: 0000-0002-0853-7959

Corresponding Author:

Professor Gin S Malhi, CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, Level 3, Main Hospital Building, St Leonards, NSW 2065, Australia. Email:

gin.malhi@sydney.edu.au

Despite its prominent position in many international clinical practice guidelines, and a renewed interest from academic psychiatry, the use of lithium to treat Bipolar Disorder (BD) has steadily declined¹. The reasons for this are threefold: First, as there is no 'patent' on lithium, it is not being marketed to physicians or patients, to the same extent or in the same manner as other agents that have similar indications; Second, compared to alternatives, lithium is generally regarded as more complicated to prescribe (necessitating regular

monitoring of serum levels) and generally less well tolerated, especially in the short term; Third, there are, arguably unfounded, concerns about its long term adverse effects, especially on renal function.

Lithium the mood stabiliser: patently obvious

Lithium has never been under patent (making it considerably cheaper than the second-generation antipsychotics (SGAs) that have been heavily marketed for the treatment of BD in recent decades) and so there has never been a pharmaceutical company to promote it *per se*. Instead, its therapeutic importance has relied solely on empirical evidence and the scientific literature. The fact that lithium lacks marketing support is not an issue that can be addressed solely by clinicians. Advocating for its use first line requires professional bodies and government agencies to promote its prescription and ensure that it has equal prominence as the newer agents being fervently promoted by major pharmaceutical companies. Such strategies also need to be supported by consumers and consumer organisations, and while clinicians cannot prevent direct to consumer marketing they can, by heeding the advice of clinical guidelines, begin to counter the misconceptions (or ‘fake news’) surrounding its use.

Guidelines almost unanimously recommend the use of lithium to treat mania, bipolar depression and maintain mood stability, and advocate its use for prophylaxis against future mood episodes. But prescribing lithium requires clinical expertise. After assessing baseline characteristics, the initiation of lithium therapy involves gradually titrating its dose, while measuring its plasma levels, which therefore need regular monitoring² until therapeutic levels are achieved. Minor, and transient, side-effects are common during titration and may lead to poor adherence; hence high-quality psychoeducation and good therapeutic skills are needed to maintain adherence.

The ‘atypicals’ are antipsychotics

In comparison, SGAs are regarded as better tolerated and have the seeming advantage of also treating comorbid symptoms that are common in BD, such as anxiety and agitation. Furthermore, SGAs do not require blood tests, either at baseline or for therapeutic monitoring*, making them easier to prescribe and manage long-term (often without the

necessary dose adjustments to minimise their long-term side-effects). As a consequence, the prescription of SGAs has increased many-fold in recent times, displacing the use of lithium and other conventional mood stabilising agents. Thus, lithium is generally regarded as being complicated to prescribe and cumbersome because of the requirement for regular monitoring. It is thought to be prone to side-effects and poorly tolerated by most patients with little benefit as regards acute symptoms of BD. But are these perceptions of lithium accurate? We argue that these views concerning lithium are misconceptions and that they have come about because the lack of specificity of SGAs has been framed as a virtue and promoted as a 'benefit'. In addition, undue importance has been attached to ease of prescribing.

Inconvenient truths

While monitoring plasma levels may seem an inconvenience, it affords an enormous advantage by providing an objective measure of compliance and ensuring appropriate therapeutic levels are achieved. It also encourages regular clinical contact ensuring that other aspects of managing a complicated illness are reviewed regularly. In our view, the potential side effects of lithium are often overstated. By and large, the early side effects of lithium therapy are transient, and provided patients are suitably forewarned, they seldom interfere with adherence to treatment. Furthermore, they can usually be adequately managed, especially once the benefits of lithium take effect³. In this regard, lithium is the most specific agent for the treatment of bipolar disorder, and it is also unique in exerting antipsychotic effects in the context of bipolar disorder without drowsiness, hypotension or direct neurological side effects. In other words, it is starkly different to most SGAs, which were first conceived to treat psychosis and then subsequently broadened their indication and 'migrated' to prescription in bipolar disorder⁴, initially to treat mania, but then bipolar depression and even maintenance (but not prophylaxis). As a consequence, antipsychotics also have significant effects on anxiety, agitation and psychosis that reflect their initial broader and more indiscriminate use. Remarkably, in practice, these effects are touted as 'additional benefits'. We disagree with these views and propose a change in perspective.

Bipolar disorder is a lifelong chronic illness for which long-term pharmacotherapy is inevitable. On this time scale, the inconvenience of monitoring plasma levels is far less a concern than the long-term consequences of inadequate treatment, with the social,

interpersonal and neurotoxic effects associated with relapses. In this window of 'lifelong management', lithium is more efficacious and better tolerated than SGAs. And while it can cause thyroid dysfunction (which can be readily managed with thyroid replacement therapy) and renal compromise (but usually only after years of treatment), compared with SGAs lithium is far *less* likely to cause metabolic syndrome, and it does not cause extrapyramidal effects. It is noteworthy that when agents such as olanzapine and quetiapine received indications for BD, the full extent of these side effects was not appreciated. But this is certainly not the case now.

Bipolar Disorder is associated with a high number of deaths from suicide, and over its course, following repeated episodes of illness, it is also thought to be associated with an increased risk of dementia. Critically, lithium reduces both the risk of suicide and is also thought to be neuroprotective⁵. These important additional 'non-mood stabilising' properties of lithium give added cause for it to be considered first line.

Counter to the foregoing views, it is often argued that lithium has limited utility because it is only effective in people with 'classic bipolar disorder', which is characterised by distinctive and recurrent episodes that are separated by periods of remission. This is partly true in that this is indeed the clinical profile in which lithium appears to be 'most' effective (not exclusively), but it is also effective more broadly, as demonstrated both by its synergistic benefits and its actions as an augmenting agent in the treatment of non-responsive major depressive disorder – where lithium can be added to antidepressants to augment their actions and exert an additional antidepressant effect in its own right. Therefore, its use should not be limited to classic bipolar disorder and it can be used across the whole spectrum of mood disorders. Furthermore, the fact that lithium may not be effective in every case of acute mania or bipolar depression, or that it may not be well tolerated in every patient when prescribed long term, does not mean that it should not even be considered, especially since the alternatives are certainly no better. This point is critical, and yet in clinical practice it is often overlooked. Treating serious mood disorders with any medication is complex; and therapeutic response, side-effect profile and tolerability will vary across patients and over time. Careful and collaborative monitoring of outcomes is

therefore a *sine qua non* of successful treatment with lithium, novel antipsychotics or any other psychotropic medication.

The misconceptions surrounding tolerability, and ease of administration, and optimal clinical phenotype, often obscure the fundamental principle that the best treatment should be utilised whenever possible and should be administered as soon as possible. In this regard, lithium *is* the best, and no other medications in direct head to head studies have shown otherwise. Undoubtedly lithium is more difficult to prescribe, and it often requires high levels of clinical expertise to manage, but this is why psychiatrists are also highly trained physicians.

Need your vote

Finally, it is common for detractors of lithium usage to cite examples of patients who have not benefited from its use, or have developed complications after decades of prescription, and while long term lithium therapy can cause thyroid and renal problems, it is important to bear in mind that in the majority of patients it is very well tolerated. Furthermore, for those in whom lithium is effective, it provides long term mood stability and prophylaxis, and a degree of functioning and wellbeing that is yet to be achieved by any other agent.

Therefore, it is imperative that we clinicians, along with the support of our professional and government bodies, level the playing field and ensure that lithium is given due consideration at every stage of BD management. Lithium is still the best medication for treating BD, by far, especially long-term, and it is critical that we prescribe it more often.

* Guidelines recommend frequent monitoring for metabolic impacts.

Declaration of Conflicting Interests:

G.S.M. has received grant or research support from National Health and Medical Research Council, Australian Rotary Health, NSW Health, American Foundation for Suicide Prevention, Ramsay Research and Teaching Fund, Elsevier, AstraZeneca, Janssen-Cilag, Lundbeck,

Otsuka and Servier; and has been a consultant for AstraZeneca, Janssen-Cilag, Lundbeck, Otsuka and Servier.

PB has received research support from the NHMRC, has received speaker fees and educational grants from Servier, and educational support from Lundbeck.

MH has received grant or research support in the last 5 years from the National Health and Medical Research Council, Medical Research Future Fund, Ramsay Health Research Foundation, Boehringer-Ingelheim, Douglas, Janssen-Cilag, Lundbeck, Lyndra, Otsuka, Praxis, and Servier; and has been a consultant for Janssen-Cilag, Lundbeck, Otsuka and Servier

R.J.P. has received support for travel to educational meetings from Servier and Lundbeck and uses software for research at no cost from Scientific Brain Training Pro.

The authors EB, PH, GM, DB, RB, BL, RM, AS and SG declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Statement

The authors received no financial support for the research, authorship, and/or publication of this article.

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