Current Treatment Options in Psychiatry (2014) 1:294–305
DOI 10.1007/s40501-014-0018-1

Mood Disorders (AH Young, Section Editor)

Current Status of Lithium in the Treatment of Mood Disorders

Gin S. Malhi, MBChB BSc(Hons) FRCPsych FRANZCP MD[1,2,*]
Claire McAulay, BA(Hons)[1,2]
Kristina Fritz, BA, PhD[1,2]

Address
*,[1]Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia
Email: gin.malhi@sydney.edu.au
[2]CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, Level 3, Acute Services Building, St Leonards, Sydney, NSW 2065, Australia

Published online: 24 May 2014

Keywords Mood stabilizer · Bipolar disorder · Unipolar depression · Suicide · Prophylaxis · Neuroprotection · Dementia

Opinion statement

Arguably, lithium is the only true mood stabilizer and the only medication developed specifically for the treatment of bipolar disorder. Providing effective long-term prophylaxis, in addition to efficacy in acute treatment of mania and bipolar depression, lithium remains a valuable first-line therapeutic choice. Up to a third of patients on lithium treatment achieve complete remission for up to a decade, markedly countering the burden exacted by the illness. Its clinical use also extends to adjunctive therapy as an augmentation strategy in the management of major depression, dysthymia and cyclothymia; contexts within which its uniquely anti-suicidal properties are apposite. Despite these advantages and a burgeoning body of both empirical and scientific research establishing its efficacy, the clinical use of lithium has diminished in recent years because of displacement by newer agents and erroneous concerns regarding long-term side effects and potential for toxicity. Currently, lithium is experiencing a resurgence of interest as researchers attempt to understand its mechanisms of action and better define its clinical efficacy. This paper briefly reviews its current status with respect to the treatment of mood disorders, and argues that its prominent positioning in clinical practice guidelines worldwide is absolutely justified.

Introduction

Following the rediscovery of its therapeutic effects by John Cade in 1949, lithium soon became a focus of clinical and basic science research. As its mood-stabilizing properties became evident, its use in the treatment of

manic–depressive illness and then bipolar disorder gradually increased. However, Cade was not the only person to have taken an interest in lithium and promulgation of its properties was facilitated by the untiring efforts of Mogens Schou, Erik Strömgren, Paul Baastrup and Samuel Gershon [1]. Collectively, these clinical scientists along with many others demonstrated lithium's effectiveness in treating acute mania and providing prophylaxis against manic or depressive relapses. An understanding of its mechanisms of action has lagged behind its clinical utility, which in recent decades declined because of perceived barriers to its use and the promotion of 'newer' alternatives. Findings from contemporary research should begin to reverse this trend given that it has been shown to have significant long-term efficacy [2••], and, in addition to providing neuroprotection, may even be able to reverse the putative neuropathology that underpins bipolar disorder. Thus, it shows no indication of relinquishing its bipolar throne and will likely remain at the forefront of mood disorders therapy, both alone and as an adjunct. Equally importantly, while its administration is undoubtedly sophisticated, its risks have been found to be exaggerated and hence its true value needs to be both recognized and reinstated [3••].

Lithium has a variety of actions on neurotransmitter systems and second messenger cascades. It inhibits apoptosis, reduces oxidative stress and promotes the transcription of neuroprotective proteins in the brain [4•]. At therapeutic levels of lithium, there are two particular targets of importance: glycogen synthase kinase 3ß and inositol monophosphate (IMPase) [5, 6]. Lithium's actions on neurotransmission of cell function are likely key to understanding the neuropathology of bipolar disorder, which is increasingly emerging as an emotion and cognition neural network disorder underpinned by neuroinflammatory dysfunction in key brain regions. This perhaps partly explains the observed delay in the response to lithium and the need for ongoing treatment to prevent recurrences and progression of the illness. Empirically, its long-term efficacy is further indirectly underscored by the increased likelihood of relapse following abrupt cessation. Clinical trials of 'newer' therapies, which initially trump the effects of lithium in the short term by virtue of anxiolytic and sedative actions, fail to allow for these differential mechanisms of action and, therefore, often incorrectly conclude that lithium lacks efficacy and effectiveness because of delay. In practice, lithium can be used alone or in combination with neuroleptics, anticonvulsants and antidepressants, and remains an optimal strategy for the treatment of both acute and maintenance phases of mood disorders.

The evidence for lithium in the management of mood disorders is sufficient and substantial and commensurate with its standing in current clinical practice guidelines. This brief review paper reappraises its current therapeutic status, especially in the management of bipolar disorder.

Current Status

Bipolar Disorder

Lithium is the archetypal treatment for bipolar disorder, but bipolar disorder can manifest in a variety of alternate forms, which tend to be less sensitive to lithium and more difficult to treat. Despite taxonomic revisions and modifications, bipolar disorder remains a challenging diagnosis – partly because it usually first emerges *forme fruste* as 'major depression'. It can also present as an admixture of manic and depressive mood symptoms superadded to which it is often accompanied by anxiety and coloured by personality. Within the spectrum of bipolar disorders, lithium is best suited to 'classic' manic–depressive patterns characterized clinically by recurrence with cyclical episodes of depression and mania punctuating sustained periods of remission and return to function [7].

The strongest predictive factors of response to lithium include a family history of bipolar or major depression; evidence of lithium response in relatives with mood disorders; later age of onset at first episode; fewer hospitalizations prior to commencing treatment; a history of recurrence with multiple past episodes; an MDI (mania followed by depression and then a well interval) pattern of illness with inter-episode recovery and an absence of mixed episodes or rapid cycling [8]. Consequently, lithium response is regarded as a marker of 'classic' bipolar disorder (or, more correctly, manic–depressive illness) and perhaps reflects the existence of a separate subset within the bipolar spectrum [9]. Duffy et al. recently found that offspring of bipolar disorder patients who developed bipolar themselves were more likely to experience an episodic course if their parents responded to lithium treatment even though lithium responsivity did not confer a higher risk of developing mood disorders overall [10••]. Bipolar I Disorder is generally more responsive to lithium therapy than Bipolar II Disorder [7], but patients in the latter group may be more generally treatment resistant, rather than specifically to lithium therapy, possibly because of greater psychosocial problems [11].

Remarkably, a third of lithium-treated patients achieve 'excellent responder' status [12], and maintain remission without relapse or recurrence for 10 or more years. These robust responders posit the possibility of distinct subtypes of bipolar disorder, and support the notion that "every bipolar disorder patient deserves a trial of lithium somewhere early in their course of illness to find out if they are in this category" [13].

Acute Mania

Evidence for lithium monotherapy in the treatment of acute mania is overwhelming [14] and hence its primacy in clinical practice guidelines [15–17]. Studies since the 1950s have consistently reinforced lithium's effectiveness compared with placebo, and indeed most other medications including neuroleptics [18]. A meta–analysis of acute mania treatment trials with lithium reported a superior response versus placebo [18]. But despite this evidence, because the effects of lithium in the treatment of a manic episode may take 6–10 days after initiation or dose increase, it is often administered alongside a neuroleptic for prompt relief from symptoms such as agitation [19]. Interestingly, an early treatment response to lithium may predict whether it will be effective longer term [20]. In sum, lithium is an effective antimanic agent.

Acute Depression

The evidence for lithium's efficacy in bipolar depressive episodes is less robust in comparison with its therapeutic effects in mania, and it is therefore not considered to be first choice as monotherapy. This phase of bipolar disorder usually presents greater treatment challenges overall, partly due to the more complex causes of depressive episodes [7]. Unfortunately, in most patients, bipolar depression is often the predominant phase of the illness, and it is the phase that confers greatest functional impairment and risk of suicide. Lithium can take 6–8 weeks before antidepressant effects achieve remission, which reduces its suitability as monotherapy in urgent cases. This delay is a distinct disadvantage in clinical trials, which often last only a matter of weeks, and this has contributed to insufficient controlled

studies, and inconclusive systematic reviews of its efficacy [21, 22]. In this context, the BALANCE (Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation) study is seminal as it managed to demonstrate unequivocally that lithium monotherapy reduces the likelihood of relapse in depression and reduces the number of depressive episodes [2••]. But in practice, lithium is often used in combination with other agents for the treatment of acute bipolar depressive episodes, because of its anti-suicidal properties and mood stabilizing effects, which also decreases the likelihood of switching to mania [15–17, 23].

Prophylaxis

A large body of evidence accumulated over 60 years supports lithium prophylaxis in bipolar disorder [2••, 19, 24–26]. A significant decrease in risk of relapse has been shown time and time again, along with prevention of suicidal behaviours and long-term maintenance of euthymic mood. A recent study by Berghöfer et al. followed 346 patients for up to 10 years and demonstrated that the prophylactic effects of lithium were stable over time [27]. Lithium is particularly potent in preventing the recurrence of mania [28, 29], but its prophylaxis does extend to depression. For example, the BALANCE study underscores lithium's effectiveness across both poles of the illness [2••]. This study also demonstrated its superiority over valproate though this was not its primary focus. The active phases of bipolar disorder have been described as 'battles' but it is successful maintenance and prophylaxis that determine the outcome of the 'war'. In this regard, lithium reigns supreme and remains the most effective agent.

Unipolar Depression

Acute Depression

Adjunctive lithium therapy is useful for treating refractory major depression, and clinical trials support its efficacy in combination with tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), tetracyclics and monoamine oxidase inhibitors (MAOIs) [30–32]. Patients with treatment-resistant depression are more likely to respond to lithium augmentation if they possess a family history of bipolar or unipolar depression, and if they have a history of more than three previous episodes of depression [33, 34]. In practice, lithium can be added to any antidepressant, whereas combination therapies with other agents are often complicated. While the extant evidence favours the use of lithium in combination with other antidepressant medications [30, 35], a recent study evaluating lithium monotherapy for unipolar depression found that 50 % responded to treatment in 4 weeks, and two thirds eventually achieved remission [36]. This is particularly noteworthy in the context of subsyndromal manic symptoms in major depression [37].

Clearly, undiagnosed bipolar disorder is a potential confounder for unipolar depression studies into lithium response, although the extent of this is difficult to determine. Sugawara and colleagues retrospectively reviewed adjunctive lithium for treatment-resistant depressed patients in a study that originally included 22 bipolar patients and an additional five from 57 patients who transmuted diagnosis from major–depressive disorder to bipolar disorder by study endpoint. Predictably, bipolar patients were more likely to achieve a superior response [33].

Corroborating this further, Inoue and colleagues demonstrated that presumed unipolar respondents often underwent a diagnostic change to bipolar disorder after follow up [38•]. This lack of longitudinal diagnostic fidelity makes it difficult to determine outcomes with confidence and suggests that lithium responsivity may be governed by 'bipolarity' per se rather than efficacy derived from major depression characteristics.

Prophylaxis

Interestingly, even though there is evidence to suggest that adjunctive lithium confers some prophylaxis against depressive episodes [39], it is seldom continued in patients with major depression much beyond remission of their acute episode, even though preventative antidepressant therapy is advocated especially in those prone to relapse [40].

Dysthymia and Cyclothymia

In addition to its use in bipolar disorder and major depression, adjunctive lithium therapy also has a role in the treatment of other mood disorders, such as dysthymia and cyclothymia (Table 1). Versiani et al. have reported on studies supporting the use of lithium in dysthymia [41], and similarly, Akiskal recommends low-dose lithium for cyclothymia [42]. Early studies suggested a significant preventative effect on depressive episodes in 26–36 % of cyclothymic patients over 2 years [43], but in recent years both cyclothymia and dysthymia have received less attention, possibly because of increasing diagnostic uncertainty, but also in a general move away from lithium use in 'milder' forms of mood disorders [44, 45].

Delivery and Dosing Considerations

The widespread use of lithium has been stifled by the increasingly popular view that it is difficult to administer. Lithium dosing has been discussed in detail elsewhere [46, 47], and despite the misconceptions regarding its administration, its efficacy demands that it is used more widely. To this end, tools such as the 'lithiumeter' (Fig. 1) can be employed to facilitate understanding and safe prescription.

Table 1. Summary of strength of evidence for lithium treatment

Indication	Evidence[a]
Bipolar Disorder	
Mania	EBR I
Depression	EBR II (Monotherapy/augmentation of antidepressants)
Maintenance	EBR I
Cyclothymia	EBR IV
Major depression	EBR I as augmentation agent
Dysthymia	EBR IV
Suicidality	EBR I

[a]Evidence-Based Research (EBR) levels adopted from the Australian NHMRC (National Health and Medical Research Council) guidelines. I – systematic review of level II studies; II – randomized controlled trial; III – other study designs using controls; IV – case series with post-test or pre-test/post-test outcomes

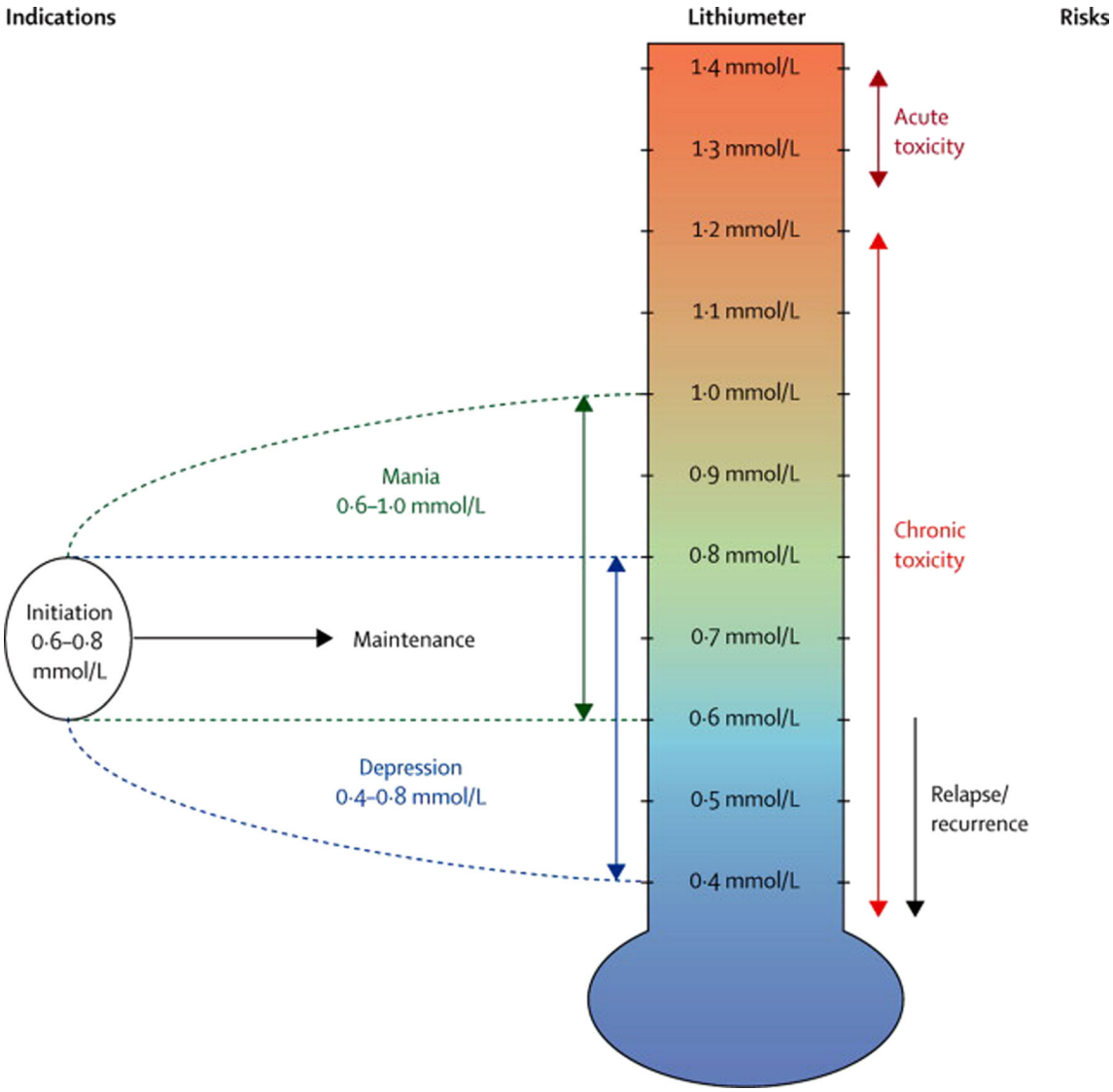

Fig. 1. 'Lithiumeter'. A schematic that can serve as a useful clinical tool to assist with understanding the appropriate therapeutic plasma concentrations of lithium indicated for different phases of illness. Reproduced with permission from Malhi GS, Berk M (2012) Is the safety of lithium no longer in the balance? Lancet 379:690–2. doi: 10.1016/S0140-6736(11)61703-0 [48].

Side Effects and Contraindications

There are a number of side effects to consider when treating with lithium, both short and long term. When lithium is initiated or increased markedly, side effects can include gastrointestinal upsets, tremor, polydipsia, polyuria, headache and fatigue; these tend to be transient. Long-term side effects are of more concern. Long-term lithium use can impact the renal system (less common but high burden), thyroid and parathyroid functioning (moderately common but also in bipolar disorder more generally and lower burden), weight (common but mild, especially compared with other agents),

and other systems more rarely. While long-term lithium use can impact various bodily systems, the population incidence of conditions in bipolar patients and the rarity of many of these effects should be taken into consideration, especially in balance with the treatment benefit in excellent responders or treatment-resistant cases [3••].

Lithium toxicity can result in serious long-term damage to the body, and may occur when kidney excretion of lithium is insufficient. An adverse reaction to high concentrations of lithium (>1.2 mmol/L) is known as acute intoxication. Chronic toxicity involves an adverse reaction despite lithium remaining at therapeutic doses, and can result after chronic lithium use and neural build-up. Haemodialysis is often used to promptly normalize lithium levels and avoid permanent kidney damage.

Lithium can increase the risk of heart defects in the foetus, though this has been overestimated previously [3••]. Effects through transfer in breast milk are unknown. Patients who become pregnant or are breastfeeding should consider the risks and benefits, as well as manage changes in filtration involved in pregnancy which may increase recurrence risk. The psychosocial effect of relapse, especially in responsive patients, should certainly be factored into management [47]. Older patients can be at higher risk of toxicity due to age-related changes in renal function and the impact of other comorbidities. This typically means that required dosages are lower than in the greater population [47]. Finally, those patients with existing kidney problems of higher severity may not be suitable for lithium therapy, while those with more manageable conditions may be suitable with more regular monitoring.

Dosing Schedules

Whether lithium should be administered twice daily or at a lower frequency continues to be a matter for debate [46]. While less frequent administration may improve compliance, reduce or delay risk of kidney damage, and minimize other adverse events, multiple dose schedules are currently recommended in many practice guidelines. Neural levels of lithium differ in their degradation to plasma levels, meaning that even as plasma levels are sometimes lower than optimal between daily doses, lithium may persist and continue to be effective in the brain. Alternate day dosing has also been shown to yield some benefits, such as decreases in some adverse events. However, the risk of suboptimal doses is higher with recurrence more likely [46], which may be alleviated with higher daily doses.

Therapeutic Plasma Concentrations

Optimal lithium concentrations in the blood depend upon which phase is being treated, although different recommendations vary substantially [46]. For initiating treatment and maintenance in bipolar disorder, lower levels of lithium between 0.6 and 0.8 mml/L are recommended. For depressive symptoms, levels of 0.4–0.8 mml/L are considered appropriate. For acute mania, greater levels of 0.6–1.0 mml/L are indicated; however, this increases risk of chronic toxicity (see Fig. 1). Appropriate levels must balance the competing concerns of ensuring efficacy while avoiding complications and minimizing risk.

Future Directions and Novel Findings

Suicidality

By definition and due to the nature of the illness, mood disorder patients are prone to suicidal thinking and are therefore at a greater risk of suicide; this is particularly true for bipolar disorder [49]. In this regard, lithium's anti-suicidal properties are particularly helpful, but research into this somewhat unique trait has inconsistent results [50]. Cipriani and colleagues (2005 and 2013 update) have established its efficacy for unipolar and bipolar patients, in both a systematic review and a sophisticated meta-analysis [51, 52••], as has Baldessarini and colleagues, who showed a 5-fold decrease in suicide risk for bipolar patients [53]. In their meta-analysis of 349 patients, Guzzetta and colleagues found reduced suicide risk in major depressive disorder patients [54]. Lithium alone or combined with neuroleptics was found to lower the risk of suicide as compared with neuroleptics alone [55].

The mechanism of lithium's anti-suicidal action remains unknown but is likely to involve moderation of impulsivity [49]. Notably, this anti-suicidal effect is independent of lithium's effect on mood and even patients with a poor response to lithium and ongoing mood instability benefit with respect to suicidal thinking [56]. Furthermore, this effect extends across different patient populations, and can also be seen at a population level in extremely low doses – for example, when found in groundwater – as illustrated by a number of epidemiological studies [57, 58, 59•, 60, 61]. Hence, the suggestion of trace levels of lithium being added to the water supply in order to achieve population-level benefits with a low risk of side effects has been posited [58].

Neuroprotection

Mood disorders have been shown to be associated with neurological dysfunction, oxidative stress, impaired cellular mechanisms and decreases in grey matter volume and neuronal cell loss. Similar changes, though usually involving different brain regions, have also been reported in bipolar disorder. Research using advanced neuroimaging techniques has shown that lithium is neuroprotective and preserves emotion-related brain regions such as the amygdala, hippocampus, and other areas in the fronto-limbic network, with increased or preserved neural volume or density reported [4•, 62•]. Again, akin to its anti-suicidal actions, this neuroprotective effect appears to occur independently of its mood-modulating actions, such that even in those that are not classified as 'excellent responders', lithium can preserve and enhance grey matter volume [63•]. In comparison, the neuroprotective effects of lithium on white matter are less clear [64•]. Regardless, these tantalizing findings point to profound properties and further reinforce lithium's suitability as an adjunctive agent, and possibly provide clues as to the functional mechanisms underpinning its clinical efficacy.

Dementia

Cognition is invariably compromised by mood disorders, and though the pattern of change is often mood-state related, naturally over time the brain receives repeated insults and accumulates trait changes. Lithium's 'neuroregenerative' actions can therefore be extended and its use in dementia holds promise. For example,

lithium has been shown to reduce the risk of dementia in bipolar patients [65], and may reduce the risk of Alzheimer's disease [66•]. There are tentative indications that lithium may slow or reverse cognitive changes, such as verbal learning, verbal memory, and psychomotor speed [67]. These benefits may, however, depend upon responsivity to lithium [68]. Some studies have found no impairment or benefit in healthy volunteers at least over the short term [69]. Lithium also causes some cognitive impairments in mood-disordered patients, which makes the effects of lithium difficult to disentangle from the impact of the disorder [69]. Therefore, more research is needed to disentangle these complex effects on cognition.

Conclusion

Despite lithium's resounding efficacy, its principal limitation remains that of tolerability, as it is toxic acutely at high doses, and chronically at therapeutic doses. The mechanisms of action of lithium suggest that second messenger systems are a key target and thus need to be better defined so as to identify opportunities for specific agents that are able to replicate its benefits but obviate its side effects. Such lithium mimetics have been designed and seem to offer promise in animal models.

Compliance with Ethics Guidelines

Conflict of Interest

Professor Malhi reports grants and/or personal fees, outside of the submitted work, from AstraZeneca, Eli Lilly, Organon, Pfizer, Servier, Wyeth, Janssen-Cilag, Lundbeck, Ranbaxy.

Dr. Kristina Fritz and Claire McAulay declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Schioldann J. History of the introduction of lithium into medicine and psychiatry: birth of modern psychopharmacology 1949. Adelaide: Adelaide Academic Press in collaboration with Brascoe Publishing; 2009.

2.•• Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010;375:385–95. doi:10.1016/S0140-6736(09)61828-6.

This seminal study reinstated lithium's long-term effectiveness as a prophylactic and maintenance agent in combination with valproate, and though the study was not designed to distinguish between valproate and lithium, it demonstrated lithium's superiority in the treatment of bipolar I disorder. This study suggests that lithium in combination with valproate should be considered first-line in the treatment of bipolar disorder, and that patients that relapse on lithium should consider switching to combination therapy.

3.•• McKnight RF, Adida M, Budge K, et al. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379:721–8. doi:10.1016/S0140-6736(11)61516-X.

This study dispelled many of the myths surrounding the risks associted with lithium treatment. It indicated that lithium is in fact much safer than initally thought but that it does re-

quire regular monitoring of blood levels and other parameters. Amongst these, a new recommendation was to monitor calcium levels for potential hypercalcaemia.

4.• Malhi GS, Tanious M, Das P, et al. Potential mechanisms of action of lithium in bipolar disorder. Current understanding. CNS Drugs. 2013;27:135–53. doi:10.1007/s40263-013-0039-0.

This comprehensive review article provides a detailed up-to-date account of potential mechanisms of action of lithium, summarizing its effects at all levels from mood and cognition to brain structure and function and cellular/intracellular changes.

5. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. Cell. 1989;59:411–9.
6. O'Brien WT, Klein PS. Validating GSK3 as an in vivo target of lithium action. Biochem Soc Trans. 2009;37:1133–8. doi:10.1042/BST0371133.
7. Gershon S, Chengappa KNR, Malhi GS. Lithium specificity in bipolar illness: a classic agent for the classic disorder. Bipolar Disord. 2009;11 Suppl 2:34–44. doi:10.1111/j.1399-5618.2009.00709.x.
8. Kleindienst N, Engel R, Greil W. Which clinical factors predict response to prophylactic lithium? A systematic review for bipolar disorders. Bipolar Disord. 2005;7:404–17. doi:10.1111/j.1399-5618.2005.00244.x.
9. Grof P. Sixty years of lithium responders. Neuropsychobiology. 2010;62:8–16. doi:10.1159/000314305.
10.•• Duffy A, Horrocks J, Doucette S, et al. The developmental trajectory of bipolar disorder. Br J Psychiatry. 2014;204:122–8. doi:10.1192/bjp.bp.113.126706.

This key research paper emphasises the importance of lithium responsivity and how this may impact the phenotypic presentation of bipolar disorder.

11. Malhi GS, Bargh DM, Cashman E, et al. The clinical management of bipolar disorder complexity using a stratified model. Bipolar Disord. 2012;14 Suppl 2:66–89. doi:10.1111/j.1399-5618.2012.00993.x.
12. Grof P. Excellent lithium responders: people whose lives have been changed by lithium prophylaxis. In: Birch NJ, Gallichio VS, Becker R, (editors) Lithium: 50 years Psychopharmacology. New Perspect. Biomed. Clin. Res. Weidner Publishing Group, Cheshire, CT; 1999. p. 36–51.
13. Sinclair L. Bipolar Disorder Expert Laments Lithium's Fading Popularity. Psychiatr News. 2012;47:11.
14. Baldessarini RJ, Tondo L. Does lithium treatment still work?: evidence of stable responses over three decades. Arch Gen Psychiatry. 2000;57:187–90.
15. Malhi GS, Adams D, Lampe L, et al. Clinical practice recommendations for bipolar disorder. Acta Psychiatr Scand Suppl. 2009;27–46. doi:10.1111/j.1600-0447.2009.01383.x.
16. Yatham L, Kennedy S. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11(3):225–55. doi:10.1111/j.1399-5618.2009.00672.x.
17. National Collaborating Centre for Mental Health. National Institute for Health and Clinical Excellence. Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. London: National Institute of Health and Clinical Excellence, The British Psychological Society and Gaskell; 2006.
18. Yildiz A, Vieta E, Leucht S, Baldessarini RJ. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. Neuropsychopharmacology. 2011;36:375–89. doi:10.1038/npp.2010.192.
19. Malhi GS, Adams D, Berk M. Is lithium in a class of its own? A brief profile of its clinical use. Aust N Z J Psychiatry. 2009;43:1096–104. doi:10.3109/00048670903279937.
20. Machado-Vieira R, Luckenbaugh DA, Soeiro-de-Souza MG, et al. Early improvement with lithium in classic mania and its association with later response. J Affect Disord. 2013;144:160–4. doi:10.1016/j.jad.2012.05.039.
21. Vieta E, Locklear J, Günther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. J Clin Psychopharmacol. 2010;30:579–90. doi:10.1097/JCP.0b013e3181f15849.
22. Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. Br J Psychiatry. 2010;196:266–73. doi:10.1192/bjp.bp.108.057612.
23. Valentí M, Pacchiarotti I, Bonnín CM, et al. Risk factors for antidepressant-related switch to mania. J Clin Psychiatry. 2012;73:e271–6. doi:10.4088/JCP.11m07166.
24. Grof P, Müller-Oerlinghausen B. A critical appraisal of lithium's efficacy and effectiveness: the last 60 years. Bipolar Disord. 2009;11 Suppl 2:10–9. doi:10.1111/j.1399-5618.2009.00707.x.
25. Nivoli AMA, Murru A, Vieta E. Lithium: still a cornerstone in the long-term treatment in bipolar disorder? Neuropsychobiology. 2010;62:27–35. doi:10.1159/000314307.
26. Hirschowitz J, Kolevzon A, Garakani A. The pharmacological treatment of bipolar disorder: the question of modern advances. Harv Rev Psychiatry. 2010;18:266–78. doi:10.3109/10673229.2010.507042.
27. Berghöfer A, Alda M, Adli M, et al. Stability of lithium treatment in bipolar disorder - long-term follow-up of 346 patients. Int J Bipolar Disord. 2013;1:11. doi:10.1186/2194-7511-1-11.

28. Coryell W. Maintenance treatment in bipolar disorder: a reassessment of lithium as the first choice. Bipolar Disord. 2009;11 Suppl 2:77–83. doi:10.1111/j.1399-5618.2009.00712.x.
29. Young AH, Hammond JM. Lithium in mood disorders: increasing evidence base, declining use? Br J Psychiatry. 2007;191:474–6. doi:10.1192/bjp.bp.107.043133.
30. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry. 2007;68:935–40. doi:10.4088/JCP.v68n0617.
31. Bschor T, Bauer M. Efficacy and mechanisms of action of lithium augmentation in refractory major depression. Curr Pharm Des. 2006;12:2985–92. doi:10.2174/138161206777947650.
32. Malhi GS, Adams D, Porter R, et al. Clinical practice recommendations for depression. Acta Psychiatr Scand Suppl. 2009;8–26. doi:10.1111/j.1600-0447.2009.01382.x.
33. Sugawara H, Sakamoto K, Harada T, Ishigooka J. Predictors of efficacy in lithium augmentation for treatment-resistant depression. J Affect Disord. 2010;125:165–8. doi:10.1016/j.jad.2009.12.025.
34. Bschor T, Uhr M, Baethge C, et al. Acute antidepressive efficacy of lithium monotherapy, not citalopram, depends on recurrent course of depression. J Clin Psychopharmacol. 2012. doi:10.1097/JCP.0b013e31827b9495.
35. Bauer M, Adli M, Bschor T, et al. Lithium's emerging role in the treatment of refractory major depressive episodes: augmentation of antidepressants. Neuropsychobiology. 2010;62:36–42. doi:10.1159/000314308.
36. Bschor T, Ritter D, Winkelmann P, et al. Lithium monotherapy increases ACTH and cortisol response in the DEX/CRH test in unipolar depressed subjects. A study with 30 treatment-naive patients. PLoS One. 2011;6:e27613.
37. Angst J, Cui L, Swendsen J, et al. Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. Am J Psychiatry. 2010;167:1194–201. doi:10.1176/appi.ajp.2010.09071011.
38.• Inoue T, Abekawa T, Nakagawa S, et al. Long-term naturalistic follow-up of lithium augmentation: relevance to bipolarity. J Affect Disord. 2011;129:64–7. doi:10.1016/j.jad.2010.08.022.
This interesting long-term study with a mean 8-year follow up of patients with treatment-resistant drepession, found that lithium responsivity predicted diagnostic depression conversion to bipolar disorder.
39. Souza FG, Goodwin GM. Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. Br J Psychiatry. 1991;158:666–75.
40. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003;361:653–61. doi:10.1016/S0140-6736(03)12599-8.
41. Versiani M, Nardi AE, Figueira I. Pharmacotherapy of dysthymia: review and new findings. Eur Psychiatry. 1998;13:203–9. doi:10.1016/S0924-9338(98)80005-9.
42. Akiskal HS. Dysthymia and cyclothymia in psychiatric practice a century after Kraepelin. J Affect Disord. 2001;62:17–31.
43. Peselow ED, Dunner DL, Fieve RR, Lautin A. Lithium prophylaxis of depression in unipolar, bipolar II, and cyclothymic patients. Am J Psychiatry. 1982;139:747–52. doi:10.1097/00004714-198212000-00022.
44. Van Meter AR, Youngstrom EA, Findling RL. Cyclothymic disorder: a critical review. Clin Psychol Rev. 2012;32:229–43. doi:10.1016/j.cpr.2012.02.001.
45. Parker G, McCraw S, Fletcher K. Cyclothymia. Depress Anxiety. 2012;29:487–94. doi:10.1002/da.21950.
46. Malhi GS, Tanious M. Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations. CNS Drugs. 2011;25:289–98. doi:10.2165/11586970-000000000-00000.
47. Malhi GS, Tanious M, Das P, Berk M. The science and practice of lithium therapy. Aust N Z J Psychiatry. 2012;46:192–211. doi:10.1177/0004867412437346.
48. Malhi GS, Berk M. Is the safety of lithium no longer in the balance? Lancet. 2012;379:690–2. doi:10.1016/S0140-6736(11)61703-0.
49. Malhi GS, Bargh DM, Kuiper S, et al. Modeling bipolar disorder suicidality. Bipolar Disord. 2013;15:559–74. doi:10.1111/bdi.12093.
50. Burgess S, Geddes J, Hawton K, et al. Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev CD003013. 2001. doi:10.1002/14651858.CD003013.
51. Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry. 2005;162:1805–19. doi:10.1176/appi.ajp.162.10.1805.
52.•• Cipriani A, Hawton K, Stockton S. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. 2013;3646:1–13. doi:10.1136/bmj.f3646.
This recent extension to Cipriani's previous (2005) review and meta-analysis included 48 randomized controlled trials, and has further bolstered the anti-suicidal efficacy of lithium, beyond its prophylactic effects. It highlights the need for further research into the mechanisms of this

effect and the potential effects of lithiun on aggression and impulsivity.

53. Baldessarini RJ, Tondo L, Davis P, et al. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord. 2006;8:625–39. doi:10.1111/j.1399-5618.2006.00344.x.
54. Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry. 2007;68:380–3. doi:10.4088/JCP.v68n0304.
55. Ahearn EP, Chen P, Hertzberg M, et al. Suicide attempts in veterans with bipolar disorder during treatment with lithium, divalproex, and atypical antipsychotics. J Affect Disord. 2013;145:77–82. doi:10.1016/j.jad.2012.07.015.
56. Müller-Oerlinghausen B. Arguments for the specificity of the antisuicidal effect of lithium. Eur Arch Psychiatry Clin Neurosci. 2001;251(Suppl):II72–5.
57. Helbich M, Leitner M, Kapusta ND. Geospatial examination of lithium in drinking water and suicide mortality. Int J Health Geogr. 2012;11:19. doi:10.1186/1476-072X-11-19.
58. Terao T, Goto S, Inagaki M, Okamoto Y. Even very low but sustained lithium intake can prevent suicide in the general population? Med Hypotheses. 2009;73:811–2. doi:10.1016/j.mehy.2009.02.043.
59.• Blüml V, Regier MD, Hlavin G, et al. Lithium in the public water supply and suicide mortality in Texas. J Psychiatr Res. 2013;47:407–11. doi:10.1016/j.jpsychires.2012.12.002.

This intriguing study investigated lithium levels in public drinking water across Texas and found a significant negative association between levels and suicide rates when adjusting for a number of additional socioeconomic factors.

60. Sugawara N, Yasui-Furukori N, Ishii N, et al. Lithium in tap water and suicide mortality in Japan. Int J Environ Res Public Health. 2013;10:6044–8. doi:10.3390/ijerph10116044.
61. Kapusta ND, Mossaheb N, Etzersdorfer E, et al. Lithium in drinking water and suicide mortality. Br J Psychiatry. 2011;198:346–50. doi:10.1192/bjp.bp.110.091041.
62.• Hallahan B, Newell J, Soares JC, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 2011;69:326–35. doi:10.1016/j.biopsych.2010.08.029.

This key study brings together data from worldwide centres and shows the specific neuroprotective effect of lithium on key emotion-related brain structures such as the hippocampus and amygdala.

63.• Hajek T, Bauer M, Simhandl C, et al. Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. Psychol Med. 2013;44:1–11. doi:10.1017/S0033291713001165.

This recent study found reduced hippocampal volume in non-lithium-treated bipolar disorder patients compared with lithium-treated bipolar disorder patients and controls. The apparent benefit for lithium treatment was independent of responsivity, as measured by episodes of illness while on treatment.

64.• Marlinge E, Bellivier F, Houenou J. White matter alterations in bipolar disorder: potential for drug discovery and development. Bipolar Disord. 2014;16:97–112. doi:10.1111/bdi.12135.

This recent review highlighted new directions in studies on white matter abnormalities in bipolar disorder and potential mechanisms of lithium, in particular GSK-3ß and IMPase inhibition, that may be implicated in these abnormalities. It recommended greater focus on white matter plasticity in developing new psychological and pharmaceutical interventions.

65. Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? Bipolar Disord. 2010;12:87–94. doi:10.1111/j.1399-5618.2009.00788.x.
66.• Forlenza OV, De Paula VJ, Machado-Vieira R, et al. Does lithium prevent Alzheimer's Disease? Drugs Aging. 2012;29:335–42.

This study presents promising findings regarding the potential impact of lithium's neuroprotective effects, and how these may be implicated in mechanisms underpinning Alzheimer's Disease and potentially other neurodegenerative disorders such as amyotrophic lateral sclerosis.

67. Arts B, Jabben N, Krabbendam L, van Os J. A 2-year naturalistic study on cognitive functioning in bipolar disorder. Acta Psychiatr Scand. 2011;123:190–205. doi:10.1111/j.1600-0447.2010.01601.x.
68. Rybakowski JK, Permoda-Osip A, Borkowska A. Response to prophylactic lithium in bipolar disorder may be associated with a preservation of executive cognitive functions. Eur Neuropsychopharmacol. 2009;19:791–5. doi:10.1016/j.euroneuro.2009.06.002.
69. Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: A meta-analysis. J Cinical Psychiatry. 2009;70:1588–97. doi:10.4088/JCP.08r04972.