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The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young. © 2025 David M. Taylor. Published 2025 by John Wiley & Sons Ltd. Chapter 2 Lithium Mechanism of action Lithium is implicated in a wide range of biological processes, with a multiplicity of effects. Consequently it has proven very difficult to ascertain the key mechanism(s) of action of lithium in regulating mood and behaviour. For example, there is some older evidence that people with bipolar illness have higher intracellular concentrations of sodium and calcium than controls and that lithium can reduce these. Interestingly, calcium-related genes have been implicated by genetic studies in bipolar disorder.1 GSK3 (glycogen synthase kinase 3), CREB (cAMP response element-binding protein) and Na+/K+ adenosine triphosphatase (ATPase) related mechanisms may be important for lithium's effects.2 Lithium may have neuroprotective effects that preserve the function of neurons and neuronal circuits.3 Lithium also promotes neurogenesis in the hippocampus, which is important for learning, memory and stress responses.4 A meta- analysis suggests lithium may prevent transition to dementia5 and lithium appears to be more effective than aducanumab in preventing cognitive decline.6 However, the largest study to date showed no beneficial effect on risk of neurocognitive disorders.7 Both reversible and irreversible neurotoxicity related to lithium are recognised adverse effects.8,9 Lithium is present in low levels in the environment (e.g. in drinking water sources) and environmental lithium concentration has been reported to be inversely related to suicide and dementia at a population level.10,11 Clinical indications Acute treatment of mania Lithium is effective for the treatment of mania, at a plasma level of 0.8–1.0mmol/L.12 If a faster onset of action is needed an adjunctive or single-agent antipsychotic with an evidence base for treating mania is recommended.12 It can be difficult to achieve Bipolar disorder

280 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 therapeutic plasma lithium levels rapidly and monitoring may be problematic if the patient is uncooperative. Treatment may be most successful in those without psychotic symptoms or evidence of rapid cycling.13 Treatment of acute mania in patients already on long-term lithium The 2016 British Association for Psychopharmacology guidelines12 suggest that in the event of relapse, an urgent plasma lithium level should be obtained to indicate the level of compliance with lithium therapy and inform possible dose adjustment. If lithium level measurement indicates non-compliance, the reason should be ascertained. If the lithium level is confirmed to be optimal, but the control of mania is inadequate, then adding a dopamine antagonist, dopamine partial agonist or valproate (given the conditions with regard to reproductive potential) is recommended.12 Bipolar depression Lithium is widely used in bipolar depression but evidence supporting robust efficacy for acute episodes is somewhat unconvincing.14,15 Evidence for prevention of depressive episodes is more compelling.

Maintenance treatment of bipolar disorder Aim for the highest tolerable lithium plasma level in the range of 0.6–0.8mmol/L12,16 with the option to reduce it to 0.4–0.6mmol/L in case of good response but poor tolerance, or to increase it to 0.8–1.0mmol/L in case of insufficient response and good tolerance. The aim of treatment is complete remission and prevention of both manic and depressive episodes.17 Lithium is the best-performing mood stabiliser for bipolar disorder in practice with a prophylactic effectiveness similar to long-acting antipsychotics.18 In 2024, it remains the gold standard treatment for bipolar disorder.19 Augmentation of antidepressants in unipolar depression Approximately 30–50% of patients fail to respond to trials of first- or second-line antidepressants and outcomes from treatment-resistant depression are poor.20 Evidence-based guidelines for treating depressive disorders with antidepressants21 suggest that either lithium or quetiapine is the agent of first choice for augmenting the existing antidepressant and that lithium augmentation is most effective at a lithium plasma level of 0.6–1.0mmol/L. Recent meta-analyses suggest robust efficacy for lithium, alongside quetiapine, D2 partial agonists and ketamine.22,23 One meta-analysis suggested lithium to be most effective.24 Clinical predictors associated with a better outcome in lithium augmentation for treatment-resistant depression included more severe depressive symptomatology, psychomotor retardation, significant weight loss, a family history of major depression or a personal experience of more than three episodes.25 Of course, compliance with lithium augmentation should also be added to this list. Lithium is widely underused in resistant depression.26

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