07 - Chapter 2 Bipolar disorder

01 - Lithium

Lithium

02 - Mechanism of action

Mechanism of action

03 - Clinical indications

Clinical indications

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

04 - Lithium and suicide

Lithium and suicide

05 - Plasma levels

Plasma levels

Bipolar disorder CHAPTER 2 Prophylaxis of unipolar depression Lithium is significantly superior to antidepressants in preventing relapses that require hospitalisation, with a relative risk of 0.34.27 Lithium prophylaxis is indicated in unipolar depression (i) if a patient has suffered two depressive episodes in 5 years; (ii) after one episode if the episode is severe and there is a strong suicide risk; (iii) with indefinite treatment if there is adherence and adverse events are not problematic, particularly if a bipolar background is suspected.28 Other uses of lithium Lithium is also used to treat aggressive and self-mutilating behaviour and studies have confirmed benefits29 to both prevent and treat steroid-induced psychosis30 and to raise the white blood cell count in patients receiving clozapine.31 Lithium and suicide It is estimated that 15% of people with bipolar disorder eventually take their own life.32 A meta-analysis of clinical trials concluded that lithium reduced the risk of both attempted and completed suicide by 80% in patients with bipolar illness,33 and large database studies have shown that lithium-treated patients are less likely to complete suicide than patients treated with other mood-stabilising drugs.34 In patients with unipolar depression, lithium also seems to protect against suicide although the mechanism of this protective effect is unknown.33 As noted, environmental lithium has been reported to be inversely related to suicide at a population level.10,35 Plasma levels The minimum effective plasma level for prophylaxis of mood disorder episodes is probably 0.4mmol/L, with the optimal concentration being in the range 0.6–-0.8mmol/L.36 Levels above 0.75mmol/L offer additional protection only against manic symptoms37 so the target range for prophylaxis is effectively 0.6–0.8mmol/L.16,38 Changes in plasma levels in either direction seem to worsen the risk of relapse.37 The optimal plasma level range in patients who have unipolar depression is less clear.39 Taking account of evidence from clinical trials, naturalistic studies and lithium in drinking water, studies seem to suggest that various benefits of lithium begin at a low concentration and increase over a narrow range up to 1.0mmol/L. Low-dose lithium regimens are under investigation but not yet clinically recommended.40 Children and adolescents may require higher plasma levels than adults to ensure that an adequate concentration of lithium is present in the central nervous system (CNS).41 Lithium is rapidly absorbed from the gastrointestinal tract but has a long distribution phase. Blood samples for plasma lithium level estimations should be taken 10–14 (ideally 12) hours post-dose in patients who are prescribed a single daily dose of a prolonged-release preparation at bedtime.12

06 - Formulations

Formulations

07 - Adverse effects

Adverse effects

08 - Lithium toxicity

Lithium toxicity

282 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Formulations There is no clinically significant difference in the pharmacokinetics of the two most widely prescribed brands of lithium in the UK: Priadel and Camcolit. In other countries, standard lithium carbonate tablets are often given twice or three times daily. The amount of elemental lithium varies by salt used. ■ ■Lithium carbonate 400mg tablets each contain 10.8mmol lithium. ■ ■Lithium citrate liquid is available in two strengths: ■ ■5.4mmol/5mL (equivalent to 200mg lithium carbonate). ■ ■10.8mmol/5mL (equivalent to 400mg lithium carbonate). Lack of clarity over which liquid preparation is intended when prescribing can lead to the patient receiving a sub-therapeutic or toxic dose. Liquid preparations need to be given 12-hourly. Adverse effects Most adverse effects are dose- and plasma level-related. These include mild gastrointestinal upset, fine tremor, polyuria and polydipsia. Polyuria may occur more frequently with twice daily dosing.42,43 Propranolol can be useful in lithium-induced tremor. Some skin conditions such as psoriasis and acne can be aggravated by lithium therapy. Lithium can also cause a metallic taste in the mouth, ankle oedema and weight gain. Lithium can cause a reduction in urinary concentrating capacity – nephrogenic diabetes insipidus – hence the occurrence of thirst and polyuria. This effect is usually reversible in the short to medium term, but renal effects may be irreversible after long- term treatment (>15 years).44 Lithium treatment can also lead to a reduction in the glomerular filtration rate (GFR) although the magnitude of the risk is uncertain.44 Lithium levels of >0.8mmol/L are associated with a higher risk of renal toxicity and prolonged lithium treatment of course requires regular monitoring of kidney function.45 Hypertension and a diagnosis of bipolar disorder worsen the risk of lithium-related chronic kidney disease.46 In the longer term, lithium increases the risk of hypothyroidism;47 in middle-aged women the risk may be up to 20%.48 A case has been made for testing thyroid autoantibodies in this group before starting lithium (to better estimate risk) and for performing thyroid function tests (TFTs) more frequently in the first year of treatment.49 Hypothyroidism is readily treated with thyroxine. TFTs usually return to normal when lithium is discontinued. Lithium also more rarely causes hyperthyroidism.50 Hyperparathyroidism causes hypercalcaemia in about 4% of patients51 and calcium levels should be monitored in patients on long-term treatment.50,52 Clinical consequences of chronically increased serum calcium include renal stones, osteoporosis, dyspepsia, hypertension and renal impairment. Lithium toxicity Toxic effects reliably occur at levels >1.5mmol/L and usually consist of gastrointestinal symptoms (increasing anorexia, nausea and diarrhoea) and CNS effects (muscle weakness, drowsiness, confusion, ataxia, coarse tremor and muscle twitching).53

09 - Pre treatment tests

Pre-treatment tests

10 - On treatment monitoring[12,58]

On-treatment monitoring[12,58]

11 - Discontinuation

Discontinuation

Bipolar disorder CHAPTER 2 Above 2mmol/L, increased disorientation and seizures usually occur, which can progress to coma and ultimately death. In the presence of more severe symptoms, osmotic or forced alkaline diuresis should be used in a medical facility. Above 3mmol/L, peritoneal or haemodialysis is often used. These plasma levels are only a guide and individuals vary in their susceptibility to symptoms of toxicity. Neurotoxicity at normal plasma levels has also been described, as brain lithium levels may not be reflected by concentration in the plasma.54,55 Most risk factors for toxicity involve changes in sodium levels or in the way the body handles sodium, for example low salt diets, dehydration, drug interactions (see later Table 2.2) and some uncommon physical illnesses such as Addison's disease. Information relating to the symptoms of toxicity and the common risk factors (especially drug interactions) should always be given to patients when treatment with lithium is initiated.56 This information should be repeated at appropriate intervals to make sure that it is clearly understood. Pre-treatment tests Before prescribing lithium, renal, thyroid and cardiac function should be checked. As a minimum, the estimated GFR (eGFR),57 urea and electrolytes (U&Es) and TFTs should be checked. A baseline calcium level is also helpful. An electrocardiogram (ECG) is also recommended in patients who have risk factors for, or existing, cardiovascular disease. A baseline measure of weight is also desirable. Lithium is a putative human teratogen. Women of child-bearing age should be advised to use a reliable form of contraception. See the section on psychotropics and pregnancy (Chapter 7). On-treatment monitoring12,58 Plasma lithium, eGFR, U&Es and TFTs should be checked every 6 months. More frequent tests may be required in those who are prescribed interacting drugs, who are elderly or who have established chronic kidney disease. Weight (or body mass index [BMI]) should also be monitored. Lithium monitoring in clinical practice in the UK is known to be suboptimal59 although there has been a modest improvement over time.60 The use of automated reminder systems has been shown to improve monitoring rates.61 Discontinuation Intermittent treatment with lithium may worsen the natural course of bipolar illness. A much greater than expected incidence of manic relapse is seen in the first few months after abruptly discontinuing lithium,62 even in patients who have been symptom-free for as long as 5 years.63 Lithium treatment should not be started unless there is a clear intention to continue it for several years and where compliance can be reasonably assured.64 This advice has obvious implications for initiating lithium treatment against a patient's will (or in a patient known to be non-compliant with medication) during a period of acute illness. The risk of relapse is probably reduced by decreasing the dose gradually over a period of at least a month65 and avoiding decremental plasma level reductions of >0.2mmol/L.37

12 - Interactions with other drugs7072

Interactions with other drugs70–72

284 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 In contrast with these recommendations, a naturalistic study found that, in patients who had been in remission for at least 2 years and had discontinued lithium very slowly, the recurrence rate was at least three times greater than in patients who continued lithium and that significant survival differences persisted for many years. Patients maintained on high lithium levels before discontinuation were particularly prone to relapse.66 One large US study based on prescription records found that half of those prescribed lithium took almost all of their prescribed doses, a quarter took between 50% and 80% and the remaining quarter took less than 50%. A third of patients took lithium for less than 6 months in total.67 A large audit found that 1 in 10 patients prescribed long-term lithium treatment had a plasma level below the therapeutic range.68 It is clear that suboptimal adherence limits the effectiveness of lithium in clinical practice. One database study suggested the extent to which lithium was taken was directly related to the risk of suicide (more prescriptions were associated with lower suicide rate).69 Less convincing data support the emergence of depressive symptoms in bipolar patients after lithium discontinuation.62 There are few data relating to patients with unipolar depression. Table 2.1 summarises the prescribing and monitoring of lithium. Interactions with other drugs70–72 Because of lithium's relatively narrow therapeutic index, pharmacokinetic interactions with other drugs can precipitate lithium toxicity. Most clinically significant interactions are largely with drugs that alter renal sodium handling. Rarely, neurotoxicity results from co-prescribing lithium and antipsychotics.73,74 ACE inhibitors Angiotensin-converting enzyme (ACE) inhibitors can (i) reduce thirst, which can lead to mild dehydration; and (ii) increase renal sodium loss leading to increased sodium reabsorption by the kidney, resulting in an increase in lithium plasma levels. The magnitude of Table 2.1 Lithium: prescribing and monitoring. Indications Mania, hypomania, prophylaxis of bipolar affective disorder and recurrent depression. Reduces aggression and suicidality. Pre-lithium work-up Estimated glomerular filtration rate (eGFR) and thyroid function tests (TFTs). ECG recommended in patients who have risk factors for, or existing, cardiovascular disease. Baseline measure of weight desirable. U&Es (including calcium). Prescribing Start at 400mg at night (200mg in the elderly). Plasma level after 7 days, then 7 days after every dose change until the desired level is reached (0.4mmol/L may be effective in unipolar depression, 0.6–1.0mmol/L in bipolar illness, slightly higher levels in

this range in difficult to treat mania). Blood should be taken 12 hours after the last dose. Take care when prescribing liquid preparations to clearly specify the strength required. Monitoring Plasma lithium every 6 months (more frequent monitoring is necessary in those prescribed interacting drugs, the elderly and those with established renal impairment or other relevant physical illness). eGFR, U&Es and TFTs every 6 months. Weight (or body mass index) should also be monitored. Stopping Reduce slowly over at least 1 month and preferably 3 months. Avoid reductions in plasma levels of

> 0.2mmol/L at a time (see section on discontinuation).

Bipolar disorder CHAPTER 2 this effect is variable, from no increase to a fourfold increase. The full effect can take several weeks to develop. The risk seems to be increased in patients with heart failure, dehydration and renal impairment (presumably because of changes in fluid balance/handling). In the elderly, ACE inhibitors increase sevenfold the risk of hospitalisation due to lithium toxicity. ACE inhibitors can also precipitate renal failure so, if co-prescribed with lithium, more frequent monitoring of eGFR and plasma lithium is required. The following drugs are ACE inhibitors: captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril and trandolapril. Care is also required with the angiotensin II receptor antagonists candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. Diuretics Diuretics can reduce the renal clearance of lithium, the magnitude of this effect being greater with thiazide than with loop diuretics. Lithium levels usually rise within 10 days of a thiazide diuretic being prescribed; the magnitude of the rise is unpredictable and can vary from an increase of 25% to 400%. The following drugs are thiazide (or related) diuretics: bendroflumethiazide, chlortalidone, cyclopenthiazide, indapamide, metolazone and xipamide. Although there are case reports of lithium toxicity induced by loop diuretics, many patients receive this combination of drugs without apparent problems. The risk of an interaction seems to be greatest in the first month after the loop diuretic has been prescribed and additional lithium plasma level monitoring during this time is recommended if these drugs are co-prescribed. Loop diuretics can increase sodium loss and subsequent reabsorption by the kidney. Patients taking loop diuretics may also have been advised to restrict their salt intake; this may contribute to the risk of lithium toxicity in these individuals. The following drugs are loop diuretics: bumetanide, furosemide and torasemide. Non-steroidal anti-inflammatory drugs Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of renal prostaglandins, thereby reducing renal blood flow and possibly increasing renal reabsorption of sodium and therefore lithium. The magnitude of the rise in lithium concentration is unpredictable for any given patient; case reports vary from increases of around 10% to over 400%. The onset of effect also seems to be variable, from a few days to several months. Risk appears to be increased in those patients who have impaired renal function, renal artery stenosis or heart failure and who are dehydrated or on a low salt diet. There are a number of case reports of an interaction between lithium and COX-2 inhibitors. NSAIDs do not appear to diminish the therapeutic effects of lithium,75 as has previously been reported. NSAIDs (or COX--2 inhibitors) can be very carefully combined with lithium, but they should be prescribed regularly, not intermittently, and more frequent plasma lithium monitoring is essential. Some NSAIDs can be purchased without a prescription, so it is particularly important that patients are aware of the potential for interaction. The following drugs are NSAIDs or COX-2 inhibitors: aceclofenac,

acemetacin, celecoxib, dexibuprofen, dexketoprofen, diclofenac, diflunisal, etodolac, etoricoxib,

13 - References

References

286 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, lumiracoxib, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid. Carbamazepine There are rare reports of neurotoxicity when carbamazepine is combined with lithium. Most reports are old and in the context of treatment involving high plasma lithium levels. It is of note though that carbamazepine can cause hyponatraemia, which may in turn lead to lithium retention and toxicity. Similarly, rare reports of CNS toxicity implicate selective serotonin reuptake inhibitors (SSRIs), another group of drugs that can cause hyponatraemia. Table 2.2 summarises drugs that may clinically interact with lithium. References

1. Bray NJ, et al. The genetics of neuropsychiatric disorders. Brain Neurosci Adv 2019; 2:2398212818799271.
2. Bortolozzi A, et al. New advances in the pharmacology and toxicology of lithium: a neurobiologically oriented overview. Pharmacol Rev 2024; 76:323–357.
3. Jope RS, et al. Lithium to the rescue. Cerebrum 2016; 2016:cer-02-16.
4. Hanson ND, et al. Lithium, but not fluoxetine or the corticotropin-releasing factor receptor 1 receptor antagonist R121919, increases cell proliferation in the adult dentate gyrus. J Pharmacol Exp Ther 2011; 337:180–186.
5. Matsunaga S, et al. Lithium as a treatment for Alzheimer’s disease: a systematic review and meta-analysis. J Alzheimers Dis 2015; 48:403–410.
6. Terao I, et al. Comparative efficacy of lithium and aducanumab for cognitive decline in patients with mild cognitive impairment or Alzheimer’s disease: a systematic review and network meta-analysis. Ageing Res Rev 2022; 81:101709.
7. Huang Q, et al. Lithium exposure and risk of major neurocognitive disorders: a systematic review and meta-analysis. J Clin Psychopharmacol 2024; 44:418–423.
8. Netto I, et al. Reversible lithium neurotoxicity: review of the literature. Prim Care Companion CNS Disord 2012; 14:PCC.11r01197.
9. Adityanjee, et al. The syndrome of irreversible lithium-effectuated neurotoxicity. Clin Neuropharmacol 2005; 28:38–49.
10. Memon A, et al. Association between naturally occurring lithium in drinking water and suicide rates: systematic review and meta-analysis of ecological studies. Br J Psychiatry 2020; 217:667–678.
11. Kessing LV, et al. Association of lithium in drinking water with the incidence of dementia. JAMA Psychiatry 2017; 74:1005–1010.
12. Goodwin GM, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J

Psychopharmacol 2016; 30:495–553.
13. Hui TP, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. Acta Psychiatr Scand 2019; 140:94–115. Table 2.2 Lithium: clinically relevant drug interactions. Drug group Magnitude of effect Timescale of effect Additional information ACE inhibitors Unpredictable Up to fourfold increases in [Li] Develops over several weeks Sevenfold increased risk of hospitalisation for lithium toxicity in the elderly Angiotensin II receptor antagonists may be associated with similar risk Thiazide diuretics Unpredictable Up to fourfold increases in [Li] Usually apparent in first 10 days Loop diuretics are safer Any effect will be apparent in the first month NSAIDs Unpredictable From 10% to over fourfold increases in [Li] Variable; few days to several months NSAIDs are widely used on a when necessary basis Can be bought without a prescription ACE, angiotensin-converting enzyme; [Li], lithium concentraction; NSAIDs, non-steroidal anti-inflammatory drugs.

Bipolar disorder CHAPTER 2 14. Bahji A, et al. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: a systematic review and network meta-analysis. J Affect Disord 2020; 269:154–184. 15. Taylor DM, et al. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta--analysis. Acta Psychiatr Scand 2014; 130:452–469. 16. Nolen WA, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord 2019; 21:394–409. 17. Severus E, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord 2014; 2:15. 18. Lähteenvuo M, et al. Real-world effectiveness of pharmacological treatments for bipolar disorder: register-based national cohort study. Br J Psychiatry 2023; 223:456–464. 19. Airainer M, et al. Lithium, the gold standard drug for bipolar disorder: analysis of current clinical studies. Naunyn Schmiedebergs Arch Pharmacol 2024; 397:9723–9743. 20. Dunner DL, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry 2006; 67:688–695. 21. Cleare A, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol 2015; 29:459–525. 22. Scott F, et al. Systematic review and meta-analysis of augmentation and combination treatments for early-stage treatment-resistant depression. J Psychopharmacol 2023; 37:268–278. 23. Nuñez NA, et al. Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. J Affect Disord 2022; 302:385–400. 24. Vázquez GH, et al. Efficacy and tolerability of combination treatments for major depression: antidepressants plus second-generation antipsychotics vs. esketamine vs. lithium. J Psychopharmacol 2021; 35:890–900. 25. Bauer M, et al. Role of lithium augmentation in the management of major depressive disorder. CNS Drugs 2014; 28:331–342. 26. Ercis M, et al. When and how to use lithium augmentation for treating major depressive disorder. J Clin Psychiatry 2023; 84:23ac14813. 27. Cipriani A, et al. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. Cochrane Database Syst Rev 2006; 4:CD003492. 28. Abou-Saleh MT, et al. Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. Int J Bipolar Disord 2017; 5:11. 29. Correll CU, et al. Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. Ann Clin Psychiatry 2017; 29:92–107. 30. Sirois F. Steroid psychosis: a review. Gen Hosp Psychiatry 2003; 25:27–33. 31. Aydin M, et al. Continuing clozapine treatment with lithium in schizophrenic

patients with neutropenia or leukopenia: brief review of literature with case reports. Ther Adv Psychopharmacol 2016; 6:33–38. 32. Harris EC, et al. Excess mortality of mental disorder. Br J Psychiatry 1998; 173:11–53. 33. Cipriani A, et al. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ 2013; 346:f3646. 34. Hayes JF, et al. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: a UK population-based electronic health records study. JAMA Psychiatry 2016; 73:630–-637. 35. Fadaei A. An investigation into the association between suicide mortality rate and lithium levels in potable water: a review study. Int Clin Psychopharmacol 2023; 38:73–80. 36. Nolen WA, et al. The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). Bipolar Disord 2013; 15:100–109. 37. Severus WE, et al. What is the optimal serum lithium level in the long-term treatment of bipolar disorder—a review? Bipolar Disord 2008; 10:231–237. 38. Manchia M, et al. Lithium and its effects: does dose matter? Int J Bipolar Disord 2024; 12:23. 39. Young AH. Lithium for long-term treatment of unipolar depression. Lancet Psychiatry 2017; 4:511–512. 40. Strawbridge R, et al. Lithium: how low can you go? Int J Bipolar Disord 2024; 12:4. 41. Moore CM, et al. Brain-to-serum lithium ratio and age: an in vivo magnetic resonance spectroscopy study. Am J Psychiatry 2002; 159:1240–-1242. 42. Bowen RC, et al. Less frequent lithium administration and lower urine volume. Am J Psychiatry 1991; 148:189–192. 43. Ljubicic D, et al. Lithium treatments: single and multiple daily dosing. Can J Psychiatry 2008; 53:323–331. 44. Gong R, et al. What we need to know about the effect of lithium on the kidney. Am J Physiol Renal Physiol 2016; 311:F1168–F1171. 45. Aiff H, et al. Effects of 10 to 30 years of lithium treatment on kidney function. J Psychopharmacol 2015; 29:608–614. 46. Parsaik AK, et al. Effects of long-term lithium therapy on kidney functioning in mood disorders: a population-based historical cohort study. Bipolar Disord 2024; doi: 10.1111/bdi.13501. 47. Frye MA, et al. Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar I maintenance studies. Acta Psychiatr Scand 2009; 120:10–13. 48. Johnston AM, et al. Lithium--associated clinical hypothyroidism. Prevalence and risk factors. Br J Psychiatry 1999; 175:336–339. 49. Livingstone C, et al. Lithium: a review of its metabolic adverse effects. J Psychopharmacol 2006; 20:347–355. 50. McKnight RF, et al. Lithium toxicity profile: a systematic review and meta-analysis. Lancet 2012; 379:721–728. 51. Vandermeulen L, et al. Lithium-associated hypercalcemia and hyperparathyroidism: a systematic review and meta-analysis. World J Biol Psychiatry 2024; 25:417–429.

 52. Czarnywojtek A, et al. Effect of lithium carbonate on the function of the thyroid gland: mechanism of action and clinical implications. J Physiol Pharmacol 2020; 71:191–199. 53. Ott M, et al. Lithium intoxication: incidence, clinical course and renal function – a population-based retrospective cohort study. J Psychopharmacol 2016; 30:1008–1019. 54. Bell AJ, et al. Lithium neurotoxicity at normal therapeutic levels. Br J Psychiatry 1993; 162:689–692. 55. Smith FE, et al. 3D 7Li magnetic resonance imaging of brain lithium distribution in bipolar disorder. Mol Psychiatry 2018; 23:2184–-2191. 56. Gerrett D, et al. Prescribing and monitoring lithium therapy: summary of a safety report from the National Patient Safety Agency. BMJ 2010; 341:c6258. 57. Morriss R, et al. Lithium and eGFR: a new routinely available tool for the prevention of chronic kidney disease. Br J Psychiatry 2008; 193:93–95. 58. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last

accessed October 2024); https://www.nice.org.uk/guidance/cg185. 59. Collins N, et al. Standards of lithium monitoring in mental health trusts in the UK. BMC Psychiatry 2010; 10:80. 60. Paton C, et al. Monitoring lithium therapy: the impact of a quality improvement programme in the UK. Bipolar Disord 2013; 15:865–875. 61. Kirkham E, et al. Impact of active monitoring on lithium management in Norfolk. Ther Adv Psychopharmacol 2013; 3:260–265. 62. Cavanagh J, et al. Relapse into mania or depression following lithium discontinuation: a 7-year follow-up. Acta Psychiatr Scand 2004; 109:91–95. 63. Yazici O, et al. Controlled lithium discontinuation in bipolar patients with good response to long-term lithium prophylaxis. J Affect Disord 2004; 80:269–271. 64. Goodwin GM. Recurrence of mania after lithium withdrawal. Implications for the use of lithium in the treatment of bipolar affective disorder. Br J Psychiatry 1994; 164:149–152. 65. Baldessarini RJ, et al. Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders. J Clin Psychiatry 1996; 57:441–448. 66. Biel MG, et al. Continuation versus discontinuation of lithium in recurrent bipolar illness: a naturalistic study. Bipolar Disord 2007; 9:435–442. 67. Sajatovic M, et al. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. Psychiatr Serv 2007; 58:855–863. 68. Paton C, et al. Lithium in bipolar and other affective disorders: prescribing practice in the UK. J Psychopharmacol 2010; 24:1739–1746. 69. Kessing LV, et al. Suicide risk in patients treated with lithium. Arch Gen Psychiatry 2005; 62:860–866. 70. Pharmaceutical Press. Medicines Complete 2024; https://www.pharmaceuticalpress.com/services/medicinescomplete/. 71. Juurlink DN, et al. Drug--induced lithium toxicity in the elderly: a population-based study. J Am Geriatr Soc 2004; 52:794–-798. 72. Finley PR. Drug interactions with lithium: an update. Clin Pharmacokinet 2016; 55:925–-941. 73. Netto I, et al. Lithium neurotoxicity due to second-generation antipsychotics combined with lithium: a systematic review. Prim Care Companion CNS Disord 2019; 21:17r02225. 74. Konieczny K, et al. The syndrome of irreversible lithium-effectuated neurotoxicity: a scoping review. Alpha Psychiatry 2024; 25:190–205. 75. Kohler-Forsberg O, et al. Nonsteroidal anti--inflammatory drugs (NSAIDs) and paracetamol do not affect 6-month mood-stabilizing treatment outcome among 482 patients with bipolar disorder. Depress Anxiety 2017; 34:281–290.

14 - Valproate

Valproate

15 - Mechanism of action1

Mechanism of action1

16 - Formulations

Formulations

17 - Indications

Indications

Bipolar disorder CHAPTER 2 Valproate Mechanism of action1 Valproate is a simple branched-chain fatty acid. Its mechanism of action is complex and not fully understood. Valproate inhibits the catabolism of gamma-aminobutyric acid (GABA), reduces the turnover of arachidonic acid, activates the extracellular signal- regulated kinase (ERK) pathway and thus alters synaptic plasticity, interferes with intracellular signalling, promotes brain-derived neurotrophic factor (BDNF) expression and reduces levels of protein kinase C. Research has focused on the ability of valproate to alter the expression of various genes that are involved in transcription regulation, cytoskeletal modifications and ion homeostasis. Other mechanisms that have been proposed include depletion of inositol and indirect effects on non-GABA pathways through the inhibition of voltage-gated sodium channels. There is a growing literature relating to the potential use of valproate as an adjunctive treatment in several types of cancer,2 a property which may also confer some effects on neuroplasticity.3 Formulations Valproate is available in the UK in three forms: sodium valproate and valproic acid (licensed for the treatment of epilepsy) and semi-sodium valproate (licensed for the treatment of acute mania). Both semi-sodium and sodium valproate are metabolised to valproic acid, which is responsible for the pharmacological activity of all three preparations.4 Clinical studies of the treatment of affective disorders variably use sodium valproate, semi-sodium valproate, ‘valproate’ or valproic acid. The great majority have used semi-sodium valproate. It is unclear if there is any difference in efficacy between valproic acid, valproate semi-sodium and sodium valproate. One large US quasi-experimental study found that in-patients who initially received the semi-sodium preparation had a hospital stay that was a third longer than patients who initially received valproic acid.5 One clear difference is that controlled-release sodium valproate (Epilim Chrono6) can be administered as a once daily dose whereas other sodium and semi-sodium valproate preparations require at least twice daily administration. Overall, there are probably no important differences between different valproate forms,7 except for the small differences in bioavailability related to valproate content. Indications Randomised controlled trials (RCTs) have shown valproate to be effective in the treatment of mania,8,9 with a response rate of 50% and a number needed to treat (NNT) of 2–4,10 although large negative studies do exist.11 One RCT found lithium to be more effective overall than valproate9 but a large (n = 300) randomised open trial of 12 weeks’ duration found lithium and valproate to be equally effective in the treatment of acute mania.12 Valproate may be effective in patients who have failed to respond to lithium.13 It may be less effective than olanzapine, both as monotherapy14 and as an adjunctive treatment to lithium12 in acute mania. One network meta-analysis reported that valproate was

18 - Plasma levels

Plasma levels

290 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 less effective but better tolerated than lithium.15 Overall, data relating to efficacy in mania are less convincing for valproate than for lithium and a range of antipsychotics.16,17 A meta-analysis of four small RCTs concluded that valproate is effective in bipolar depression with a small to medium effect size.18 A 2020 meta-analysis placed divalproex fifth out of 21 treatments for bipolar depression.19 Valproate has limited utility in rapid-cycling bipolar disorder.20 Although open-label studies suggest that valproate is effective in the prophylaxis of bipolar affective disorder,21 RCT data are limited.22,23 Bowden et al.24 found no difference between lithium, valproate and placebo in the primary outcome measure, time to any mood episode, although valproate was superior to lithium and placebo on some secondary outcome measures. In another RCT22 there was no difference in relapse rates between valproate and olanzapine. A post-hoc analysis of data from this study found that patients with rapid-cycling illness had a better very early response to valproate than to olanzapine but that this advantage was not maintained.23 Outcomes with respect to manic symptoms for those who did not have a rapid-cycling illness were better at 1 year with olanzapine than with valproate. In a further 20-month RCT of lithium versus valproate in patients with rapid-cycling illness, both the relapse and attrition rates were high, and no difference in efficacy between valproate and lithium was apparent.25 The independent BALANCE study found lithium to be numerically superior to valproate, and the combination of lithium and valproate statistically superior to valproate alone.26 Aripiprazole in combination with valproate is superior to valproate alone.27 Overall, data suggest that adjunctive valproate provides additional protection against relapse.28 In the UK, the National Institute for Health and Care Excellence (NICE) recommends valproate as a first-line option for the treatment of acute episodes of mania, in combination with an antidepressant for the treatment of acute episodes of depression, and for prophylaxis,29 but importantly NOT in women of child-bearing potential.29,30 A Cochrane review concluded that the evidence supporting the use of valproate as prophylaxis is limited.31 Valproate is sometimes used to treat aggressive behaviours of variable aetiology.32 One RCT (n = 16) failed to detect any advantage for risperidone augmented with valproate over risperidone alone in reducing hostility in patients with schizophrenia.33 A mirror-image study found that, in patients with schizophrenia or bipolar disorder in a secure setting, valproate decreased agitation.34 There is a small positive placebo-controlled RCT of valproate in generalised anxiety disorder.35 Valproate may also have preventive benefits against COVID-19.36 Plasma levels The pharmacokinetics of valproate are complex, following a three-compartmental model and showing protein-binding saturation. Plasma level monitoring is supposedly of more limited use than with lithium or carbamazepine.37 There may be a linear association between valproate serum levels and response in acute mania, with serum levels <55mg/L being no more effective than placebo, and levels >94mg/L being associated with the most robust response.38 Optimal serum levels during the maintenance phase are

unknown, but are likely to be at least 50mg/L.39 Achieving therapeutic plasma levels rapidly using a loading dose regimen is generally well tolerated. Plasma levels can also be used to detect non--compliance or toxicity. Using total valproate concentration (the standard method) is no less useful than free valproate levels in most situations.40

19 - Adverse effects

Adverse effects

20 - Pre treatment tests

Pre-treatment tests

21 - On treatment monitoring

On-treatment monitoring

22 - Discontinuation

Discontinuation

Bipolar disorder CHAPTER 2 Adverse effects Valproate can cause both gastric irritation and hyperammonaemia,41 both of which can lead to nausea. Lethargy and confusion can occasionally occur with starting doses above 750mg/day. Weight gain can be significant,42 particularly when valproate is used in combination with clozapine. Valproate causes dose-related tremor in up to a quarter of patients.43 In most of these patients, it is intention/postural tremor that is problematic, but a very small proportion develop parkinsonism associated with cognitive decline; these symptoms are reversible when valproate is discontinued.44 Hair loss (with curly regrowth)45 and peripheral oedema can occur, as can thrombocytopenia, leucopenia, red cell hypoplasia and pancreatitis.46 Valproate can cause hyperandrogenism in women47 and has been linked with the development of polycystic ovaries although the evidence supporting this association is conflicting. Valproate is a major human teratogen (see Chapter 7). Valproate may also affect male fertility48 but its teratogenic effect in men is disputed.49–51 Valproate may very rarely cause fulminant hepatic failure. Young children receiving multiple anticonvulsants are most at risk. Any patient with raised liver function tests (LFTs; common in early treatment52) should be evaluated clinically and other markers of hepatic function such as albumin and clotting time should be checked. Many adverse effects of valproate are dose-related (and often peak plasma level related) and increase sharply in frequency and severity when the plasma concentration is >100mg/L. The once daily modified-release form of sodium valproate does not produce as high peak plasma levels as the conventional formulation, and so may be better tolerated. Valproate and other antiseizure medications have been associated with an increased risk of suicidal behaviour53 but this finding is not consistent across studies.54 Patients with depression55 or who take another antiseizure medication that increases the risk of developing depression may be a subgroup at greater risk.56 Pre-treatment tests Baseline full blood count (FBC), LFTs and weight or BMI are recommended by NICE in the UK. On-treatment monitoring In the UK, NICE recommends that an FBC and LFTs should be repeated after 6 months, and that BMI should be monitored. Valproate summary of product characteristics (SPCs) recommends more frequent LFTs during the first 6 months with albumin and clotting measured if enzyme levels are abnormal. Where there is clear hypalbuminaemia, free valproate levels should be measured. Discontinuation It is unknown if abrupt discontinuation of valproate worsens the natural course of bipolar illness in the same manner as lithium. One small naturalistic retrospective study suggested that it might.57 Until further data are available, if valproate is to be discontinued, it should be done slowly over at least a month, preferably longer. In people with epilepsy, valproate withdrawal is associated with depression, falls and hospital admissions.58

23 - Use in women of child bearing age

Use in women of child-bearing age

24 - Interactions with other drugs

Interactions with other drugs

292 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Use in women of child-bearing age Valproate is an established human teratogen. NICE recommends that alternative antiseizure medications are preferred in women with epilepsy59 and that valproate should not be used to treat bipolar illness in women of child-bearing age.29 The teratogenic potential of valproate is not widely appreciated and in the past many women of child-bearing age were not advised of the need for contraception or prophylactic folate.60,61 Valproate may also cause impaired cognitive function in children exposed to valproate in utero.62 Valproate is now contraindicated in women of child--bearing potential in many countries (see Chapter 7). Interactions with other drugs Valproate is highly protein bound and can be displaced by other protein bound drugs such as aspirin, leading to toxicity. Aspirin also inhibits the metabolism of valproate; a dose of at least 300mg aspirin is required.63 Other, less strongly protein bound drugs such as warfarin can be displaced by valproate, leading to higher free levels and toxicity. Valproate is hepatically metabolised; drugs that inhibit CYP enzymes can increase valproate levels (e.g. erythromycin, fluoxetine and cimetidine). Valproate can increase the plasma levels of some drugs by inhibition of glucuronidation. Examples include tricyclic antidepressants (TCAs; particularly clomipramine64), lamotrigine,65 quetiapine,66 warfarin67 and phenobarbital. Valproate may also significantly lower plasma olanzapine concentrations although the mechanism is unknown.68 Pharmacodynamic interactions also occur. The anticonvulsant effect of valproate is antagonised by drugs that lower the seizure threshold (e.g. antipsychotics). Weight gain can be exacerbated by other drugs such as clozapine and olanzapine. Table 2.3 summarises the prescribing and monitoring of valproate. Table 2.3 Valproate: prescribing and monitoring. Indications Mania, hypomania, bipolar depression and prophylaxis of bipolar affective disorder. May reduce aggression in a range of psychiatric disorders (although data are weak). Pre-valproate work-up FBC and LFTs. Baseline measure of weight desirable. Prescribing Titrate dose upwards against response and adverse effects. Loading doses can be used and are generally well tolerated. Modified-release sodium valproate (Epilim Chrono6) can be given once daily. All other formulations must be administered at least twice daily. Plasma levels can be used to assure adequate dosing and treatment compliance. Blood should be taken immediately before the next dose. Monitoring FBC and LFTs if clinically indicated. Weight (or body mass index). Stopping Reduce slowly over at least 1 month, preferably longer.

25 - References

References

Bipolar disorder CHAPTER 2 References

1. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? Cell Mol Life Sci 2007; 64:2090–2103.
2. Natale G, et al. Valproate and lithium: old drugs for new pharmacological approaches in brain tumors? Cancer Lett 2023; 560:216125.
3. Gervain J, et al. Valproate reopens critical-period learning of absolute pitch. Front Syst Neurosci 2013; 7:1–11.
4. Fisher C, et al. Sodium valproate or valproate semisodium: is there a difference in the treatment of bipolar disorder? Psychiatric Bulletin 2003; 27:446–448.
5. Wassef AA, et al. Lower effectiveness of divalproex versus valproic acid in a prospective, quasi-experimental clinical trial involving 9,260 psychiatric admissions. Am J Psychiatry 2005; 162:330–339.
6. SANOFI. Summary of product characteristics. Epilim Chrono (valproic acid, sodium valproate) 500mg. 2024 (last accessed October 2024); https://www.medicines.org.uk/emc/medicine/6779.
7. Delage C, et al. Valproate, divalproex, valpromide: are the differences in indications justified? Biomed Pharmacother 2023; 158:114051.
8. Bowden CL, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA 1994; 271:918–924.
9. Freeman TW, et al. A double-blind comparison of valproate and lithium in the treatment of acute mania. Am J Psychiatry 1992; 149:108–111.
10. Nasrallah HA, et al. Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. J Affect Disord 2006; 95:69–78.
11. Hirschfeld RM, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended-release in the acute treatment of mania. J Clin Psychiatry 2010; 71:426–432.
12. Bowden C, et al. A 12-week, open, randomized trial comparing sodium valproate to lithium in patients with bipolar I disorder suffering from a manic episode. Int Clin Psychopharmacol 2008; 23:254–262.
13. Pope HG, Jr, et al. Valproate in the treatment of acute mania. A placebo-controlled study. Arch Gen Psychiatry 1991; 48:62–68.
14. Novick D, et al. Translation of randomised controlled trial findings into clinical practice: comparison of olanzapine and valproate in the EMBLEM study. Pharmacopsychiatry 2009; 42:145–152.

15. Cipriani A, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011; 378:1306–1315.
16. Kishi T, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. Mol Psychiatry 2022; 27:1136–1144.
17. Hsu TW, et al. Variability and efficacy in treatment effects on manic symptoms with lithium, anticonvulsants, and antipsychotics in acute bipolar mania: a systematic review and meta-analysis. EClinicalMedicine 2022; 54:101690.
18. Smith LA, et al. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord 2010; 122:1–9.
19. Bahji A, et al. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: a systematic review and network meta-analysis. J Affect Disord 2020; 269:154–184.
20. Strawbridge R, et al. A systematic review and meta-analysis of treatments for rapid cycling bipolar disorder. Acta Psychiatr Scand 2022; 146:290–311.
21. Calabrese JR, et al. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990; 147:431–434.
22. Tohen M, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry 2003; 160:1263–1271.
23. Suppes T, et al. Rapid versus non-rapid cycling as a predictor of response to olanzapine and divalproex sodium for bipolar mania and maintenance of remission: post hoc analyses of 47-week data. J Affect Disord 2005; 89:69–77.
24. Bowden CL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. Arch Gen Psychiatry 2000; 57:481–489.
25. Calabrese JR, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. Am J Psychiatry 2005; 162:2152–2161.
26. Geddes JR, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010; 375:385–395.
27. Marcus R, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disord 2011; 13:133–144.
28. Nestsiarovich A, et al. Preventing new episodes of bipolar disorder in adults: systematic review and meta-analysis of randomized controlled trials. Eur Neuropsychopharmacol 2022; 54:75–89.
29. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last accessed October 2024); https://www.nice.org.uk/guidance/cg185.
30. National Institute for Health and Care Excellence. Antenatal and postnatal mental health: clinical management and service guidance. Clinical guideline [CG192]. 2014 (last updated February 2020, last accessed October 2024); https://www.nice.org.uk/guidance/cg192.
31. Cipriani A, et al. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev 2013; 10:CD003196.

32. Lindenmayer JP, et al. Use of sodium valproate in violent and aggressive behaviors: a critical review. J Clin Psychiatry 2000; 61:123–128.

 33. Citrome L, et al. Risperidone alone versus risperidone plus valproate in the treatment of patients with schizophrenia and hostility. Int Clin Psychopharmacol 2007; 22:356–362. 34. Gobbi G, et al. Efficacy of topiramate, valproate, and their combination on aggression/agitation behavior in patients with psychosis. J Clin Psychopharmacol 2006; 26:467–473. 35. Aliyev NA, et al. Valproate (depakine--chrono) in the acute treatment of outpatients with generalized anxiety disorder without psychiatric comorbidity: randomized, double-blind placebo-controlled study. Eur Psychiatry 2008; 23:109–114. 36. Watson A, et al. Valproic acid use is associated with diminished risk of contracting COVID-19, and diminished disease severity: epidemiologic and in vitro analysis reveal mechanistic insights. PLoS One 2024; 19:e0307154. 37. Haymond J, et al. Does valproic acid warrant therapeutic drug monitoring in bipolar affective disorder? Ther Drug Monit 2010; 32:19–29. 38. Allen MH, et al. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry 2006; 163:272–275. 39. Taylor D, et al. Doses of carbamazepine and valproate in bipolar affective disorder. Psychiatric Bulletin 1997; 21:221–223. 40. Krishna MBN, et al. Total valproate versus free valproate in therapeutic drug monitoring for bipolar disorder: a cross-sectional study. Asia Pac Psychiatry 2024; 16:e12555. 41. Segura-Bruna N, et al. Valproate--induced hyperammonemic encephalopathy. Acta Neurol Scand 2006; 114:1–7. 42. El-Khatib F, et al. Valproate, weight gain and carbohydrate craving: a gender study. Seizure 2007; 16:226–232. 43. Zadikoff C, et al. Movement disorders in patients taking anticonvulsants. J Neurol Neurosurg Psychiatry 2007; 78:147–151. 44. Ristic AJ, et al. The frequency of reversible parkinsonism and cognitive decline associated with valproate treatment: a study of 364 patients with different types of epilepsy. Epilepsia 2006; 47:2183–2185. 45. Praharaj SK, et al. Valproate-associated hair abnormalities: pathophysiology and management strategies. Hum Psychopharmacol 2022; 37:e2814. 46. Gerstner T, et al. Valproic acid-induced pancreatitis: 16 new cases and a review of the literature. J Gastroenterol 2007; 42:39–48. 47. Joffe H, et al. Valproate is associated with new--onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. Biol Psychiatry 2006; 59:1078–1086. 48. Asghar MA, et al. Understanding the impact of valproate on male fertility: insights from preclinical and clinical meta-analysis. BMC Pharmacol Toxicol 2024; 25:69. 49. Garey JD, et al. Paternal valproate treatment and risk of childhood neurodevelopmental disorders: precautionary regulatory measures are insufficiently substantiated. Birth Defects Res 2024; 116:e2392. 50. Christensen J, et al. Valproate use during spermatogenesis and risk to offspring. JAMA Netw Open 2024; 7:e2414709. 51. Angus-Leppan H, et al. New valproate regulations, informed choice and seizure risk. J Neurol 2024; 271:5671–5686. 52. Bjornsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scand 2008; 118:281–290. 53. Patorno E, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010; 303:1401–1409. 54. Gibbons RD, et al. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. Arch Gen Psychiatry 2009; 66:1354–1360. 55. Arana A, et al. Suicide-related events in patients treated with antiepileptic drugs. N Engl J Med 2010; 363:542–551. 56. Andersohn F, et al. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. Neurology 2010; 75:335–340. 57. Franks MA, et al. Bouncing back: is the bipolar rebound phenomenon peculiar to lithium? A retrospective naturalistic study. J Psychopharmacol 2008; 22:452–456. 58. Mbizvo GK, et al. Morbidity and mortality risks associated with valproate withdrawal in young adults with epilepsy. Brain 2024; 147:3426–3441. 59. National

Institute for Health and Care Excellence. Epilepsies in children, young people and adults. NICE guideline [NG217]. 2022 (last accessed October 2024); https://www.nice.org.uk/guidance/ng217. 60. James L, et al. Informing patients of the teratogenic potential of mood stabilising drugs; a case notes review of the practice of psychiatrists. J Psychopharmacol 2007; 21:815–819. 61. James L, et al. Mood stabilizers and teratogenicity – prescribing practice and awareness amongst practising psychiatrists. J Mental Health 2009; 18:137–143. 62. Meador KJ, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009; 360:1597–1605. 63. Sandson NB, et al. An interaction between aspirin and valproate: the relevance of plasma protein displacement drug-drug interactions. Am J Psychiatry 2006; 163:1891–1896. 64. Fehr C, et al. Increase in serum clomipramine concentrations caused by valproate. J Clin Psychopharmacol 2000; 20:493–494. 65. Morris RG, et al. Clinical study of lamotrigine and valproic acid in patients with epilepsy: using a drug interaction to advantage? Ther Drug Monit 2000; 22:656–660. 66. Aichhorn W, et al. Influence of age, gender, body weight and valproate comedication on quetiapine plasma concentrations. Int Clin Psychopharmacol 2006; 21:81–85. 67. Gunes A, et al. Inhibitory effect of valproic acid on cytochrome P450 2C9 activity in epilepsy patients. Basic Clin Pharmacol Toxicol 2007; 100:383–386. 68. Bergemann N, et al. Valproate lowers plasma concentration of olanzapine. J Clin Psychopharmacol 2006; 26:432–434.

26 - Carbamazepine

Carbamazepine

27 - Mechanism of action1

Mechanism of action1

28 - Formulations

Formulations

29 - Indications

Indications

Bipolar disorder CHAPTER 2 Carbamazepine Mechanism of action1 Carbamazepine blocks voltage--dependent sodium channels, thus inhibiting repetitive neuronal firing. It reduces glutamate release and decreases the turnover of dopamine and noradrenaline. While carbamazepine has a similar molecular structure to TCAs, it is radically different in respect to both therapeutic and adverse effects. Oxcarbazepine (a structural derivative of carbamazepine), as well as blocking voltage--dependent sodium channels, also increases potassium conductance and modulates high-voltage activated calcium channels. Eslicarbazepine is available in some countries. Like oxcarbazepine it acts as a pro-drug for licarbazepine, the likely active molecule of all three drugs. Formulations Carbamazepine is available as a liquid, chewable and immediate-release and controlled- release tablets. Non-modified release formulations generally have to be administered two to three times daily. The controlled-release preparation can be given once or twice daily, and the reduced fluctuation in serum levels usually leads to improved tolerability. This modified-release preparation has a lower bioavailability and an increase in dose of 10–15% may be required. Indications Carbamazepine is primarily used as an antiseizure medication. It is also used in the treatment of trigeminal neuralgia and, in the UK and elsewhere, is licensed for the treatment of bipolar illness in patients who do not respond to lithium. With respect to the treatment of mania, two placebo--controlled randomised studies have found the extended-release formulation of carbamazepine to be effective. In both studies, the response rate in the carbamazepine arm was twice that in the placebo arm.2,3 Carbamazepine was not particularly well tolerated – the incidence of dizziness, somnolence and nausea was high. Another study found carbamazepine alone to be as effective as carbamazepine plus olanzapine.4 Most formal guidelines do not recommend carbamazepine as a first-line treatment for mania.5 A Cochrane review concluded that there were insufficient trials of adequate methodological quality of oxcarbazepine in the acute treatment of bipolar disorder to inform its efficacy and acceptability.6 More recent reviews suggest oxcarbazepine has useful efficacy in mania.7 Two 2022 network meta-analyses8,9 confirmed the efficacy and relatively poor tolerability of carbamazepine. Open studies suggest that carbamazepine monotherapy has some efficacy in bipolar depression10 but evidence supporting other strategies is stronger (see section on treatment of bipolar depression later in this chapter). Carbamazepine may also be useful in unipolar depression either alone11 or as an augmentation strategy.12 Carbamazepine is generally considered to be less effective than lithium in the prophylaxis of bipolar illness.13 A 2009 meta--analysis failed to find a significant difference in efficacy between lithium and carbamazepine, but those who received carbamazepine were more likely to drop out of treatment because of adverse effects.14 Lithium is

30 - Plasma levels

Plasma levels

31 - Adverse effects1

Adverse effects1

296 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 considered to be superior to carbamazepine in reducing suicidal behaviour,15 although data are not consistent16 and carbamazepine may have anti-suicidal properties.17 In the UK, NICE considers carbamazepine to be a third-line prophylactic agent5 and data emerging since this guidance support this positioning.18 Three small studies suggest the related oxcarbazepine may have some prophylactic efficacy when used in combination with other mood-stabilising drugs.19–21 There are data supporting the use of carbamazepine in the management of alcohol withdrawal symptoms,22 although the high initial doses required are often poorly tolerated. A Cochrane review did not consider the evidence strong enough to support the use of carbamazepine for this indication.23 Carbamazepine has also been used to manage aggressive behaviour in patients with schizophrenia;24 the quality of data is weak and the mode of action unknown. There are a number of case reports and open case series that report on the use of carbamazepine in various psychiatric illnesses such as panic disorder, borderline personality disorder and episodic dyscontrol syndrome. Plasma levels When carbamazepine is used as an antiseizure medication, the therapeutic range is generally considered to be 4–12mg/L, although the supporting evidence is not strong. In patients with affective illness, a dose of at least 600mg/day and a plasma level of at least 7mg/L may be required,25 although this is not a consistent finding.4,11,26 Levels above 12mg/L are associated with a higher adverse effect burden. Carbamazepine blood concentrations vary markedly within the dosage interval. It is therefore important to sample at a point in time where levels are likely to be reproducible for any given individual. The most appropriate way of monitoring is to take a trough level before the first dose of the day. Carbamazepine metabolism is genetically determined and so genetic testing may be helpful before starting carbamazepine.27 Carbamazepine is a hepatic enzyme inducer that induces its own metabolism as well as that of other drugs, including some antipsychotics.28 An initial plasma half-life of around 30 hours is reduced to around 12 hours on chronic dosing. For this reason, plasma levels should be checked 2–4 weeks after starting or after an increase in dose to ensure that the desired level is still being obtained. Most published clinical trials that demonstrated the efficacy of carbamazepine as a mood stabiliser used doses that are significantly higher (800–1200mg/day) than those commonly prescribed in UK clinical practice.29 Adverse effects1 The main adverse effects associated with carbamazepine therapy are dizziness, diplopia, drowsiness, ataxia, nausea and headaches. They can sometimes be avoided by starting with a low dose and increasing slowly. Avoiding high peak blood levels by splitting the dose throughout the day or using a controlled-release formulation may also help. Dry mouth, oedema and hyponatraemia are also common. Sexual dysfunction can occur, probably mediated through reduced testosterone levels.30 Around 3% of patients treated with carbamazepine develop a generalised erythematous rash. Serious exfoliative dermatological reactions can rarely occur and vulnerability is genetically determined.31 The human lymphocyte antigen (HLA) variant

B*15:02 has a sensitivity of around 70%

32 - Pre treatment tests

Pre-treatment tests

33 - On treatment monitoring

On-treatment monitoring

34 - Discontinuation

Discontinuation

35 - Use in women of child bearing age

Use in women of child-bearing age

36 - Interactions with other drugs4144

Interactions with other drugs41–44

Bipolar disorder CHAPTER 2 and a specificity approaching 100% in certain populations.32 Genetic testing in people from South-East Asia is recommended before carbamazepine is prescribed. Carbamazepine is a known human teratogen (see Chapter 7). Carbamazepine commonly causes a chronic low white blood cell (WBC) count. One patient in 20,000 develops agranulocytosis and/or aplastic anaemia.33 Raised alkaline phosphate (ALP) and gamma-glutamyl transferase (GGT) are common (a GGT of 2–3 times normal is rarely a cause for concern34). A delayed multiorgan hypersensitivity reaction rarely occurs, mainly manifesting itself as various skin reactions, a low WBC count and abnormal LFTs. Fatalities have been reported.34,35 There is no clear timescale for these events. Some antiseizure drugs have been associated with an increased risk of suicidal behaviour. Carbamazepine has not been implicated, either in general36,37 or more specifically in those with bipolar illness.38 Pre-treatment tests Baseline U&Es, FBC and LFTs are recommended by NICE. A baseline measure of weight is also desirable. On-treatment monitoring In the UK, NICE recommends that U&Es, FBC and LFTs should be repeated after 6 months, and that weight (or BMI) should also be monitored. Discontinuation It is not known if abrupt discontinuation of carbamazepine worsens the natural course of bipolar illness in the same way that abrupt cessation of lithium does. In one small case series (n = 6), one patient developed depression within a month of discontinuation,39 while in another small case series (n = 4), three patients had a recurrence of their mood disorder within 3 months.40 Until further data are available, if carbamazepine is to be discontinued, it should be done slowly (over at least a month). Use in women of child-bearing age Carbamazepine is an established human teratogen (see Chapter 7). Women who have mania are likely to be sexually disinhibited. The risk of unplanned pregnancy is likely to be above population norms (where 50% of pregnancies are unplanned). If carbamazepine cannot be avoided, adequate contraception should be ensured (note the interaction between carbamazepine and oral contraceptives outlined in the next section) and prophylactic folate prescribed. Interactions with other drugs41–44 Carbamazepine is a potent inducer of hepatic cytochrome enzymes and is metabolised by CYP3A4. Plasma levels of most antidepressants, most antipsychotics, benzodiazepines, warfarin, zolpidem, some cholinesterase inhibitors, methadone, thyroxine, theophylline, oestrogens and other steroids may be reduced by carbamazepine, possibly

37 - References

References

298 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 resulting in treatment failure. Patients requiring contraception should either receive a preparation containing not less than 50mcg oestrogen or use a non-hormonal method. Drugs that inhibit CYP3A4 will increase carbamazepine plasma levels and may precipitate toxicity. Examples include fluconazole, cimetidine, diltiazem, verapamil, erythromycin and some SSRIs. Pharmacodynamic interactions also occur. The antiseizure activity of carbamazepine is reduced by drugs that lower the seizure threshold (e.g. antipsychotics and antidepressants); the potential for carbamazepine to cause neutropenia may be increased by other drugs that depress the bone marrow function (e.g. clozapine); and the risk of hyponatraemia may be increased by other drugs that have the potential to deplete sodium (e.g. diuretics). Neurotoxicity has very rarely been reported when carbamazepine is used in combination with lithium. As carbamazepine is structurally similar to TCAs, in theory it should not be given within 14 days of discontinuing a monoamine oxidase inhibitor (MAOI). There seems to be no clinical basis to this restriction. Table 2.4 summarises the prescribing and monitoring of carbamazepine. References

1. Novartis Pharmaceuticals UK Ltd. Summary of product characteristics. Tegretol tablets 100mg, 200mg, 400mg. 2024 (last accessed October 2024); https://www.medicines.org.uk/emc/medicine/1328.
2. Weisler RH, et al. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry 2004; 65:478–484.
3. Weisler RH, et al. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2005; 66:323–330.
4. Tohen M, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. Br J Psychiatry 2008; 192:135–143.
5. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last accessed October 2024); https://www.nice.org.uk/guidance/cg185.
6. Vasudev A, et al. Oxcarbazepine for acute affective episodes in bipolar disorder. Cochrane Database Syst Rev 2011; 12:CD004857.
7. Grunze A, et al. Efficacy of carbamazepine and its derivatives in the treatment of bipolar disorder. Medicina (Kaunas) 2021; 57:433. Table 2.4 Carbamazepine: prescribing and monitoring. Indications Mania (not first line), bipolar depression (evidence weak), unipolar depression (evidence weak) and prophylaxis of bipolar disorder (third line after antipsychotics and valproate). Alcohol withdrawal (may be poorly tolerated).

> Carbamazepine is licensed for the treatment of bipolar illness in patients who do not respond to lithium. Pre-carbamazepine work-up U&Es, FBC and LFTs. Baseline measure of weight desirable. HLA genotyping. CYP3A4 genotyping. Prescribing Titrate dose upwards against response and adverse effects; start with 100–200mg twice a day and aim for 400mg twice a day (some patients will require higher doses). The modified-release formulation (Tegretol Retard) can be given once to twice daily, is associated with less severe fluctuations in serum levels and is generally better tolerated. Plasma levels can be used to assure adequate dosing and treatment compliance. Blood should be taken immediately before the next dose. Carbamazepine induces its own metabolism. Blood levels should be re-checked 2 weeks after an increase in dose. Monitoring U&Es, FBC and LFTs yearly and when clinically indicated. Weight (or body mass index). Stopping Reduce slowly over at least 1 month, preferably longer. Hyperbolic tapering has theoretical support.

Bipolar disorder CHAPTER 2 8. Kishi T, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. Mol Psychiatry 2022; 27:1136–1144. 9. Hong Y, et al. A cumulative Bayesian network meta-analysis on the comparative efficacy of pharmacotherapies for mania over the last 40 years. Psychopharmacology (Berl) 2022; 239:3367–3375. 10. Dilsaver SC, et al. Treatment of bipolar depression with carbamazepine: results of an open study. Biol Psychiatry 1996; 40:935–937. 11. Zhang ZJ, et al. The effectiveness of carbamazepine in unipolar depression: a double-blind, randomized, placebo-controlled study. J Affect Disord 2008; 109:91–97. 12. Kramlinger KG, et al. The addition of lithium to carbamazepine. Antidepressant efficacy in treatment-resistant depression. Arch Gen Psychiatry 1989; 46:794–800. 13. Nasrallah HA, et al. Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. J Affect Disord 2006; 95:69–78. 14. Ceron-Litvoc D, et al. Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. Hum Psychopharmacol 2009; 24:19–28. 15. Kleindienst N, et al. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. Neuropsychobiology 2000; 42 Suppl 1:2–-10. 16. Yerevanian BI, et al. Bipolar pharmacotherapy and suicidal behavior. Part I: Lithium, divalproex and carbamazepine. J Affect Disord 2007; 103:5–11. 17. Tsai CJ, et al. The rapid suicide protection of mood stabilizers on patients with bipolar disorder: a nationwide observational cohort study in Taiwan. J Affect Disord 2016; 196:71–77. 18. Peselow ED, et al. Prophylactic efficacy of lithium, valproic acid, and carbamazepine in the maintenance phase of bipolar disorder: a naturalistic study. Int Clin Psychopharmacol 2016; 31:218–223. 19. Vieta E, et al. A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. Int J Neuropsychopharmacol 2008; 11:445–452. 20. Conway CR, et al. An open-label trial of adjunctive oxcarbazepine for bipolar disorder. J Clin Psychopharmacol 2006; 26:95–97. 21. Juruena MF, et al. Bipolar I and II disorder residual symptoms: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33:94–99. 22. Malcolm R, et al. The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. J Gen Intern Med 2002; 17:349–355. 23. Minozzi S, et al. Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev 2010; 3:CD005064. 24. Brieden T, et al. Psychopharmacological treatment of aggression in schizophrenic patients. Pharmacopsychiatry 2002; 35:83–89. 25. Taylor D, et al. Doses of carbamazepine and valproate in

bipolar affective disorder. Psychiatric Bulletin 1997; 21:221–223. 26. Simhandl C, et al. The comparative efficacy of carbamazepine low and high serum level and lithium carbonate in the prophylaxis of affective disorders. J Affect Disord 1993; 28:221–231. 27. Riffi R, et al. Pharmacogenetics of carbamazepine: a systematic review on CYP3A4 and CYP3A5 polymorphisms. CNS Neurol Disord Drug Targets 2024; 23:1463–1473. 28. Cohen H, et al. The extent of cytochrome P450 3A induction by antiseizure medications: a systematic review and network meta-analysis. Epilepsia 2024; 65:445–455. 29. Taylor DM, et al. Prescribing and monitoring of carbamazepine and valproate – a case note review. Psychiatric Bulletin 2000; 24:174–177. 30. Lossius MI, et al. Reversible effects of antiepileptic drugs on reproductive endocrine function in men and women with epilepsy – a prospective randomized double-blind withdrawal study. Epilepsia 2007; 48:1875–-1882. 31. Hung SI, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 2006; 16:297–306. 32. Moutaouakkil Y, et al. Diagnostic utility of human leukocyte antigen B*15:02 screening in severe carbamazepine hypersensitivity syndrome. Ann Indian Acad Neurol 2019; 22:377–383. 33. Kaufman DW, et al. Drugs in the aetiology of agranulocytosis and aplastic anaemia. Eur J Haematol Suppl 1996; 60:23–30. 34. Bjornsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scand 2008; 118:281–-290. 35. Ganeva M, et al. Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: report of four cases and brief review. Int J Dermatol 2008; 47:853–-860. 36. Patorno E, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010; 303:1401–1409. 37. Andersohn F, et al. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. Neurology 2010; 75:335–340. 38. Gibbons RD, et al. Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. Arch Gen Psychiatry 2009; 66:1354–1360. 39. Macritchie KA, et al. Does ‘rebound mania’ occur after stopping carbamazepine? A pilot study. J Psychopharmacol 2000; 14:266–268. 40. Franks MA, et al. Bouncing back: is the bipolar rebound phenomenon peculiar to lithium? A retrospective naturalistic study. J Psychopharmacol 2008; 22:452–456. 41. Spina E, et al. Clinical significance of pharmacokinetic interactions between antiepileptic and psychotropic drugs. Epilepsia 2002; 43 Suppl 2:37–44. 42. Patsalos PN, et al. The importance of drug interactions in epilepsy therapy. Epilepsia 2002; 43:365–385. 43. Crawford P. Interactions between antiepileptic drugs and hormonal contraception. CNS Drugs 2002; 16:263–272. 44. Citrome L, et al. Pharmacokinetics of aripiprazole and concomitant carbamazepine. J Clin Psychopharmacol 2007; 27:279–283.

38 - Antipsychotic drugs in bipolar disorder

Antipsychotic drugs in bipolar disorder

39 - First generation antipsychotics

First-generation antipsychotics

40 - Second generation antipsychotics

Second-generation antipsychotics

300 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Antipsychotic drugs in bipolar disorder Antipsychotic drugs not only have activity that reduces psychotic symptoms,1 individual antipsychotics variously possess sedative, anxiolytic, anti-manic, mood-stabilising and antidepressant properties. Some antipsychotics (quetiapine and olanzapine) show all of these activities. Antipsychotics licensed by the US Food and Drug Administration (FDA) for use in bipolar disorder include aripiprazole (mania, mixed episodes, maintenance treatment), asenapine (mania, mixed states), cariprazine and lumateperone (bipolar depression), lurasidone (bipolar depression), olanzapine (mania, mixed episodes, maintenance), olanzapine and fluoxetine (bipolar depression), quetiapine (mania, maintenance, bipolar depression), risperidone (mania, mixed episodes) and ziprasidone (mania, maintenance). Risperidone LAI has been approved for monotherapy or adjunctive maintenance, and aripiprazole depot for monotherapy maintenance treatment. EU labelling is similar except that olanzapine/fluoxetine in combination is not licensed for any indication and no second-generation antipsychotic (SGA) long-acting injection (LAI) has a licence for maintenance. First-generation antipsychotics These agents have long been used in mania and several studies support their use in the acute phase of illness, with superiority over placebo and comparable effects to lithium.2,3 Their effectiveness is enhanced by combination with lithium.4,5 In the longer term maintenance treatment of bipolar disorder, first-generation antipsychotics (FGAs) are widely used6 but modern, robust supporting data are absent.7 FGAs are relatively more often associated with both depression and tardive dyskinesia in bipolar disorder7–9 and their use is declining. The higher rate of tardive dyskinesia with FGAs is not in doubt, but the greater risk of depression,10,11 while less well supported, is certainly worthy of consideration. Second-generation antipsychotics Mania Network meta-analyses indicate superiority of antipsychotics over placebo in mania, with similar activity to so-called mood stabilisers.12–14 In a 2023 network meta-analysis, efficacy of individual antipsychotics was broadly similar,15 with a suggestion of superiority of risperidone. Adjunctive treatment with antipsychotics is more effective than monotherapy with mood stabiliser medication, and augmentation with mood stabiliser medication is more effective than antipsychotic monotherapy. The combination is associated with more adverse effects, especially somnolence.16 Interpretation of outcomes is made difficult by trials including patients whose mania occurred in the context of failed mood stabiliser treatment. Participants receive either

a failed mood stabiliser or a mood stabiliser plus an antipsychotic. The superior effect of the combination is not surprising in this context. Although the mechanism is difficult to discern, converging evidence suggests anti- manic effects of antipsychotics are related to their effects on the dopamine system.17,18

41 - Specific antipsychotics

Specific antipsychotics

Bipolar disorder CHAPTER 2 Bipolar depression In acute treatment of bipolar depression, antipsychotics found to be effective include cariprazine, lumateperone, lurasidone, olanzapine (± fluoxetine) and quetiapine.14,19,20 In terms of mechanism, this does not appear to be a dopamine-mediated effect as aripiprazole and most dopamine-blocking antipsychotics do not show efficacy in acute bipolar depression.19 Efficacy is similar among those shown to be effective, although lurasidone may be superior to cariprazine.21,22 Maintenance Compounds that have efficacy in the acute phase of bipolar disorder, whether that be mania or depression, seem to exert effects in maintenance treatment.23 This is borne out by a network meta-analysis of maintenance treatments in bipolar disorder, in which olanzapine, quetiapine and risperidone LAIs showed effects against relapse.24 This analysis did not include more recent (positive) trials of aripiprazole (see next section),24 nor studies of cariprazine25 which may not be effective as maintenance treatment. Specific antipsychotics Aripiprazole Aripiprazole is effective in acute treatment of mania both alone,26–28 as an add-on agent29 and in long-term prophylaxis.30,31 No difference is seen when directly compared with lithium or haloperidol although one small RCT suggested lithium was more effective in mania.32 In trials in mania, aripiprazole is associated with nausea and movement disorder (mainly akathisia).33 Aripiprazole LAI is also effective for prophylaxis in bipolar I disorder with the effect predominantly on prevention of manic episodes.34 Asenapine Asenapine is given by the sublingual route and is effective in mania.35,36 Efficacy seems to be maintained in the longer term,37 with RCT evidence showing efficacy in preventing depression and manic episodes in people with bipolar I disorder.38 Asenapine is less likely to cause weight gain and metabolic disturbance39 than some other antipsychotics. Cariprazine Cariprazine is efficacious for treating mania as well as depression symptoms in people with mania with mixed features40 and has a low propensity for weight gain.39 Clozapine The earliest observational study of antipsychotics for maintenance treatment in bipolar disorder examined clozapine in people attending a service for resistant mood disorders.41 There is evidence from at least 15 trials to suggest improvements in treatment-resistant bipolar disorder (TRBD) (where two treatments have failed,

302 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 despite adequate dose and duration) and in depression, mania, rapid-cycling states and psychotic symptoms.42 Clozapine is fairly widely used in bipolar disorder, particularly in South-East Asia.43 Lurasidone Lurasidone is licensed by the FDA as monotherapy and adjunctive treatment to lithium and divalproex for acute treatment of bipolar depression, on the basis of RCTs of monotherapy versus placebo,44 and as an adjunct to lithium or valproate.45 The main adverse effects include nausea and akathisia, with minimal effects on weight and metabolic parameters.39 Olanzapine Olanzapine is effective in mania.46,47 As with other FGAs, olanzapine is most effective when used in combination with a mood stabiliser in acute mania and for symptomatic (though not syndromal) relapse

prevention,48,49 although in one study, olanzapine + carbamazepine was no better than carbamazepine alone.50 Data suggest olanzapine may offer benefits in longer-term treatment.51,52 It may be more effective than lithium.53,54 Olanzapine is, of course, associated with significant metabolic effects, including weight gain, effects that are minimised by the use of the olanzapine/samidorphan combination available in some countries.55,56 Quetiapine Data relating to quetiapine57–59 suggest robust efficacy in all aspects of bipolar disorder including prevention of mania and bipolar depression.60 It has low propensity for extrapyramidal side effects (EPSEs), though there are significant effects on weight and metabolic parameters. Risperidone Risperidone has shown efficacy in mania,61 particularly in combination with a mood - stabiliser.62,63 Risperidone LAI (as Risperdal Consta) is also effective64 (note though that the pharmacokinetics of this formulation generally render it an unsuitable choice for the acute treatment of mania). The long-acting version is used as prophylaxis (an unlicensed use in most countries). It is effective as prophylaxis against mania in the longer term.23 Paliperidone can be assumed to have similar effects, although prospective, controlled data are lacking.65 Other antipsychotics There are few data for amisulpride66 and rather more for ziprasidone,67 which is sometimes used for mania in the USA. Iloperidone may be effective in mixed episodes68 but data are insufficient to support its use. Lumateperone is effective in bipolar depression.69,70

42 - References

References

Bipolar disorder CHAPTER 2 References

1. ECNP. Neuroscience-based nomenclature (NbN). 2024; https://www.ecnp.eu/research--innovation/nomenclature.
2. Cipriani A, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011; 378:1306–1315.
3. Goodwin GM, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016; 30:495–553.
4. Chou JC, et al. Acute mania: haloperidol dose and augmentation with lithium or lorazepam. J Clin Psychopharmacol 1999; 19:500–505.
5. Small JG, et al. A placebo-controlled study of lithium combined with neuroleptics in chronic schizophrenic patients. Am J Psychiatry 1975; 132:1315–1317.
6. Soares JC, et al. Adjunctive antipsychotic use in bipolar patients: an open 6-month prospective study following an acute episode. J Affect Disord 1999; 56:1–8.
7. Keck PE, Jr, et al. Anticonvulsants and antipsychotics in the treatment of bipolar disorder. J Clin Psychiatry 1998; 59 Suppl 6:74–81.
8. Tohen M, et al. Antipsychotic agents and bipolar disorder. J Clin Psychiatry 1998; 59 Suppl 1:38–48.
9. Zarate CA, Jr, et al. Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. Am J Psychiatry 2004; 161:169–171.
10. Gigante AD, et al. Long-acting injectable antipsychotics for the maintenance treatment of bipolar disorder. CNS Drugs 2012; 26:403–420.
11. Goikolea JM, et al. Lower rate of depressive switch following antimanic treatment with second-generation antipsychotics versus haloperidol. J Affect Disord 2013; 144:191–198.
12. Yildiz A, et al. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychol Med 2015; 45:299–317.
13. Kishi T, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. Mol Psychiatry 2022; 27:1136–1144.
14. Baldessarini RJ, et al. Pharmacological treatment of adult bipolar disorder. Mol Psychiatry 2019; 24:198–217.
15. Yu CL, et al. Comparison of antipsychotic dose equivalents for acute bipolar mania and schizophrenia. BMJ Ment Health 2023; 26:e300546.

16. Ogawa Y, et al. Mood stabilizers and antipsychotics for acute mania: a systematic review and meta-analysis of combination/augmentation therapy versus monotherapy. CNS Drugs 2014; 28:989–1003.
17. Ashok AH, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. Mol Psychiatry 2017; 22:666–679.
18. Jauhar S, et al. A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. JAMA Psychiatry 2017; 74:1206–1213.
19. Taylor DM, et al. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. Acta Psychiatr Scand 2014; 130:452––469.
20. Yildiz A, et al. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis. Lancet Psychiatry 2023; 10:693–705.
21. Kadakia A, et al. Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. BMC Psychiatry 2021; 21:249.
22. Martins-Correia J, et al. Cariprazine in the acute treatment of unipolar and bipolar depression: a systematic review and meta-analysis. J Affect Disord 2024; 362:297–307.
23. Taylor MJ. Bipolar treatment efficacy. Lancet Psychiatry 2014; 1:418.
24. Miura T, 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; 1:351–359.
25. McIntyre RS, et al. Cariprazine as a maintenance therapy in the prevention of mood episodes in adults with bipolar I disorder. Bipolar Disord 2024; 26:442–453.
26. Sachs G, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. J Psychopharmacol 2006; 20:536–546.
27. Keck PE, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium- controlled study. J Affect Disord 2009; 112:36–49.
28. Young AH, et al. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. Br J Psychiatry 2009; 194:40–48.
29. Vieta E, et al. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/ lithium monotherapy: a placebo--controlled study. Am J Psychiatry 2008; 165:1316–1325.
30. Keck PE, Jr, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007; 68:1480–1491.
31. Vieta E, et al. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. Curr Med Res Opin 2010; 26:1485–1496.
32. Shafti SS. Aripiprazole versus lithium in management of acute mania: a randomized clinical trial. East Asian Arch Psychiatry 2018; 28:80–84.
33. Brown R, et al. Aripiprazole alone or in combination for acute mania. Cochrane Database Syst Rev 2013; 12:CD005000.
34. Calabrese JR, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized

withdrawal study. J Clin Psychiatry 2017; 78:324–331.

 35. McIntyre RS, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J Affect Disord 2010; 122:27–38. 36. McIntyre RS, et al. Asenapine versus olanzapine in acute mania: a double-blind extension study. Bipolar Disord 2009; 11:815–826. 37. McIntyre RS, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. J Affect Disord 2010; 126:358–365. 38. Szegedi A, et al. Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder. Am J Psychiatry 2018; 175:71–79. 39. Pillinger T, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020; 7:64–77. 40. McIntyre RS, et al. Cariprazine for the treatment of bipolar mania with mixed features: a post hoc pooled analysis of 3 trials. J Affect Disord 2019; 257:600–606. 41. Zarate CA, Jr, et al. Clozapine in severe mood disorders. J Clin Psychiatry 1995; 56:411–417. 42. Li XB, et al. Clozapine for treatment-resistant bipolar disorder: a systematic review. Bipolar Disord 2015; 17:235–247. 43. Loo LWJ, et al. Clozapine use for bipolar disorder: an Asian Psychotropic Prescription Patterns Consortium Study. J Clin Psychopharmacol 2023; 43:278–282. 44. Loebel A, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014; 171:160–-168. 45. Loebel A, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double- blind, placebo-controlled study. Am J Psychiatry 2014; 171:169–177. 46. Tohen M, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry 1999; 156:702–709. 47. Tohen M, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. Arch Gen Psychiatry 2000; 57:841–849. 48. Tohen M, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002; 59:62–69. 49. Tohen M, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry 2004; 184:337–345. 50. Tohen M, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. Br J Psychiatry 2008; 192:135–143. 51. Sanger TM, et al. Long-term olanzapine therapy in the treatment of bipolar I disorder: an open-label continuation phase study. J Clin Psychiatry 2001; 62:273–281. 52. Vieta E, et al. Olanzapine as long-term adjunctive therapy in treatment-resistant bipolar disorder. J Clin Psychopharmacol 2001; 21:469–473. 53. Tohen M, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005; 162:1281–1290. 54. McKnight RF, et al. Lithium for acute mania. Cochrane Database Syst Rev 2019; 6:CD004048. 55. Corrao MM, et al. Olanzapine/samidorphan: a new combination treatment for schizophrenia and bipolar I disorder intended to reduce weight gain. CNS Drugs 2022; 36:605–616. 56. Faden J, et al. Olanzapine--samidorphan combination tablets for the treatment of schizophrenia and bipolar I disorder – what is it, and will it be used? Expert Rev Neurother 2022; 22:365–376. 57. Ghaemi SN, et al. The use of quetiapine for treatment-resistant bipolar disorder: a case series. Ann Clin Psychiatry 1999; 11:137–140. 58. Sachs G, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2004; 6:213–223. 59. Altamura AC, et al. Efficacy and tolerability of quetiapine in the treatment of bipolar disorder:

preliminary evidence from a 12-month open label study. J Affect Disord 2003; 76:267–271. 60. Young AH, et al. A randomised, placebo-controlled 52-week trial of continued quetiapine treatment in recently depressed patients with bipolar I and bipolar II disorder. World J Biol Psychiatry 2014; 15:96–112. 61. Segal J, et al. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol 1998; 21:176–180. 62. Sachs GS, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo- controlled comparison of efficacy and safety. Am J Psychiatry 2002; 159:1146–1154. 63. Vieta E, et al. Risperidone in the treatment of mania: efficacy and safety results from a large, multicentre, open study in Spain. J Affect Disord 2002; 72:15–19. 64. Quiroz JA, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry 2010; 68:156–162. 65. Taylor DM, et al. Paliperidone palmitate: factors predicting continuation with treatment at 2 years. Eur Neuropsychopharmacol 2016; 26:2011–-2017. 66. Vieta E, et al. An open-label study of amisulpride in the treatment of mania. J Clin Psychiatry 2005; 66:575–578. 67. Vieta E, et al. Ziprasidone in the treatment of acute mania: a 12--week, placebo-controlled, haloperidol-referenced study. J Psychopharmacol 2010; 24:547–558. 68. Singh V, et al. An open trial of iloperidone for mixed episodes in bipolar disorder. J Clin Psychopharmacol 2017; 37:615–619. 69. McIntyre RS, et al. The efficacy of lumateperone in patients with bipolar depression with mixed features. J Clin Psychiatry 2023; 84:22m14739. 70. Calabrese JR, et al. Efficacy and safety of lumateperone for major depressive episodes associated with bipolar I or bipolar II disorder: a phase 3 randomized placebo-controlled trial. Am J Psychiatry 2021; 178:1098–1106.

43 - Antipsychotic long acting injections in bipol

Antipsychotic long-acting injections in bipolar disorder

Bipolar disorder CHAPTER 2 Antipsychotic long-acting injections in bipolar disorder LAIs are widely used in bipolar disorder although none is formally licensed in the UK for this indication (Abilify Maintena is approved by the FDA in the USA). Support for their use is rather limited: there have been dozens of open-label trials or case series published, but few included more than a handful of subjects.1–3 Retrospective cohort studies, mirror-image studies and population-level studies do, nonetheless, offer some support for the use of LAIs (mainly SGAs) in bipolar maintenance.1 Mirror--image studies uniformly show a reduction in admissions and bed days when patients are switched from oral medication to LAI formulations of aripiprazole4–6 and paliperidone,6,7 although study numbers were small. Prospective open-label studies also support the prophylactic effect of aripiprazole LAI, both monthly and two-monthly.8,9 There have also been seven RCTs, only five of which were sufficiently powered to produce interpretable results (the remaining two trials included only 30 subjects in total10,11). These five RCTs represent the highest level of evidence for LAIs in bipolar disorder. Their details are set out in Table 2.5. Few firm conclusions can be drawn from the controlled trials outlined in Table 2.5. Risperidone LAI is clearly effective either as the sole treatment or as an adjunct but provides protection only against manic, hypomanic and mixed--manic episodes and Table 2.5 Randomised controlled trials (RCTs) of the use of long-acting injections (LAIs) in bipolar affective disorder. Reference Number LAI Comparator Duration Outcome Ahlfors et al., 198112 (19/14) Flupentixol decanoate Lithium 18 months Neither treatment improved main outcome (number of mood episodes) Macfadden et al., 200913* (65/59) Risperidone (adjunct) Placebo (adjunct) 12 months Risperidone LAI reduced rate of relapse compared with placebo (relative risk 2.3) Quiroz et al., 201014* (154/149) Risperidone monotherapy Placebo monotherapy 24 months Overall relapse rate was 30% with risperidone, 56% with placebo. Risperidone did not protect against depressive relapse. Vieta et al., 201215* (132/135/131) Risperidone monotherapy Placebo or oral olanzapine monotherapy 18 months Recurrence of any mood episode: oral olanzapine 23.8%; risperidone LAI 38.9%; placebo 56.4%. Olanzapine and risperidone reduced risk of elevated mood episode but only olanzapine reduced risk of depression. Calabrese et al., 201716* (133/133) Aripiprazole monotherapy Placebo monotherapy 12 months Relapse to any mood episode 26.5% with aripiprazole; 51.1% with placebo. No clear effect on recurrence of depression. An open follow-on study of this RCT (that also

included patients newly prescribed aripiprazole) showed somewhat better levels of protection: 87–98% of participants remained well over 12 months.17 *Trial sponsored by manufacturer.

44 - Conclusion

Conclusion

306 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 neither decreases nor increases the risk of depressive relapse. Risperidone LAI may be less effective than oral olanzapine. It might be assumed that paliperidone LAI has similar effects to risperidone LAI. Oral paliperidone prevents manic relapse in bipolar disorder,18 there are a few supportive mirror-image studies6,7 and case reports describe good outcomes with the LAI form.19,20 Aripiprazole LAI protects against manic relapse but does not appear to affect risk of depression. Data for FGAs in bipolar disorder are scarce and generally of low quality (open trials, case series and retrospective analyses). In these studies, FGA LAIs seem to reduce the risk of relapse compared with prior treatments. The largest (open) study12 (n = 85) suggested flupentixol decanoate (20mg every 2–3 weeks) reduced the risk of elevated mood episodes. Reports describe similar effects for other FGA LAIs. The one RCT conducted with flupentixol LAI12 showed no effect and no superiority over lithium. Considering this single RCT and all of the small and uncontrolled observations, there is very little evidence to support the often-repeated lore that flupentixol LAI increases the risk of manic relapse and haloperidol LAI and fluphenazine LAI increase the risk of depressive relapse (or that FGAs provoke depression). It is notable that authors of systematic reviews21,22 reiterate this view, which seems to be based on solely the observed increase in depressive episodes in the open study conducted by Ahlfors and colleagues.12 In fact, this increase occurred only in subjects whose lithium treatment had been stopped immediately before the study began. Nonetheless, oral haloperidol, when used for mania, is more likely than oral SGAs to cause a switch to depression23 so some caution is clearly required. There are no controlled comparisons of FGA and SGA LAIs.1–3 A Taiwanese retrospective cohort study24 reported a higher risk of depressive episode recurrence and a higher likelihood of hospitalisation in those prescribed FGA LAIs (50% were prescribed flupentixol, 25% haloperidol and 25% other drugs) compared with those prescribed risperidone LAI. Of particular note was the substantial rate of treatment discontinuation. At 1 year only 7.2% of those initially prescribed risperidone and 2.2% of those initiated on FGA LAIs remained on the original treatment. Another observational study found both SGA and FGA LAIs to be effective but only when treatment continued for at least 6 months.25 Conclusion ■ ■Support for the use of FGA LAIs in bipolar disorder is weak. ■ ■Very limited evidence suggests FGA LAIs may be effective in reducing recurrence of mania/hypomania but they do not prevent recurrence of depression and may increase the risk. ■ ■Risperidone LAI and aripiprazole LAI are robustly associated with a reduced risk of recurrence of episodes of mania/hypomania compared with placebo. ■ ■Risperidone LAI and aripiprazole LAI have no effect on the risk of depressive recurrence. ■ ■There is limited evidence to support the benefit of LAIs over oral antipsychotic treatment in bipolar maintenance. ■ ■As with other conditions, the use of LAIs offers the advantage of transparency in respect to compliance: the LAI injection is either given or it is not.

45 - References

References

Bipolar disorder CHAPTER 2 References

1. Keramatian K, et al. Long-acting injectable second-generation/atypical antipsychotics for the management of bipolar disorder: a systematic review. CNS Drugs 2019; 33:431–456.
2. Pacchiarotti I, et al. Long-acting injectable antipsychotics (LAIs) for maintenance treatment of bipolar and schizoaffective disorders: a systematic review. Eur Neuropsychopharmacol 2019; 29:457–470.
3. Prajapati AR, et al. Second-generation antipsychotic long-acting injections in bipolar disorder: systematic review and meta-analysis. Bipolar Disord 2018; 20:687–696.
4. Goto J, et al. Preventive effect of aripiprazole once monthly on rehospitalization for bipolar disorder: a multicenter 1-year retrospective mirror image study. Neuropsychopharmacol Rep 2023; 43:425–433.
5. Woo YS, et al. Preventive effect of aripiprazole once-monthly on relapse into mood episodes in bipolar disorder: a multicenter, one-year, retrospective, mirror image study. J Affect Disord 2024; 351:381–386.
6. Yıldızhan E, et al. Effect of long acting injectable antipsychotics on course and hospitalizations in bipolar disorder – a naturalistic mirror image study. Nord J Psychiatry 2022; 76:37–43.
7. Caliskan AM, et al. Impact of initiating long-acting injectable paliperidone palmitate on relapse and hospitalization in patients with bipolar I disorder: a mirror image retrospective study. Asian J Psychiatr 2020; 54:102457.
8. Harlin M, et al. A randomized, open-label, multiple-dose, parallel-arm, pivotal study to evaluate the safety, tolerability, and pharmacokinetics of aripiprazole 2-month long-acting injectable in adults with schizophrenia or bipolar I disorder. CNS Drugs 2023; 37:337–350.
9. McIntyre RS, et al. Safety and efficacy of aripiprazole 2-month ready-to-use 960 mg: secondary analysis of outcomes in adult patients with bipolar I disorder in a randomized, open-label, parallel-arm, pivotal study. Curr Med Res Opin 2023; 39:1021–1030.
10. Esparon J, et al. Comparison of the prophylactic action of flupenthixol with placebo in lithium treated manic-depressive patients. Br J Psychiatry 1986; 148:723–725.
11. Yatham L, et al. Randomised trial of oral vs. injectable antipsychotics in bipolar disorder. Presented at the 6th International Conference on Bipolar Disorder: 16–18 June 2005, Pittsburgh, PA.
12. Ahlfors UG, et al. Flupenthixol decanoate in recurrent manic-depressive illness. A comparison with lithium. Acta Psychiatr Scand 1981; 64:226–237.
13. Macfadden W, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I

disorder who relapse frequently. Bipolar Disord 2009; 11:827–839.
14. Quiroz JA, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry 2010; 68:156–162.
15. Vieta E, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. Eur Neuropsychopharmacol 2012; 22:825–835.
16. Calabrese JR, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psychiatry 2017; 78:324–331.
17. Calabrese JR, et al. Aripiprazole once-monthly as maintenance treatment for bipolar I disorder: a 52-week, multicenter, open-label study. Int J Bipolar Disord 2018; 6:14.
18. Berwaerts J, et al. A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. J Affect Disord 2012; 138:247–258.
19. Buoli M, et al. Paliperidone palmitate depot in the long-term treatment of psychotic bipolar disorder: a case series. Clin Neuropharmacol 2015; 38:209–211.
20. Li K, et al. Case report: paliperidone palmitate in the management of bipolar I disorder with non-compliance. Front Psychiatry 2020; 11:529672.
21. Bond DJ, et al. Depot antipsychotic medications in bipolar disorder: a review of the literature. Acta Psychiatr Scand Suppl 2007; 2007:3–16.
22. Gigante AD, et al. Long-acting injectable antipsychotics for the maintenance treatment of bipolar disorder. CNS Drugs 2012; 26:403–420.
23. Goikolea JM, et al. Lower rate of depressive switch following antimanic treatment with second-generation antipsychotics versus haloperidol. J Affect Disord 2013; 144:191–198.
24. Wu CS, et al. Comparative effectiveness of long-acting injectable risperidone vs. long--acting injectable first-generation antipsychotics in bipolar disorder. J Affect Disord 2016; 197:189–195.
25. Bartoli F, et al. Effect of long-acting injectable antipsychotics on 1-year hospitalization in bipolar disorder: a mirror-image study. Eur Arch Psychiatry Clin Neurosci 2023; 273:1579–-1586.

46 - Physical monitoring for people with bipolar d

Physical monitoring for people with bipolar disorder1,2

Physical monitoring for people with bipolar disorder1,2 Monitoring for all patients Additional monitoring for specific drugs Test or measurement Initial health check Annual check-up Antipsychotics Lithium Valproate Carbamazepine Thyroid function Yes Yes At start and every 6 months. More often if evidence of change. Liver function tests (LFTs) Yes Yes Every 3 months for the first year then annually Monthly for the first 3 months then annually Renal function (eGFR) Yes Yes At start and every 6 months. More often if there is evidence of deterioration or the patient starts taking interacting drugs. Electrolytes, urea and creatinine (EUC) Yes Yes At start and then every 3–6 months (include serum calcium) Monthly for the first 3 months then annually Full blood count (FBC) Yes Yes Only if clinically indicated Every 3 months for the first year then annually Monthly for the first 3 months then annually Blood (plasma) glucose Yes Yes, as part of a routine physical health check At start and then every 4–6 months (and at 1 month if taking olanzapine); more often if evidence of elevated levels Lipid profile Yes Yes, as part of a routine physical health check At start and at 3 months; more often initially if evidence of elevated levels Blood pressure and pulse Yes Yes, as part of a routine physical health check During dosage titration if antipsychotic prescribed is associated with postural hypotension

47 - References

References

Prolactin Children and adolescents only At start and if symptoms of raised prolactin develop Raised prolactin unlikely with quetiapine or aripiprazole. Very occasionally seen with olanzapine and asenapine. Very common with risperidone and FGAs. ECG If indicated by cardiovascular disease or risk factors At start if there are risk factors for or existing cardiovascular disease (or haloperidol is prescribed). If relevant abnormalities are detected, re-check after each dose increase. At start if risk factors for or existing cardiovascular disease. If relevant abnormalities are detected re-check after each dose increase. At start if risk factors for or existing cardiovascular disease. If relevant abnormalities are detected, re-check after each dose increase. Waist circumference and/or body mass index Yes Yes, as part of a routine physical health check Monthly for the first 3 months then annually At start, and then every 6 months Every 3 months for the first year then annually At start and when needed if the patient gains weight rapidly Plasma levels of drug At least 3–4 days after initiation and 3–4 days after every dose change until levels stable, then every 3 months in the first year, then every 6 months for most patients (see NICE2) Titrate by effect and tolerability. Do not routinely measure unless there is evidence of lack of effectiveness, poor adherence or toxicity. Two weeks after initiation and 2 weeks after dose change. Thereafter, do not routinely measure unless there is evidence of lack of effectiveness, poor adherence or toxicity. For patients on lamotrigine, do an annual health check, but no special monitoring tests are needed although blood levels may indicate if high doses might be considered. References

1. Ng F, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord 2009; 11:559–595.
2. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last accessed October 2024); https://www.nice.org. uk/guidance/cg185.

48 - Treatment of acute mania or hypomania

Treatment of acute mania or hypomania

310 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Treatment of acute mania or hypomania Drug treatment is the mainstay of therapy for mania and hypomania. Both antipsychotics and mood stabilisers are effective (although the nomenclature here is unhelpful – most, possibly all, antipsychotics are anti-manic and most mood stabilisers reduce psychotic symptoms in mania). Sedative and anxiolytic drugs (e.g. benzodiazepines) may add to the effects of these treatments. Drug choice is made difficult by the small number of direct comparisons, such that no one individual drug can be recommended over another on efficacy grounds. However, an early network meta-analysis1 suggested that olanzapine, risperidone, haloperidol and quetiapine had the best combination of efficacy and acceptability. Cochrane reviews suggested olanzapine is more effective than both lithium2 and valproate3 when used as monotherapy. Olanzapine may also be more effective than asenapine.4 A 2024 network meta-analysis concluded that tamoxifen was the most effective individual drug.5 The benefit of antipsychotic mood stabiliser combinations (compared with a mood stabiliser alone) is established for those relapsing while on mood stabilisers but less clear for those presenting on no treatment.6–10 The most common study design is for participants to be randomised to continued mood stabiliser alone (a treatment that allows the emergence of mania) or to the failed mood stabiliser with a (newly introduced) No Stop antidepressant treatment Is patient taking anti-manic* medication? Yes *In this context anti-manic = antipsychotic or mood stabiliser. **Lithium may be somewhat less effective in mixed states27 or substance misuse28 and in those with rapid cycling or exhibiting psychotic symptoms.29 Consider: An antipsychotic (if symptoms severe or behaviour disturbed) Or Valproate (avoid in women of child-bearing potential) Or Lithium (if future adherence likely) If response is inadequate after 1–2 weeks Combine antipsychotic and valproate or lithium All patients: consider adding short-term benzodiazepine22–24 (lorazepam or clonazepam) If taking an antipsychotic, check compliance and dose. Increase if necessary. Consider adding lithium or valproate If taking lithium,** check plasma levels, consider increasing the dose to give levels 1.0–1.2mmol/L (to treat the acute episode) and/or adding an antipsychotic If taking valproate, check plasma levels,8,9,25,26 increase dose to give levels up to 125mg/L if tolerated. Consider adding an antipsychotic If taking lithium or valproate and mania is severe, check level, add an antipsychotic6 If taking carbamazepine, consider adding

an antipsychotic (higher doses may be needed as antipsychotic levels reduced) All patients: consider adding short-term benzodiazepine22–24 (lorazepam or clonazepam) Figure 2.1 Treatment of acute mania or hypomania.6–21

Bipolar disorder CHAPTER 2 antipsychotic. Overall, combination treatment with an antipsychotic and a mood stabiliser is more effective and quicker to act than either individual drug used alone.5,30 Most formal guidelines recommend drug combinations as the first choice in mania,31 although single drug treatment may be considered, at least initially, for people presenting on no prior treatment. Figure 2.1 outlines a treatment strategy for mania and hypomania. These recommendations are based on somewhat dated UK NICE guidelines,7 British Association for Psychopharmacology (BAP) guidelines32 and individual references cited in the diagram. Where an antipsychotic is recommended, choose from those licensed for mania/bipolar disorder (i.e. most conventional drugs, aripiprazole, asenapine, olanzapine, risperidone and quetiapine). Valproate use is now heavily restricted, so lithium is likely to be the mood stabiliser most commonly used, at least in younger men and women. An alternative is carbamazepine, but this, like valproate, is teratogenic. Lamotrigine has no activity in mania33 and should not be used. Suggested doses and alternative treatments are outlined in Tables 2.6 and 2.7. Table 2.6 Mania: suggested drug doses. Drug Dose Mood stabilisers Carbamazepine 400mg MR twice daily increasing to 800–-1600mg/day.34,35 Dose may need to be increased after 2 weeks owing to induction of metabolism. Lithium 400mg/day, increasing every 3–4 days according to plasma levels. At least one study has used 800mg as a starting dose.36 Valproate As semi-sodium – 250mg three times daily increasing according to tolerability and plasma levels. Slow-release semi-sodium valproate may also be effective (at 15–30mg/kg)37 but there is one failed study.38 As slow-release sodium valproate – 500mg/day increasing as above. Higher, ‘loading doses’ have been used, both oral39–-41 and intravenous.42–44 The dose is 20–30mg/kg/day. Antipsychotics Aripiprazole 15mg/day increasing up to 30mg/day as required.45 Doses lower than 15mg may not be effective.46 Asenapine 5mg twice daily increasing to 10mg twice daily as required Cariprazine 3mg/day increasing up to 12mg a day as required47 Olanzapine 10mg/day increasing to 15 or 20mg as required Risperidone 2 or 3mg/day increasing to 6mg/day as required. The use of paliperidone in mania is not well supported.48 Quetiapine IR – 100mg/day increasing to 800mg as required. Higher starting doses have been used.49 XL – 300mg/day increasing to 600mg/day on day 2 Haloperidol 5–10mg/day increasing to 15mg if required Benzodiazepines Lorazepam23,24 Up to 4mg/day (some centres use higher doses) Clonzapam22,24 Up to 8mg/day

49 - References

References

1. Cipriani A, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011; 378:1306–1315.
2. McKnight RF, et al. Lithium for acute mania. Cochrane Database Syst Rev 2019; 6:CD004048.
3. Jochim J, et al. Valproate for acute mania. Cochrane Database Syst Rev 2019; 10:CD004052.
4. Mahajan V, et al. Efficacy and safety of asenapine versus olanzapine in combination with divalproex for acute mania: a randomized controlled trial. J Clin Psychopharmacol 2019; 39:305–311.
5. Huang W, et al. Comparative efficacy, safety, and tolerability of pharmacotherapies for acute mania in adults: a systematic review and network meta-analysis of randomized controlled trials. Mol Psychiatry 2024; doi: 10.1038/s41380-024-02705-3. Table 2.7 Mania: other possible treatments.* Treatment Comments Allopurinol (300–600mg/day) A meta--analysis of five studies of adjunct allopurinol found an effect size of just less than 0.3.50 Celecoxib (400mg/day)51 Small RCT (n = 46) suggests benefit when used as adjunct to valproate. Clonidine (450–900mcg/day)52 Limited data Clozapine53–55 Established treatment option for refractory mania/bipolar disorder. Rapid titration has been reported.56 Endoxifen57 (4–8mg/day) RCT evidence of efficacy. Major metabolite of tamoxifen. Gabapentin58 (up to 2.4g/day) Probably only effective by virtue of an anxiolytic effect. Rarely used. Possibly useful as prophylaxis.59 Levetiracetam (up to 1500mg/day) Effective as adjunctive treatment in two RCTs.60,61 One case of levetiracetam causing mania.62 Melatonin (6mg/day)67 Preliminary evidence of benefit as an adjunct to standard treatment. One small negative study.68 Memantine63 (10–-30mg/day) Conflicting evidence64–66 Oxcarbazepine69–76 (around 300–3000mg/day) Probably effective acutely and as prophylaxis although one controlled study (conducted in youths) was negative.77 Phenytoin78 (300–400mg/day) Rarely used. Limited data. Complex kinetics with narrow therapeutic range. Ritanserin79 (10mg/day) Supported by a single RCT. Well tolerated. May protect against EPSEs. Tamoxifen80 (20–140mg/day) Good evidence for efficacy as adjunct and as monotherapy, with large effect size. May provoke switch to depression. Topiramate81 (up to 300mg/day) Probably not effective. Less effective than lithium.2 Tryptophan depletion82 Supported by a small RCT. Ziprasidone83–85 Supported by three RCTs. Widely used outside UK. *Entries are given in alphabetical order; no preference is implied by order in the table. Consult specialist and primary literature before using any treatment listed. EPSEs, extrapyramidal side effects;

RCT, randomised controlled trial.

Bipolar disorder CHAPTER 2 6. Smith LA, et al. Acute bipolar mania: a systematic review and meta--analysis of co-therapy vs. monotherapy. Acta Psychiatr Scand 2007; 115:12–20. 7. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last accessed October 2024); https://www.nice.org.uk/guidance/cg185. 8. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2009; 23:346–388. 9. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002; 159:1–50. 10. Sachs GS. Decision tree for the treatment of bipolar disorder. J Clin Psychiatry 2003; 64 Suppl 8:35–40. 11. Tohen M, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. Arch Gen Psychiatry 2003; 60:1218–1226. 12. Baldessarini RJ, et al. Olanzapine versus placebo in acute mania treatment responses in subgroups. J Clin Psychopharmacol 2003; 23:370–376. 13. Sachs G, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2004; 6:213–223. 14. Yatham LN, et al. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. J Clin Psychopharmacol 2004; 24:599–606. 15. Yatham LN, et al. Risperidone plus lithium versus risperidone plus valproate in acute and continuation treatment of mania. Int Clin Psychopharmacol 2004; 19:103–109. 16. Bowden CL, et al. Risperidone in combination with mood stabilizers: a 10-week continuation phase study in bipolar I disorder. J Clin Psychiatry 2004; 65:707–714. 17. Hirschfeld RM, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo--controlled trial. Am J Psychiatry 2004; 161:1057–1065. 18. Bowden CL, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry 2005; 66:111–121. 19. Khanna S, et al. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. Br J Psychiatry 2005; 187:229–234. 20. Young RC, et al. GERI-BD: a randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. Am J Psychiatry 2017; 174:1086–1093. 21. Conus P, et al. Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: an 8-week randomised controlled trial. Eur Psychiatry 2015; 30:975–982. 22. Sachs GS, et al. Adjunctive clonazepam for maintenance treatment of bipolar affective disorder. J Clin Psychopharmacol 1990; 10:42–47. 23. Modell JG, et al. Inpatient clinical trial of lorazepam for the management of manic agitation. J Clin Psychopharmacol 1985; 5:109–113. 24. Curtin F, et al. Clonazepam and lorazepam in acute mania: a Bayesian meta-analysis. J Affect Disord 2004; 78:201–208. 25. Taylor D, et al. Doses of carbamazepine and valproate in bipolar affective disorder. Psychiatric Bulletin 1997; 21:221–223. 26. Allen MH, et al. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry 2006; 163:272–275. 27. Swann AC, et al. Lithium treatment of mania: clinical characteristics, specificity of symptom change, and outcome. Psychiatry Res 1986; 18:127–141. 28. Goldberg JF, et al. A history of substance abuse complicates remission from acute mania in bipolar disorder. J Clin Psychiatry 1999; 60:733–740. 29. Hui TP, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. Acta Psychiatr Scand 2019; 140:94–115. 30. Tajika A, et al. Mood stabilizers and antipsychotics for acute mania: systematic review and meta-analysis of augmentation therapy vs monotherapy from the perspective of time to the onset of treatment effects. Int J Neuropsychopharmacol 2022; 25:839–852. 31. Yatham LN, et al. Canadian Network for

Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20:97–-170. 32. Goodwin GM, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016; 30:495–553. 33. Besag FMC, et al. Efficacy and safety of lamotrigine in the treatment of bipolar disorder across the lifespan: a systematic review. Ther Adv Psychopharmacol 2021; 11:20451253211045870. 34. Weisler RH, et al. A multicenter, randomized, double-blind, placebo--controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry 2004; 65:478–484. 35. Weisler RH, et al. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2005; 66:323–330. 36. Bowden CL, et al. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. Int Clin Psychopharmacol 2010; 25:60–67. 37. McElroy SL, et al. Randomized, double-blind, placebo-controlled study of divalproex extended release loading monotherapy in ambulatory bipolar spectrum disorder patients with moderate-to-severe hypomania or mild mania. J Clin Psychiatry 2010; 71:557–565. 38. Hirschfeld RM, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended-release in the acute treatment of mania. J Clin Psychiatry 2010; 71:426–432. 39. McElroy SL, et al. A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. J Clin Psychiatry 1996; 57:142–146. 40. Hirschfeld RM, et al. Safety and tolerability of oral loading divalproex sodium in acutely manic bipolar patients. J Clin Psychiatry 1999; 60:815–818.

 41. Hirschfeld RM, et al. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. J Clin Psychiatry 2003; 64:841–846. 42. Jagadheesan K, et al. Acute antimanic efficacy and safety of intravenous valproate loading therapy: an open-label study. Neuropsychobiology 2003; 47:90–93. 43. Sekhar S, et al. Efficacy of sodium valproate and haloperidol in the management of acute mania: a randomized open-label comparative study. J Clin Pharmacol 2010; 50:688–692. 44. Fontana E, et al. Intravenous valproate in the treatment of acute manic episode in bipolar disorder: a review. J Affect Disord 2020; 260:738–743. 45. Li DJ, et al. Efficacy, safety and tolerability of aripiprazole in bipolar disorder: an updated systematic review and meta-analysis of randomized controlled trials. Prog Neuropsychopharmacol Biol Psychiatry 2017; 79:289–301. 46. Romeo B, et al. Meta-analysis and review of dopamine agonists in acute episodes of mood disorder: efficacy and safety. J Psychopharmacol 2018; 32:385–396. 47. Vieta E, et al. Effect of cariprazine across the symptoms of mania in bipolar I disorder: analyses of pooled data from phase II/III trials. Eur Neuropsychopharmacol 2015; 25:1882–1891. 48. Chang HY, et al. The efficacy and tolerability of paliperidone in mania of bipolar disorder: a preliminary meta-analysis. Exp Clin Psychopharmacol 2017; 25:422–433. 49. Pajonk FG, et al. Rapid dose titration of quetiapine for the treatment of acute schizophrenia and acute mania: a case series. J Psychopharmacol 2006; 20:119–124. 50. Chen AT, et al. Allopurinol augmentation in acute mania: a meta-analysis of placebo-controlled trials. J Affect Disord 2018; 226:245–250. 51. Arabzadeh S, et al. Celecoxib adjunctive therapy for acute bipolar mania: a randomized, double-blind, placebo-controlled trial. Bipolar Disord 2015; 17:606–614. 52. Singal P, et al. Efficacy and safety of clonidine in the treatment of acute mania in bipolar disorder: a systematic review. Brain Sci 2023; 13:547. 53. Mahmood T, et al. Clozapine in the management of bipolar and schizoaffective manic episodes resistant to standard treatment.

Aust NZ J Psychiatry 1997; 31:424–426. 54. Green AI, et al. Clozapine in the treatment of refractory psychotic mania. Am J Psychiatry 2000; 157:982–986. 55. Ifteni P, et al. Switching bipolar disorder patients treated with clozapine to another antipsychotic medication: a mirror image study. Neuropsychiatr Dis Treat 2017; 13:201–204. 56. Aksoy Poyraz C, et al. Effectiveness of ultra-rapid dose titration of clozapine for treatment-resistant bipolar mania: case series. Ther Adv Psychopharmacol 2015; 5:237–242. 57. Joseph JT, et al. Efficacy and safety of endoxifen in bipolar disorder: a systematic review. Hum Psychopharmacol 2024; 39:e2899. 58. Ng QX, et al. A systematic review of the clinical use of gabapentin and pregabalin in bipolar disorder. Pharmaceuticals (Basel) 2021; 14:834. 59. Vieta E, et al. A double-blind, randomized, placebo--controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. J Clin Psychiatry 2006; 67:473–477. 60. Zarezadeh F, et al. Levetiracetam adjunct to quetiapine for the acute manic phase of bipolar disorder: a randomized, double-blind and placebo-controlled clinical trial of efficacy, safety and tolerability. Int Clin Psychopharmacol 2022; 37:46–53. 61. Keshavarzi A, et al. Levetiracetam as an adjunctive treatment for mania: a double-blind, randomized, placebo--controlled trial. Neuropsychobiology 2022; 81:192–203. 62. Park EM, et al. Acute mania associated with levetiracetam treatment. Psychosomatics 2014; 55:98–100. 63. Koukopoulos A, et al. Antimanic and mood-stabilizing effect of memantine as an augmenting agent in treatment--resistant bipolar disorder. Bipolar Disord 2010; 12:348–349. 64. Veronese N, et al. Acetylcholinesterase inhibitors and memantine in bipolar disorder: a systematic review and best evidence synthesis of the efficacy and safety for multiple disease dimensions. J Affect Disord 2016; 197:268–280. 65. Serra G, et al. Three-year, naturalistic, mirror-image assessment of adding memantine to the treatment of 30 treatment-resistant patients with bipolar disorder. J Clin Psychiatry 2015; 76:e91–97. 66. Omranifard V, et al. Evaluation of the effect of memantine supplementation in the treatment of acute phase of mania in bipolar disorder of elderly patients: a double-blind randomized controlled trial. Adv Biomed Res 2018; 7:148. 67. Moghaddam HS, et al. Efficacy of melatonin as an adjunct in the treatment of acute mania: a double-blind and placebo--controlled trial. Int Clin Psychopharmacol 2020; 35:81–88. 68. Quested DJ, et al. Melatonin In Acute Mania Investigation (MIAMI-UK). A randomized controlled trial of add-on melatonin in bipolar disorder. Bipolar Disord 2021; 23:176–185. 69. Benedetti A, et al. Oxcarbazepine as add-on treatment in patients with bipolar manic, mixed or depressive episode. J Affect Disord 2004; 79:273–277. 70. Lande RG. Oxcarbazepine: efficacy, safety, and tolerability in the treatment of mania. Int J Psychiatry Clin Pract 2004; 8:37–40. 71. Ghaemi SN, et al. Oxcarbazepine treatment of bipolar disorder. J Clin Psychiatry 2003; 64:943–945. 72. Pratoomsri W, et al. Oxcarbazepine in the treatment of bipolar disorder: a review. Can J Psychiatry 2006; 51:540–545. 73. Juruena MF, et al. Bipolar I and II disorder residual symptoms: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double- blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33:94–99. 74. Suppes T, et al. Comparison of two anticonvulsants in a randomized, single-blind treatment of hypomanic symptoms in patients with bipolar disorder. Aust NZ J Psychiatry 2007; 41:397–402. 75. Vieta E, et al. A double-blind, randomized, placebo--controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. Int J Neuropsychopharmacol 2008; 11:445–452.

 76. Talaei A, et al. Oxcarbazepine versus sodium valproate in treatment of acute mania: a double-blind randomized clinical trial. Int Clin Psychopharmacol 2022; 37:116–121. 77. Wagner KD, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. Am J Psychiatry

2006; 163:1179–1186. 78. Mishory A, et al. Phenytoin as an antimanic anticonvulsant: a controlled study. Am J Psychiatry 2000; 157:463–465. 79. Akhondzadeh S, et al. Ritanserin as an adjunct to lithium and haloperidol for the treatment of medication-naive patients with acute mania: a double blind and placebo controlled trial. BMC Psychiatry 2003; 3:7. 80. Carmassi C, et al. Prescribing tamoxifen in patients with mood disorders: a systematic review of potential antimanic versus depressive effects. J Clin Psychopharmacol 2021; 41:450–460. 81. Pigott K, et al. Topiramate for acute affective episodes in bipolar disorder in adults. Cochrane Database Syst Rev 2016; 9:CD003384. 82. Applebaum J, et al. Rapid tryptophan depletion as a treatment for acute mania: a double-blind, pilot-controlled study. Bipolar Disord 2007; 9:884–887. 83. Keck PE, Jr, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double--blind, randomized trial. Am J Psychiatry 2003; 160:741–748. 84. Potkin SG, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. J Clin Psychopharmacol 2005; 25:301–310. 85. Vieta E, et al. Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. J Psychopharmacol 2010; 24:547–558.

50 - Rapid cycling bipolar affective disorder

Rapid-cycling bipolar affective disorder

316 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Rapid-cycling bipolar affective disorder Rapid-cycling bipolar affective disorder is usually defined as bipolar disorder in which four or more episodes of (hypo-)mania or depression (or four clear switches in polarity) occur in a 12--month period. It is generally considered to be less responsive to drug treatment than non-rapid--cycling bipolar illness1 and entails considerable depressive morbidity and suicide risk.2 Bipolar patients with rapid cycling have more depressive morbidity, a higher incidence of anxiety disorders, addiction, bulimia and borderline personality disorder, as well as atypical features during depression and symptoms such as irritability, risky behaviour, impulsivity and agitation. Rapid--cycling patients have poorer overall functioning, more obesity and are treated with a greater number of drugs.3 Drug doses tend to be somewhat higher in rapid-cycling than in other bipolar patients.4 Recent electroconvulsive therapy (ECT) treatment is associated with greater risk of rapid cycling.5 Table 2.8 outlines a treatment strategy for rapid cycling based on rather limited data and few direct comparisons of drugs.6 This strategy is broadly in line with the findings of published systematic reviews.7,8 NICE concluded that there is no evidence to support rapid-cycling illness being managed any differently from that with a more conventional course.9 There is no formal first choice agent or combination – prescribing depends partly on what treatments have already been used to prevent or treat mood episodes. Lithium is less likely to be effective in rapid cycling than in non-rapid cycling,10 a finding supported by psychiatrists' experiences.11 In practice, response to treatment is sometimes idiosyncratic: individuals may show significant response to a particular drug. Spontaneous or treatment-related remissions occur in around a third of rapid cyclers12 and rapid cycling may come and go in many patients.13

51 - References

References

Bipolar disorder CHAPTER 2 References

1. Miola A, et al. Prevalence and outcomes of rapid cycling bipolar disorder: mixed method systematic meta-review. J Psychiatr Res 2023; 164:404–415.
2. Coryell W, et al. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 2003; 60:914–920.
3. Furio M, et al. Characterization of rapid cycling bipolar patients presenting with major depressive episode within the BRIDGE-II-MIX study. Bipolar Disord 2020; 23:391–399.
4. Yasui-Furukori N, et al. Factors associated with doses of mood stabilizers in real-world outpatients with bipolar disorder. Clin Psychopharmacol Neurosci 2020; 18:599–606.
5. Xu JJ, et al. Sociodemographic, clinical and treatment characteristics of current rapid--cycling bipolar disorder: a multicenter Chinese study. Int J Bipolar Disord 2024; 12:11.
6. Miola A, et al. Current status and treatment of rapid cycling bipolar disorder. J Clin Psychopharmacol 2024; 44:86–88.
7. Strawbridge R, et al. A systematic review and meta-analysis of treatments for rapid cycling bipolar disorder. Acta Psychiatr Scand 2022; 146:290–311.
8. Roosen L, et al. Evidence-based treatment strategies for rapid cycling bipolar disorder, a systematic review. J Affect Disord 2022; 311:69–77.
9. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last accessed October 2024); https://www.nice.org.uk/guidance/cg185.
10. Hui TP, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. Acta Psychiatr Scand 2019; 140:94–115.
11. Montlahuc C, et al. Response to lithium in patients with bipolar disorder: what are psychiatrists’ experiences and practices compared to literature review? Pharmacopsychiatry 2019; 52:70–77.
12. Koukopoulos A, et al. Duration and stability of the rapid-cycling course: a long-term personal follow-up of 109 patients. J Affect Disord 2003; 73:75–85.
13. Carvalho AF, et al. Rapid cycling in bipolar disorder: a systematic review. J Clin Psychiatry 2014; 75:e578–e586. Table 2.8 Recommended treatment strategy fo rapid-cycling bipolar disorder. Step Suggested treatment Step 1 Withdraw antidepressants in all patients10,11 (some controversial evidence supports continuation of SSRIs12,13) Step 2 Evaluate possible precipitants e.g. alcohol, thyroid dysfunction (including antithyroid antibodies14), external stressors15 Step 3 Optimise mood stabiliser treatment16–19 (using plasma levels) and Consider combining mood stabilisers e.g. lithium + valproate, lithium + lamotrigine, valproate + carbamazepine or go to Step 4 Step 4 Consider other (usually

adjunctive) treatment options (alphabetical order; preferred treatment options in bold8) Aripiprazole20,21 (15–30mg/day) Clozapine22 (usual doses) ECT23 Lamotrigine24–26 (up to 225mg/day) Levetiracetam27 (up to 2000mg/day) Lurasidone28,29 (40–120mg/day) Nimodipine30–32 (180mg/day) Olanzapine33 (usual doses) Quetiapine34–37 (300–-600mg/day) Risperidone38,39 (up to 6mg/day) Thyroxine40,41 (150–400mcg/day) Topiramate42 (up to 300mg/day) Transcranial magnetic stimulation (rTMS)43,44 The choice of drug is determined by patient factors – there are few comparative efficacy data to guide choice at the time of writing. Quetiapine probably has the best supporting data34–36 but it has similar efficacy to aripiprazole or olanzapine. Supporting data for levetiracetam, nimodipine, thyroxine and topiramate are relatively limited. Clozapine has a clear role in treatment-resistant bipolar disorder,45 a definition that might include rapid cycling, in which it shows some acute and long-term efficacy.22,46

14. Wehr TA, et al. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987; 144:1403–1411. 15. El-Mallakh RS, et al. Antidepressants worsen rapid-cycling course in bipolar depression: a STEP-BD randomized clinical trial. J Affect Disord 2015; 184:318–321. 16. Amsterdam JD, et al. Efficacy and mood conversion rate during long-term fluoxetine v. lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder. Br J Psychiatry 2013; 202:301–306. 17. Amsterdam JD, et al. Effectiveness and mood conversion rate of short-term fluoxetine monotherapy in patients with rapid cycling bipolar II depression versus patients with nonrapid cycling bipolar II depression. J Clin Psychopharmacol 2013; 33:420–424. 18. Gan Z, et al. Rapid cycling bipolar disorder is associated with antithyroid antibodies, instead of thyroid dysfunction. BMC Psychiatry 2019; 19:378. 19. Kupka RW, et al. Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. J Clin Psychiatry 2003; 64:1483–1494. 20. Kemp DE, et al. A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and co-occurring substance abuse or dependence. J Clin Psychiatry 2009; 70:113–121. 21. Da Rocha FF, et al. Addition of lamotrigine to valproic acid: a successful outcome in a case of rapid-cycling bipolar affective disorder. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31:1548–1549. 22. Woo YS, et al. Lamotrigine added to valproate successfully treated a case of ultra-rapid cycling bipolar disorder. Psychiatry Clin Neurosci 2007; 61:130–131. 23. Zhihan G, et al. Lamotrigine and lithium combination for treatment of rapid cycling bipolar disorder: results from meta-analysis. Front Psychiatry 2022; 13:913051. 24. Suppes T, et al. Efficacy and safety of aripiprazole in subpopulations with acute manic or mixed episodes of bipolar I disorder. J Affect Disord 2008; 107:145–154. 25. Muzina DJ, et al. Aripiprazole monotherapy in patients with rapid-cycling bipolar I disorder: an analysis from a long-term, double-blind, placebo--controlled study. Int J Clin Pract 2008; 62:679–687. 26. Calabrese JR, et al. Clozapine prophylaxis in rapid cycling bipolar disorder. J Clin Psychopharmacol 1991; 11:396–397. 27. Mosolov S, et al. Electroconvulsive therapy (ECT) in bipolar disorder patients with ultra-rapid cycling and unstable mixed states. Medicina (Kaunas) 2021; 57:624. 28. Fatemi SH, et al. Lamotrigine in rapid-cycling bipolar disorder. J Clin Psychiatry 1997; 58:522–527. 29. Calabrese JR, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. J Clin Psychiatry 2000; 61:841–850. 30. Wang Z, et al. Lamotrigine adjunctive therapy to lithium and divalproex in depressed patients with rapid cycling bipolar disorder and a recent substance use disorder: a 12-week, double-blind, placebo-controlled pilot study. Psychopharmacol Bull 2010; 43:5–21. 31. Braunig P, et al. Levetiracetam in the treatment of rapid cycling bipolar

disorder. J Psychopharmacol 2003; 17:239–241. 32. Siwek M, et al. Lurasidone in therapy of treatment-resistant ultra-rapid cycling bipolar disorder: case report. Clin Psychopharmacol Neurosci 2021; 19:568–571. 33. Kato M, et al. The efficacy and safety of lurasidone in bipolar I depression with and without rapid cycling: a pooled post-hoc analysis of two randomized, placebo-controlled trials. J Affect Disord 2023; 337:150–158. 34. Goodnick PJ. Nimodipine treatment of rapid cycling bipolar disorder. J Clin Psychiatry 1995; 56:330. 35. Pazzaglia PJ, et al. Preliminary controlled trial of nimodipine in ultra-rapid cycling affective dysregulation. Psychiatry Res 1993; 49:257–272. 36. Romanov DV, et al. [Nimodipine in treatment of bipolar disorder]. Zh Nevrol Psikhiatr Im S S Korsakova 2023; 123:20–26. 37. Sanger TM, et al. Olanzapine in the acute treatment of bipolar I disorder with a history of rapid cycling. J Affect Disord 2003; 73:155–161. 38. Goldberg JF, et al. Effectiveness of quetiapine in rapid cycling bipolar disorder: a preliminary study. J Affect Disord 2008; 105:305–310. 39. Vieta E, et al. Quetiapine monotherapy in the treatment of patients with bipolar I or II depression and a rapid-cycling disease course: a randomized, double-blind, placebo--controlled study. Bipolar Disord 2007; 9:413–425. 40. Langosch JM, et al. Efficacy of quetiapine monotherapy in rapid-cycling bipolar disorder in comparison with sodium valproate. J Clin Psychopharmacol 2008; 28:555–560. 41. Vieta E, et al. Quetiapine in the treatment of rapid cycling bipolar disorder. Bipolar Disord 2002; 4:335–340. 42. Bobo WV, et al. A randomized open comparison of long-acting injectable risperidone and treatment as usual for prevention of relapse, rehospitalization, and urgent care referral in community-treated patients with rapid cycling bipolar disorder. Clin Neuropharmacol 2011; 34:224–233. 43. Vieta E, et al. Treatment of refractory rapid cycling bipolar disorder with risperidone. J Clin Psychopharmacol 1998; 18:172–174. 44. Extein IL. High doses of levothyroxine for refractory rapid cycling. Am J Psychiatry 2000; 157:1704–1705. 45. Walshaw PD, et al. Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: a double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3). Bipolar Disord 2018; 20:594–603. 46. Chen CK, et al. Combination treatment of clozapine and topiramate in resistant rapid-cycling bipolar disorder. Clin Neuropharmacol 2005; 28:136–138. 47. Zamar AC, et al. A new treatment protocol of combined high-dose levothyroxine and repetitive transcranial magnetic stimulation for the treatment of rapid-cycling bipolar spectrum disorders: a cohort evaluation of 55 patients. J Clin Med 2022; 11:5830. 48. Tao S, et al. Case report: rTMS in combination with aripiprazole and sodium valproate for the maintenance treatment of rapid cycling bipolar disorder. Front Psychiatry 2023; 14:1070046. 49. Delgado A, et al. Clozapine in bipolar disorder: a systematic review and meta-analysis. J Psychiatr Res 2020; 125:21–27. 50. Kılınçel O, et al. The role of clozapine as a mood regulator in the treatment of rapid cycling bipolar affective disorder. Turk Psikiyatri Derg 2019; 30:268–271.

52 - Bipolar depression

Bipolar depression

53 - Meta analysis in bipolar depression

Meta-analysis in bipolar depression

Bipolar disorder CHAPTER 2 Bipolar depression Bipolar depression shares the diagnostic criteria for an episode of major depressive disorder, but episodes may differ in severity, time course, liability to recurrence and response to drug treatment. Episodes of bipolar depression are, compared with unipolar depression, more rapid in onset, more frequent, more severe, shorter and more likely to involve delusions and reverse neuro-vegetative symptoms such as hyperphagia and hypersomnia.1–3 Around 15% of people with bipolar disorder commit suicide,4 a statistic that reflects the severity and frequency of depressive episodes. Bipolar depression affords greater socioeconomic burden than either mania or unipolar major depression5 and comprises the majority of symptomatic illness in bipolar affective disorder with respect to time.6,7 In the UK, NICE recommends the combination of fluoxetine with olanzapine or quetiapine on its own (assuming an antipsychotic is not already prescribed).8 Lamotrigine is considered to be second-line treatment. BAP guidelines9 have lamotrigine as a first- line option, albeit with the caveat that a mood stabiliser or antipsychotic will be needed to protect against mania in the longer term. Lurasidone is also a first-line option in the BAP guidelines. The 2020 RANZCP guidelines10 recommend the use of lithium, lamotrigine, valproate, quetiapine, lurasidone and cariprazine either as individual agents or in combinations of two or three different drugs (including the addition of an antidepressant). Olanzapine and carbamazepine are considered second-line drugs. Similar recommendations are made in the more recent (2023) Canadian guidelines.11 Differences include the relegation of valproate to a second-line treatment and the inclusion of lumateperone (also as a second- line drug). Lurasidone is suggested as a first-line agent but only as an adjunct. Olanzapine plus fluoxetine is second line but olanzapine itself is demoted to third-line use. Tables 2.9, 2.10 and 2.11 give some broad guidance on treatment options in bipolar depression. Meta-analysis in bipolar depression Meta-analytical studies in bipolar depression are constrained by the variety of methods used to assess efficacy. This means that many scientifically robust studies cannot be included in some meta-analyses because their parameters (outcomes, duration, etc.) are not shared with other studies and so cannot be compared with them. Early lithium studies are an important example – their short duration and cross-over design preclude their inclusion in meta-analysis. BAP guidelines are somewhat dismissive (perhaps correctly) of network meta-analyses because outcome is heavily influenced by inclusion criteria and because findings often contradict direct comparisons.9 A

2021 network meta-analysis of 18 RCTs found that, looking only at antipsychotic drugs, lurasidone, quetiapine, olanzapine and cariprazine were all effective, with cariprazine having the smallest effect size.12 A more recent (2024) review13 of 16 RCTs of FDA-licensed antipsychotics added lumateperone to the list of robustly effective agents. Olanzapine showed the lowest rate of withdrawals from trials and quetiapine was the least well tolerated. The largest network meta--analysis (101 RCTs) was published in 2023.14 In this, olanzapine plus fluoxetine was the most effective, followed in order by quetiapine, olanzapine alone, lurasidone, lumateperone, cariprazine and lamotrigine (the least effective). Recent meta-analyses of ketamine and esketamine15,16 have concluded that ketamine formulations are probably effective in bipolar depression but with a low certainty of evidence.

320 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Table 2.9 Established treatments (listed in alphabetical order). Drug/regimen Comments Lamotrigine1,17–21 Lamotrigine appears to be effective both as a treatment for bipolar depression and as prophylaxis against further episodes. It does not induce switching or rapid cycling. It is as effective as citalopram and causes less weight gain than lithium. Overall, the effect of lamotrigine is difficult to be clear about, with numerous equivocal trials22 that perhaps failed to allow for the time taken for full titration of the drug. It may be useful as an adjunct to lithium23 or as an alternative to it in pregnancy.24 A later trial25 suggested robust efficacy when combined with quetiapine. There is a small anti-manic effect of lamotrigine.26 Treatment is somewhat complicated by the small risk of rash, which is associated with speed of dose titration. The necessity for titration may limit clinical utility. A further complication is the question of dose: 50mg/day has efficacy, but 200mg/day is probably better. In the USA, doses of up to 1200mg/day have been used (mean around 250mg/day). Plasma concentrations (only the range for anti-convulsant effects is known) may guide the need for higher doses. Lithium1,17,27–29 Lithium is probably effective in treating bipolar depression but supporting data are methodologically questionable.30 There is some evidence that lithium prevents depressive relapse but its effects on manic relapse are considered more robust. There is fairly strong support for lithium in reducing suicidality in bipolar disorder.31,32 Lurasidone Three RCTs show a good effect for lurasidone either alone33 or as an adjunct to mood stabilisers.34,35 A further RCT reported good outcome in bipolar depression with sub- syndromal hypomanic symptoms.36 Pooled analysis suggests response is dose-related.37 A network meta-analysis suggested lurasidone is more effective than aripiprazole and ziprasidone but not quetiapine or olanzapine.38 Mood stabiliser + antidepressant39–45 Antidepressants are still widely used in bipolar depression, particularly for breakthrough episodes occurring in those on mood stabilisers. They have been assumed to be effective, although there is a risk of cycle acceleration and/or switching. Studies suggest mood stabilisers alone are just as effective as mood stabilisers/antidepressant combination although subanalysis suggested higher doses of antidepressants may be effective.46–48 Tricyclics and MAOIs are usually best avoided. SSRIs are generally recommended if an antidepressant is to be prescribed. Venlafaxine and bupropion (amfebutamone) have also been used. Venlafaxine may be more likely to induce a switch to mania.49,50 Continuing antidepressant treatment after resolution of symptoms may protect against depressive relapse51,52 although only in the absence of a mood stabiliser.53 At the time of writing, there is no consensus on whether or not to continue antidepressants long term.54 The most recent findings suggest that switch rates are no higher with sertraline alone than with lithium + sertraline,55 but also that there may be no protective effect against depressive episodes.56 Some guidelines recommend the use of antidepressants in bipolar II depression57 and there is

evidence that sertraline does not increase switch rates in these patients.55 Olanzapine ± fluoxetine17,30,58–61 This combination (Symbyax®) is more effective than both placebo and olanzapine alone in treating bipolar depression. The dose is 6 and 25mg or 12 and 50mg/day (so presumably 5/20mg and 10/40mg are effective). It may be more effective than lamotrigine. There is reasonable evidence of prophylactic effect. It is recommended as first-line treatment by NICE8 but not in other guidelines. Olanzapine alone is effective when compared with placebo62 but the combination with fluoxetine is more effective. (This is possibly the strongest evidence for a beneficial effect for an antidepressant in bipolar depression.)

Bipolar disorder CHAPTER 2 Table 2.10 Alternative treatments (refer to primary literature before using). Drug/regimen Comments Antidepressants76–84 ‘Unopposed’ antidepressants (i.e. without mood-stabiliser protection) are generally to be avoided in bipolar depression because of the risk of switching and inducing rapid cycling. There is also evidence that they are relatively less effective (perhaps not effective at all) in bipolar depression than in unipolar depression although dose may be critical.48 Short-term use of fluoxetine, venlafaxine and moclobemide seems reasonably effective and safe even as monotherapy. A meta-analysis suggested a large effect size for tranylcypromine in the absence of any risk of switching.85 Overall, however, unopposed antidepressant treatment should be avoided, especially in bipolar I disorder.54 Cariprazine86 One RCT suggests that cariprazine at 1.5mg/day is effective in bipolar I depression. A second, larger study showed 1.5 and 3mg/day to be effective.87 The most recent study87 found benefit for 1.5mg/day but not 3mg/day. Usually has lowest efficacy among effective drugs in meta-analyses. Ketamine88–91 An IV dose of 0.5mg/kg is effective in refractory bipolar depression with a very high response rate. Dissociative symptoms are common but brief. Now accepted as standard treatment for refractory bipolar depression.92,93 IV racemate is possibly more effective than intranasal esketamine.94 Switching to mania is a potential problem95 although probably a remote risk. Pramipexole96,97 Two small placebo-controlled trials suggested useful efficacy in bipolar depression. Effective dose averages around 1.7mg/day. Both studies used pramipexole as an adjunct to existing mood-stabiliser treatment. Neither study detected an increased risk of switching to mania/hypomania (a theoretical consideration) but data are insufficient to exclude this possibility. A meta-analysis of studies showed a robust effect on response but not remission.98 RCT, randomised controlled trial. Drug/regimen Comments Quetiapine63–67 Five large RCTs have demonstrated clear efficacy for doses of 300 and 600mg daily (as monotherapy) in bipolar I and bipolar II depression. A later study in Chinese patients demonstrated the efficacy of 300mg/day68 in bipolar I depression. It may be superior to both lithium and paroxetine. Quetiapine also prevents relapse into depression and mania69,70 and so is one of the treatments of choice in bipolar depression. It appears not to be associated with switching to mania. Valproate1,17,71–75 Limited evidence of efficacy as monotherapy but recommended in some guidelines. Several very small RCTs but many are negative; however meta-analyses do support antidepressant efficacy.74 Probably protects against depressive relapse but database is small. Not recommended because of its teratogenic effects in both men and women. MAOIs, monoamine oxidase inhibitors; RCT, randomised controlled trial. Table 2.9 (Continued)

54 - Summary of drug choice

Summary of drug choice

55 - References

References

322 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Summary of drug choice The combination of olanzapine + fluoxetine is probably the most effective treatment available for bipolar depression but its use is constrained by the well-known adverse effect profile of olanzapine. SSRIs other than fluoxetine may be effective but should probably be avoided unless clear individual benefit is obvious.54 Alternative first-line choices are quetiapine, olanzapine, lurasidone, lamotrigine and cariprazine (and lumateperone in North America). These drugs differ substantially in adverse effect profile, tolerability and cost, each of which needs to be considered when prescribing for an individual. Lithium is also effective but supporting evidence is relatively weak. Second-line drugs include ketamine and, increasingly, modafinil. Aripiprazole, risperidone, ziprasidone, tricyclics (with the exception of imipramine) and MAOIs (with the exception of tranylcypromine) are probably not effective and should not be used routinely.114 References

1. Malhi GS, et al. Bipolar depression: management options. CNS Drugs 2003; 17:9–25.
2. Perlis RH, et al. Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. Am J Psychiatry 2006; 163:225–231.
3. Mitchell PB, et al. Comparison of depressive episodes in bipolar disorder and in major depressive disorder within bipolar disorder pedigrees. Br J Psychiatry 2011; 199:303–309.
4. Haddad P, et al. Pharmacological management of bipolar depression. Acta Psychiatr Scand 2002; 105:401–403.
5. Hirschfeld RM. Bipolar depression: the real challenge. Eur Neuropsychopharmacol 2004; 14 Suppl 2:S83–S88.
6. Judd LL, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59:530–537.
7. Judd LL, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003; 60:261–269.
8. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last accessed October 2024); https://www.nice.org.uk/guidance/cg185. Table 2.11 Other possible treatments (seek specialist advice before using). Drug/regimen Comments Aripiprazole99–102 Limited support from open studies as add-on treatment. One RCT was negative. Possibly not effective.98 Carbamazepine1,17,103 Occasionally recommended but database is poor and effect modest. May have useful activity when added to other mood stabilisers. Gabapentin1,104,105 Open studies suggest modest effect when added to mood stabilisers or antipsychotics. Doses average around 1750mg/day. Anxiolytic effect may account for apparent effect in bipolar depression. Inositol106 Small, randomised, pilot study suggests that 12g/day inositol is effective in bipolar depression.

Mifepristone107,108 Some evidence of mood-elevating properties in bipolar depression although this was not replicated in a larger trial. Improved cognitive function in both trials. Dose used was 600mg/day. Modafinil109 Meta-analysis of five studies of modafinil/armodafinil suggests robust benefit on response and remission with good tolerability and no evidence of increased risk of switching. Some evidence of safety from a later study.110 Omega-3 fatty acids111–113 One positive RCT (1g/2g a day) and one negative (6g a day). The ratio of omega-6 may determine efficacy.113 RCT, randomised controlled trial.

Bipolar disorder CHAPTER 2 9. Goodwin GM, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016; 30:495–553. 10. Malhi GS, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust NZ J Psychiatry 2021; 55:7–117. 11. Keramatian K, et al. The CANMAT and ISBD guidelines for the treatment of bipolar disorder: summary and a 2023 update of evidence. Focus (Am Psychiatr Publ) 2023; 21:344–353. 12. Kadakia A, et al. Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. BMC Psychiatry 2021; 21:249. 13. Li S, et al. Efficacy and tolerability of FDA-approved atypical antipsychotics for the treatment of bipolar depression: a systematic review and network meta-analysis. Eur Psychiatry 2024; 67:e29. 14. Yildiz A, et al. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis. Lancet Psychiatry 2023; 10:693–705. 15. Zhan Z, et al. Comparative efficacy and side-effect profile of ketamine and esketamine in the treatment of unipolar and bipolar depression: protocol for a systematic review and network meta-analysis. BMJ Open 2021; 11:e043457. 16. Rodolico A, et al. Efficacy and safety of ketamine and esketamine for unipolar and bipolar depression: an overview of systematic reviews with meta-analysis. Front Psychiatry 2024; 15:1325399. 17. Yatham LN, et al. Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options. Bipolar Disord 2003; 5:85–97. 18. Calabrese JR, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry 1999; 60:79–88. 19. Bowden CL, et al. Lamotrigine in the treatment of bipolar depression. Eur Neuropsychopharmacol 1999; 9 Suppl 4:S113–S117. 20. Marangell LB, et al. Lamotrigine treatment of bipolar disorder: data from the first 500 patients in STEP-BD. Bipolar Disord 2004; 6:139–143. 21. Schaffer A, et al. Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression. J Affect Disord 2006; 96:95–99. 22. Calabrese JR, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disord 2008; 10:323–333. 23. Van der Loos ML, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry 2009; 70:223–231. 24. Newport DJ, et al. Lamotrigine in bipolar disorder: efficacy during pregnancy. Bipolar Disord 2008; 10:432–-436. 25. Geddes JR, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 x 2 factorial randomised trial. Lancet Psychiatry 2016; 3:31–39. 26. Goodwin GM, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004; 65:432–441. 27. Geddes JR, et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004; 161:217–222. 28. Calabrese JR, et al. A placebo-controlled 18-month trial of

lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003; 64:1013–1024. 29. Prien RF, et al. Lithium carbonate and imipramine in prevention of affective episodes. A comparison in recurrent affective illness. Arch Gen Psychiatry 1973; 29:420–425. 30. Grunze H, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry 2010; 11:81–109. 31. Goodwin FK, et al. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003; 290:1467–1473. 32. Kessing LV, et al. Suicide risk in patients treated with lithium. Arch Gen Psychiatry 2005; 62:860–866. 33. Loebel A, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014; 171:160–168. 34. Loebel A, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double- blind, placebo-controlled study. Am J Psychiatry 2014; 171:169–177. 35. Suppes T, et al. Lurasidone adjunctive with lithium or valproate for bipolar depression: a placebo-controlled trial utilizing prospective and retrospective enrolment cohorts. J Psychiatr Res 2016; 78:86–93. 36. Suppes T, et al. Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo- controlled study. Am J Psychiatry 2016; 173:400–407. 37. Chapel S, et al. Lurasidone dose response in bipolar depression: a population dose-response analysis. Clin Ther 2016; 38:4–15. 38. Ostacher M, et al. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: a systematic review and network meta-analysis. World J Biol Psychiatry 2018; 19:586–601. 39. Calabrese JR, et al. International Consensus Group on Bipolar I Depression Treatment Guidelines. J Clin Psychiatry 2004; 65:571–579. 40. Nemeroff CB, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001; 158:906–912. 41. Vieta E, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 2002; 63:508–512. 42. Young LT, et al. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry 2000; 157:124–126. 43. Fawcett JA. Lithium combinations in acute and maintenance treatment of unipolar and bipolar depression. J Clin Psychiatry 2003; 64 Suppl 5:32–-37.

 44. Altshuler L, et al. The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: a retrospective chart review. J Clin Psychiatry 2001; 62:612–616. 45. Erfurth A, et al. Bupropion as add-on strategy in difficult-to-treat bipolar depressive patients. Neuropsychobiology 2002; 45 Suppl 1:33–36. 46. Sachs GS, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007; 356:1711–1722. 47. Goldberg JF, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. Am J Psychiatry 2007; 164:1348–1355. 48. Tada M, et al. Antidepressant dose and treatment response in bipolar depression: reanalysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) data. J Psychiatr Res 2015; 68:151–156. 49. Post RM, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006; 189:124–131. 50. Leverich GS, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006; 163:232–239. 51. Salvi V, et al.

The use of antidepressants in bipolar disorder. J Clin Psychiatry 2008; 69:1307–1318. 52. Altshuler LL, et al. Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: a blinded, randomized study. J Clin Psychiatry 2009; 70:450–457. 53. Ghaemi SN, et al. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand 2008; 118:347–356. 54. Pacchiarotti I, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013; 170:1249–1262. 55. Altshuler LL, et al. Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. Am J Psychiatry 2017; 174:266–276. 56. Yatham LN, et al. Duration of adjunctive antidepressant maintenance in bipolar I depression. N Engl J Med 2023; 389:430–440. 57. Yatham LN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20:97–170. 58. Tohen M, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003; 60:1079–1088. 59. Brown EB, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry 2006; 67:1025–1033. 60. Corya SA, et al. A 24-week open-label extension study of olanzapine-fluoxetine combination and olanzapine monotherapy in the treatment of bipolar depression. J Clin Psychiatry 2006; 67:798–806. 61. Dube S, et al. Onset of antidepressant effect of olanzapine and olanzapine/fluoxetine combination in bipolar depression. Bipolar Disord 2007; 9:618–627. 62. Tohen M, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. Br J Psychiatry 2012; 201:376–382. 63. Calabrese JR, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005; 162:1351–1360. 64. Thase ME, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006; 26:600–609. 65. Suppes T, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J Affect Disord 2010; 121:106–115. 66. Young AH, et al. A double-blind, placebo--controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry 2010; 71:150–162. 67. McElroy SL, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry 2010; 71:163–174. 68. Li H, et al. Efficacy and safety of quetiapine extended release monotherapy in bipolar depression: a multi-center, randomized, double-blind, placebo-controlled trial. Psychopharmacology (Berl) 2016; 233:1289–1297. 69. Vieta E, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). J Affect Disord 2008; 109:251–263. 70. Suppes T, et al. Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). Am J Psychiatry 2009; 166:476–488. 71. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2009; 23:346–388. 72. Davis LL, et al. Divalproex in the treatment of bipolar depression: a placebo-controlled study. J Affect Disord 2005; 85:259–266. 73. Ghaemi SN, et al. Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. J Clin Psychiatry 2007; 68:1840–1844. 74. Smith LA, et al. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord 2010; 122:1–9. 75. Muzina DJ, et al. Acute efficacy of divalproex sodium versus placebo in mood

stabilizer-naive bipolar I or II depression: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 2011; 72:813–819. 76. Amsterdam JD, et al. Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression – low manic switch rate. Bipolar Disord 2004; 6:75–-81. 77. Amsterdam JD, et al. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. J Clin Psychopharmacol 1998; 18:435–440.

Bipolar disorder CHAPTER 2 78. Amsterdam J. Efficacy and safety of venlafaxine in the treatment of bipolar II major depressive episode. J Clin Psychopharmacol 1998; 18:414–417. 79. Amsterdam JD, et al. Venlafaxine monotherapy in women with bipolar II and unipolar major depression. J Affect Disord 2000; 59:225–229. 80. Silverstone T. Moclobemide vs. imipramine in bipolar depression: a multicentre double-blind clinical trial. Acta Psychiatr Scand 2001; 104:104–109. 81. Ghaemi SN, et al. Antidepressant treatment in bipolar versus unipolar depression. Am J Psychiatry 2004; 161:163–165. 82. Post RM, et al. A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. Bipolar Disord 2003; 5:396–-406. 83. Amsterdam JD, et al. Comparison of fluoxetine, olanzapine, and combined fluoxetine plus olanzapine initial therapy of bipolar type I and type II major depression – lack of manic induction. J Affect Disord 2005; 87:121–130. 84. Amsterdam JD, et al. Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study. Int Clin Psychopharmacol 2005; 20:257–264. 85. Heijnen WT, et al. Efficacy of tranylcypromine in bipolar depression: a systematic review. J Clin Psychopharmacol 2015; 35:700–705. 86. Durgam S, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry 2016; 173:271–281. 87. Earley W, et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. Am J Psychiatry 2019; 176:439–448. 88. Diazgranados N, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010; 67:793–802. 89. Shahani R, et al. Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 2007; 69:810–812. 90. Zarate CA, Jr, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry 2012; 71:939–946. 91. Permoda-Osip A, et al. Single ketamine infusion and neurocognitive performance in bipolar depression. Pharmacopsychiatry 2015; 48:78–79. 92. Jha MK, et al. Psychopharmacology and experimental therapeutics for bipolar depression. Focus (Am Psychiatr Publ) 2019; 17:232–237. 93. Włodarczyk A, et al. Safety and tolerability of ketamine use in treatment-resistant bipolar depression patients with regard to central nervous system symptomatology: literature review and analysis. Medicina (Kaunas) 2020; 56:67. 94. Bahji A, et al. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord 2021; 278:542–555. 95. Alison McInnes L, et al. Possible affective switch associated with intravenous ketamine treatment in a patient with bipolar I disorder. Biol Psychiatry 2016; 79:e71–e72. 96. Goldberg JF, et al. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment- resistant bipolar depression. Am J Psychiatry 2004; 161:564–566. 97. Zarate CA, Jr, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biol Psychiatry 2004; 56:54–60. 98. Romeo B, et al. Meta-analysis and review of dopamine agonists in acute episodes of mood disorder: efficacy and safety. J Psychopharmacol 2018; 32:385–396. 99. Ketter TA, et al. Adjunctive aripiprazole in treatment-resistant bipolar depression. Ann Clin Psychiatry 2006; 18:169–172. 100. Mazza M, et al. Beneficial acute antidepressant effects of aripiprazole as an adjunctive treatment or monotherapy in bipolar patients unresponsive to mood stabilizers: results from a 16-week open--

label trial. Expert Opin Pharmacother 2008; 9:3145–3149. 101. Sidor MM, et al. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry 2011; 72:156–167. 102. Cruz N, et al. Efficacy of modern antipsychotics in placebo-controlled trials in bipolar depression: a meta-analysis. Int J Neuropsychopharmacol 2010; 13:5–14. 103. Dilsaver SC, et al. Treatment of bipolar depression with carbamazepine: results of an open study. Biol Psychiatry 1996; 40:935–937. 104. Wang PW, et al. Gabapentin augmentation therapy in bipolar depression. Bipolar Disord 2002; 4:296–301. 105. Ashton H, et al. GABA-ergic drugs: exit stage left, enter stage right. J Psychopharmacol 2003; 17:174–178. 106. Chengappa KN, et al. Inositol as an add-on treatment for bipolar depression. Bipolar Disord 2000; 2:47–55. 107. Young AH, et al. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. Neuropsychopharmacology 2004; 29:1538–1545. 108. Watson S, et al. A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. Biol Psychiatry 2012; 72:943–949. 109. Nunez NA, et al. Efficacy and tolerability of adjunctive modafinil/armodafinil in bipolar depression: a meta-analysis of randomized controlled trials. Bipolar Disord 2020; 22:109–120. 110. Lipschitz JM, et al. Modafinil’s effects on cognition and sleep quality in affectively-stable patients with bipolar disorder: a pilot study. Front Psychiatry 2023; 14:1246149. 111. Frangou S, et al. Efficacy of ethyl--eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry 2006; 188:46–50. 112. Keck PE, Jr, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biol Psychiatry 2006; 60:1020–1022. 113. Zhang M, et al. Assessment of causal relationships between omega-3 and omega-6 polyunsaturated fatty acids in bipolar disorder: a 2--sample bidirectional mendelian randomization study. Food Funct 2023; 14:6200–6211. 114. Taylor DM, et al. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. Acta Psychiatr Scand 2014; 130:452–469.

56 - Prophylaxis in bipolar disorder

Prophylaxis in bipolar disorder

326 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Prophylaxis in bipolar disorder Any successful drug regimen used for an acute episode should be continued as prophylaxis. To a large extent, therefore, the choice of maintenance treatment for individual patients is dictated by the efficacy and tolerability of acute treatment. Possible exceptions include the consideration of withdrawing antipsychotic treatment from a mood-stabiliser combination after an episode of mania (recommended by some authorities1) and the withdrawal of antidepressants after the successful treatment of an acute episode of bipolar depression, assuming a mood stabiliser is continued (recommended by most authorities, at least implicitly2). Withdrawing antipsychotics from combination regimens with lithium or valproate may worsen the risk of relapse.3 Residual mood symptoms after an acute episode are a strong predictor of recurrence.4,5 In respect to monotherapy, most evidence supports the efficacy of lithium6,7 in preventing episodes of mania and depression.8 Carbamazepine is somewhat less effective6,9 and the long-term efficacy of valproate is uncertain,7,10–12 although it too may protect against relapse both into depression and mania.6,13 Lithium has the advantage of a proven anti-suicidal effect14–16 but perhaps, relative to other mood stabilisers, the disadvantage of a worsened outcome following abrupt discontinuation17–20 (although the effect of abrupt discontinuation of other drugs may be similar20). Early use of lithium might increase the likelihood of efficacy.21 The independent BALANCE study found that valproate as monotherapy was relatively less effective than lithium or the combination of lithium and valproate,11 casting doubt on its use as a first-line single treatment. Also, a large observational study has shown that lithium is much more effective than valproate in preventing relapse to any condition and in preventing rehospitalisation.22 Given this, valproate’s relative contraindication in women of child-bearing age and the fact that valproate is not licensed for prophylaxis, valproate should be considered a second- or third-line treatment. Conventional antipsychotics have traditionally been used and are perceived to be effective although the objective evidence base is rather weak.23,24 FGA depots probably protect against mania but may worsen depression25 (see ‘Antipsychotic long-acting injections in bipolar disorder’ earlier in this chapter). Evidence supports the efficacy of many SGAs particularly olanzapine,26,27 quetiapine,28 aripiprazole29 and risperidone.30 Most studies examine combinations with mood stabilisers and there are fewer supportive monotherapy trials, although asenapine, aripiprazole, olanzapine,

quetiapine and risperidone monotherapy are all more effective than placebo. Olanzapine, quetiapine and aripiprazole are licensed for prophylaxis in many countries although only olanzapine and quetiapine offer protection against depression.7 Asenapine may also be effective,31 as may ziprasidone.32 There is some evidence to support maintenance treatment with lurasidone when added to valproate or lithium,33 but there are only acute data for lumateperone.34 Cariprazine may be ineffective as maintenance.35 All antipsychotic + mood - stabiliser combinations were more effective than mood stabilisers alone in a meta-analysis of 41 studies and 9821 participants.36 Aripiprazole

- valproate was numerically the best maintenance treatment (in terms of risk of relapse to any episode) in this analysis. A later meta-analysis of 14 monotherapy studies found that monotherapy with aripiprazole, olanzapine, lurasidone, risperidone or quetiapine was more effective than placebo over 6 months or longer.37 A 2022 network meta- analysis found the order of effectiveness to be olanzapine (most effective), quetiapine, aripiprazole, risperidone, lurasidone and paliperidone (least effective).7 Long-acting aripiprazole has been shown to delay the time to, and reduced the rate of recurrence of, manic episodes and was generally safe and well tolerated.38 The use of

57 - Optimising lithium treatment45

Optimising lithium treatment45

58 - Combination treatment

Combination treatment

Bipolar disorder CHAPTER 2 risperidone LAI is well supported by RCTs39 and naturalistic studies.40 The prescribing of LAI SGAs is generally encouraged despite some labelling restrictions41–44 (see ‘Antipsychotic long-acting injections in bipolar disorder’ earlier in this chapter). Box 2.1 summarises recommendations from NICE for prescribing in bipolar disorder. Optimising lithium treatment45 For adults with bipolar disorder the standard lithium plasma level should be 0.6–0.8mmol/L with the option to reduce it to 0.4–0.6mmol/L in cases of good response but poor tolerance, or to increase it to 0.8–1.0mmol/L in cases of insufficient response and good tolerance. For children and adolescents no consensus exists, but the majority of the International Society for Bipolar Disorders (ISBD)/International Study Group on Lithium (IGSLI) task force endorsed this same recommendation. For the elderly, a more conservative approach may be adopted, usually aiming for 0.4–0.6mmol/L, with the option to go to, at most, 0.7 or 0.8mmol/L at age 65–79 years, and only to 0.7mmol/L over age 80 years. Combination treatment A significant proportion of patients with bipolar illness fail to be treated adequately with a single mood stabiliser,11 so combinations of mood stabilisers46,47 or a mood stabiliser and an antipsychotic47,48 are commonly used.49 Also, there is evidence that where combination treatments are effective in mania or depression, then continuation with the same combination provides optimal prophylaxis.28,48 Overall, combination treatments offer better protection against relapse than monotherapy.7 The use of polypharmacy needs to be balanced against the likely increased adverse effect burden. Combinations of olanzapine, risperidone, quetiapine or haloperidol with lithium or valproate are recommended by NICE27 and by BAP guidelines.6 Alternative antipsychotics (e.g. aripiprazole) are also options in combinations with lithium or valproate, particularly if these have been found to be effective during the treatment of an acute episode of mania or depression.28,50 Carbamazepine is considered to be third line. Lamotrigine may be useful in bipolar II disorder27 but seems only to prevent recurrence of depression.51 Lurasidone may have broadly similar long-term efficacy, both as monotherapy and when combined with a mood stabiliser.33,52 Extrapolation of currently available data suggests that lithium plus an SGA is probably the polypharmacy regimen of choice. There are naturalistic data to support combinations of three treatments; in one study53 the two best treatments were lithium + valproate + quetiapine followed by lithium + valproate + olanzapine. Box 2.1 NICE recommendations27 ■ ■When planning long-term pharmacological interventions to prevent relapse, take into account drugs that have been effective during episodes of mania or bipolar depression. Discuss with the person whether they prefer to continue this treatment or switch to lithium, and explain that lithium is the most effective long-term treatment for bipolar disorder. ■ ■Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder and if lithium is insufficiently effective, consider adding valproate. If lithium is poorly tolerated, consider valproate or olanzapine instead, or if it has been effective during an episode of mania or bipolar depression, quetiapine. ■ ■Do not offer valproate to women of child-bearing potential.

Ensure adequate contraception in men taking valproate. ■ ■Discuss with the person the possible benefits and risks of each drug for them.

328 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Monotherapy with antipsychotics can be considered where mood stabilisers are poorly tolerated or where adherence cannot be assured.54 A meta-analysis of long-term antidepressant treatment found that continued treatment was more likely to induce a switch to mania than prevent a depressive episode.55 The STEP-BD study found no significant benefit for continuing (compared with discontinuing) an antidepressant and worse outcomes in those with rapid-cycling illness.56 A more recent study found that neither escitalopram nor bupropion had any effect on relapse of depression.57 There is thus essentially no strong support for long-term use of antidepressants in bipolar illness although some bipolar patients may relapse into depression when antidepressants are discontinued.20 Box 2.2 and Table 2.12 summarise prophylaxis and maintenance treatment, respectively, in bipolar disorder. Box 2.2 Summary of prophylaxis in bipolar disorder First line: lithium monotherapy Second line: olanzapine, aripiprazole, risperidone or quetiapine in combination with valproate* or lithium Third line: alternative antipsychotic (lurasidone, asenapine or ziprasidone) or alternative mood stabiliser (carbamazepine or lamotrigine) in combination Fourth line: antipsychotic with two mood stabilisers ■ ■Always maintain successful acute treatment regimens (e.g. mood stabiliser + antipsychotic) as prophylaxis ■ ■Avoid long-term antidepressants if possible *Not in women of child-bearing potential. Table 2.12 Summary of maintenance in bipolar disorder.7,57 Prevents mania Prevents depression Monotherapy Antipsychotics Aripiprazole Yes No Asenapine Yes No Olanzapine Yes Yes Paliperidone Yes No Risperidone Yes No Quetiapine Yes Yes Mood stabilisers (MS) Lamotrigine No Yes Lithium Yes Yes Valproate Yes (?) Yes Antidepressants No No Combination treatment Antipsychotic + MS Yes Yes Valproate + lamotrigine Yes (?) Yes

59 - References

References

Bipolar disorder CHAPTER 2 References

1. Malhi GS, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders: bipolar disorder summary. Bipolar Disord 2020; 22:805–821.
2. Yatham LN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20:97–170.
3. Kang MG, et al. Lithium vs valproate in the maintenance treatment of bipolar I disorder: a post-hoc analysis of a randomized double-blind placebo-controlled trial. Aust NZ J Psychiatry 2020; 54:298–307.
4. Solomon DA, et al. Longitudinal course of bipolar I disorder: duration of mood episodes. Arch Gen Psychiatry 2010; 67:339–347.
5. Perlis RH, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006; 163:217–224.
6. Goodwin GM, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016; 30:495–553.
7. Nestsiarovich A, et al. Preventing new episodes of bipolar disorder in adults: systematic review and meta-analysis of randomized controlled trials. Eur Neuropsychopharmacol 2022; 54:75–89.
8. Sani G, et al. Treatment of bipolar disorder in a lifetime perspective: is lithium still the best choice? Clin Drug Investig 2017; 37:713–727.
9. Hartong EG, et al. Prophylactic efficacy of lithium versus carbamazepine in treatment--naive bipolar patients. J Clin Psychiatry 2003; 64:144–151.
10. Cipriani A, et al. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev 2013; 10:CD003196.
11. Geddes JR, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010; 375:385–395.
12. Kemp DE, et al. A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and co--occurring substance abuse or dependence. J Clin Psychiatry 2009; 70:113–121.
13. Smith LA, et al. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. Bipolar

Disord 2007; 9:394–412.
14. Cipriani A, et al. 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; 162:1805–1819.
15. Kessing LV, et al. Suicide risk in patients treated with lithium. Arch Gen Psychiatry 2005; 62:860–866.
16. Song J, et al. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. Am J Psychiatry 2017; 174:795–802.
17. Mander AJ, et al. Rapid recurrence of mania following abrupt discontinuation of lithium. Lancet 1988; 2:15–17.
18. Faedda GL, et al. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry 1993; 50:448–455.
19. Macritchie KA, et al. Does ‘rebound mania’ occur after stopping carbamazepine? A pilot study. J Psychopharmacol 2000; 14:266–268.
20. Franks MA, et al. Bouncing back: is the bipolar rebound phenomenon peculiar to lithium? A retrospective naturalistic study. J Psychopharmacol 2008; 22:452–456.
21. Kessing LV, et al. Starting lithium prophylaxis early v. late in bipolar disorder. Br J Psychiatry 2014; 205:214–220.
22. Kessing LV, et al. Valproate v. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study. Br J Psychiatry 2011; 199:57–63.
23. Gao K, et al. Typical and atypical antipsychotics in bipolar depression. J Clin Psychiatry 2005; 66:1376–1385.
24. Hellewell JS. A review of the evidence for the use of antipsychotics in the maintenance treatment of bipolar disorders. J Psychopharmacol 2006; 20:39–45.
25. Gigante AD, et al. Long-acting injectable antipsychotics for the maintenance treatment of bipolar disorder. CNS Drugs 2012; 26:403–420.
26. Tohen M, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry 2003; 160:1263–1271.
27. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last accessed October 2024); https://www.nice.org.uk/guidance/cg185.
28. Vieta E, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). J Affect Disord 2008; 109:251–263.
29. McIntyre RS. Aripiprazole for the maintenance treatment of bipolar I disorder: a review. Clin Ther 2010; 32 Suppl 1:S32–S38.
30. Ghaemi SN, et al. Long-term risperidone treatment in bipolar disorder: 6-month follow up. Int Clin Psychopharmacol 1997; 12:333–338.
31. Szegedi A, et al. Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder. Am J Psychiatry 2017; 175:71–79.
32. Bowden CL, et al. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. Int Clin Psychopharmacol 2010; 25:60–67.

33. Calabrese JR, et al. Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder. Eur Neuropsychopharmacol 2017; 27:865–876.
34. McIntyre RS, et al. The efficacy of lumateperone in patients with bipolar depression with mixed features. J Clin Psychiatry 2023; 84:22m14739.
35. McIntyre RS, et al. Cariprazine as a maintenance therapy in the prevention of mood episodes in adults with bipolar I disorder. Bipolar Disord 2024; 26:442–453.
36. Kishi T, et al. Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta- analysis of randomized controlled trials. Mol Psychiatry 2021; 26:4146–4157.
37. Escudero MAG, et al. Second generation antipsychotics monotherapy as maintenance treatment for bipolar disorder: a systematic review of long-term studies. Psychiatr Q 2020; 91:1047–1060.

 38. Calabrese JR, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psychiatry 2017; 78:324–331. 39. Kishi T, et al. Long-acting injectable antipsychotics for prevention of relapse in bipolar disorder: a systematic review and meta-analyses of randomized controlled trials. Int J Neuropsychopharmacol 2016; 19:pyw038. 40. Hsieh MH, et al. Bipolar patients treated with long--acting injectable risperidone in Taiwan: a 1-year mirror-image study using a national claims database. J Affect Disord 2017; 218:327–334. 41. Belge JB, et al. Long-acting second-generation injectable antipsychotics for the maintenance treatment of bipolar disorder: a narrative review. Expert Opin Pharmacother 2024; 25:295–299. 42. Kishi T, et al. A comparison of recurrence rates after discontinuation of second-generation antipsychotic long-acting injectable versus corresponding oral antipsychotic in the maintenance treatment of bipolar disorder: a systematic review. Psychiatry Res 2024; 333:115761. 43. Pacchiarotti I, et al. Long-acting injectable antipsychotics (LAIs) for maintenance treatment of bipolar and schizoaffective disorders: a systematic review. Eur Neuropsychopharmacol 2019; 29:457–470. 44. Yıldızhan E, et al. Effect of long acting injectable antipsychotics on course and hospitalizations in bipolar disorder – a naturalistic mirror image study. Nord J Psychiatry 2022; 76:37–43. 45. Nolen WA, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord 2019; 21:394–409. 46. Freeman MP, et al. Mood stabilizer combinations: a review of safety and efficacy. Am J Psychiatry 1998; 155:12–21. 47. Muzina DJ, et al. Maintenance therapies in bipolar disorder: focus on randomized controlled trials. Aust NZ J Psychiatry 2005; 39:652–661. 48. Tohen M, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry 2004; 184:337–345. 49. Paton C, et al. Lithium in bipolar and other affective disorders: prescribing practice in the UK. J Psychopharmacol 2010; 24:1739–1746. 50. Marcus R, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disord 2011; 13:133–144. 51. Bowden CL, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003; 60:392–400. 52. Pikalov A, et al. Long-term use of lurasidone in patients with bipolar disorder: safety and effectiveness over 2 years of treatment. Int J Bipolar Disord 2017;

5:9. 53. Wingård L, et al. Monotherapy vs. combination therapy for post mania maintenance treatment: a population based cohort study. Eur Neuropsychopharmacol 2019; 29:691–700. 54. Jauhar S, et al. Controversies in bipolar disorder; role of second-generation antipsychotic for maintenance therapy. Int J Bipolar Disord 2019; 7:10. 55. Ghaemi SN, et al. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand 2008; 118:347–356. 56. Ghaemi SN, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry 2010; 71:372–380. 57. Yatham LN, et al. Duration of adjunctive antidepressant maintenance in bipolar I depression. N Engl J Med 2023; 389:430–440.

60 - Stopping lithium and mood stabilisers

Stopping lithium and mood stabilisers

61 - Rationale for stopping

Rationale forÂ stopping

62 - Withdrawal effects from lithium and other moo

Withdrawal effects from lithium and other mood stabilisers

Bipolar disorder CHAPTER 2 Stopping lithium and mood stabilisers Rationale for stopping Patients may ask to stop lithium and other mood stabilisers because of the range of adverse effects experienced. In one cohort 54% of patients discontinued lithium, mostly because of tolerability problems, including diarrhoea (13%), tremor (11%), polyuria/ polydipsia/diabetes insipidus (9%), creatinine increase (9%) and weight gain (7%).1 Alternatively, although lithium and mood stabilisers are useful in controlling acute symptoms and in preventing relapse, a clinician may judge that the balance of risks and benefits has shifted over time (e.g. adverse physical effects accumulate, alternative coping strategies developed) such that dose reduction or stopping may be considered. Other patients may be prescribed mood stabilisers for conditions such as personality disorders, for which there is a lack of evidence. Stopping should be done in a manner that minimises the risk of both withdrawal effects and relapse (the two key risks). Withdrawal effects from lithium and other mood stabilisers Discontinuation of lithium can cause withdrawal effects, including both physical and psychological symptoms (Table 2.13). These withdrawal effects include mood episodes (depression, but more commonly mania) and are sometimes called ‘rebound’ effects.2,3 The risk of relapse in the period following abrupt cessation greatly exceeds the rate of relapse in the untreated disorder.2 For example, a review of studies of lithium discontinuation in people with bipolar disorder found that the untreated disorder had a mean cycle length (the average time between episodes) of 11.6 months, whereas the time to a new episode following lithium discontinuation was 1.7 months.2 This represents a sevenfold increase in the rate of relapse and suggests that manic and depressive symptoms that occur following lithium withdrawal are largely because of lithium withdrawal effects rather than because of the untreated disorder. Nonetheless, it is to be expected that the withdrawal of an effective mood stabiliser leads to mood destabilisation simply because of the removal of an effective treatment for the condition. Relapse may sometimes indicate the need for continued treatment. Distinguishing between withdrawal--related rebound and true relapse of the underlying condition is made easier by extending the

withdrawal period (so as to help rule out withdrawal effects). Withdrawal effects are thought to be due to the development of dopaminergic hypersensitivity6 and changes in neuronal membranes, cell transport function or other neurotransmitter systems during lithium treatment.7 Other mood stabilisers have also been associated with a withdrawal syndrome.8 Table 2.13 Withdrawal effects of lithium.3–5 Physical effects Psychological effects Tremor Polyuria Muscular weakness Polydipsia Dryness of mouth Anxiety Nervousness Irritability Alertness Sleep disturbances Elated mood/mania Depressed mood

63 - Evidence for long term treatment

Evidence for long-term treatment

64 - Duration of tapering

Duration ofÂ tapering

65 - Pattern of tapering

Pattern of tapering

332 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 2 Evidence for long-term treatment Although lithium is accepted as the first-line choice for prophylaxis in bipolar disorder,9 evidence for long-term treatment with lithium and other mood stabilisers is derived from discontinuation studies where patients established on these medications were randomised to either continue or cease treatment.10,11 In these studies, lithium was sometimes stopped abruptly. As mentioned, rapid stopping of lithium is likely to produce withdrawal effects, which can include precipitating mood episodes.2 Indeed, in one study abruptly stopping lithium in patients with depression provoked manic episodes in 13%.12 There is evidence that abrupt cessation of other mood stabilisers can also precipitate mood episodes.3 Patients who are discontinued from these medications often demonstrate relapse rates that are greater than in the untreated disorder, suggesting that withdrawal effects may inflate the apparent rate and extent of relapse.2,13 Few maintenance studies extend beyond a 2-year follow-up period. Observational studies (over longer periods) have found lithium to be more effective than other mood stabilisers but these studies are somewhat limited by confounding effects.14 Duration of tapering With lithium, rapid discontinuation (1–14 days) has been shown to produce a much greater risk of relapse than gradual tapering over 15–30 days.15–17 Time to relapse is decreased and the proportion of patients relapsed at study end is greatly increased in the rapid discontinuation group. These robust and reproducible findings support a recommendation that lithium should not be stopped abruptly unless a serious adverse effect occurs, and that withdrawal should take place over at least a month or preferably longer. There are few studies examining the optimal rate or duration of tapering lithium. However, the finding that 50% of relapses occur in the first 3 months after lithium is stopped but then lessen over time2 suggests that this period of 3 months might be required for underlying adaptations to lithium to resolve. One study that discontinued lithium over 2–5 months found higher relapse rates in these patients than in those who stayed on lithium.18 This might conceivably suggest that tapering should be even slower than the 4-week to 3-month period suggested by NICE in the UK.19 Long withdrawal schedules are not unusual in different areas of medicine. Antiseizure drugs are tapered over between 1 month and 4 years in non-psychiatric conditions, with relapse rates increased in the first 6 months before converging with patients continuing with the antiseizure drugs.8 Pattern of tapering Lithium, like all pharmacological agents, conforms to the law of mass action and therefore demonstrates a hyperbolic pattern between dose and pharmacological effect.12 The mode of action of lithium is unknown, however it is known to affect GSK-3. The relationship between the dose of lithium and effect on this target is hyperbolic.13 As for other psychotropic agents this justifies a hyperbolically reducing dose pattern (in order to produce linearly reducing effects on its target receptors), which may be clinically approximated by a proportionate dose reduction (a reduction by the same proportion each step, so that the size of the reduction becomes smaller and smaller as the total dose gets lower) (Box 2.3).

66 - Practice guide to tapering

Practice guide to tapering

67 - References

References

Bipolar disorder CHAPTER 2 Practice guide to tapering ■ ■Patients should be told that there is the possibility of withdrawal effects, and that there may be an increased risk of affective relapse from stopping lithium or mood stabilisers more quickly. These effects will be reduced if these medications are reduced in a more gradual fashion. ■ ■There is no clear evidence on how to taper (or for how long), but following principles from other psychotropic medications, an initial reduction of 10–25% of the current dose should be offered, with withdrawal symptoms (Table 2.13) and symptoms monitored for at least 4 weeks to ensure stability. ■ ■Further reductions should be titrated against the tolerability of this dose decrease. Reductions should probably be made according to an exponentially reducing pattern, whereby each reduction is calculated as a fixed proportion (e.g. 10% or 25%) of the most recent dose (effectively becoming smaller and smaller as the total dose becomes lower) each month, or until stability is assured. ■ ■For a very few patients the final dose before completely stopping may be very small, because small doses have relatively large effects on target receptors. This may be as small as 1% of therapeutic doses, for example <10mg for lithium. To achieve small doses, liquid preparations (lithium) will be required. ■ ■As the process of reducing lithium or mood stabilisers might be destabilising it may be wise to pursue other strategies during the tapering period.20 Ongoing monitoring may be necessary for a number of months after complete cessation to ensure mood stability. ■ ■If withdrawal symptoms or symptoms of relapse emerge at any point, pausing the reduction, a small increase in dose or returning to a previously effective dose are all possible responses. Difficulty reducing medication does not preclude a further attempt at reduction but might indicate the need for a more gradual reduction regimen. ■ ■Other modalities for people with bipolar disorder, including family therapy, interpersonal therapy, cognitive behavioural therapy, psychoeducation and social rhythm therapy, may be considered as well as more individualised, idiosyncratic coping strategies.21–23 References

1. Öhlund L, et al. Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. BMC Psychiatry 2018; 18:37.
2. Suppes T, et al. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991; 48:1082–1088.
3. Franks MA, et al. Bouncing back: is the bipolar rebound phenomenon peculiar to lithium? A retrospective naturalistic study. J Psychopharmacol 2008; 22:452–456.
4. Baastrup PC, et al. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. Lancet 1970; 2:326–330. Box 2.3 Suggested slow reduction regimen for lithium ■ ■Reduce by 200mg every month until dose is 800mg daily, then ■ ■Reduce by 100mg every month until dose is 400mg daily, then ■ ■Reduce by 50mg every month until dose is 100mg daily, then ■ ■Reduce by 25mg every month until completely stopped

5. Klein E, et al. Discontinuation of lithium treatment in remitted bipolar patients: relationship between clinical outcome and changes in sleep-wake cycles. J Nerv Ment Dis 1991; 179:499–501. 6. Ferrie L, et al. Effect of chronic lithium and withdrawal from chronic lithium on presynaptic dopamine function in the rat. J Psychopharmacol 2005; 19:229–234. 7. Balon R, et al. Lithium discontinuation: withdrawal or relapse? Compr Psychiatry 1988; 29:330–334. 8. Vernachio K, et al. A review of withdraw strategies for discontinuing antiepileptic therapy in epilepsy and pain management. Pharm Pharmacol Int J 2015; 3:232–235. 9. Nolen WA, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord 2019; 21:394–409. 10. Geddes JR, et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004; 161:217–222. 11. Moncrieff J. Lithium: evidence reconsidered. Br J Psychiatry 1997; 171:113–119. 12. Faedda GL, et al. Lithium discontinuation: uncovering latent bipolar disorder? Am J Psychiatry 2001; 158:1337–1339. 13. Goodwin GM. Recurrence of mania after lithium withdrawal. Implications for the use of lithium in the treatment of bipolar affective disorder. Br J Psychiatry 1994; 164:149–152. 14. Kessing LV, et al. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord 2018; 20:419–431. 15. Faedda GL, et al. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry 1993; 50:448–455. 16. Baldessarini RJ, et al. Illness risk following rapid versus gradual discontinuation of antidepressants. Am J Psychiatry 2010; 167:934–941. 17. Baldessarini RJ, et al. Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders. J Clin Psychiatry 1996; 57:441–448. 18. Biel MG, et al. Continuation versus discontinuation of lithium in recurrent bipolar illness: a naturalistic study. Bipolar Disord 2007; 9:435–442. 19. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. Clinical guideline [CG185]. 2014 (last updated December 2023, last checked July 2024); https://www.nice.org.uk/guidance/cg185. 20. Guy. A, et al. Guidance for Psychological Therapists: Enabling Conversations with Clients Taking or Withdrawing from Prescribed Psychiatric Drugs. London: APPG for Prescribed Drug Dependence, 2019. 21. Reinares M, et al. Psychosocial interventions in bipolar disorder: what, for whom, and when. J Affect Disord 2014; 156:46–55. 22. Cappleman R, et al. Managing bipolar moods without medication: a qualitative investigation. J Affect Disord 2015; 174:241–249. 23. Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. Am J Psychiatry 2008; 165:1408–1419.