

Mood stabilisers

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SUMMARY

Many of the drugs used to treat bipolar disorder can be considered to stabilise specific mood phases.

Based on current evidence, lithium and perhaps sodium valproate are the only drugs effective for both acute treatment and the prevention of future episodes.

Quetiapine might also have true mood stabilising properties.

Other anticonvulsants and antipsychotics have evidence to show that they stabilise certain mood states or illness trajectories. They may be used in acute treatment of bipolar disorder, but there is less evidence for their role in maintenance treatment to prevent recurrence.

Introduction

The bipolar disorders are characterised by irregular acute episodes of depression, mania, hypomania and mixed states (various admixtures of elevated and depressed mood). Bipolar disorder is the sixth leading cause of disability worldwide,¹ with a lifetime prevalence of 1–4%.² The lifetime risk of death by suicide is as high as 19%.³ The impact of bipolar disorder on patients' lives is similar to multiple sclerosis, and greater than end-stage renal disease or rheumatoid arthritis.⁴ Most of the burden of illness results from depression, low-level symptoms between episodes and comorbidities such as anxiety and substance use.

People with bipolar disorders present commonly to general practitioners. In one primary care study, 9.8% of patients screened positive for bipolar disorder,⁵ but only 6.5% were taking mood stabilising treatment. Misdiagnosis is the norm and more than one-third of Australians with bipolar disorder are symptomatic for 10 or more years before diagnosis.⁶ Early diagnosis is critical as it allows early intervention. The disorder is almost universally recurrent, so adequate maintenance treatment for prophylaxis should begin during the treatment of the acute episode. All episodes should be treated aggressively to full remission where possible.

What is a mood stabiliser?

Bipolar disorders have different illness phases. To be considered a mood stabiliser, a drug should:

- treat acute depression
- treat acute mania
- prevent depression
- prevent mania.

Some drugs are 'phase-specific treatments'. They work better in some phases than other phases of the illness (Table 1). Most phase-specific treatments are not truly mood stabilising. Current evidence maintains that only drugs such as lithium and perhaps valproate and quetiapine provide acute and long-term illness attenuation, but other anticonvulsants and antipsychotics are also used in treatment.

How mood stabilisers work

There is no specific psychopharmacological mechanism, so how mood stabilisers work is unknown. The possible mechanisms of action of lithium are complex and include:

- altered cell membrane sodium transport
- inhibition of inositol monophosphatase
- reduced protein kinase C activity
- neurogenic/neurotrophic actions
- alterations in serotonin metabolism
- modulation of intracellular signal transduction.⁷

The anticonvulsant drugs used in bipolar disorders may have mechanisms of action which include voltage-sensitive sodium and calcium channels, gamma-aminobutyric acid enhancement, glutamate blockade, or downstream signal transduction cascades.⁷

Atypical antipsychotics are believed to exert a mood stabilising effect through their monoaminergic actions in treating bipolar depression. In psychotic mania they may have dopamine D₂ antagonism or partial agonism and serotonin 5HT_{2a} antagonism.⁷

Current evidence

Most of the available treatments (Table 1) perform equally well in the elevated phase of bipolar disorder, and do so relatively quickly. Most available research data are for acute treatment of bipolar mania. This is despite the depressive phase being less amenable to treatment, more frequent and longer lasting. Bipolar

depression causes more suffering and functional impairment and has a greater adverse impact on prognosis.

The selection of drugs is based on their efficacy against the phase, type and stage of bipolar disorder. Comorbidity (physical, psychiatric, substance abuse), tolerability and safety should also be considered.

In practice, effectiveness is limited by poor patient compliance. This is due primarily to tremor, metabolic disturbance, cognitive dysfunction, sedation and yearning for the perceived pleasure of euphoric mood.

Lithium

Despite being discovered 60 years ago, lithium remains the gold standard for mood stabilisation. Lithium has proven efficacy in the treatment of mania, being more effective against classical (euphoric) mania than mixed (dysphoric) variants. It is also moderately effective against the depressive phase. Placebo-controlled trials confirm lithium’s prophylactic effect against mania and depression.

Recent meta-analyses^{8,9} and longer-term follow-up studies continue to support the preventative efficacy and effectiveness of lithium monotherapy. Lithium also has a specific and strong anti-suicide effect.

Serum lithium concentration is taken as a trough level, 12 hours after a dose for twice-daily dosing, and 24 hours for single-daily dosing. In general, the target range for treating acute phase disturbance should be 0.6–1.2 mmol/L. For maintenance therapy 0.4–0.8 mmol/L will often be adequate. There is a quite large individual variation in the dose required to achieve these targets. The elderly and those with renal impairment usually require lower doses than other patients.

Adverse effects within the therapeutic range are common. Tremor, hypothyroidism, weight gain and sedation are problematic. The most concerning adverse reactions include lithium toxicity, interstitial nephritis, nephrogenic diabetes insipidus and arrhythmia. These occur rarely and adequate monitoring and investigation should allow early intervention.

Serum lithium concentrations can be increased when lithium is co-prescribed with non-steroidal anti-inflammatory drugs, diuretics, ACE inhibitors and metronidazole, risking possible lithium toxicity. Toxicity can also be increased with methyl dopa, carbamazepine and calcium channel blockers.

Considering the evidence, and the harm–benefit ratio, lithium is probably underused. Perhaps this is because of perceived difficulties with

uptitration, concern regarding rare adverse events or unfamiliarity with the drug. There is also no active marketing for lithium.

Anticonvulsants

Only three anticonvulsants – valproate, lamotrigine and carbamazepine – have any demonstrated mood stabilising effect. The other anticonvulsants do not have the necessary evidence to support their use in treating bipolar disorder. In general, anticonvulsant dosage is determined by clinical effect and tolerability.

Sodium valproate

Valproate appears to be equivalent to lithium against the manic phase,¹⁰ but better against mixed mania.¹¹ There is only limited evidence of efficacy in depression or maintenance prevention. Meta-analysis shows valproate is superior to placebo for maintenance.⁸

Sedation is often problematic and weight gain is at least as common as with lithium. Hepatotoxicity or pancreatitis can occur rarely. Concern exists regarding whether valproate might be implicated in polycystic ovary syndrome. The teratogenic effects of valproate mean it should not be used by pregnant women or women planning pregnancy.

Valproate concentrations can be increased by fluoxetine, fluvoxamine, topiramate, chlorpromazine, cimetidine, erythromycin and ibuprofen.

Table 1 Efficacy of drugs used in bipolar disorder

	Treatment of acute mania	Treatment of acute depression	Mania relapse-prevention	Depression relapse-prevention
Lithium	++	++	++	++
Valproate	++	+	++	+
Carbamazepine	+	0	+	0
Lamotrigine	-	++	+	++
Olanzapine	++	+(¹)	++	+
Quetiapine	++	++	++	++
Risperidone	++	-	++ ²	-
Ziprasidone	++	-	++	-
Aripiprazole	++	-	++	-
Paliperidone	++	0	0	0
Asenapine	+	0	+	0
Antidepressants	-	-	-	-

++ good double-blind, placebo-controlled evidence

+ limited supportive double-blind, placebo-controlled evidence

0 no good double-blind, placebo-controlled evidence

- negative studies exist

¹ including olanzapine-fluoxetine combination

² risperidone long-acting injection (depot)

Lamotrigine

Lamotrigine lacks acute antimanic efficacy but has modest antidepressant efficacy as monotherapy or in combination with other drugs. It has prophylactic efficacy against both manic and depressive relapse.

Although lamotrigine is not approved for bipolar disorder in Australia, internationally it is considered a first-line treatment for bipolar depression.⁷ Australian clinical practice guidelines support its use in acute bipolar depression and in maintenance prophylaxis.¹²

Lamotrigine is generally well tolerated, with little to no sedation or weight gain.⁷ There is a small risk of severe dermatological reactions (Stevens-Johnson syndrome), so patients need slow dose titration. Stop treatment if any rash appears.

Carbamazepine

There is reasonable evidence supporting an antimanic effect of carbamazepine, but lithium, valproate or atypical antipsychotics are often preferred. This is because there are no placebo-controlled data supporting carbamazepine's use in bipolar depression or in the maintenance phase. Furthermore, the adverse effect burden, drug interactions and enzyme induction complicate dosing. Carbamazepine tends to be used only when other treatments have failed.

Antipsychotics

In acute mania, the atypical antipsychotics olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, paliperidone and asenapine have placebo-controlled trials to support them as monotherapies. All but paliperidone have studies which show antimanic equivalence to other mood stabilisers and typical antipsychotics. On meta-analysis, lithium, valproate and antipsychotics are more effective than placebo and have similar effect sizes^{13,14} in treating mania.

Atypical antipsychotics (olanzapine, quetiapine, risperidone and asenapine) added to mood stabilisers are more effective than mood stabilisers alone in mania. Meta-analysis^{14,15} shows a faster and greater response to combination treatment, but at the cost of more adverse effects.

Regarding acute antidepressant effect, the best placebo-controlled evidence is for quetiapine^{16,17} and then for olanzapine.¹⁸ No other atypical antipsychotics have evidence of superiority over placebo in treating acute bipolar depression.

Some studies show that atypical antipsychotic drugs (except paliperidone) may protect against relapse, but this is mainly because of their ability to prevent manic episodes. They are less effective in preventing depressive relapse. Atypical antipsychotics demonstrate acute-phase efficacy alone or in

combination and assist with relapse prevention when used with mood stabilisers.

Cognitive and metabolic adverse effects (elevations in triglycerides, glucose and cholesterol, appetite increase and weight gain), sedation and somnolence are most problematic. The frequency, severity and extent of these adverse effects varies between treatments. Although they are less frequent than with typical antipsychotics, there may be extrapyramidal adverse effects. Tardive dyskinesia can also occur.

Antidepressants

Antidepressants are not mood stabilising in bipolar disorder. The largest and most rigorous studies of antidepressants in bipolar depression fail to show any benefit.¹⁹ On meta-analysis, there is no evidence of antidepressant efficacy in acute bipolar depression²⁰ or of relapse prevention over the longer term.²¹ Any potential gains need to be weighed against the risks of inducing mood elevation, cycle acceleration and mixed episodes. However, antidepressants remain one of the most prescribed treatments for bipolar disorder and much controversy surrounds their use. Antidepressants are necessary in a proportion of patients, but should only be prescribed with a mood stabiliser, with close monitoring, and should be discontinued sooner than would usually be considered in unipolar depression.

Combination therapy

Patients with bipolar depression, mixed episodes, psychotic features, rapid-cycling and comorbid dysthymia, anxiety or substance use disorders often do not respond, let alone remit, on monotherapy. The vast majority of patients need combination therapy. The combination of lithium and valproate has recently been shown to be superior in maintenance to either drug alone.²² Clinicians need to be aware of the greater adverse effect burden and potential interactions associated with combination treatment.

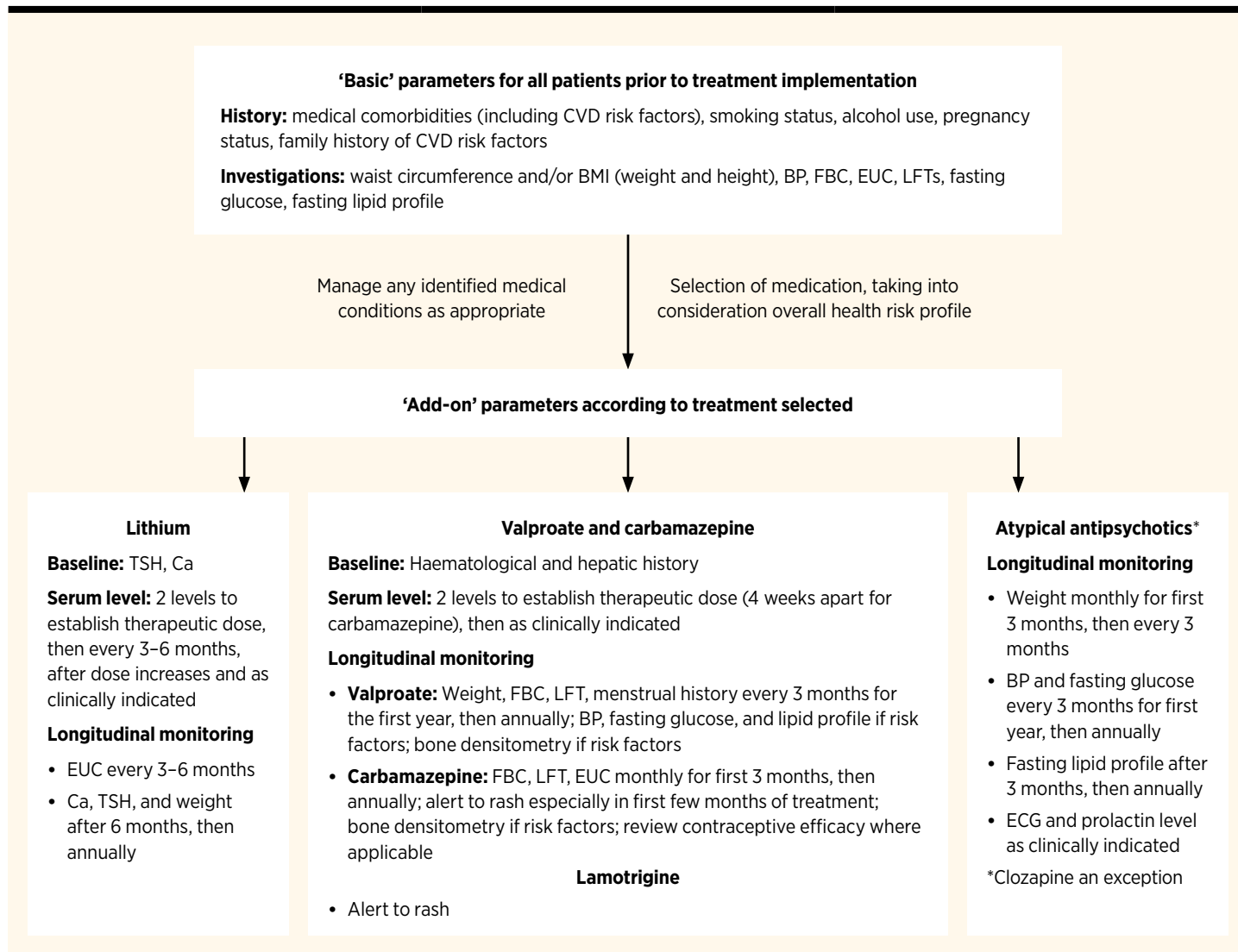
Treatment monitoring

The prescriber needs to ensure that appropriate pre-treatment evaluation, baseline investigations and longitudinal monitoring occur. The International Society for Bipolar Disorders consensus guidelines for safety monitoring²³ are an excellent guide to investigation and monitoring (Fig. 1).

Pregnancy and lactation

Pregnancy and the postpartum are times of increased risk of a bipolar episode. The risks of treatment need to be weighed against the risks to the mother and her child, if there is an untreated episode or mood instability during pregnancy and afterwards.

Fig. 1 Algorithm for safety monitoring in bipolar disorder †



CVD cardiovascular disease
 BMI body mass index
 BP blood pressure

FBC full blood count
 EUC electrolytes, urea and creatinine
 LFT liver function tests

TSH thyroid stimulating hormone
 Ca calcium
 ECG electrocardiogram

† Reproduced with permission from the International Society for Bipolar Disorders consensus guidelines for safety monitoring of bipolar disorder treatments²³

Detailed review, discussion and planning should occur pre-conception, where possible. Although all mood-stabilising treatments can be used during pregnancy, if considered necessary, there are risks of teratogenicity and increased obstetric and neonatal complications.²⁴ Specialist ongoing care is recommended to monitor medicines during pregnancy and breastfeeding.

Non-pharmacological 'mood stabilisers'

There is a growing body of evidence identifying various non-pharmacological treatments with phase-specific and relapse-prevention efficacy (see Box). These should be used to augment pharmacological strategies where possible.

Non-pharmacological 'mood stabilisers'

- Sleep-wake cycle stabilisation, exercise
- Substance abstinence (illicit drugs, alcohol, nicotine and caffeine)
- Specific psychological interventions (cognitive behavioural therapy, interpersonal-social rhythm therapy, family-focused therapy, mindfulness-based therapies and psychoeducation)
- Non-specific psychosocial interventions (for example, activity scheduling, sleep hygiene, social skills training, therapeutic engagement, supportive therapies, compliance strategies, problem-solving and basic stress management)



SELF-TEST QUESTIONS

True or false?

9. When used to treat bipolar disorder, atypical antipsychotics do not cause weight gain.

10. Lithium treatment can cause hypothyroidism in patients with bipolar disorder.

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Conclusion

Bipolar disorder is a complex and difficult disorder to treat. An awareness of available treatments and their specific benefits and hazards, along with early and accurate diagnosis, will hopefully facilitate better outcomes for those suffering this extremely distressing and disabling chronic illness. Lithium remains the most useful drug for acute treatment and prevention. ◀

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