

Graylands Hospital Drug Bulletin

Pharmacological treatment of Bipolar Disorder

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Bipolar Disorder

Bipolar disorder (BD) occurs in approximately 1% to 2% of the population and is characterised by distinct episodes of mania and depression.¹ The existence of mania, hypomania and mixed states differentiate BD from unipolar depression.²

The impact of the illness is severe, and can affect relationships, career, self-esteem and longevity.¹ Peak onset is usually in early adult life (late adolescence to early 20s) and it has a strong genetic basis.¹ Rapid-cycling and psychotic features are associated with greater treatment resistance.²

Most randomised controlled trials (RCTs) and treatment recommendations focus on bipolar-I disorder, but results are often extrapolated to include bipolar-II disorder.¹ Bipolar-I disorder is diagnosed when a patient has one or more episodes of mania, with or without major depressive episodes.³ A patient is diagnosed with bipolar-II disorder when they experience one or more episodes of hypomania, as well as at least one major depressive episode.³

Treatment of Bipolar Disorder

The general aim of treatment of BD is to reduce the morbidity associated with the disease and limit the disability it confers.² This requires prompt and effective treatment of acute episodes, and prevention of relapse or recurrence.² A summary of the treatment options for BD is represented in Figure 1. These medications must be used cautiously in women of childbearing potential because of possible effects on the foetus.⁴

Acute mania

The treatment of acute mania has been extensively studied.⁵ Multiple treatment options are available, and must be selected according to their efficacy, safety and tolerability.⁶

Lithium

Lithium remains a first line treatment option for acute mania¹ though the mechanism of action is still unclear.⁷ The relatively slow response in the acute phase may be problematic,⁷ however, continuing lithium treatment after the manic episode has resolved is beneficial.⁵

The therapeutic concentration of lithium required in acute mania is usually 0.8-1.2mmol/L - higher than for maintenance therapy.¹ Clinical vigilance is required at

these levels as adverse effects are more likely.⁵

Sodium valproate

The efficacy of sodium valproate has been demonstrated in several RCTs. It has equivalent efficacy to lithium in acute mania, but may be less effective than olanzapine.⁸ A plasma concentration of at least 43mg/L is necessary to benefit from sodium valproate, while toxicity is likely at concentrations above 122mg/L.¹ Within this range, dose should be adjusted according to clinical response.¹

The effect of sodium valproate can be accelerated by using loading doses.² This is generally well tolerated, and allows therapeutic serum levels to be achieved earlier in therapy. Doses of 30mg/kg/day for the first two days have been used, and then reduced to 20mg/kg/day.⁹

Other Anticonvulsants

Carbamazepine has demonstrated efficacy in treating mania, but is rarely used as first line therapy.⁵ It interacts with many drugs and also causes autoinduction.⁵ Thus the dose may need to be increased after a few weeks of therapy to ensure adequate serum concentration.

Oxcarbazepine has shown some efficacy in a few RCTs with very small sample sizes.¹⁰ A recent 7-week study found no improvement in manic symptoms after oxcarbazepine treatment.¹⁰

Gabapentin showed some evidence in open-labelled trials, but not in placebo-controlled trials.⁷

Topiramate has also failed to show efficacy in RCTs.⁷

Antipsychotics

First generation antipsychotics (FGAs), such as haloperidol, have been used to treat acute mania but due to the risk of extra-pyramidal side effects are not a preferred first line agent.⁵ However, if other treatment options have failed, use of FGAs is recommended.²

Substantial RCT data supports the efficacy of second generation antipsychotics (SGAs) in the treatment of acute mania.¹⁰ Their indications according to the Pharmaceutical Benefits Scheme (PBS) are listed in Table 1.

Olanzapine, quetiapine, risperidone and ziprasidone have demonstrated efficacy as monotherapy treatment options for acute mania.¹⁰ There is also

some evidence to suggest aripiprazole is effective,¹⁰ however it is not approved by the Therapeutic Goods Administration (TGA) in Australia for use in BD.¹¹ Quetiapine extended release has also proven to be effective in a 3-week trial, improving manic symptoms from day 4.¹⁰ This formulation is not listed on the PBS for BD.

Table 1: Atypical antipsychotics' bipolar disorder PBS indication in Australia¹²

Antipsychotic	PBS Indication
Olanzapine (tablets, wafers)	Maintenance treatment of bipolar I disorder.
Risperidone (liquid, tablets, quicklets®)	Adjunctive therapy to mood stabilisers for up to 6 months, of an episode of acute mania associated with bipolar I disorder.
Quetiapine (not extended release tablets)	Monotherapy, for up to 6 months, of an episode of acute mania associated with bipolar I disorder. Maintenance treatment of bipolar I disorder, in combination with lithium or sodium valproate.
Ziprasidone	Monotherapy, for up to 6 months, of an episode of acute mania or mixed episodes associated with bipolar I disorder.

Benzodiazepines

Benzodiazepines, such as diazepam, clonazepam and lorazepam are useful in acutely agitated patients. They are indicated when sedation and tranquillisation are a priority. They lack significant pharmacokinetic drug interactions which is beneficial when used in combination with other agents.⁵

Benzodiazepines can also help minimise the antipsychotic dose required and therefore reduce the risk of side effects such as movement disorders.⁵

Combination treatment

Recent studies have shown that the combination of lithium or sodium valproate with an antipsychotic (haloperidol, olanzapine, risperidone, quetiapine, aripiprazole) is more effective than treatment with either lithium or sodium valproate alone.^{2, 10}

Acute depression

Bipolar depression accounts for much of the morbidity and mortality associated with BD.¹³ Although most of the research is focussed on treating mania, data suggests that patients with BD spend much more time depressed (32%) than manic (9%).¹⁴ However, for the majority of the time the symptoms are subthreshold.¹⁴ It also takes longer to recover from the depressive phase than the manic phase.¹⁵

During the course of BD, depression occurs earlier, recurs more often and lasts longer compared to mania.¹⁶

Traditionally, bipolar depression is considered to be

more refractory, with a less favourable response to antidepressants than unipolar depression.¹⁴ Atypical features, such as hypersomnia, melancholia, psychotic symptoms and psychomotor changes are also more likely in bipolar depression.²

Antidepressants

The use of antidepressants in BD is a controversial issue, with some reports of it inducing a switch into mania, hypomania or mixed episodes.¹⁷ Recent reports, however, have challenged this assumption and conflicting evidence exists in regards to their efficacy and usefulness in bipolar depression.^{1, 14}

In general, antidepressants should only be prescribed in patients with BD if a mood stabilising agent is also used to prevent a manic switch.¹⁴

There is currently limited evidence that supports the modest efficacy of antidepressants in bipolar depression.⁵ Tricyclic antidepressants and serotonin and noradrenaline reuptake inhibitors, which have a dual action on serotonin and noradrenaline, carry a greater risk of inducing a manic episode than selective serotonin reuptake inhibitors.⁵ They are only recommended in patients who inadequately respond to initial treatment.⁵

Long-term treatment with antidepressants occurs in clinical practice in bipolar patients though the evidence supporting this is unclear.⁵ Clinical judgement should be used to determine whether the antidepressant should be continued.⁵

Fluoxetine, in combination with olanzapine, currently has the greatest amount of data supporting its efficacy in bipolar depression.¹⁷

Lithium

Conflicting data exists regarding the efficacy of lithium in bipolar depression. Some reports suggest that lithium is more useful in the treatment of mania compared to depression, while there are controlled trials supporting its antidepressant and anti-suicidal effectiveness.¹⁴

Lithium could be considered when depressive symptoms are less severe.⁵

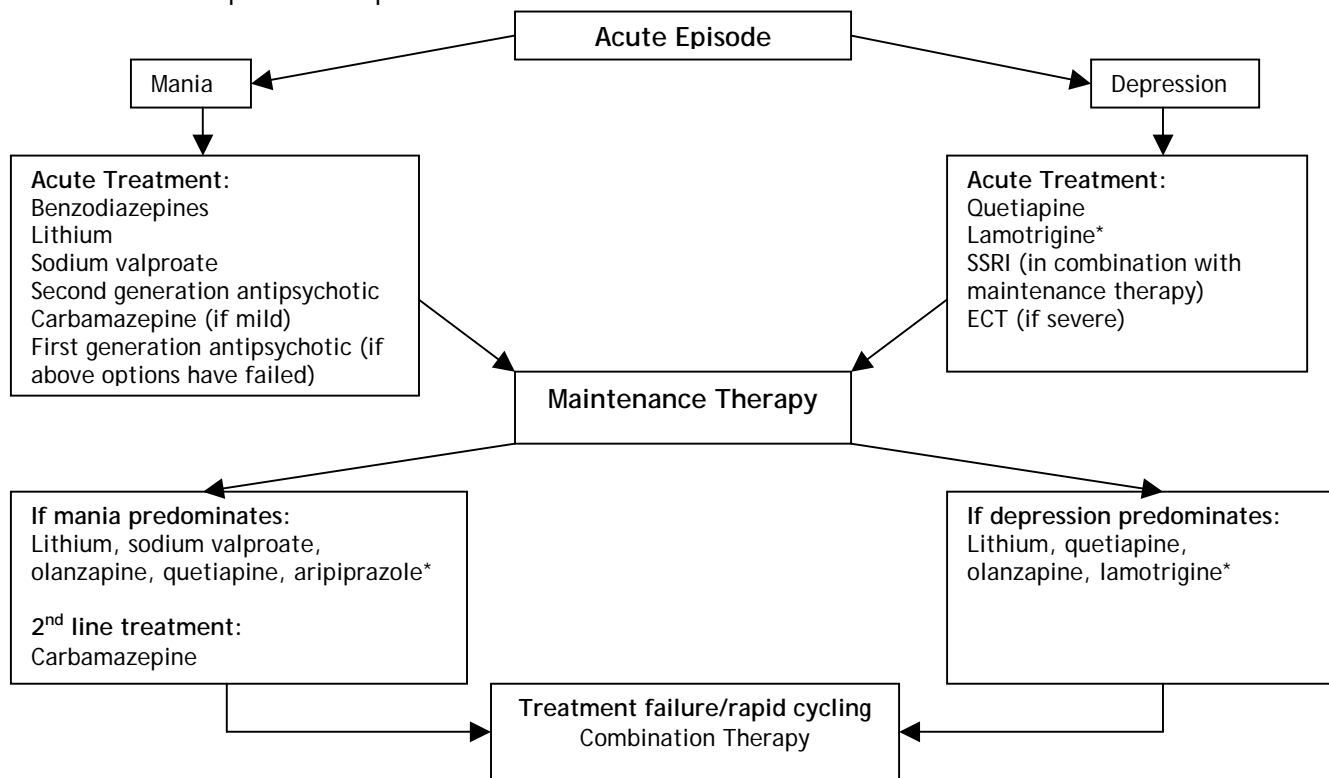
Sodium Valproate

There have been four small, placebo-controlled studies focussing on sodium valproate in the treatment of bipolar depression.¹⁷ Sodium valproate was found to be significantly superior to placebo in three of these trials.¹⁷ Larger RCTs are required to confirm these results.¹⁷

Lamotrigine

Lamotrigine has been studied as an acute treatment for bipolar depression in five RCTs.¹⁶ Lamotrigine was significantly more effective than placebo in the first study but not in the other four studies. A large placebo response rate may have been responsible for

Figure 1: Treatment options for Bipolar Disorder^{# 5}



* Not TGA approved for BD use in Australia

Please check the PBS for individual medication PBS approvals

the inability to detect differences between lamotrigine and placebo in the latter four studies.¹⁶ Slow dose titration, due to the risk of rash, results in up to 6 weeks of treatment being required before an adequate dose is achieved.⁵ Trials indicate this may be a reason for early drop-out.⁵

Lamotrigine should be considered if previous treatment with an antidepressant provoked mood instability or was ineffective.⁵

Lamotrigine is not approved by the TGA for use in BD.¹¹

Antipsychotics

Quetiapine, at doses of 300mg and 600mg daily, has demonstrated efficacy in reducing depressive symptoms in patients with BD compared to placebo.⁵ Analysis of four RCTs showed efficacy of quetiapine monotherapy in bipolar-I disorder,¹⁰ with slightly lower response rates in bipolar-II disorder.¹⁸

Short-term treatment with quetiapine can cause somnolence and sedation, which may result in substantial dropout from initial treatment.⁵ Long-term treatment carries the risk of metabolic disturbances, which must be considered when quetiapine is started.⁵ Olanzapine monotherapy appears to produce a modest effect in bipolar depression, while the olanzapine-fluoxetine combination has been shown to provide an even greater effect.¹⁵ The risk of metabolic disturbances is higher with olanzapine compared to quetiapine.

Electro-convulsive Therapy

Electro-convulsive therapy (ECT) appears to be equally

effective in bipolar and unipolar depression.⁵ However, trials exclusively in BD do not exist and evidence is limited.⁵

Maintenance treatment

The goal of maintenance treatment is to prevent relapse of BD.¹⁹ It should be considered after stabilisation of the first manic episode, as prevention of relapse early in the course of the illness may lead to fewer relapses in the future.¹⁹

Non-compliance with prescribed maintenance treatment is a major cause of relapse in BD.

The number of evidence-based options for long-term prophylactic treatment of BD has increased in recent years.⁵

Lithium

Lithium continues to be the gold standard of maintenance therapy in BD,²⁰ and the standard for comparison of new therapies.¹⁹ Evidence suggests that lithium is better at preventing mania than depression.⁷ For most patients, the target lithium concentration during maintenance therapy is 0.6-0.8mmol/L,¹ though there is considerable inter-patient variability.¹

Lithium has also been shown to reduce the risk of suicide (both completed and deliberate self harm) in patients with BD.⁷

Although lithium is effective in maintenance treatment, limitations exist in regards to the burden of side effects and tolerability. Hypothyroidism,

decreasing kidney function, cognitive impairment and tremor can occur and result in cessation of lithium.¹⁹

Discontinuation of lithium within a 2-week interval is associated with increased risk of manic relapse.⁵ The dose should be tapered over at least 2-4 weeks except in medical emergency or overdose.⁵

Sodium Valproate

Considering its widespread use in BD, there are very few RCTs evaluating the efficacy of sodium valproate as maintenance therapy.^{8,19} It has shown comparable efficacy to olanzapine although placebo-controlled evidence is lacking.⁸ Despite this, sodium valproate is extensively used in clinical practice for maintenance therapy of BD.⁷

The greatest advantage of sodium valproate may be that it is both well tolerated and effective in patients who do not respond to lithium.¹⁹ Sodium valproate has a larger therapeutic window than lithium, and side effects can be lessened with dose adjustments.¹⁹ Common side effects include weight gain, sedation and hair loss and more rarely liver and pancreatic dysfunction can occur.¹⁹

Other Anticonvulsants

Lamotrigine is more effective against depression than mania in long-term treatment. Lamotrigine can be considered when depression is the major burden of BD and the risk of manic relapse is low.⁵

Carbamazepine has demonstrated efficacy in the maintenance treatment of BD, though this efficacy may fade with longer-term treatment.⁷ Two recent trials comparing lithium to carbamazepine showed substantial benefit to lithium in preventing relapse.⁵

A RCT comparing oxcarbazepine to placebo in maintenance treatment of BD showed a lower, but not statistically significant risk of mood recurrence with oxcarbazepine.¹⁰ More RCTs are required in this area.¹⁰

There is currently insufficient evidence to support the use of gabapentin or topiramate in BD.⁷

Antipsychotics

Only olanzapine and quetiapine are indicated on the PBS for maintenance treatment in BD.¹² They may be appropriate in the management of bipolar patients, particularly when psychotic features are also present.⁵

Olanzapine has been shown to be effective as a maintenance treatment in a placebo-controlled relapse prevention trial.⁵

Quetiapine has shown to be effective as monotherapy or in combination with lithium or sodium valproate in the prevention of relapse into mania or depression.¹⁰ This combination was also significantly more effective than lithium or sodium valproate alone.¹⁰

Risperidone long acting injection has demonstrated efficacy in the maintenance treatment of BD in two RCTs, as both monotherapy and adjunctive

treatment.¹⁰ However, this indication is not approved in Australia.

Combination Treatments

Increasingly, combinations of agents are being prescribed in patients who do not respond to monotherapy.⁵ Large, controlled trials are needed to determine which combinations offer the most benefit in patients with BD.⁵

Rapid Cycling

Rapid cycling is associated with long-term treatment problems, as it is generally less responsive to drug treatment than non-rapid cycling BD.²¹ It also confers higher rates of morbidity and increased suicide risk.²

It is important to identify and treat any conditions, such as hypothyroidism or substance misuse, which may be contributing to the rapid cycling.⁵ Antidepressants should be tapered then discontinued as they may also contribute to cycling.⁵

There is little data available on treatment options for rapid cycling. Carbamazepine has been shown to be more effective than lithium in one study,²² though not proven in another.²¹ For many patients combinations of medications, such as lithium plus sodium valproate, are required.^{5,21}

Mixed States

Mixed states are often hard to diagnose and differentiate from both mania and agitated depression.² Antidepressants and other medications, such as stimulants, which may cause a mood-elevating effect or switch, should be ceased.

Olanzapine, quetiapine or sodium valproate may be effective as monotherapy. Alternatively, olanzapine in combination with sodium valproate may be considered.²

Conclusion

BD is a life-long illness and prevention of recurrent mood episodes is the goal of treatment. Despite the recent introduction of new therapies, such as the SGAs, lithium remains first line treatment and the standard for comparison.¹⁹

Clinicians must not only consider what treatment is effective for a patient, but also take into account the safety and tolerability of each medication.⁶

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References available on request

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