Mood stabilisers in bipolar disorder

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Pharmacotherapy is the centrepiece of management for bipolar disorder. GPs have an important role in caring for patients with this chronic condition, particularly during the maintenance phase.

Bipolar disorder (formerly known as manic depression) is a chronic, recurrent illness with a peak onset in early adulthood. It is characterised by episodes of depression and either mania (bipolar I disorder) or hypomania (bipolar II disorder); psychotic features may or may not be present. Diagnostic criteria are outlined in *Diagnostic and statistical manual of mental disorders*, fourth edition.[1] Hypomania is often overlooked, leading to a high rate of misdiagnosis of bipolar II disorder as recurrent depression.

What are mood stabilisers?

The term 'mood stabiliser' was initially used to describe the action of lithium (Lithicarb, Quilonum SR) in preventing recurrence of illness, and was extended to include anticonvulsants with mood stabilising properties – i.e. carbamazepine (Tegretol, Teril), sodium valproate (Epilim, Valpro) and lamotrigine. The antipsychotic drug olanzapine (Zyprexa) also has mood stabilising properties and is now indicated for maintenance treatment of bipolar disorder. Treatment should not worsen the course of the illness or induce a mood switch, such as from depression to hypomania or mania.

How are mood stabilisers used?

Mood stabilisers have a spectrum of action that enables the treatment of mania and bipolar depression and long term prevention of recurrent episodes. Lithium has the strongest evidence of efficacy across all phases of the illness and is the benchmark against which newer agents are judged. The clinical trial evidence of efficacy for mood stabilisers in treating bipolar I disorder is summarised in the Table below; the evidence for bipolar II disorder is less robust.

Guidelines for the treatment of bipolar disorder and use of mood stabilisers are widely available – see, for example, *Therapeutic guidelines: psychotropic*[2] or the Royal Australian and New Zealand College of Psychiatrists' clinical practice guidelines.[3] GPs have an important role to play in caring for patients during the maintenance phase, and a lesser role in treating acute episodes.

Mania

Many agents are available for treating mania and hypomania. There is evidence that combination therapy has greater efficacy than monotherapy in acute mania, and, therefore, lithium and/or sodium valproate are commonly used together with a new antipsychotic such as olanzapine, risperidone (Risperdal) or quetiapine (Seroquel).

Experts are divided in their approach to selecting maintenance treatment following an acute episode. Some argue that 'the drug that got you well, keeps you well', whereas others believe that evidence of long term efficacy should guide treatment choice.

Bipolar depression

There is clinical trial evidence for the efficacy of lithium and lamotrigine, respectively, in treating bipolar depression.[4] Antidepressants are widely used and effective, but they have a variable risk of switching the patient into hypomania or mania and, therefore, should be combined with a mood stabiliser – lithium is the first choice. For patients taking a mood stabiliser who present with a 'breakthrough' episode of bipolar depression, the first step is to optimise the dose and plasma level of the mood stabiliser prior to adding an antidepressant. Newer antidepressants, such as SSRIs, have a

Table. Mood stabilisers in bipolar disorder: strength of evidence for efficacy*

Drug	Mania	Bipolar depression	Maintenance
Lithium	Very strong	Strong	Very strong
Sodium valproate	Very strong	Inconsistent or inadequate	Weak
Carbamazepine	Strong	Inconsistent or inadequate	Weak
Lamotrigine	Inconsistent or inadequate	Strong	Very strong
Olanzapine	Very strong	Weak	Strong

* Highest level of evidence from prospective, randomised placebo controlled trials: very strong.

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lower risk of mood switching than the older tricyclics and monoamine oxidase inhibitors. Suicide risk should always be assessed because patients with bipolar disorder have a risk of suicide that is 15 to 20 times the population risk.

Maintenance treatment

The use of lithium in preventing recurrence of illness has revolutionised the outcome for patients with bipolar disorder, and it remains the treatment of choice.[5] Placebo controlled trials comparing lithium and lamotrigine show a differing profile of action, with lithium being more effective in delaying time to a manic episode and lamotrigine being more effective in delaying time to a depressive episode compared with placebo. This differential effect provides options for long term maintenance therapy, depending on the polarity of recurrences.

Although monotherapy is generally preferable for the maintenance phase, combination therapy may be required to achieve optimum outcome. Benefits must be balanced against the burden of side effects. Most patients require lifelong treatment to maintain mood stability. If medication needs to be discontinued then it should be tapered off because stopping abruptly increases the risk of early recurrence. Antidepressants used long term may increase the risk of rapid cycling (more than four to six episodes per year) and 'breakthrough' episodes of mania, and should be taken in combination with a mood stabiliser.

Up to 50% of bipolar disorder sufferers spend a substantial proportion of time between episodes with minor or subsyndromal symptoms, particularly depression. There is a high rate of concomitant medical problems, such as cardiovascular disease and diabetes, and comorbidity due to alcohol abuse and dependence. Recovery of occupational, social and family function may be protracted and incomplete. Several studies have reported a reduced risk of mortality in patients maintained on lithium, largely achieved by a reduction in suicide rates. No similar data have been reported for other mood stabilisers.[6]

What monitoring is required?

Regular monitoring of psychiatric and medical status of patients during maintenance treatment is critical.[6]

Lithium

For lithium, monitoring of plasma levels every one to three months is mandatory: maintenance plasma levels of 0.5 to 0.8 mmol/L are recommended, and 'fine tuning' will minimise side effects such as tremor and increased thirst and urination. Pretreatment and annual serum creatinine, electrolyte and calcium levels and thyroid function tests are recommended to monitor effects on renal, thyroid and parathyroid function.

Anticonvulsants

The anticonvulsant plasma levels recommended for bipolar disorder are those recommended for epilepsy. They are less informative in terms of therapeutic effects and toxicity in bipolar disorder, but helpful in assessing compliance. For patients who are taking sodium valproate and carbamazepine, it is advisable to obtain pretreatment and follow up blood counts and liver function tests, where indicated.

Olanzapine

Olanzapine may contribute to the risk of type 2 diabetes, and monitoring of weight, plasma glucose and lipids is recommended.

What about important precautions and drug interactions?

Lamotrigine

Skin rashes have been reported in patients taking lamotrigine, with an incidence of 10% in adults with a mood disorder. Risk factors include a high starting dose, rapid dose escalation and concurrent use of sodium valproate. Unless the rash is clearly not drug related, lamotrigine should be discontinued at the first sign of rash because it may be potentially life threatening. Metabolism of lamotrigine is inhibited by sodium valproate and induced by carbamazepine, and dosage adjustment is required when these agents are used in combination.

Lithium

Illness or surgery affecting fluid and electrolyte balance or administration of drugs that decrease elimination of lithium by the kidney (e.g. diuretics, NSAIDs or angiotensin converting enzyme inhibitors) raise lithium levels. This may precipitate neurotoxicity, which may be potentially life threatening. MT

References

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DECLARATION OF INTEREST: Professor Johnson has been an investigator in clinical trials in mood disorders and schizophrenia with numerous pharmaceutical sponsors. Current trials include maintenance studies in bipolar disorder with lamotrigine (GlaxoSmithKline) and quetiapine (AstraZeneca). He is a member of advisory boards for Eli Lilly, Sanofi and Servier. He is a consultant to the TGA and a previous member of the PBAC.