



Philip B Mitchell

# Bipolar disorder

## Background

Bipolar disorder affects about 1% of Australians and impacts severely on relationships, careers and general functional capacity. General practitioners are central in the management of patients with bipolar disorder.

## Objective

To update clinicians on the recognition, diagnosis and management of bipolar disorder in light of recent research.

## Discussion

There is growing concern about the over-diagnosis of bipolar disorder, and increasing evidence that bipolar depression may present differently to unipolar depression. Antipsychotics are the initial agents of choice for the acute treatment of mania. For preventive treatment, lithium and atypical antipsychotics have the strongest evidence base. Lithium has been shown to be more effective than valproate. The main effect of lithium and most of the atypical antipsychotics is on prevention of manic relapse; only olanzapine and quetiapine also protect against depression. Lamotrigine is an agent with evidence for prevention of depressive relapse, but have minimal activity against mania. The role of antidepressants remains contentious, while there is strong support for quetiapine. Finally, there is growing evidence from randomised controlled trials of the benefit of psychological therapies in conjunction with medications.

## Keywords

bipolar disorder; lithium; antipsychotics; antidepressants



Patients with bipolar disorder present major opportunities and challenges for the general practitioner (GP). On the one hand, the potential for a dramatic benefit of treatment is perhaps greater for bipolar disorder than for most other psychiatric disorders. Finding the appropriate mix of medications and psychological assistance to reduce or abolish the frequency of recurrences can make an enormous difference to people's lives. On the other hand, the common reluctance to engage in therapy, loss of insight during mania and tendency to frequent recurrence make this a difficult condition to manage within the confines of the primary care setting.

## Epidemiology

In Australia, about 1% of the community have bipolar disorder.<sup>1</sup> This condition has a major impact on the average patient.<sup>1</sup> Patients are more likely to experience broken relationships and make suicide attempts than even those with unipolar depression (major depressive disorder).<sup>1</sup> Compared to the general population they are also more likely to be on government benefits, have comorbid anxiety disorders or substance abuse, and spend more days disabled.<sup>1</sup> The latter finding is consistent with the international experience: the recently published 2010 Global Burden of Disease Study reported bipolar disorder to be the eighteenth most disabling health condition internationally.<sup>2</sup>

## Diagnosis

The hallmark characteristic of bipolar disorder is the tendency to swing between the two contrasting 'poles' of elevated mood and depression, with a return to largely normal functioning in between these episodes.

The periods of elevated mood are termed mania or hypomania. These share common characteristic symptoms, which are detailed in *Table 1*. Mania is distinguished from hypomania in being more prolonged (most diagnostic systems require a minimum duration of 7 days for mania and a minimum of 4 days for hypomania) and leading to marked impairment of functioning, unlike hypomania in which the mood is distinctly different from normal, but there is no substantial impairment. Mania (unlike hypomania) may also be characterised by the presence of delusions and/or hallucinations, or by the need for hospitalisation. Patients who have experienced an episode of mania are diagnosed as having bipolar I disorder, whereas those with only hypomanic episodes are said to have bipolar II disorder.



**Table 1. Symptoms of mania and hypomania (symptoms need to be present for at least 4 days for hypomania and 7 days for mania)**

- Abnormally elevated or euphoric mood, frequently associated with an increased tendency to irritability
- Increased energy and activity (more 'wired')
- Reduced need for sleep (as distinct from insomnia)
- An inflated sense of one's own abilities (grandiosity)
- Disinhibited behaviour: increased sexual drive; increased spending or excessive generosity; tendency to make overly frank comments about others
- Increased subjective speed of thoughts ('my thoughts are too quick for my tongue to keep up with'); more talkative; speaking more loudly
- Increased distractibility: reduced ability to focus and complete tasks (despite having many plans or projects)
- Enhanced perceptual experiences: eg. sounds are more harmonious, colours richer than usual.

For most patients with bipolar disorder, more of their lives are spent in depressed mood than in periods of elevation, even for those with bipolar I disorder. Furthermore, the illness usually first presents with a depressive episode, meaning that some young people with depressive episodes may go on to have hypo/manic episodes in the future.

It is critical that the depressive episodes of bipolar disorder are recognised early and treated vigorously, as most suicides occur during depressive episodes.<sup>3</sup> One aspect of improving recognition of bipolar depressive episodes has been clarifying if there are symptoms more commonly observed in bipolar than unipolar depression. The work of our group at the University of New South Wales, Black Dog Institute<sup>4,5</sup> and others has demonstrated that some symptoms are more likely to occur in bipolar depression, thereby assisting clinicians in considering this possibility in cases where the history of past hypo/manic episodes is uncertain or ambiguous. We have termed this a 'probabilistic approach', thereby emphasising that there are no pathognomonic characteristics of bipolar depression, rather differing likelihoods of the occurrence of particular symptoms. Those features more common in bipolar depression are listed in *Table 2*. Some patients present with a mixture of depressive and hypo/manic symptoms.

While 10 years ago there was concern that bipolar disorder was being under-diagnosed, there is now growing evidence that the pendulum has swung to the opposite direction of overdiagnosis, particularly for bipolar II disorder.<sup>6</sup> The first evidence for this came from two US centres in 2008,<sup>7,8</sup> which reported that a high proportion of patients presenting to clinical services with a diagnosis of bipolar disorder were unable to have that diagnosis verified by formal structured interviews. It appeared that the diagnosis was being made in many people with transient mood instability. The formal interviews demonstrated that many of these patients had other conditions such as borderline personality disorder, unipolar depression and impulse control disorders.

## Management of bipolar disorder

While the mainstay of treatment for bipolar disorder is medication, there is growing evidence of the importance of adjunctive psychological treatments.<sup>9</sup>

Those medications approved in Australia for the treatment of acute mania and the preventive treatment of bipolar disorder (indicating those which are Pharmaceutical Benefits Scheme [PBS]-listed) are detailed in *Table 3* and *Table 4*, respectively. No medications have been approved for the acute treatment of bipolar depression.

### Acute treatment of mania

A recent meta-analysis<sup>10</sup> has confirmed that the most efficacious acute treatments for mania are the antipsychotics rather than the traditional 'mood stabilisers' lithium, valproate and carbamazepine. Specifically, that report found that the preferred options – after taking into account both efficacy and tolerability – were risperidone, olanzapine and haloperidol.<sup>10</sup>

What ramifications does this study have for GPs needing to urgently treat manic patients in the community? While it highlights the clear benefit of these antipsychotics, clinicians need to weigh this information against some of the potential adverse effects of these medications, such as metabolic syndrome with olanzapine and extrapyramidal side effects with haloperidol. Furthermore, some patients will be considered for long-term treatment with other medications such as lithium (see below), so those agents may be initiated early in conjunction with the antipsychotic.

### Acute treatment of bipolar depression

This is the most contentious management issue for patients with bipolar disorder. The main debate concerns the role of the antidepressants as the various national and international guidelines differ in their recommendations. Unfortunately, there is conflicting data on both the efficacy of antidepressants in bipolar depression, and the rates of antidepressant-induced hypo/manic episodes.<sup>9</sup> It is the author's own opinion that there is a legitimate role for antidepressants in treating acute bipolar depression, as long as patients are also concurrently prescribed an agent to reduce

**Table 2. Features more common in bipolar depression than unipolar depression**

- Physical slowing (psychomotor retardation)
- Increased sleep (hypersomnia) and/or increased appetite (hyperphagia)
- Early morning waking/diurnal mood variation (worse in morning)
- Delusions and hallucinations; excessive (pathological) guilt
- Lability of mood (interspersed hypomanic symptoms)
- Early onset of first depression (<25 years)
- Multiple prior depressive episodes
- Positive family history of bipolar disorder.



the risk of inducing hypo/mania, such as lithium, valproate or an antipsychotic. There is now also clear evidence of the efficacy of quetiapine monotherapy in the acute treatment of bipolar depression<sup>11</sup> and some evidence for the combination of olanzapine and fluoxetine.<sup>12</sup>

### Preventive treatment

The strongest evidence for prevention of recurrences is for lithium.<sup>13</sup> There is also solid evidence for all of the atypical antipsychotics.<sup>14</sup> However, for lithium and most atypical antipsychotics, the most clear-cut effect is for prevention of manic episodes. Among the antipsychotics, quetiapine and olanzapine stand out as also preventing recurrence of depressive episodes, though for both agents this evidence is based on only one trial.<sup>15,16</sup> Lamotrigine, on the other hand, has been demonstrated in two major trials to be effective in preventing depressive relapse,<sup>17,18</sup> though with only minimal effect on preventing hypo/manic episodes.<sup>19</sup>

<b>Table 3. Medications approved in Australia for the acute treatment of mania</b>
• Lithium*
Anticonvulsants
• Valproate*
• Carbamazepine*
First-generation antipsychotics
• Chlorpromazine*
• Haloperidol*
Second-generation antipsychotics
• Aripiprazole
• Asenapine*
• Olanzapine
• Quetiapine*
• Risperidone* (as adjunct to mood stabiliser)
• Ziprasidone*
*PBS listed for acute treatment of mania as of July 2013

<b>Table 4. Medications approved in Australian for the preventive treatment of bipolar disorder</b>
• Lithium*
Anticonvulsants
• Carbamazepine*
• Lamotrigine
Second generation antipsychotics
• Aripiprazole
• Asenapine*
• Olanzapine*
• Quetiapine*
• Risperidone depot injection (in combination with lithium or valproate)*
*PBS listed for preventive treatment of bipolar disorder as of July 2013

While there has been no convincing controlled evidence for the efficacy of valproate in preventive treatment of bipolar disorder, the clinical experience has been that this is often an effective prophylactic agent. A recent randomised comparison of lithium and valproate monotherapies with the combination of these treatments reported lithium to be as effective as the combination, and more effective than valproate monotherapy.<sup>20</sup>

### Safety of lithium

The first meta-analysis of the side effects of lithium has been recently reported,<sup>21</sup> and provides useful guidance for the clinician whose treatment choices will be determined by consideration of both efficacy and safety. That report did not find evidence of significant renal impairment, though the reduction in urinary concentrating ability (leading to polyuria) was confirmed. The reader may also be interested in an excellent review of lithium and renal function published several years ago,<sup>22</sup> which provides clinically helpful flowcharts on clinical decision making when renal function is either minimally, moderately or severely impaired. It is the author's own clinical observation that lithium may lead to significant chronic renal impairment in a small number of patients, and this is more likely with long-term usage.

The other major findings of the McKnight meta-analysis<sup>21</sup> were that lithium is associated with an increased risk of hypothyroidism, hyperparathyroidism (with elevated calcium and parathyroid hormone concentrations) and weight gain. While the study did not find significantly higher rates of teratogenesis with lithium, the author recommends that lithium still be considered a potentially teratogenic treatment that should preferably be ceased in women planning to conceive, though the absolute risk of teratogenesis is much less than that found with valproate, carbamazepine and lamotrigine.

### Psychological treatments

There is growing evidence of the importance of psychological factors in predisposition to bipolar disorder, triggering individual episodes, and complicating the patient's response to developing this illness. To address this, a number of tailored therapies have been developed for bipolar disorder. There is now strong evidence from individual controlled trials and meta-analyses<sup>9</sup> for the efficacy of a number of psychological therapies including cognitive behavioural therapy, psycho-education, interpersonal and social rhythms therapy and family focused approaches. Social rhythms therapy, for example, focuses upon the importance of regularising daily habits such as sleep, meal times and activity levels.<sup>23</sup> These should not be considered an alternative to medications, but adjunctive to those.

### Conclusion

There have been important advances in the management of bipolar disorder in recent years. The GP is the central figure in the management of patients with this condition, in conjunction with specialist mental health service providers, and is in the strongest position to understand the critical balance between biological and psychosocial factors for the individual patient.



## Resources

- Black Dog Institute: [www.blackdoginstitute.org.au/](http://www.blackdoginstitute.org.au/)
- Beyondblue: [www.beyondblue.org.au/](http://www.beyondblue.org.au/)
- US National Institute of Mental Health: [www.nimh.nih.gov/health/publications/bipolar-disorder/index.shtml](http://www.nimh.nih.gov/health/publications/bipolar-disorder/index.shtml)

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