Bipolar disorder
Focus on depression

Patients with bipolar disorder that is not severe or is very treatment-responsive may be managed primarily in the general practice setting, with occasional clinical review and support by psychiatric services when complications or major recurrences occur.

PHILIP B. MITCHELL
MB BS, MD, FRANZCP, FRCPsych

BRONWYN GOULD
AM, MB BS, DipPaed, MPsycholMed

Professor Mitchell is Scientia Professor and Head of the School of Psychiatry, University of NSW, and Director of the Bipolar Disorders Clinic, Black Dog Institute, Prince of Wales Hospital, Sydney. Dr Gould is a General Practitioner in Sydney, NSW.

There has been growing public and professional interest in bipolar disorder in recent times, with a number of high-profile people openly acknowledging that they suffer from this condition. In Australia, this illness afflicts 1.3% of the population at some stage of their life, and 0.9% in any 12-month period.[1] Although there has been valid concern about under-recognition of bipolar disorder in the past,[2] there is now concern that the pendulum has swung too far and that the condition may be being overdiagnosed by clinicians, particularly in those patients presenting with depression.[3]

Bipolar disorder is the sixth most disabling condition across the whole of medicine, and its impact on affected individuals, and those close to them, is profound.[4] Disrupted relationships are common among those with bipolar disorder, rates of unemployment are high, achievement of career aspirations may be significantly hampered and many are forced onto government benefits. Additionally, mortality rates are substantially increased, mainly due to higher rates of cardiovascular and cerebrovascular disease, diabetes and obesity.[5] At least a quarter of affected individuals will

IN SUMMARY

- **Patients with bipolar disorder spend more of their lives in depressed than elevated mood. The marked disability and high suicide rates linked to bipolar disorder are associated with these depressive episodes.**
- **There is concern that bipolar disorder, and particularly bipolar II disorder, may be becoming overdiagnosed.**
- **Patients with bipolar disorder that is not severe or is very treatment-responsive can be managed by GPs, with psychiatrists providing occasional clinical review and 'back-up' when complications or major recurrences occur.**
- **There is evidence for the use in acute bipolar depression of lamotrigine, lithium, olanzapine (particularly in conjunction with fluoxetine) and quetiapine.**
- **Definite preventive effects against bipolar depression have been demonstrated for lamotrigine, lithium, olanzapine and quetiapine (in conjunction with lithium and sodium valproate).**
- **Although evidence is conflicting regarding the efficacy of antidepressants in bipolar depression and their tendency to induce mania or rapid cycling, the authors consider they have a valid role when they are used in conjunction with appropriate preventive therapy (i.e. mood stabilisers).**
- **Cognitive behavioural therapy, psychoeducation and interpersonal and social rhythms therapy have been shown to be of value in bipolar depression.**

attempt suicide on one or more occasions, and suicide rates are greatly increased compared with the general population.[6]

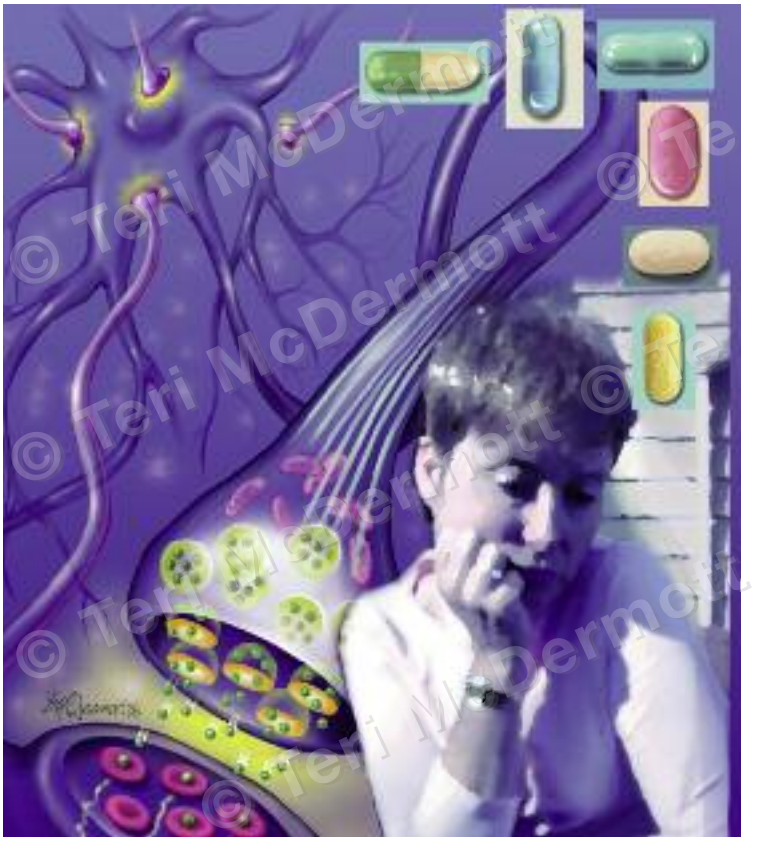
The marked disability and mortality in individuals with bipolar disorder mean that health practitioners should be on the alert for the condition so it can be diagnosed early and an appropriate ongoing management strategy can be implemented. It is a highly recurrent condition for the vast majority of patients, and because it usually initially presents in late adolescence or early adulthood, the potential for long-lasting damage to many aspects of day-to-day functioning is considerable.

The care of patients with mental health conditions is now increasingly being shared between the primary and secondary care sectors. Bipolar disorder is a complex mental illness and, unlike with conditions such as depression, anxiety and substance use, the average GP would treat relatively few patients with bipolar disorder over a professional career. It is the authors' opinion that a psychiatrist should assess most patients with bipolar disorder at least once, initially early in the course of their illness, and make recommendations for appropriate pharmacological and psychological treatments.

Episodes of acute mania are medical emergencies and affected patients should, when possible, be referred urgently to a psychiatrist or community mental health team. The ongoing care of patients with severe and/or markedly recurrent illness is probably best managed in the mental health sector. Those patients with less severe or very treatment-responsive illness are probably best cared for primarily by the GP, with the psychiatrist providing occasional clinical review and 'back-up' when complications or major recurrences occur.

This article provides an update on the diagnosis and management (acute and preventive) of the depressive phase of bipolar disorder, bipolar depression. A previously published article (in the August 2009 issue of *Medicine Today*) considers the manic phase of the condition, and future articles will focus on the distinguishing of bipolar depression from unipolar depression and maintenance therapy for bipolar disorder.[7]

Bipolar disorder: depression



Bipolar disorder is a highly recurrent condition for most patients and usually first presents in late adolescence or early adulthood. Patients with the condition have marked disability and mortality, and also increased rates of suicide compared with the general population.

Clinical presentation

Patients with bipolar disorder may have distinct periods of mania or hypomania and of bipolar depression or may have concurrent manic/hypomanic and depressed symptoms (mixed episodes, also known as dysphoric mania). Bipolar disorder is usually categorised into types I and II: bipolar I disorder is diagnosed if the patient has had at least one episode of mania, and bipolar II disorder if there have only been hypomanic and depressive episodes. Individuals with bipolar I disorder usually also have major depressive episodes but a small proportion (about 5%) will only experience mania.

Depression is more likely to be the first presentation of bipolar disorder than is mania or hypomania. Furthermore, although mania and

Table 1. Medications demonstrated to be effective in bipolar depression*

Acute treatment

- Antidepressants (in conjunction with a long-term preventive medication) – e.g. SSRIs, SNRIs
- Lamotrigine
- Lithium
- Olanzapine (particularly in conjunction with fluoxetine)
- Quetiapine

Long-term preventive treatment†

- Lamotrigine‡
- Lithium
- Olanzapine
- Quetiapine (in conjunction with lithium or sodium valproate)

* Demonstrated in randomised controlled trials to be effective.

† Although carbamazepine and sodium valproate have not been demonstrated to be effective in long-term placebo-controlled trials for the prevention of bipolar depression, widespread clinical experience would suggest that they are effective.

‡ Lamotrigine prevents both manic and depressive episodes in bipolar disorder but has a much stronger effect against depressive episodes.

ABBREVIATIONS: SNRIs = serotonin and noradrenaline reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

hypomania are the hallmark diagnostic characteristics, depression is the most common experience of the illness for most patients over their life. Those patients with bipolar I disorder report three times as many days in depression than in mania or hypomania, while those with bipolar II disorder have 37 depressed days for every day hypomanic.

The suicide rate is high in patients with bipolar disorder – at over 100 cases per 100,000 person years, it is at least 15 times the rate in the general population. The suicides most often occur during periods of depression. Overall, suicidal thoughts and attempts are more common in bipolar-associated depression than in unipolar depression, occurring at about twice the rate.[8]

There is now a growing recognition that certain clinical features are more common in bipolar depression than unipolar depression, and vice versa.[9] In particular, patients with bipolar depression are more likely to manifest psychomotor retardation, hypersomnia, hyperphagia and psychosis. Also, the first presentation of depression is earlier in those with bipolar disorder than in those who do not have the condition, and depressive episodes tend to be both shorter and more likely to recur.

These differences between bipolar and unipolar depression are useful to take into account when making treatment decisions for certain depressed patients. These patients include those with an ambiguous past history of manic or hypomanic episodes, 'unipolar depressed' patients with a family history of bipolar disorder, and young patients presenting only with recurrent depressive episodes and in whom it is unclear whether this represents unipolar depression or a first presentation of bipolar disorder.

Many patients also have ongoing mild 'subsyndromal' depressive symptoms between the frank major episodes of mania and depression. These mild depressive symptoms contribute much of the disability due to bipolar disorder.

Comorbid conditions

It has become increasingly apparent that comorbidity of bipolar disorder with anxiety disorders and substance abuse is common.[8] About 50% of patients with bipolar disorder have a concurrent anxiety condition, with panic disorder, generalised anxiety disorder and social phobia being the most common forms; and about 40% have a concurrent substance use disorder (alcohol or drugs).

Underdiagnosis of bipolar disorder

The most common misdiagnoses for patients with 'true' bipolar disorder are schizophrenia (particularly in men) and unipolar depression (particularly in women). The misdiagnosis of schizophrenia probably reflects similarities between the psychotic features of acute mania and paranoid schizophrenia. Unipolar depression is more likely to be misdiagnosed when past episodes of hypomania or mania are not actively explored in individuals presenting with depression.

Other common misdiagnoses are anxiety and substance abuse, perhaps reflecting a lack of appreciation that these disorders frequently coexist with bipolar disorder. Sometimes patients are misdiagnosed with personality disorders, particularly borderline and antisocial types.

Overdiagnosis of bipolar disorder

As mentioned earlier, there is concern that bipolar disorder, and particularly bipolar II disorder, may be becoming overdiagnosed, particularly in those patients with unipolar depression or borderline personality disorder.[3] Some authorities recommend diagnosing hypomania even for brief periods of elevated mood (i.e. of only hours in duration), rather than the generally used criterion of hypomania lasting at least two to four days.[7] Such a diagnostic shift risks either labelling normal exuberance and enthusiasm as pathological mood disturbance, or misconstruing the mood instability common in those with borderline personality traits or disorder.

This is not a mere esoteric academic debate. Overdiagnosis could mean inappropriate and excessive use of 'mood stabilising' therapies, with consequent insufficient attention paid to the psychological aspects of unipolar depression or personality disorder.

Treatment of bipolar depression

Medications

Bipolar disorder is a very biological condition, with strong genetic roots (heritable factors account for 70 to 85% of the cause), and it is therefore not surprising

continued

Table 2. TGA and PBS status of medications used in patients with bipolar depression

Drug*	Acute treatment of bipolar depression		Preventive treatment of bipolar depression	
	TGA approved indication	PBS listed	TGA approved indication	PBS listed
Antidepressants (e.g. SSRIs, SNRIs)†	No	No	No	No
Carbamazepine	No	No	Yes‡	Yes‡
Lamotrigine	No	No	No	No
Lithium	Yes	Yes	Yes	Yes
Olanzapine	No	No	Yes§	Yes§
Quetiapine	Yes	No	Yes (adjunctive therapy, with lithium or sodium valproate)§	Yes (adjunctive therapy, with lithium or sodium valproate)§
Sodium valproate	No	No	No	No

* Lamotrigine, lithium, olanzapine and quetiapine have been demonstrated in randomised controlled trials to be effective in bipolar depression. Carbamazepine and sodium valproate have not been demonstrated to be effective in long-term placebo-controlled trials for the prevention of bipolar depression but widespread clinical experience suggests that they are effective.

† There is currently substantial controversy about the role of antidepressants in the treatment of bipolar depression. They may be considered to be of use, as long as they are used in conjunction with a long-term preventive therapy (i.e. mood stabilisers).

‡ For maintenance treatment of bipolar affective disorder.

§ For prevention of manic, depressive or mixed episode recurrence in bipolar I disorder.

ABBREVIATIONS: SNRIs = serotonin and noradrenaline reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

that the centrepiece of treatment is pharmacological. A wide range of medications has been shown in randomised controlled trials to be effective for this condition. Those of value in the acute and preventive treatment of bipolar depression are listed in Table 1, and the current status of TGA approval and PBS listing of these drugs for these indications is given in Table 2.

Further details on pharmacological options for the treatment of depressive and manic episodes of bipolar disorder, and also of mixed episodes and rapid cycling bipolar disorder, can be obtained from the Royal Australian and New Zealand College of Psychiatrists' clinical practice guidelines for the treatment of bipolar disorder (*Bipolar Disorder Clinical Version*, available in pdf format from the College) and *Therapeutic Guidelines: Psychotropic, Version* 6.[10,11]

Acute treatment

There is currently substantial controversy about the role of antidepressants in the management of bipolar depression. The evidence is conflicting regarding both their efficacy and their tendency to induce switches into mania or rapid cycling (four or more episodes of mania or hypomania and/or depression in a 12-month period).

It is the authors' contention from both clinical experience and reading of the scientific literature that there is a valid role for antidepressants in bipolar depression, as long as they are used in conjunction with appropriate preventive therapy (i.e. mood stabilisers). Although antidepressants may induce manic episodes or a rapid-cycling pattern, it would appear that the likelihood of this is not as high as previously suggested, particularly for the selective serotonin reuptake inhibitor (SSRI) antidepressants. The tricyclic antidepressants, the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine and the older monoamine oxidase inhibitors such as phenelzine and tranylcypromine appear to be more likely to precipitate mania than the SSRIs. At present it is not known if the SNRIs desvenlafaxine and duloxetine have the same effect as venlafaxine, although it would be surprising if this was not the case.

There is growing evidence from randomised controlled trials for the role of some of the second-generation (or atypical) antipsychotics and the antiepileptic agent lamotrigine in the acute treatment of bipolar depression. Currently there is support for the use of quetiapine, olanzapine (particularly in conjunction with the SSRI fluoxetine) and lamotrigine. With regard to lamotrigine, a recent meta-analysis has confirmed a positive effect, albeit weak, in acute bipolar depression. Additionally, there is an older literature supporting efficacy of lithium in this context.

It should also be noted that electroconvulsive therapy is an extremely effective and sometimes life-saving treatment for the small proportion of patients with bipolar depression who do not respond to medications.

Preventive (maintenance) treatment of bipolar depression

Medications with broad prophylactic efficacy for bipolar disorder include lithium, sodium valproate, carbamazepine, olanzapine, quetiapine, lamotrigine and aripiprazole. Definite preventive effects against bipolar depression have been demonstrated only for lamotrigine, olanzapine, quetiapine (in conjunction with lithium or sodium valproate) and lithium. Lamotrigine has a much stronger preventive effect against depressive episodes than

it has against manic episodes, whereas lithium has a stronger preventive effect against manic episodes than against depressive episodes.

Psychological therapies

There are major psychological issues relevant to bipolar disorder. Manic and depressive episodes are frequently triggered by acute stresses or changes in daily patterns or rhythms (such as sleep–wake cycles). Furthermore, there are considerable difficulties for most patients in adjusting psychologically to living with a major mental illness and in coping with the ramifications of their behaviour, especially during episodes of mania.

The development of focused psychological therapies for the acute or preventive treatment of bipolar depression has been a major advance in the management of this condition in recent years, as it has also for mania.[12,13] These treatments are not alternatives to medications; rather, they should be used in conjunction with pharmacotherapy. Generally, they are most effective when initiated during periods of wellness, as a means of reducing the likelihood of future relapse of depression. The psychological therapies demonstrated in randomised controlled trials to be effective in patients with bipolar depression are listed in Table 3.

The major areas of focus in the psychological treatment of bipolar depression have been on:

- education of the patient and his or her family about the condition and its treatment
- cognitive behavioural therapy dealing with symptoms and the impact on the individual of having this illness – for example, identifying triggers to depressive episodes and planning how to minimise or avoid them, accurately labelling emotions, identifying thoughts and reframing them into more positive rational responses, and dealing with adjustment/self-esteem issues and long-term vulnerabilities

Table 3. Psychotherapies demonstrated to be effective in bipolar depression*

- Cognitive behavioural therapy
- Psychoeducation
- Interpersonal and social rhythms therapy

* Demonstrated to be effective in randomised controlled trials.

Table 4. Recommended monitoring of medications used in patients with bipolar disorder

Drug	Serum concentration of drug	Liver function tests	Full blood count	Other
Carbamazepine	Every three to six months; aim for 17 to 50 µmol/L	Every three to six months; to exclude hepatotoxicity	Every three to six months; to exclude aplastic anaemia and other haematological dyscrasias	Electrolytes – every three to six months; to exclude hyponatraemia
Lamotrigine	No utility in serum level monitoring as no apparent relation between serum concentration and clinical efficacy	–	–	No regular testing necessary
Lithium	Every three to six months for patients on regular dosage; aim for 0.6 to 0.8 mmol/L in acute depression and maintenance therapies and 0.8 to 1.2 mmol/L in acute mania therapy	–	–	TSH and electrolytes/urea/creatinine/eGFR – every six to 12 months; to exclude hypothyroidism and declining renal function
Second-generation antipsychotics – e.g. olanzapine	No target levels	–	–	Blood glucose levels and serum lipids – every six months; to exclude diabetes and hyperlipidaemias
Sodium valproate	Every three months; aim for 300 to 700 µmol/L	Every three to six months; to exclude hepatotoxicity	Every three to six months; to exclude thrombocytopenia	–

ABBREVIATIONS: eGFR = estimated glomerular filtration rate; TSH = thyroid-stimulating hormone.

Sources of information on bipolar disorder for patients, families and friends

Books

Berk L, Berk M, Castle D, Lauder S. Living with bipolar: a guide to understanding and managing the disorder. Sydney: Allen & Unwin; 2008.

Eyers K, Parker G. Mastering bipolar disorder: an insider's guide to managing mood swings and finding balance. Sydney: Allen & Unwin; 2008.

Rowe P, Rowe J. The best of times, the worst of times: our family's journey with bipolar. Sydney: Allen & Unwin; 2005.

Russell S. A lifelong journey: staying well with manic–depression/bipolar disorder. Melbourne: Michelle Anderson Publishing; 2005.

DVDs

Manic–depressive illness: a guide to living with it. Monkey See Productions (http://www.monkeysee.com.au).

Troubled minds: the lithium revolution. SBS Productions/Film Australia. (Available for purchase by educational institutions from Enhance TV, at http://www.enhancetv.com.au.)

Websites

Beyondblue: The National Depression Initiative – http://www.beyondblue.org.au

Black Dog Institute – http://www.blackdoginstitute.org.au

- interpersonal and social rhythms therapy – teaches patients to be more effective in handling relationships and to make graded lifestyle changes to increase stability, and highlights the importance of routine and sleep.

Any psychological therapy should also address the presence of comorbid conditions such as anxiety or substance use disorders.

Specific issues for management in the general practice setting

Roles of GPs, psychiatrists and psychologists

Patients with less severe or very treatment-responsive bipolar disorder may be managed primarily by the GP, with the psychiatrist providing occasional clinical review and 'back-up' when complications or major recurrences occur.

Patients and all the professionals involved in their care can benefit from the use of management plans. As these plans are developed, they need to involve the GP, psychiatrist, psychologist (if relevant) and patient. Such plans should provide specific strategies to follow should manic or depressive relapse occur, and it can be helpful if they include agreed guidelines for contacting relations or friends, and the circumstances that should precipitate involuntary intervention during a manic relapse with loss of insight. After consultation, the plan should be distributed to all the health professionals involved in the patient's care, the patient and his or her carers or family. Any major change in treatment is probably best undertaken after review by the specialist.

With the advent in recent years of the Commonwealth Better Access to Mental Health Care program, which has provided Medicare items for psychological services for people with mental health disorders, the previous financial hurdles to accessing evidence-based psychological interventions from skilled clinical psychologists no longer exist.

Poor adherence with treatment

Poor adherence with medications is common in patients with bipolar disorder. Rates of nonadherence of up to 50% are frequently reported for both bipolar I and bipolar II disorders. These high rates mainly reflect the difficulty most patients have in accepting the diagnosis and the

need for treatment. Other issues include particular side effects of treatment (such as weight gain, tremor, subtle effects on co-ordination and an attenuation of the normal emotional range) and a yearning for the 'lost pleasures' of mania.

The practitioner should address poor adherence, openly exploring relevant issues with the patient and devising strategies to deal with these, such as reducing medication dosage to reduce side effects. A critical issue in enhancing patient engagement in therapy and adherence to treatment is educating and informing the patient and his or her family about bipolar disorder. There are now many sources of quality information on this condition, some of which are detailed in the box on page 24.

Monitoring of physical status and medications

Premature mortality, largely due to cardiovascular and cerebrovascular disease, has recently been recognised in patients with bipolar disorder and the physical status of such patients should therefore be monitored regularly (at least annually). Particular attention should be given to monitoring lipid levels (including cholesterol) in patients aged over 40 years, blood glucose levels, weight, smoking status, alcohol use and blood pressure. Exercise participation should also be considered.

Recommendations on the frequency of blood monitoring for patients taking certain medications are given in Table 4.

Conclusion

Patients with bipolar disorder spend more of their lives in depressed than elevated mood. Although the chaos and disruption of manic episodes leads to major concern for friends and relatives, the marked disability and the high suicide rates linked to the disorder are associated with the depressive episodes and the ongoing mild depressive symptoms between the frank major episodes of mania and depression.

Bipolar depression is often complex to diagnose and treat but effective management can make a profound difference to the lives of both sufferers and their families. GPs, psychiatrists and psychologists are all critical players in this process, and patients with less severe or very treatment-responsive bipolar disorder may be managed by the GP, with the psychiatrist providing occasional clinical review and support when complications or major recurrences occur. MT

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Further reading

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Joyce PR, Mitchell PB, eds. Mood disorders: recognition and treatment. Sydney: UNSW Press; 2005.

COMPETING INTERESTS: In the past three years, Professor Mitchell has received remuneration for advisory board membership from Eli Lilly and AstraZeneca; and consultative fees or lecture honoraria from AstraZeneca, Eli Lilly, Janssen-Cilag and Lundbeck. He is not currently a member of any pharmaceutical company advisory board. Dr Gould: None.