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Bipolar disorder

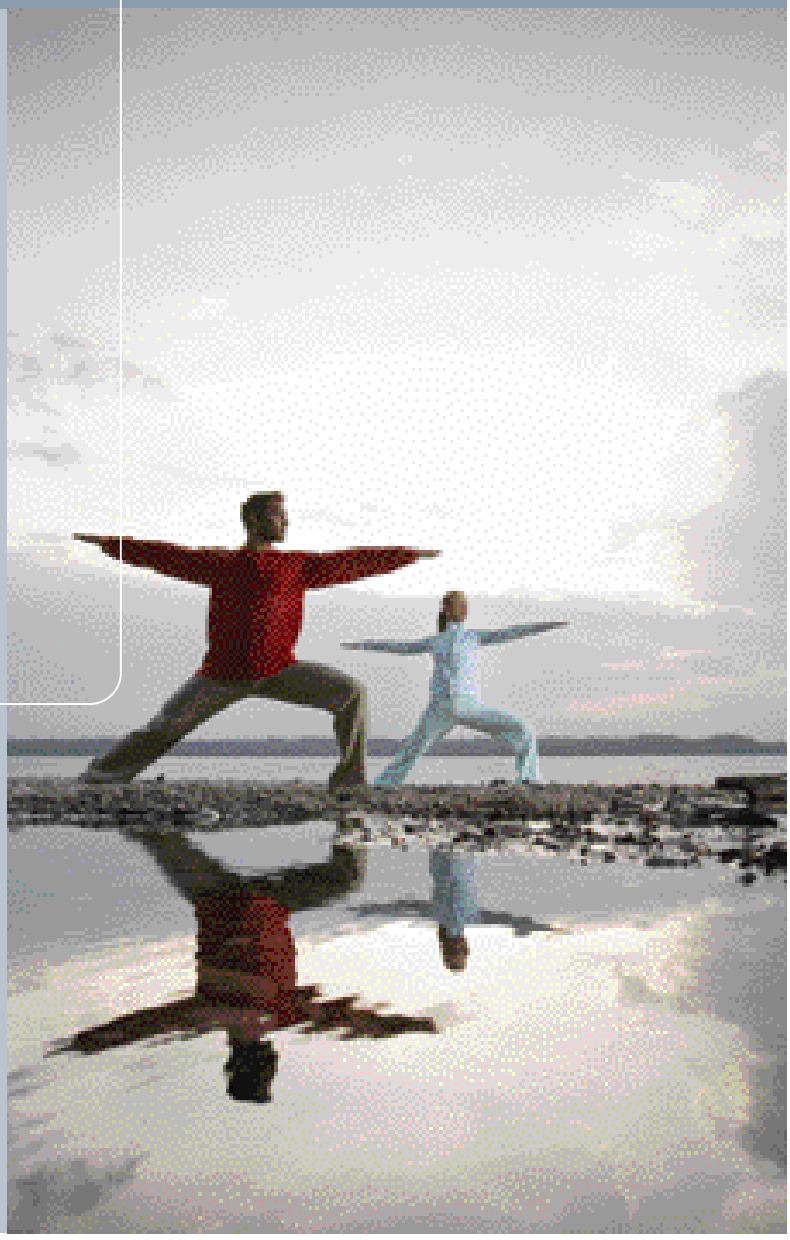
Reprint Collection

Focus on depression

Is it possible to distinguish bipolar depression from unipolar depression?

Focus on mania

Focus on maintenance



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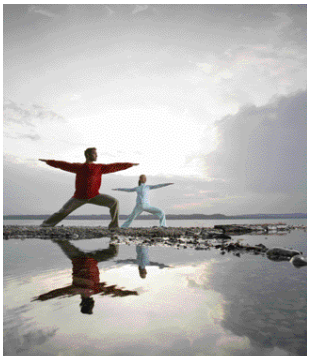

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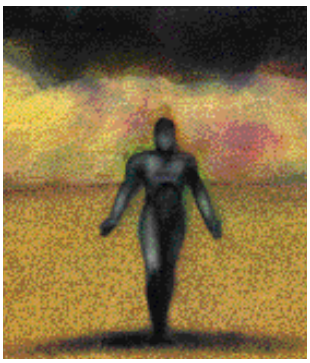

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Bipolar disorder
Focus on depression

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.

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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]

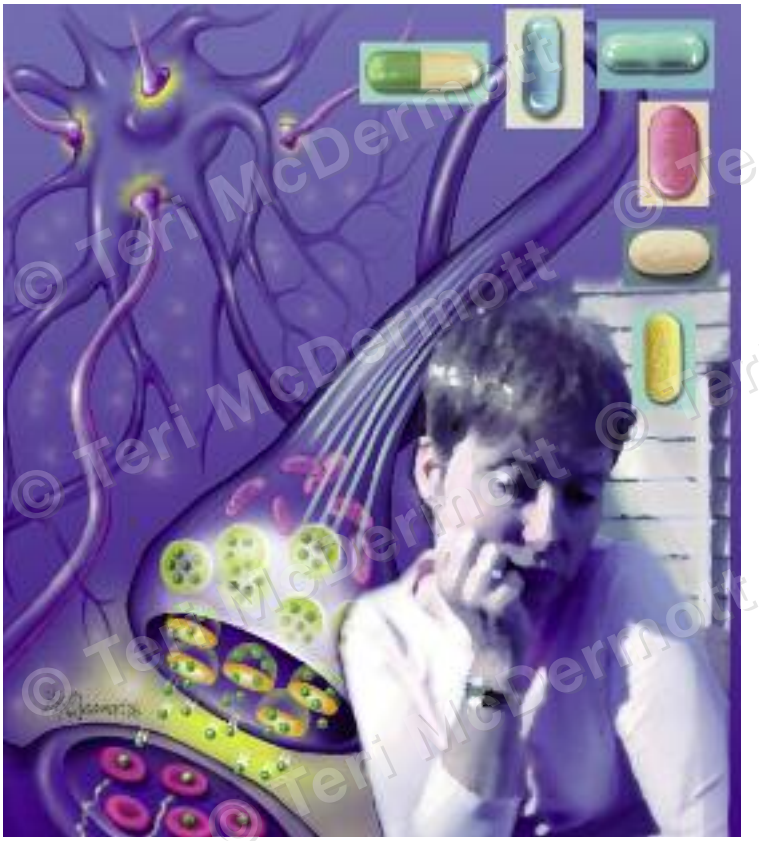
The marked disability and mortality in individuals with bipolar disorder mean that health practitioners should be on the alert for the condition so it can be diagnosed early and an appropriate ongoing management strategy can be implemented. It is a highly recurrent condition for the vast majority of 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. Other articles in this supplement consider the manic phase of the condition, 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

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]

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 (monotherapy and 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.

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

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.

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

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.

more positive rational responses, and dealing with adjustment/self-esteem issues and long-term vulnerabilities
- 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 this page.

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.

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

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.

Is it possible to distinguish bipolar depression from unipolar depression?

Clinical features can help determine whether a patient's depressive episode is more likely to be unipolar depression or a presentation of bipolar disorder. The likely diagnosis influences the treatment decisions made.

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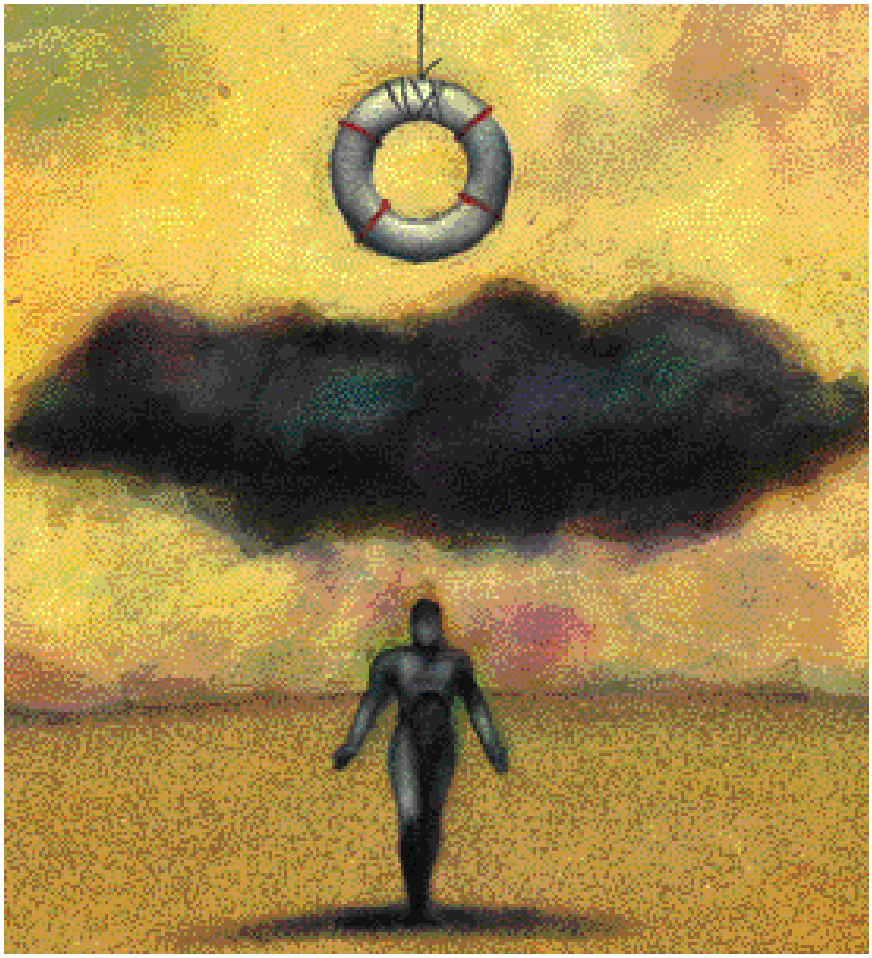
The hallmark characteristic of bipolar disorder is pathologically elevated mood but depression is now recognised to comprise the predominant affect over time, and to make a major contribution to the disability related to this condition.

A depressive episode is the first manifestation of bipolar disorder in at least half of patients with the condition and most studies report that the majority of patients first present to medical practitioners in this phase of the illness. There are currently no accepted diagnostic criteria for bipolar depression for either research or clinical purposes, and depressed patients with bipolar disorder are often misdiagnosed as having unipolar depression (major depressive disorder). There is, however, growing recognition that there are clinical features that are more common in bipolar depression than in unipolar depression, and vice versa.[1-3] These features have the potential for use in determining whether a depression is more likely to be unipolar depression or a presentation of bipolar disorder. This is important to know because the treatments of unipolar depression and bipolar depression differ, with treatment of bipolar depression being complex and involving the use of various combinations of antipsychotics, lithium, antidepressants

IN SUMMARY

- **Knowing whether a depression is more likely to be unipolar depression or a presentation of bipolar disorder is important because the treatments of unipolar depression and bipolar depression differ.**
- **There are currently no accepted diagnostic criteria for bipolar depression and depressed patients with bipolar disorder are often misdiagnosed as having unipolar depression (major depressive disorder).**
- **Diagnostic uncertainty is likely in depressed patients with ambiguous past histories of hypomania or mania or family histories of bipolar disorder and in young patients presenting only with recurrent depressive episodes.**
- **Certain clinical features (signs or symptoms and various characteristics of illness course and family history) are more common in bipolar depression than in unipolar depression, and vice versa.**
- **A 'probabilistic' approach is suggested to the diagnosis of bipolar I depression in a patient with a major depressive episode and no clear prior episodes of hypomania or mania, based on the differential likelihood of specific depressive clinical features being experienced.**



and other medications rather than antidepressants alone. Also, suicidal thoughts and attempts are more common in patients with bipolar disorder-associated depression than in patients with unipolar depression, occurring at about twice the rate. [5]

Clinical scenarios in which there may be diagnostic uncertainty include depressed patients with an ambiguous past history of episodes of hypomania or mania or a family history of bipolar disorder and young patients presenting only with recurrent depressive episodes.

This article presents a suggested 'probabilistic' approach to the diagnosis of bipolar I depression based on the differential likelihood of a patient experiencing various clinical features.[6] Although the immediate definitive diagnosis of bipolar I disorder on the basis of this approach is not recommended, practitioners are encouraged to consider such a diagnosis, particularly if patients develop hypomanic or manic episodes when taking antidepressants, or respond poorly to standard antidepressant therapies. The manic and depressive phases of bipolar disorder and maintenance therapy for the condition are considered in separate articles in this supplement.[4,7]

Issues in diagnosis

Patients with bipolar disorder report that delays in diagnosis and incorrect diagnoses are common. A study of participants in a bipolar disorder support group revealed that more than one-third of these patients had sought professional help within a year of the onset of symptoms, but 69% were misdiagnosed, most frequently with unipolar depression.[8] Other frequently reported misdiagnoses were anxiety disorder, schizophrenia, borderline or antisocial personality disorder, alcohol or substance misuse and/or dependence, and schizoaffective disorder. Over a third of the patients who were misdiagnosed waited 10 years or more before receiving an accurate diagnosis. Notably, respondents rarely reported all their manic symptoms to a doctor; for example, less than one-third admitted symptoms such as reckless behaviour, excessive spending and increased sexual interest or activity.

The results of the described study would suggest two reasons for the original common 'misdiagnosis' of unipolar depression: firstly, many patients with bipolar disorder might not have experienced an episode of hypomania or mania by the time of 'misdiagnosis'; and secondly, for some patients with bipolar disorder, the occurrence of hypomanic or manic symptoms was either not elicited by clinicians or not acknowledged by the patients. Mania and hypomania may have overt and subtle presentations, and some patients with hypomania may not view them as abnormal, rather perhaps perceiving them as normal or even desirable (especially the feelings of being energised and needing less sleep).[7]

Clinical differences between bipolar depression and unipolar depression

The age of onset of the first depressive episode and the numbers of depressive episodes experienced are generally different for patients with bipolar depression and those with unipolar depression. The age of onset of the first depressive episode in bipolar disorder has been found in many studies to be earlier than that found in unipolar depression, and patients with bipolar disorder tend to experience more depressive episodes over a lifetime than those with unipolar depression. There does not, however, appear to be any

significant difference in the severities of the depressions.

Bipolar I depression versus unipolar depression

There have now been a relatively large number of studies comparing the clinical characteristics of bipolar I depression (depression occurring during bipolar I disorder) and unipolar depression.[6] Features with potential clinical utility for diagnosing bipolar depression have been suggested by various studies, including Australian research reports such as those of Mitchell and colleagues and Parker and colleagues.[1,9] These features are:

- signs of psychomotor retardation
- melancholic symptoms such as worthlessness, unvarying mood and marked anhedonia
- 'atypical' depressive symptoms such as hypersomnia and leaden paralysis
- a past history of psychotic depression
- the absence of anxiety, initial insomnia, tearfulness and tendency to blame others.

Mitchell and colleagues acknowledged that these features reflected differing group means and were not pathognomonic of bipolar depression.[1]

The studies of Mitchell and Parker suggest that bipolar I depression is characterised by an admixture of melancholic, atypical and (less commonly) psychotic features.[1,9] This pattern suggests that the clinical presentation of bipolar I depression is distinct from the 'pure' atypical depression of, for example, seasonal affective disorder or the 'pure' melancholic presentation of some patients with severe unipolar depression.

Bipolar II depression versus unipolar depression

There have been relatively few studies of bipolar II depression (depression in bipolar II disorder). In one large study, the Italian researcher Benazzi reported on a comparison of the symptoms of depression in 379 outpatients with bipolar II depression and 271 outpatients with unipolar depression.[10] The features found in this study to be more common in the patients with bipolar II depression were weight gain, increased eating, hypersomnia, psychomotor agitation, worthlessness and a diminished ability to concentrate.

This small literature suggests that patients with bipolar II depression, like patients with bipolar I depression, manifest with 'atypical' features such as increased sleep and appetite, but unlike patients with bipolar I depression, do not have psychomotor slowing (rather they may be more likely to be agitated).

Table. A probabilistic approach to the diagnosis of bipolar I depression*

Clinical features more common with bipolar I depression	Clinical features more common with unipolar depression
Symptoms and signs	
Increased sleep and/or increased daytime napping	Initial insomnia/reduced sleep
Increased appetite and/or weight gain	Decrease appetite and/or weight loss
'Leaden paralysis' (sensation of heavy limbs)	–
Psychomotor retardation (physical and mental slowing)	Normal or increased activity levels
Psychotic features and/or pathologically excessive guilt	Somatic / hypochondriacal complaints
Lability of mood, manic symptoms	–
Course of illness	
Early onset of first depression	Later onset of first depression
Multiple prior episodes of depression	Long duration of episodes
Family history	
Positive family history of bipolar disorder	Negative family history of bipolar disorder

* Premised on a current major depressive episode in patients with no clear prior episodes of hypomania or mania.

Clinical characteristics of 'converters' from unipolar depression to bipolar disorder

Another means of defining the characteristics of bipolar depression is by identifying apparent 'unipolar' patients who on long-term follow up 'convert' to bipolar I or II disorder. Angst and Preisig reported that about 1% of patients with unipolar depression initially identified while hospitalised convert from depression to bipolar I disorder each year.[11]

Akiskal and colleagues reported that the predictors of a later emergence of bipolar I disorder in patients with unipolar depression were onset of depression prior to age 25 years, hypersomnia and motor retardation, a family history of bipolar disorder, medication-precipitated manic episodes and postpartum depression.[12] The NIMH Collaborative Programme on the Psychobiology of Depression 11-year prospective follow up found that 4% of participants 'converted' to bipolar I disorder and 9% to bipolar II disorder.[13] Those who switched to bipolar I disorder were

more likely to have been psychotic or hospitalised at the index depressive assessment, compared with those who continued to have a diagnosis of major depressive disorder.[14] Mood lability in the depressive state was the most specific predictor of switching to bipolar II disorder.[13]

A proposed probabilistic approach to the diagnosis of bipolar I disorder

It is apparent that there are no pathognomonic characteristics of bipolar depression compared with unipolar depression. There are, however, replicated findings of clinical characteristics that are more common in patients with bipolar I depression than in those with unipolar depression, and vice versa, or that are observed in patients with unipolar depression who 'convert' to bipolar I disorder over time.

Drawing on the previously mentioned studies comparing the clinical characteristics of bipolar I depression and unipolar depression, the clinical features that have been most commonly and consistently reported to be more common in patients with bipolar I depression (or in unipolar-depressed 'converters' to bipolar I disorder) are:[6]

- course of illness: earlier age of onset, shorter duration of episodes and more prior episodes
- symptomatology: worthlessness, low self-esteem, social withdrawal, hypersomnia, hyperphagia/weight gain, 'atypical features' (such as leaden paralysis), lability of mood and psychotic features
- mental state signs: psychomotor retardation (lower activity levels)
- family history: positive for bipolar disorder.

Some other features of depression said to be indicative of the future development of bipolar disorder include induction of hypomania or mixed states by antidepressants, abrupt onset of depression, seasonal pattern, mixed presentations with hypomanic symptoms and postnatal onset.

Conversely, those clinical features that have been most commonly and consistently reported to be more common in patients with unipolar depression are:[6]

- course of illness: later age of onset, longer duration of episodes and fewer prior episodes
- symptomatology: initial insomnia, appetite loss and/or weight loss, and somatic complaints
- mental state signs: normal or higher activity levels
- family history: negative for bipolar disorder.

Rather than proposing a categorical diagnostic distinction between bipolar I depression and unipolar depression, we have recommended a probabilistic (or likelihood) approach to the distinction.[4] There is no 'point of rarity' between the two presentations, but rather a differential likelihood of experiencing the symptoms and signs of depression listed above. As some of the features (such as worthlessness, low self-esteem and social withdrawal) are common in depression, we have considered these to be of low diagnostic specificity and have therefore not included these in the final probabilistic approach to the diagnosis of bipolar depression.

The suggested criteria for this probabilistic approach are detailed in the Table. We have utilised specific depressive clinical signs or symptoms (as well as characteristics of illness course and family history), rather than proposing a requirement for particular syndromal presentations of depression such as 'atypical' or 'melancholic' depression. This table is premised on a current major depressive episode in patients with no clear prior episodes of hypomania or mania. We specify features that indicate the greater likelihood of bipolar I depression or unipolar depression, respectively.

Conclusion

A probabilistic approach has been developed to assist clinicians in identifying depressed patients who have an increased likelihood of going on to develop bipolar I disorder. This approach is based on the differential likelihood of specific depressive clinical features being experienced by patients. As yet, there have been no formal treatment studies using the approach. At present, we do not recommend that clinicians immediately diagnose and treat depressed patients with these features as definitely having bipolar I disorder. However, we commend practitioners to seriously consider this possibility for such individuals as treatment progresses, particularly if patients develop hypomanic or manic episodes when taking antidepressants or respond poorly to standard antidepressant therapies. MT

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Bipolar disorder
Focus on mania

An episode of acute mania is a medical emergency. The GP can play a pivotal role in its early identification and prevention, and may need to initiate treatment if there are limited local mental health services.

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In Australia, bipolar disorder afflicts 1.3% of the population at some stage of their life, and 0.9% in any 12-month period.[1] The peak onset of illness is usually in early adult life (late adolescence to late 20s) and there is a strong genetic basis.

The impact of bipolar disorder on affected individuals, and those close to them, is profound; this is the sixth most disabling condition across the whole of medicine.[2] Disrupted relationships are common, rates of unemployment are high (at the least, achievement of career aspirations may be significantly hampered) and many are forced onto government benefits. Furthermore, mortality rates are substantially increased, mainly due to higher rates of cardiovascular and cerebrovascular disease, diabetes and obesity.[3] At least a quarter of affected individuals will attempt suicide on one or more occasions, and at over 100 cases per 100,000 person years, suicide rates are greatly increased compared with the general population.[4]

The marked disability and mortality in individuals with bipolar disorder mean that GPs need to be on the alert for early diagnosis and the implementation of an appropriate ongoing management strategy. As bipolar disorder usually initially presents in late adolescence or early adulthood, the potential for long-lasting damage to many aspects of day-to-day functioning is profound. For

IN SUMMARY

- **An episode of acute mania is a medical emergency. Insight and judgement are usually impaired early and urgent involuntary hospitalisation under the relevant mental health legislation is frequently required to protect the patient.**
- **GPs have an important role in early identification and prevention of mania, and may need to initiate treatment if there are limited local mental health services.**
- **The two components of the pharmacological management of acute mania are primary treatment of the pathologically elevated mood and short-term containment of any associated behavioural disturbance such as aggression or violence, agitation or over-activity, and disinhibition.**
- **Primary treatment of the pathologically elevated mood is with lithium, sodium valproate, carbamazepine or a second-generation antipsychotic. This treatment will usually be continued for prophylaxis.**
- **Short-term containment of associated behavioural disturbance comprises calming or sedating the patient until their mood stabilises, and usually involves temporary use of supplementary antipsychotics or benzodiazepines.**
- **Psychological therapies have a critical role in preventing relapse into mania and stopping mild elevations of mood progressing to full manic presentations.**

the vast majority of patients, this is a highly recurrent condition.

There is a welcome and increasing interest in shared care between the primary and secondary care sectors for patients with mental health conditions. The authors suggest that a psychiatrist should assess most patients with bipolar disorder at least once, early in the course of their treatment program, with recommendations being made for appropriate pharmacological and psychological treatments. 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.

For those patients with severe and/or markedly recurrent illness, ongoing care is probably best managed in the mental health sector. Those patients with either less severe or very treatment-responsive illness are probably best managed primarily by the GP, with the psychiatrist providing occasional clinical review and 'back-up' when complications or major recurrences occur. However, an episode of acute mania is a medical emergency and requires urgent referral to a psychiatrist and/or community mental health team.

Patients with bipolar disorder may have periods of mania or hypomania and periods of bipolar depression or may have depressive symptoms intertwined with the mania ('mixed episode' or 'dysphoric mania'). The illness is usually categorised into bipolar I and bipolar II types: 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. Comorbidity with substance dependence or abuse is common, occurring in about 50% of subjects.

This article focuses on the management of mania in patients with bipolar disorder. The general principles for managing mania, the medications approved for this presentation and psychological treatments developed for use early in the manic process to prevent relapse are described. The management of depression, the distinguishing of bipolar depression from unipolar depression and maintenance therapy for bipolar disorder are considered in other articles in this supplement.

Table 1. Features of mania, hypomania and mixed episodes

Mania

- Excessively elevated or euphoric and/or irritable mood
- Duration of at least one week
- Characteristic symptoms and behavioural change:
  - inflated sense of own abilities/ capabilities (grandiosity)
  - disinhibition – may manifest as increased libido, increased spending, overly frank comments about others, impaired judgement in work or relationships
  - increased speed of thoughts, increasingly talkative (perhaps associated with 'flight of ideas')
  - increased activity levels and increased subjective energy (occasionally associated with physical agitation)
  - lack of focus, distractibility
  - reduced need for sleep
- Evidence of marked impairment in functioning, with or without psychotic features (delusions, hallucinations), and possibly with hospitalisation

Hypomania

- Excessively elevated or euphoric and/or irritable mood – same as in mania
- Duration of at least two to four days – shorter than in mania
- Characteristic symptoms and behavioural change – same as in mania
- Mood and behaviour distinctly different to normal, but not severely impairing and no psychotic features or hospitalisation – less extreme than in mania

Mixed episodes

- Presentations characterised by concurrent presence of manic or hypomanic symptoms and depressive symptoms
- Usually the manic or hypomanic features predominate
- Sometimes referred to as 'dysphoric mania'

Clinical features and diagnosis

The clinical features of mania are elevated, expansive or irritable mood, accelerated speech, racing thoughts with flight of ideas, increased activity and reduced need for sleep. Patients may develop grandiose ideas, act recklessly (including increased spending) and show increased sexual drive and activity. Symptoms often appear abruptly. Where symptoms are less severe and of shorter duration, the term 'hypomania' is used. The clinical features of mania, hypomania and mixed episodes, based on the formal *DSM-IV-TR* criteria, are compared in Table 1, and broad 'clinical clues' for identifying patients in the manic or hypomanic phase of bipolar disorder are listed in Table 2.

For patients with a first presentation of mania, particularly when the initial onset occurs after the age of 40 years, organic causes such as medications (e.g. corticosteroids or dopaminergic agents for Parkinson's disease), endocrine disorders (e.g. hyperthyroidism) or neurological conditions (e.g. frontal lobe tumours or cerebrovascular disease) should be excluded. In practice, however, such organic aetiologies are very uncommon. In younger first presentations, psychiatric

continued

Table 2. Clinical clues for identifying mania and hypomania[7]

Symptoms and signs include the following behaviours if out of character for the individual:

- Feeling energised and 'wired'
- Excessively seeking stimulation
- Overly driven in pursuit of goals
- Needing less sleep
- Irritable if stopped from carrying out ideas
- Disinhibited and flirtatious
- Offensive or insensitive to the needs of others
- Spending money in an unusual manner or inappropriately
- Indiscreet and disregarding social boundaries
- Having poor self-regulation
- Making excessively creative and grandiose plans
- Having difficulty discussing issues rationally or maturely
- Reporting enhanced sensory experiences

differential diagnoses include schizophrenia, schizoaffective disorder and substance abuse.

General principles in the management of mania

An episode of acute mania is a medical emergency. Patients have the capacity to destroy their reputations, relationships and finances within hours or days. Insight and judgement are usually impaired early, even in the absence of delusions, and urgent involuntary hospitalisation under the relevant mental health legislation is frequently required to protect the patient. However, the decision to admit may be traumatic for the patient and family members, all of whom will need support.

If community or outpatient treatment occurs, it is essential to monitor risky behaviour, such as financial indiscretion or potential harm to others, such as from hazardous driving. A financial power of attorney may be necessary. Outpatient attendance is often erratic, and a legally enforceable community treatment order may be required.

It has been said that patients with acute mania are 'always worse than they seem'. An apparently reasonable level of function during a brief assessment may mask more serious dysfunction. Reports from family and friends should be taken seriously, but interpreted with an understanding of the patient's normal function and the nature of these relationships. Irrespective of whether inpatient or community treatment is required, the occurrence of mania will require urgent referral to a psychiatrist and/or community mental health team.

Manic relapses in patients with established bipolar disorder are often due to poor medication adherence, so serum concentrations of medications should be checked where this is relevant. Other common causes of relapse include substance abuse (particularly that involving cannabis, cocaine or amphetamines), use of antidepressants and stressful life events. If the patient is taking an antidepressant, this should be ceased.

Medications

The two components of the pharmacological management of acute mania are primary treatment of the pathologically elevated mood and short-term containment of any associated behavioural disturbance such as aggression or violence, agitation or overactivity, and disinhibition (see the box on this page).[5]

Primary treatment of the pathologically elevated mood involves the commencement of lithium, sodium valproate, carbamazepine or a second-generation antipsychotic. There is usually a delay of effect of one to two weeks, although some improvement often occurs within the first few days. This treatment will usually be continued for prophylaxis.

Principles of medication treatment of acute mania and hypomania[5]

Primary treatment of the pathologically elevated mood

The following medications are used as mood stabilisers:

- Lithium
- Anticonvulsants: sodium valproate, carbamazepine
- Second-generation antipsychotics: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone

Short-term containment of any associated behavioural disturbance

The following medications are used until the mood becomes stabilised:

- Supplemental antipsychotics (first- or second-generation) – if not already chosen as a mood stabiliser
- Supplemental benzodiazepines

Short-term containment of any associated behavioural disturbance comprises calming or sedating the patient as an interim measure until his or her mood stabilises. It usually involves the temporary use of supplementary antipsychotics (first- or second-generation) or benzodiazepines (e.g. diazepam or clonazepam). The aim should be to gradually withdraw these once the mania settles.

The medications demonstrated to be of value in the acute management of mania are listed in Table 3, and the current status of TGA approval and PBS listing for the treatment of acute mania for these drugs is given in Table 4. Further details on pharmacological options 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 http://www.ranzcp.org/resources/clinical-practice-guidelines.html)

Table 3. Medications demonstrated to be effective in the acute treatment of mania*

Mood stabiliser
- Lithium

Anticonvulsants
- Sodium valproate
- Carbamazepine

First-generation antipsychotics
- Chlorpromazine
- Haloperidol

Second-generation antipsychotics
- Aripiprazole
- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone

* Demonstrated to be effective in randomised controlled trials.

or *Therapeutic Guidelines: Psychotropic*, Version 6.[5,6]

Psychological therapies

There is growing evidence for the benefits of psychological therapies in bipolar disorder. These treatments play a critical role (in conjunction with medications) in either preventing relapse into mania or stopping mild elevations of mood progressing to full manic presentations. However, they are not useful once the patient is in the full manic episode.

Psychological therapies shown to be useful in this role include:[7]

- education about the condition and its treatment
- cognitive behavioural techniques – for example, identifying triggers 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
- interpersonal and social rhythms therapy – teaches patients to be more effective in handling relationships and make graded lifestyle changes to increase stability, and highlights the importance of routine and sleep
- schema-focused cognitive therapy – this is a more lengthy process necessary for some patients whose core beliefs are embedded in feelings of inadequacy, failure or unrelenting standards that continue to drive self-defeating behaviours
- mindfulness meditation
- supportive psychotherapy – this is particularly useful in identifying interpersonal triggers that affect the patient's mood, and may include problem-solving approaches; it is most useful in the maintenance stage of treatment, once the skills of cognitive behavioural therapy have been learned
- exercise, yoga, relaxation therapy and similar 'mind–body' interventions individualised to the needs and lifestyle of the patient (these may also be beneficial in the maintenance stage).

Table 4. TGA and PBS status of medications demonstrated to be effective in acute mania

Drug effective in acute mania*	TGA approved for acute mania	PBS listed for acute mania
Mood stabiliser		
Lithium	Yes	Yes
Anticonvulsants (used to stabilise mood)		
Sodium valproate	Yes	Yes
Carbamazepine	Yes	Yes
First-generation antipsychotics		
Chlorpromazine	Yes	Yes
Haloperidol	Yes	Yes
Second-generation antipsychotics		
Aripiprazole	No	No
Olanzapine	Yes (monotherapy, adjunctive therapy)	No
Quetiapine	Yes (monotherapy, adjunctive therapy)	Yes (monotherapy)
Risperidone	Yes	Yes (adjunctive therapy)
Ziprasidone	Yes (monotherapy, mixed episodes)	Yes (monotherapy, mixed episodes)

* Demonstrated to be effective in randomised controlled trials.

Specific issues for management in the general practice setting

Identification of early warning signs to prevent relapse

Some patients switch into mania rapidly and without warning, losing insight

Table 5. Early warning signs for manic relapse – the relapse profile[7]

- Increasing activities and busyness
- Reduced need for sleep
- Impulsive behaviour
- Speaking in a caustic manner
- Telephoning friends indiscriminately

quickly. A considerable proportion, however, have a 'transitional' phase with early warning signs that begin hours, days or weeks prior to the onset of frank manic symptoms. (Interestingly, early warning signs rarely occur prior to the development of a bipolar depressive episode.) With training, both the patient and his or her family can often identify the behaviour changes in this transitional phase.

Common early warning signs are insomnia, a reduced need for sleep, increased energy and irritability. If such signs can be reliably identified, counteracting strategies can be developed. For example, behavioural means of improving sleep can be instituted, associated stresses (such as relationship or work difficulties) addressed, or medications such as hypnotics or antipsychotics commenced with the intent of aborting progression to a full manic episode. As the GP has a greater awareness of the day-to-day clinical status and life context of the patient, he or she is often in a better situation than the specialist to identify and deal with such early signs.

Other techniques such as the patient completing daily mood charts may assist in identifying early features of a 'slide' into a manic or depressive relapse. Active collaboration with a skilled psychologist will help the GP in designing and carrying out such interventions. More details on identifying these 'early warning signs' and on strategies for preventing progression into a manic relapse are detailed in Tables 5 and 6. Guidance on when to refer the patient to psychological services is provided in Table 7.

There are now a large number of quality information sources on this condition for patients, families and friends, some of which are detailed in the box on page 22.

Confidentiality during mania or hypomania

An issue central to the nature of bipolar disorder is the loss of insight during the course of mania or hypomania. It should be noted that some patients rarely lose insight during hypomania.

The GP must consider as paramount the ongoing welfare of patients as behaviour may be markedly disturbed during episodes. Patients may engage in behaviour with severe future ramifications, such as embarking upon unwise business schemes, spending large amounts of money or becoming aggressive with a real potential of physical harm to others. Despite the patient's protestations at the time, it is imperative for the clinician to intervene in such situations, although this may arouse considerable patient anger or irritation.

It may be necessary to invoke local mental health act legislation to enforce treatment. Sometimes, however, the patient will reluctantly comply with the instructions of the clinician and/or family to avoid involuntary treatment; such a response is more likely where strong prior trust in the doctor–patient relationship has been nurtured. The GP should always be aware that the patient's behaviour in the surgery might appear more normal than that actually occurring in his or her day-to-day life. As a general principle, an account of disturbed or disrupted behaviour by a sensible friend or relative should always be taken seriously if it conflicts with the claims of the patient with mania.

A related and complex issue is what should be communicated to the patient's

Table 6. Strategies for patients to prevent progression into a manic relapse[7]

- Establish a regular routine for eating and sleeping
- Minimise sleep disruption and other stressors and triggers
- Spend nights in your bedroom even if you are not sleeping — lie down and rest as much as you can
- Prioritise and reduce the number of tasks you are involved in
- Modify excessive behaviour — slow down
- Engage in calming activities and be aware of how you are thinking, feeling and behaving
- Carefully follow through the consequences of your actions — consider the costs and benefits
- Delay impulsive actions — if it is still a good idea in a few days time, it might really be a good idea
- Spend time on your own to reduce stimulation, for example by avoiding crowds, busy shops, intense movies and parties
- Find a quiet, restful place to pass the time
- Keep a diary of your moods and reactions
- Reframe your overly inflated thoughts as symptoms
- Recognise if you are getting into destructive situations
- Talk to someone you can trust
- Avoid drinking tea, coffee, cola and other drinks that contain caffeine
- Avoid alcohol, marijuana and other drugs
- See a doctor to review your medications and current state

Table 7. When to refer patients with mania to psychological services[7]

- Patient is having difficulty understanding or accepting the diagnosis
- Medication adherence is less than optimal
- Relapses occur, suggesting the need for symptom management skills to supplement medication
- Patient has unresolved issues or trauma resulting from the phase of the illness or hospitalisation
- Patient has difficulty in adjusting to relationships or work
- Cognitive distortions act to destabilise mood
- Patient has difficulty identifying stressors or triggers leading to relapse
- Patient has sustained feelings of loss of direction or meaning
- Personality difficulties hinder recovery

Table 8. Recommended physical monitoring and testing of patients with bipolar disorder taking mood stabilisers

Monitoring of all patients

At least once a year:*

- Lipid levels, including cholesterol, in patients aged over 40 years
- Plasma glucose levels
- Weight
- Smoking status and alcohol use
- Blood pressure

Monitoring for specific drugs

Lithium

- Serum lithium concentrations – every three to six months for patients on regular dosage; aim for 0.6 to 0.8 mmol/L
- TSH and electrolytes/urea/creatinine/eGFR – every six to 12 months; to exclude hypothyroidism or declining renal function

Carbamazepine

- Serum carbamazepine concentrations – every three to six months; aim for 17 to 50 µmol/L
- Liver function tests – every three to six months; to exclude hepatotoxicity
- Full blood count – every three to six months; to exclude aplastic anaemia and other haematological dyscrasias
- Electrolytes – every three to six months; to exclude hyponatraemia

Sodium valproate

- Serum sodium valproate concentrations – every three months; aim for 300 to 700 µmol/L
- Liver function tests – every three to six months; to exclude hepatotoxicity
- Full blood count – every three to six months; to exclude thrombocytopenia

Second-generation antipsychotics

- Blood sugar levels and serum lipids – every six months; to exclude diabetes and hyperlipidaemias

* As recommended by the UK National Institute of Health and Clinical Excellence[8]

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

family if the manic patient refuses contact with them, or when family members attempt to speak to the practitioner without the patient's approval or awareness. In traditional health legislation, the rights of the patient to privacy are given primacy in these situations. The authors would contend, however, that respect of such 'rights' may not always be appropriate, or in the patient's long-term interest – particularly when the patient lives with the family or the family has ongoing financial or other responsibilities. In such situations, it may be more appropriate to consider the whole family context as 'the patient'. It would, therefore, be wise for clinicians to inform patients early in their contact that if their behaviour is destructive to themselves or others, practitioners involved in their management and family members may need to be notified without their consent if necessary. On the other hand, for those who have been estranged from family for prolonged periods when well, such engagement of the family during illness may be inappropriate. Recognition of the necessity to involve designated 'primary care givers' has been formalised under some state mental health legislations. (Note that mental health legislation differs from state to state.)

For those patients who are prone to spending or borrowing large amounts of money during manic episodes, serious consideration should be given to strategies such as:

- arranging for a power-of-attorney by a family member
- using relevant state bodies to take over the patient's financial affairs
- simple actions for reducing ease of spending large amounts of money such as encouraging the patient to give up the use of credit cards.

Monitoring of physical status and medications

In view of the recent recognition of premature mortality in the bipolar disorder population, largely due to cardiovascular and cerebrovascular disease, the physical status of patients should be monitored regularly (at least annually).

Particular attention should be given to monitoring lipid and glucose levels, as well as weight, smoking status, alcohol use and exercise participation, as listed

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 www.enhancetv.com.au).

Websites

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

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

in Table 8.[8] Recommendations on the frequency of blood monitoring for patients on the various mood stabilising medications are also detailed in this table.

Conclusion

Mania is a medical emergency with drastic consequences for the patient and family if poorly managed. The GP can play a pivotal role in early identification and prevention of the condition and may need to initiate treatment if there are limited local mental health services. MT

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

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Bipolar disorder
Focus on maintenance

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Bipolar disorder is a highly recurrent and potentially disabling disorder, and prevention of recurrence with maintenance therapy is a predominant focus of management. GPs are well placed to provide this long-term care.

Bipolar disorder is a highly recurrent disorder for the majority of affected individuals, and is associated with significant disability and mortality, mainly due to increased rates of cardiovascular and cerebrovascular disease, diabetes and obesity.

Whereas elevated, expansive or irritable mood in mania or hypomania is the hallmark feature of the disorder, the bulk of the disability and most of the time spent in illness are in the depressive phase. Both poles of the disorder tend to be time limited but mania tends to settle more quickly than depression; the index polarity tends to predict the polarity of recurrence. Psychotic features may be present in patients with bipolar I disorder (those who have had at least one episode of mania) but are not typically experienced by patients with bipolar II disorder (those who have had hypomanic and depressive episodes but no manic episodes).

The highly recurrent nature of the illness implies that prevention of recurrence with maintenance therapy is a predominant focus of management in patients with bipolar disorder. Although acute treatment of depression and mania are inevitably the tickets into treatment, the ultimate treatment focus is the maintenance of therapeutic benefits and prevention of recurrence. Once an accurate diagnosis has been made and the index presentation managed, it is the adequacy of maintenance therapy that is likely to determine the individual's long-term outcome and quality of life.

Maintenance therapy in patients with bipolar disorder therefore begins with the acute treatment

IN SUMMARY

- **Despite bipolar disorder being a complex illness to manage, most individuals with the disorder derive substantial benefit from optimal management and have the potential to lead rich and fulfilling lives.**
- **The highly recurrent nature of bipolar disorder means that prevention of recurrence with maintenance therapy is a predominant focus of management. Such therapy involves both polypharmacy and the combination of pharmacotherapy with psychological and lifestyle interventions.**
- **The agents used in the acute treatment of bipolar disorder are likely to be continued as maintenance therapy.**
- **Lithium is the benchmark in the maintenance therapy of bipolar disorder, and has an extensive evidence base. There is also evidence for the effectiveness in relapse prevention of sodium valproate, lamotrigine, carbamazepine, olanzapine and quetiapine.**
- **It is important to address comorbidities such as medical factors, personality, smoking and substance use. Re-evaluation of the diagnosis may be necessary because comorbidities and psychosocial stressors can, with time, have a greater role than initially appreciated.**

Table 1. Medication efficacy in maintenance therapy of bipolar disorder

Medications with evidence of efficacy in maintenance*

In general, medications that are effective for the index presentation of bipolar disorder are likely to be continued as maintenance therapy.

Clear evidence (level I or II)*

- Lithium†
- Lamotrigine‡
- Sodium valproate
- Olanzapine§
- Quetiapine§
- Aripiprazole§ ||

Limited evidence (level III)*

- Carbamazepine
- Risperidone, extended-release formulation (depot)||
- Ziprasidone

Medications with no clear evidence of efficacy in maintenance

- Antidepressants
- Gabapentin
- Topiramate
- Typical antipsychotics

* Level I and level II evidence are obtained from systematic review of all relevant randomised controlled trials (RCTs) and from at least one properly designed RCT, respectively. Level III evidence is obtained from well-designed pseudo RCTs (alternate allocation or some other method), and from comparative studies with concurrent controls (nonrandomised trials, cohort studies, case-control studies and interrupted time series with control groups) or without concurrent controls (historical control studies, two or more single-arm studies and interrupted time series without parallel control groups).

† Lithium is more effective in preventing manic episodes than depressive episodes.

‡ Lamotrigine is more effective in preventing depressive episodes than manic episodes although it prevents both types.

§ Second-generation antipsychotics are effective for treating core mood symptoms, independent of their effects on psychosis.

|| Effective in preventing manic but not depressive episodes.

of the condition. As the agents that settle the index presentation are likely to be continued as maintenance therapy, the choice of acute treatments is critical and it is necessary to treat acute illness with maintenance in mind. The subjective experience of acute treatment shapes the individual's propensity to see treatment as beneficial or, conversely, poorly tolerable or imposed unwillingly, and therefore influences future participation in long-term management. The quality and availability of services, continuity of care and therapeutic alliance are powerful determinants of outcome.

General principles of maintenance management

Bipolar disorder is a complicated illness to manage, being predictably unpredictable, pleomorphic and associated with extensive comorbidity. It requires sophisticated management, which is best achieved using a multidisciplinary approach. The broad aim of treatment is to reduce the morbidity associated with the disorder and thereby limit the associated disability. Achieving this involves prompt and effective treatment of acute episodes as well as the prevention of relapse and recurrence. Optimal management requires attention to patients' individual problems, and should address biological, medication, psychological, social and lifestyle issues. Optimal long-term management should engage the patient's family members or other key carer supports and typically involves a range of mental health specialists and a primary care physician.[1]

Given the long-term and multifaceted nature of the disorder, primary care physicians are optimally placed to be the nexus of the management team. A trusting collaborative partnership between physician and patient enables close monitoring of symptoms to allow detection and management of early warning signs, and is critical in treatment adherence. A strong therapeutic alliance between physician and patient can aid education of the patient about the condition (psychoeducation), and also provide emotional support to the patient. The quality of this alliance is an important determinant of outcome, a stronger treatment alliance being associated with more positive attitudes about medication and a reduced sense of stigma among patients with bipolar disorder, and fewer manic symptoms at six months of follow up.[2,3]

Many individuals with bipolar disorder achieve a durable recovery and maintain a high level of functioning. A significant number, however, remain chronically ill despite appropriate management. Certain treatment patterns are associated with a poorer prognosis, particularly rapid cycling, mixed states and psychotic features, as well as comorbid substance use (including smoking) and personality disorders.[4] Mood stabilisers, particularly lithium, may significantly reduce the risk of suicide.[5]

Once a diagnosis of bipolar disorder has been confirmed, ongoing treatment is likely to be necessary. There is evidence that each episode of illness increases the risk of subsequent recurrence. In addition, response to treatment reduces with recurrence. There is further evidence that there are significant brain volume changes and neuropsychological differences between first-episode and chronically ill cohorts.[6,7] The treatment plan needs to be adaptable to changing clinical realities but it is equally important that hasty treatment changes are not made for unstable mood because response to mood stabilisers tends to be slow and it can take many months for the full effects of treatment to become evident.

After remission of the acute manic or depressive phase, it is particularly important to treat subsyndromal depressive symptoms because disability is predominantly linked to this more chronic aspect of the illness.[8] Monitoring treatment (including those aspects of physical health impacted by either treatment or illness, particularly the metabolic syndrome, clinical response to medications, blood levels and safety monitoring), adherence

and side effects are critical components of maintenance.

Pharmacotherapy

Maintenance agents are likely to be used for an extended time and should therefore be selected taking into account the balance of efficacy and tolerability profiles. This consideration needs to be interwoven with individual patient factors, including preference, past response and safety factors.[9]

Lithium is the best established agent for maintenance therapy, and there is also evidence for the effectiveness of the anticonvulsants (antiepileptics) sodium valproate, carbamazepine, lamotrigine and some atypical antipsychotics in relapse prevention.[10-12] Lithium tends to be most useful for treating patients with classic euphoric mania. Second-generation (atypical) antipsychotics have utility in treating patients' core mood symptoms, independent of the effects of the drugs on psychosis. There is no good evidence that first-generation (conventional) antipsychotics are of value in maintenance.

The medications shown to be of value in the pharmacological maintenance treatment of patients with bipolar disorder are listed in Table 1. The current status of TGA approval and PBS listing of these drugs for this use is given in Table 2.

Monotherapy is ideal but many people do not respond to monotherapy and have to take multiple mood-stabilising agents. It needs to be stressed that mood stabilisation with pharmacotherapy takes time, often many months, and a trial of a mood stabiliser should be given for a correspondingly lengthy period. As mentioned previously, acute treatment should be planned with maintenance in mind because there is a tendency to continue agents used in the acute phase.

Further details on pharmacological options can be obtained from the Canadian Network for Mood and Anxiety Treatments (CANMAT)/International Society for Bipolar Disorders (ISBD) guidelines, 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.[12-14]

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

Drug*	Maintenance treatment of bipolar disorder	
	TGA approved	PBS listed
Recommended – as monotherapy, or in combination with lithium if inadequate response		
Lithium	Yes	Yes
Lamotrigine	No	No
Sodium valproate	No	No
Carbamazepine	Yes	Yes
Olanzapine	Yes†	Yes†
Quetiapine	Yes (monotherapy and adjunctive therapy)†	Yes (adjunctive therapy)†
Others		
Aripiprazole	No	No
Risperidone, extended release formulation (depot)	No	No
Ziprasidone	No	No
Antidepressants (e.g. SSRIs, SNRIs)‡	No	No

* Lithium, carbamazepine, lamotrigine, sodium valproate, olanzapine and quetiapine have been demonstrated in randomised controlled trials to be effective in preventing relapse in patients with bipolar disorder; lithium is the best established agent, and appears to be more effective at preventing manic than depressive episodes; lamotrigine has a stronger effect on preventing depressive episodes than manic episodes; aripiprazole prevents manic but not depressive episodes. Evidence for risperidone as an adjunctive maintenance therapy is from open trials; there is controlled data for extended-release (depot) risperidone. There is no placebo-controlled trial evidence for ziprasidone as maintenance therapy.

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

‡ There is currently substantial controversy about the role of antidepressants in the treatment of bipolar depression. There is no evidence for maintenance efficacy of antidepressants; however, if they are used, this needs to be in conjunction with a long-term antimanic therapy (i.e. a mood stabiliser).

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

Lithium

Lithium remains the benchmark in the maintenance of bipolar disorder, and has an extensive evidence base. It may be more effective in preventing recurrences of mania than depression in bipolar disorder, and it has also been clearly shown to have a prophylactic action in recurrent unipolar depression.

Lithium needs to be maintained at stable blood levels, around 0.6 to 0.8 mmol/L, and safety monitoring is essential.[15]

Anticonvulsants

Sodium valproate

Sodium valproate is used widely as maintenance therapy (off-label use), despite there being relatively limited evidence in support of its efficacy as a maintenance agent. The first randomised placebo-controlled trial of sodium valproate in the maintenance of bipolar disorder showed equivocal results. Two randomised comparator trials are published, one showing similar efficacy between sodium valproate and olanzapine, and the other that sodium

valproate was as effective as lithium in the maintenance of rapid-cycling bipolar disorder. More recently, the Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) trial has shown lithium to be superior to sodium valproate in maintenance, with the combination of lithium and sodium valproate being more effective than either monotherapy.[16]

Lamotrigine

Although there is soft evidence for the treatment of acute depression with lamotrigine, its efficacy in preventing recurrence of mood episodes, particularly depression, has been confirmed in two trials. There is a trend for lamotrigine (off-label use) to outperform lithium in the prevention of bipolar depression, whereas lithium is more effective in preventing mania.

Carbamazepine

There are some data supporting the utility of carbamazepine in maintenance. Randomised maintenance studies comparing carbamazepine against lithium have, however, favoured lithium.

Second-generation antipsychotics

Olanzapine and quetiapine

Of the second-generation (or atypical) antipsychotics, olanzapine has a strong evidence base (four randomised controlled trials) for its use as a maintenance treatment for bipolar disorder. Like lithium, olanzapine has been shown to be more effective at preventing the recurrence of manic or mixed episodes than depressive episodes.

Quetiapine appears to be superior to placebo in maintenance treatment up to a year when used in conjunction with lithium or sodium valproate. Interestingly, available data suggest that quetiapine has similar effectiveness in preventing relapse into depression as it has in preventing relapse into mania. Both olanzapine and quetiapine appear to confer additional benefit and to increase the time to recurrence of mania or depression when added to lithium or sodium valproate therapy.

Aripiprazole

Aripiprazole has been shown in two trials to prevent manic but not depressive episodes in patients with bipolar disorders. It has a role in the maintenance therapy of bipolar disorder (off-label use).

Risperidone

There are no published placebo-controlled data of risperidone maintenance treatment in bipolar disorder. Open-label data, however, suggested that risperidone adjunctive to sodium valproate or lithium improves depressive symptomatology. Unpublished controlled trials provide support for adjunctive depot risperidone in maintenance therapy of treatment-resistant bipolar disorder.

Depot risperidone is currently used off-label in the maintenance therapy of bipolar I disorder, especially in the presence of adherence difficulties.

Ziprasidone

There are no published controlled trials of ziprasidone in maintenance therapy. It is, however, occasionally used as maintenance therapy (off-label use).

Antidepressants

The use of antidepressants in continuation treatment or the maintenance phase of bipolar disorder is controversial because of the risk of inducing mania (switching) or cycle acceleration. A review of published data found no evidence to support the long-term use of antidepressants in bipolar disorder. Provisional data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study suggested modest benefits with the continuation of antidepressant treatment , such as reduced depressive morbidity, and an increased risk of relapse when antidepressants are discontinued.[17]

Antidepressants do not appear to significantly reduce the risk of recurrent depressive episodes or reduce the severity of episodes. Placebo-controlled data of the use of antidepressants in maintenance are needed.

Other drugs

There is no evidence for the efficacy of the anticonvulsants gabapentin and topiramate in the maintenance treatment of bipolar disorder.

Monitoring of physical status and medications

Regular safety monitoring is a core part of most bipolar maintenance treatment. For example, individuals on lithium treatment require regular lithium level monitoring, as well as monitoring of renal and thyroid functions.

Patients need to be warned about the increased rates of diabetes and hyperlipidaemia in patients with bipolar disorder and the risks associated with these conditions, and metabolic monitoring is essential for maintenance treatment given the long-term nature of therapy. Detailed guidelines for safety monitoring are available.[15]

Psychotherapy

As an adjunct to medications, psychological interventions enhance treatment adherence and also have an independent therapeutic effect. A key aspect of therapy includes establishing a healthy therapeutic relationship that also facilitates psychoeducation and encourages the involvement of family and partners where necessary. This is as true of integrated management in a primary care setting as of formal psychological therapy.[18]

Almost all data on psychosocial interventions in bipolar disorder are derived from studies carried out in patients in the maintenance phase. Psychosocial interventions as an adjunct to medications appear to reduce the risk of relapse and improve functioning. The benefit appears to be greater in patients who receive the psychosocial therapies when in a non-depressed or nonmanic mood (euthymia), and treatment may be less effective in

those individuals with a high number of prior mood episodes (more than 12 episodes).[19]

There is evidence supporting the use of interventions focused on the recognition of early warning signs and the use of group psychoeducation, cognitive behavioural therapy, family-focused therapy and interpersonal and social rhythm therapy (Table 3). Internet-based treatments are being developed, such as the beyondblue-funded self-help program for people with bipolar disorder available at www.moodswings.net.au.[20,21]

Supportive therapy is of probable value, although no formal studies have been conducted.

Lifestyle interventions

Simple and practical measures involving a healthy lifestyle and promotion of a more structured routine as well as more formal therapy are of significant benefit to treatment outcomes. These measures need to be combined with optimum pharmacotherapy. Psychosocial stressors need to be addressed, and the person assisted with problem-solving skills. The quality of social supports and networks is an important determinant, and assistance should be given in the development and maintenance of social support and networks. Occupational support is important, as work has a core function in most peoples' lives.

Psychoeducation is documented to reduce recurrence risk and should be part of integrated care. Family or carer support has been shown to reduce relapse risk.

It is essential to support a healthy lifestyle.[22] Social rhythm regularity, particularly with regard to sleep habits, is important. Most people benefit from structure around their daily activities, so this social rhythm regularity should extend to daily routines. It is also useful to discuss the principle of acting contrary to mood; when the person feels low and feels like withdrawing, pushing to maintain routine is generally beneficial, and equally if the person feels up and capable of taking on far more than usual, they should be advised to stick to their routine. Exercise is of particular value in bipolar disorder, again interwoven into a routine.[23]

It is important to address comorbidities, particularly substance misuse. Consideration should be given to smoking cessation, as there is a suggestion that smokers have a poorer response to treatment and worse long-term outcomes.[24,25]

Clinicians also need to be mindful of safety and risk issues. Monitoring for early warning signs of relapse and having an action plan to deal with these is important.

Management of nonresponse

Many individuals with bipolar disorder struggle to achieve a satisfactory response to treatment despite having undergone appropriate assessment and management. Steps that can be taken with such patients include the following:

- use of mood monitoring and structured rating scales to measure treatment response, as part of clinical assessment
- reassessment of adherence and satisfaction with the treatment plan; it is necessary to see that the person's treatment goals are concordant with the treatment plan
- if the patient is taking a mood stabiliser, confirmation that adequate blood levels of medications are attained.

Re-evaluation of the diagnosis may be necessary because comorbidities (e.g. medical factors, personality and substance use) or psychosocial stressors can, with time, have a greater role than initially appreciated.

Specialist consultation or referral to a specialist clinic should be considered when novel treatments are prescribed, in particularly complex cases, or where there has been partial or no response to multiple evidence-based treatment trials.

Conclusion

Bipolar disorder is a particularly complex illness to manage because of its multiphasic nature, intrinsic instability and high rates of comorbidity and the necessity for both polypharmacy and the combination of pharmacotherapy with psychological and lifestyle management. Principles of chronic disease management that have been developed in other medical disorders can be extended to bipolar disorder. Most individuals with the disorder will, however, derive substantial benefit from optimal management, and have the potential to lead rich and fulfilling lives. MT

Table 3. Psychosocial interventions with evidence as adjunctive treatment in maintenance

- **Monitoring early warning signs** – use of psychoeducation, mood monitoring and relapse prevention plans to identify and manage early warning signs
- **Cognitive behavioural therapy (CBT)** – combines cognitive and behavioural strategies to target maladaptive thinking patterns that predispose patients to and perpetuate depression
- **Interpersonal and social rhythm therapy (IPSRT)** – focuses on the link between social relationships and mood, the maintenance of stability in daily routines and identification and management of rhythm disruption
- **Family-focused therapy (FFT)** – includes communication enhancement training, problem-solving skills and skills-based training as well as psychoeducation aimed at the patient and family
- **Group psychoeducation** – provides information and emotional support, assists with adjustment to chronic illness and targets treatment adherence

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