Improving recognition and management of bipolar disorder

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More than 200,000 people in Australia live with bipolar disorder throughout their adult lives, and poor management of this episodic illness significantly impairs social, emotional and economic wellbeing, to the detriment of both the patient and the community. GPs are key to an integrated biopsychosocial approach to bipolar disorder. This article describes the core components of early detection and effective management in the light of recent evidence.

Bipolar disorder can have a severe impact on the relationships, careers and general health of the people who live with the condition. Frequent recurrences, comorbid disorders and a lack of insight during episodes of mania can make managing patients with bipolar disorder in general practice especially challenging. Nevertheless, GPs who find the right combination of psychological intervention and medications to diminish or abolish recurrences of this episodic illness can make an enormous difference to their patients' lives.

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Epidemiology

About 1 to 1.5% of people in Australia will develop bipolar disorder, irrespective of ethnicity or socioeconomic status.[1] This is an illness usually diagnosed in young adulthood and although bipolar II disorder is more common in women, bipolar I disorder affects both sexes equally.[2] Those with bipolar disorder are more likely to be receiving government benefits and have poorer psychosocial functioning than the general population.[1] They are symptomatic almost half the time,[3] not only due to the bipolar disorder but also as a result of common comorbidities such as substance misuse and anxiety disorders (present in 45% of cases).[4] Moreover, those with bipolar disorder on average die many years earlier than the rest of the population.[5]

Depressive symptoms account for most of the disability incurred due to this illness, and suicide occurs in 10 to 15% of patients with bipolar disorder, most often during depressive episodes.[6]

Diagnosis and investigations

No diagnostic tests are as yet available for the detection of bipolar disorder. The characteristic clinical feature is a pattern of mood swings between the two 'poles' of depression and elevation (Box 1).[7,8]

Unipolar depression versus bipolar depression

Unipolar depression is 10 to 15 times more common than bipolar disorder. Patients with bipolar illness usually first present with an episode of depression.[7] It is unsurprising, therefore, that only 20% of patients with bipolar disorder are correctly diagnosed within the first year of seeking treatment for depression.[2] However, as the mean delay

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between the first episode of depression and the correct diagnosis of bipolar disorder is an unacceptable five to 10 years,[9] doctors should be alert to the features more common to bipolar depression than unipolar depression (Box 2).[10]

It is essential to enquire carefully about possible episodes of hypomania in patients with depression that proves difficult to treat.[11,12] Tools such as the Hypomania Checklist 32 (HCL-32) can assist the GP to identify a history of hypomanic symptoms in patients with a major depressive episode.[13] Once bipolar disorder has been diagnosed, scales such as the Young Mania Rating Scale (YMRS) can help clarify the severity of periods of elevated mood.[14]

Comorbidities

Early diagnosis is made more difficult by the frequent presence of comorbid anxiety, substance misuse and personality disorders (especially borderline personality disorder).[15] These conditions require their own evidence-based treatments if the patient with bipolar disorder is to be well managed.

KEY POINTS

- Bipolar disorder is more common than schizophrenia and associated with considerable morbidity and economic cost to affected individuals and their families.
- Pharmacotherapy and psychological management, aimed at reducing the frequency and intensity of episodes of illness, can make a major difference to the wellbeing of those living with bipolar disorder.
- There are as yet no diagnostic tests for bipolar disorder so the clinical evaluation of mood swings and associated symptoms of the two 'poles' of mood elevation and depression is crucial.
- Doctors should be alert to the features more commonly associated with bipolar (rather than unipolar) depression, enquire about episodes of hypomania in patients with difficult to treat depression, and be mindful of the possibilities of overdiagnosis of bipolar disorder in some patients.
- Doctors should also be aware that episodes of predominantly hypomania/mania or depression can occur with mixed features of the opposite 'pole'.
- Appropriate investigation and physical examination is crucial as many physical illnesses may first present with severe secondary disturbances of mood and the unwanted effects of some medications used to treat patients with bipolar disorder can cause physical problems.
- Although pharmacotherapy is necessary for acute and maintenance management of affected patients, specific adjunctive psychological therapies have also been found to promote better mood stability and reduce the frequency of hospitalisation.

Differential diagnoses

Anxiety and substance use disorders, together with attention deficit hyperactivity disorder and oppositional defiant disorder in children and adolescents, are common differential diagnoses of bipolar disorder, as are schizophrenia and major depression. In addition, several medical illnesses can cause or contribute to the development of mood disorders, so the patient should be examined for the presence of conditions such as sleep apnoea, chronic pain, hyperthyroidism and hypothyroidism (Table 1).[11]

For older people who present for the first

1. SYMPTOMS OF MANIA AND HYPOMANIA*[7]

Symptoms need to be present for at least four days for hypomania and seven days for mania.

- Abnormally elevated or euphoric mood, often associated with irritability
- Increased energy and activity despite needing little sleep
- A sense of heightened or special abilities (grandiosity)
- Disinhibited behaviour such as increased sex drive, overspending or a tendency to be overly frank or uncharacteristically rude in the appraisal of others
- Racing thoughts, associated with speaking more quickly and/or loudly
- Increased distractibility with a tendency to flit from task to task, leaving many uncompleted or poorly executed
- Enhanced perceptual experiences so that colours and sounds are more vivid or one's thinking feels sharper than usual

* Bipolar I disorder is defined by episodes of mania, which in turn are defined by marked impairment of functioning, psychotic features or hospitalisation. Bipolar II disorder is defined by the occurrence of hypomanic episodes only, the symptoms of which, though clearly distinct from the person's normal functioning, are not characterised by severe impairment, psychotic features or hospitalisation. About 75% of those presenting with mania will also have psychotic symptoms such as hallucinations or delusions.[2]

2. FEATURES MORE COMMON IN PATIENTS WITH BIPOLAR DEPRESSION THAN UNIPOLAR DEPRESSION[10]

- More frequent episodes of shorter duration with abrupt onset and offset
- Positive family history of bipolar disorder
- First episode of depression before the age of 25 years with multiple episodes of depression before a first episode of hypomania/mania
- Physical and mental slowing
- Increased sleep and/or appetite
- Early morning wakening with mood worse in morning
- Delusions and hallucinations
- Excessive guilt and labile mood

TABLE 1. A GUIDE TO EXAMINATION AND INVESTIGATION OF PATIENTS PRESENTING FOR THE FIRST TIME WITH EVIDENCE OF A MOOD DISORDER, INCLUDING THOSE ALREADY TAKING PSYCHOTROPIC MEDICATIONS*[11]

Conditions	Examinations/investigations†
Abnormal vital signs	Sinus tachycardia may reflect anxiety Blood pressure may be altered by psychotropic medications Bradycardia may be an indication of hypothyroidism
Overweight/obesity	Commonly prescribed medications for bipolar disorder can cause weight gain
Self-harm	Scars may indicate a history of self-harm
Endocrine disorders	Thyroid disease and Cushing's syndrome may first present with signs and symptoms of affective disorders so check for goitre, hyper/hypothyroid features and Cushingoid features
Respiratory disorders	Comorbid anxiety and depression commonly present with, and in some cases are causally related to, sleep apnoea, snoring, restless leg syndrome, COPD features, wheeze/asthma and lung malignancy Disturbed sleep is particularly a risk factor for episodes of hypomania/mania
Neurological disorders	Parkinsonism, motor/sensory deficits, cerebrovascular disease features, motor tics and Tourette's disorder may all present with symptoms of depression or hypomania/mania
Organ insufficiency	Poor hepatic, renal, cardiac and pulmonary function are associated with a greater risk for depression Check for jaundice, arteriovenous fistula for dialysis, dyspnoea and peripheral oedema In addition, organ insufficiency and its management may impair the pharmacokinetics of medications used to treat patients with bipolar disorder and heighten the potential for drug–drug interactions

* Adapted from: RANZCP Clinical Practice Guidelines for Mood Disorders. Aust N Z J Psychiatry 2015; 49: 1087-1206.[11]
† The following investigations should be included in the examination of all patients presenting with a mood disorder: thyroid function tests and measurement of thyroid antibodies; full blood count and erythrocyte sedimentation rate; measurement of vitamin D, fasting blood sugar and serum prolactin levels; renal and liver function tests; and screening of antinuclear antibodies and anti-double-stranded DNA to exclude systemic lupus erythematosus. The following may also be necessary: measurement of vitamin B12, folate and beta human chorionic gonadotrophin levels; testing for sexually transmitted disease; urine and blood screening for benzodiazepines, opioids, psychostimulants, cannabis and hallucinogens; and cerebral imaging to exclude underlying causative neurological lesions.

3. FEATURES OF CYCLOTHYMIA, MIXED AFFECTIVE STATES AND RAPID CYCLING BIPOLAR DISORDER THAT CAN CLOUD THE DIAGNOSTIC PICTURE OF BIPOLAR DISORDER

Cyclothymia
Patients with cyclothymia experience subthreshold episodes of hypomania/mania and depression, and in some patients this is difficult to distinguish from their temperament or personality. Pharmacological approaches are not recommended when the distress and dysfunction occasioned by the disorder is mild. However, cognitive behavioural therapy augmented with wellbeing therapy and family involvement are likely to be beneficial.[16,17] If mood cycling leads to significant dysfunction then pharmacotherapy should be guided by the recommended strategies for the management of patients with bipolar II disorder.

Mixed affective states
Patients exhibit depression or hypomania/mania together with three or more symptoms from the opposite pole. For depressed patients with mixed features, consider olanzapine, quetiapine or sodium valproate as monotherapy or sodium valproate in combination with an antidepressant. In patients with dysphoric mania, second-generation antipsychotics in conjunction with a mood stabiliser are preferred.[18]

Rapid cycling bipolar disorder
Rapid cycling bipolar disorder refers to the presence of at least four mood episodes of hypomania/mania or depression in the previous 12 months. Patients with this condition are difficult to manage and the focus is on treating the presenting mood state and reducing the frequency of cycling. Antidepressants are best avoided because they may worsen mood cycling. The choice of available mood stabilisers includes lithium, sodium valproate, olanzapine, lamotrigine, quetiapine and aripiprazole.[11]

time with a mood disorder, underlying neurodegenerative disorders such as frontotemporal dementia should also be considered.[11] On occasion, patients will develop hypomania/mania in response to antidepressant medication; however, not all of these patients will go on to develop bipolar disorder.

Examination and investigations

A guide to examination and investigations in patients presenting with a possible mood disorder is given in Table 1.[11]

Overdiagnosis of bipolar disorder

Given the complexity of comorbidities and differential diagnoses, it is perhaps unsurprising that clinical exploration of the possibility of bipolar disorder can lead to overdiagnosis. This is especially true when hypomania is assumed to be evidenced by transient or rapidly shifting mood instability, which is also a feature of conditions such as borderline personality disorder and impulse control disorder.[2,7] Cyclothymia, mixed affective states and rapid cycling bipolar disorder can also cloud the diagnostic picture (Box 3).[11,16-18]

If doubt remains about the diagnosis of bipolar disorder, we recommend referral of the patient to a psychiatrist or a tertiary assessment centre for diagnostic clarification.

Acute management of bipolar disorder

Mania

On rare occasions, GPs will be required to initiate management of patients with acute mania in the community. The evidence is clear that antipsychotic medications such as quetiapine, risperidone, olanzapine, aripiprazole and haloperidol are both effective and acceptable, although extrapyramidal side effects can limit the clinical usefulness of haloperidol.[2,19,20]

Several factors will influence the choice of medication, including clinician familiarity with one or more of these medications, patient preference (especially with regard to side effects such as sedation, weight gain or extrapyramidal symptoms) and subsidisation by the PBS (Tables 2 and 3).

Electroconvulsive therapy (ECT) is another useful treatment for patients with mania, as well as for those with depression. It is especially useful for patients who cannot tolerate or do not respond to medications.

It is important to be aware that mania is often provoked or exacerbated by stressors and that relief from these assists recovery. Patients experiencing mania often require hospitalisation, and the GP can greatly assist such patients and their families, before and after admission, with basic information about the illness and simple advice aimed at reducing conflict and enhancing family functioning.[2]

Hypomania

Hypomania is, by definition, self-limiting and much less functionally impairing than mania. If intervention is required then the principles of medication and psychosocial interventions recommended above for mania apply.[21-23]

Bipolar depression

The increased risk of suicide in patients with bipolar disorder is almost always a consequence of depression, which is of concern as the acute management of bipolar depression continues to prove difficult. The second-generation antipsychotics quetiapine, lurasidone (off-label use) and olanzapine (off-label use) have shown evidence of effectiveness in the treatment of patients with bipolar depression (Tables 2 and 4). Lurasidone, although the least likely of these three medications to lead to metabolic syndrome, is approved and subsidised only for the treatment of people with schizophrenia in Australia.[24,25]

There is also evidence that the combination of olanzapine and fluoxetine is effective in the acute treatment of patients with bipolar depression. However, this combined preparation is not available in Australia, although clearly the individual medications can be used in combination.[26]

TABLE 2. PHARMACOLOGICAL MANAGEMENT OF BIPOLAR DISORDER IN MANIA, DEPRESSION AND MAINTENANCE PHASES[2]

Drug	Clinical management			Advantages	Disadvantages
	Mania	Depression	Maintenance		
Mood stabilisers					
Sodium valproate	+++	+	++*	Useful in episodes with mixed features	CYP450 inhibitor, not recommended in women of childbearing age
Lamotrigine	– – –	++	+++	Bipolar II disorder or depressive predominant	Slow titration
Lithium	+++	++	+++	Antisuicidal properties	Not recommended in renal failure
Carbamazepine	+++	+	++	Effective in bipolar disorder with nonclassic features	CYP450 inducer
Antipsychotics					
Aripiprazole	+++	–	++	Manic predominant polarity, good metabolic profile	Akathisia
Asenapine	+++	+	+	Possible treatment for depressive symptoms	Moderate metabolic syndrome
Lurasidone	+	+++	+	Lack of anticholinergic effects	Efficacy related to feeding, akathisia, sedation
Olanzapine	+++	+++	++	Rapid efficacy	Severe metabolic syndrome
Quetiapine	+++	+++	+++	Only antipsychotic drug with indications for treatment of acute manic and depressive episodes and maintenance	Sedation
Risperidone	++	–	++	Intramuscular administration every two weeks	Risk of switch to depression, extrapyramidal symptoms
Ziprasidone	++	–	++	Manic predominant polarity, good metabolic profile	Efficacy related to feeding
Antidepressants					
Antidepressants	– –	+ +		Applicable in resistant bipolar depression combined with mood stabilisers	Risk of switch to mania

* Although sodium valproate is not TGA approved for maintenance treatment of patients with bipolar disorder, the positive clinical experience worldwide supports its use for this indication.

Adjunctive antidepressants for bipolar depression

The use of adjunctive antidepressant medication in the treatment of patients with bipolar depression remains contentious.[27-30] Two recent studies illustrate this, with contradictory findings. El-Mallakh's group found that long-term continuation of antidepressants in patients with rapid-cycling bipolar disorder led to a threefold increase in mood episodes during the first year of follow up.[31] In contrast, Amsterdam and colleagues found that continuation of antidepressant monotherapy in patients with bipolar II disorder is prophylactic, with little risk of switching.[32]

An influential report from the major bipolar disorder international society recommended that although antidepressant monotherapy should be avoided in the treatment of patients with bipolar depression, use of adjunct antidepressants with a mood-stabilising agent (such as lithium, sodium valproate or lamotrigine) or an antipsychotic such as quetiapine can be helpful in promoting rapid recovery from bipolar depression.[33] The selective serotonin reuptake inhibitors (SSRIs) may have lower rates of manic switch than serotonin and noradrenaline reuptake inhibitors (SNRIs) and tricyclic and tetracyclic antidepressants. Patients should be monitored for the development of mixed states, emergence or exacerbation of mood instability and, of course, signs of hypomania/mania. Patients with treatment-resistant bipolar depression generally require the supervision of a specialist.

ECT for bipolar depression

ECT has been shown to be equally effective for the rapid treatment of patients with bipolar and unipolar depression, with some

evidence suggesting a more rapid response in those with bipolar depression.[34] Reports of switching in controlled studies of ECT in patients with bipolar depression are uncommon.[11]

Repetitive transcranial magnetic stimulation

Although there have been no studies of the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in patients with bipolar depression, many depressed patients with bipolar disorder have been included in trials of rTMS with no evidence that those with bipolar depression are less likely to respond to rTMS than patients with unipolar depression.[35] Overall, the rate of manic switch with rTMS appears to be low.[11]

Psychological treatments

Online interventions for patients with bipolar disorder are being developed but are not yet clinically available.[36,37] Guidelines from the UK National Institute for Health Care and Excellence (www.nice.org.uk) and the Royal Australian and New Zealand College of Psychiatrists (RANZCP) concur that adjunctive structured psychological interventions (such as cognitive behavioural therapy and family focused therapy) should be offered to help stabilise episodes of bipolar depression.[38-42] However, it has been argued recently that this advice is underpinned by less robust evidence than may be inferred by the recommendations.[43]

TABLE 3. TGA AND PBS STATUS OF MEDICATIONS USED FOR TREATMENT OF ACUTE MANIA AND MAINTENANCE TREATMENT OF BIPOLAR DISORDER

Drug	Acute treatment of mania		Maintenance treatment of bipolar disorder	
	TGA approved	PBS listed	TGA approved	PBS listed
Aripiprazole	Yes*	No	Yes*	No
Asenapine	Yes*	Yes	Yes*	Yes
Carbamazepine	Yes	Yes	Yes	Yes
Lamotrigine	No	No	Yes	No
Lithium	Yes	Yes	Yes	Yes
Olanzapine	Yes	No	Yes	Yes
Quetiapine	Yes	Yes	Yes	Yes
Risperidone	Yes	Yes†	No	No
Risperidone long-acting injectable form	No	No	Yes‡	Yes*
Sodium valproate	Yes	Yes	No	No
Ziprasidone	Yes*	Yes*	No	No

* Also for mixed episodes.
† As an adjunct to lithium or sodium valproate.
‡ For treatment refractory bipolar disorder in combination with lithium or sodium valproate.

Nevertheless, there is a strong clinical consensus that a comprehensive biopsychosocial approach to the management of patients with bipolar depression is, as with the treatment of those with unipolar depression, likely to enhance treatment adherence, speed recovery and produce better psychosocial outcomes for most patients.[38,39]

TABLE 4. TGA AND PBS STATUS OF MEDICATIONS USED FOR TREATMENT OF BIPOLAR DEPRESSION

Drug	Acute treatment of bipolar depression		Prevention of bipolar depression	
	TGA approved	PBS listed	TGA approved	PBS listed
Carbamazepine	No	No	Yes	Yes
Lamotrigine	No	No	Yes	No
Lithium	Yes	Yes	Yes	Yes
Olanzapine	No	No	Yes	Yes
Quetiapine	Yes	No	Yes*	Yes*

* Adjunctive to lithium or sodium valproate

Prevention of relapse in bipolar disorder

The aim of prevention in the management of patients with bipolar disorder is the achievement of good mood stability that minimises the frequency of relapse into either mood state and allows, in euthymia, psychosocial interventions that improve adherence to treatment and promote wellbeing.[44]

Pharmacotherapy

Pharmacotherapy for the prevention of relapse usually consists of a mood stabiliser alone or in combination with an antipsychotic or antidepressant (Table 2).[45] Lithium has the strongest evidence for the prevention of recurrences, followed closely by the second-generation antipsychotics.

In a network meta-analysis, lithium was highlighted as one of the most effective treatments for the prevention of both manic and depressive episodes, despite being potentially associated with a decline in renal function (although not renal failure),

hypothyroidism and hypercalcaemia.[46]

Quetiapine has similar effectiveness to lithium in the prevention of hypomania/mania and depression.[47]

When depression is the chief concern, (as in nearly all cases of bipolar II disorder), lamotrigine is likely to be the mood stabiliser of choice because it has strong evidence for effectiveness in the prevention of bipolar depression and is generally well tolerated, the rare but dangerous possibility of Stevens–Johnson syndrome not withstanding.[48] In Australia, lamotrigine is approved, but not subsidised, for the prevention of episodes of bipolar depression (see Table 4).

Sodium valproate monotherapy has been found to be less effective in relapse prevention than both lithium monotherapy and combined sodium valproate and lithium.[49] Nevertheless, sodium valproate can be useful prophylactically and when mixed episodes are a feature of the condition.

Safety of lithium

A meta-analysis by McKnight and colleagues of the side effects of lithium did not find any evidence of significant renal impairment, although it is the authors' experience that a small number of patients taking lithium (especially in the longer term) will experience chronic renal impairment.[50]

However, the meta-analysis did find that lithium is associated with an increased risk of weight gain, hypothyroidism and hyperparathyroidism (with elevated calcium and parathyroid hormone concentrations). Regular measurement of indices of these unwanted effects should continue to be part of routine management of patients taking lithium.[1]

Pregnancy

Careful preconception counselling for women with bipolar disorder and their partners is essential and GPs may wish to collaborate with the patient's psychiatrist in the management of the condition during pregnancy and the postpartum period. Carbamazepine and sodium valproate increase the risk of spina bifida and low IQ, and the rate of teratogenicity for lamotrigine is similar to that for carbamazepine so these three drugs should be avoided in pregnancy.[51] Although the teratogenicity of lithium is less than previously thought, in the authors' view lithium should be tapered and ceased, if possible, in women planning to conceive.[50]

The risk of relapse is highest in the postpartum period (and for primiparous women), and treatment should recommence as soon as possible after delivery. Preconception counselling should also explain that breastfeeding is generally contraindicated in women with bipolar disorder taking psychotropic medications.[52]

Psychological therapy

The first comprehensive review and meta-analysis of studies examining the effectiveness of psychological interventions for the treatment of patients with bipolar disorder was published in 2016.[3] Although Oud and colleagues noted that the quality of the data was often low, they nevertheless found that some psychological therapies reduce hospital admissions and relapse rates and may also improve depressive symptoms.[3] They found that structured individual psychological interventions reduced the risk of relapse by 35%, and that family psychoeducation also substantially reduced relapse rates.[3] However, they did not confirm the work of Frank and colleagues, finding instead no evidence of effectiveness for interpersonal and social rhythm therapy.[53]

Complementary therapies

Adjuvant agents reported as helpful for patients with bipolar depression, but not mania, include omega-3 fatty acids, chromium and N-acetyl cysteine, although the evidence for most of these is scarce.[54-57] Initial randomised controlled trials suggest that adjunctive choline, magnesium, folate and tryptophan may be beneficial for reducing symptoms of mania.[55]

Lifestyle interventions

Although there is robust evidence for the positive effect of exercise on mood and fitness in patients with unipolar depression, evidence for the beneficial effect of exercise in those with bipolar disorder is more scant, but promising.[58] For example, regular physical activity is associated with better sleep quality in individuals with bipolar disorder.[59,60]

As sleep disturbance can be a prodromal symptom of mania, GPs should warn patients considering choices that disrupt the sleep–wake cycle such as shift-work or overseas travel.[61,62]

Conclusion

In recent years there have been important developments in the management of patients with bipolar disorder, including an enhancement and targeting of the indicated pharmacopoeia, a comprehensive meta-analysis of the effectiveness of psychological therapies and a detailed set of guidelines developed by the RANZCP for the Australian setting. GPs are well placed, in conjunction with mental healthcare specialists, to integrate these new tools and data to promote the mental and physical health and wellbeing of the many people in Australia living with bipolar disorder. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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