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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 or adjunctive therapy)†	Yes (adjunctive therapy)†
Others		
Aripiprazole	No	No
Risperidone	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 is 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. Risperidone is used in the maintenance therapy of bipolar disorder (off-label use), but not often.

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 nondepressed 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]

continued

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

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 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

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