Acute management of bipolar disorders

Ajeet Singh, Consultant Psychiatrist, The Geelong Clinic, and Department of Clinical and Biomedical Sciences, Barwon Health, University of Melbourne, Geelong; and Michael Berk, Consultant Psychiatrist, The Geelong Clinic, Department of Clinical and Biomedical Sciences, Barwon Health, University of Melbourne, Geelong, ORYGEN Research Centre, Melbourne, and Mental Health Research Institute, Melbourne

Summary

Acute bipolar presentations include manic, hypomanic, mixed, and depressive states. Manic presentations cannot be contained in a primary care setting and require psychiatric assessment for hospitalisation. Several drugs that have mood stabilising actions are now available, providing more treatment options for clinicians. Antidepressant use in bipolar depression remains controversial, but if considered clinically appropriate must be administered with a drug that stabilises mood. Psychosocial interventions help patients with recovery and to cope with residual symptoms of illness.

Key words: depression, hypomania, management, mania.

(Aust Prescr 2008;31:73–6)

Introduction

Patients with bipolar disorders face significant risks of morbidity and mortality and present medical practitioners with considerable diagnostic and management challenges. The lifetime prevalence of bipolar disorders is estimated at 1–4% of the general population.[1] Suicide is attempted by 25–50% of sufferers[2], and overall 15% of people with bipolar disorders die by suicide.[3]

Accurate diagnosis depends on recognising often under-reported symptoms of elevated mood. Mixed states (combined depressive and elevated symptoms) and comorbid substance misuse frequently cloud the initial diagnosis. These diagnostic complexities along with often impaired patient insight lead to a third of Australian patients suffering illness for more than ten years before accurate diagnosis is made and appropriate treatment given.[4]

Bipolar disorders

These are characterised by episodic depressions and elevations of mood. Bipolar I involves manic symptoms which last for at least a week and are severe enough to markedly impair functioning or require hospitalisation. In contrast, bipolar II involves hypomania in which elevated symptoms are less severe but still clearly different from usual mood and last for at least four days. In both forms of the illness, depressive episodes tend to be more frequent and disabling than mania. Sufferers spend 32–50% of follow-up in depressive episodes and only 1–9% in elevated states.[5] Most patients have inter-episode periods of recovery, but over 90% relapse without medications.[6]

Risk assessment

It is necessary to determine the most appropriate settings for patient care, and assess for suicidal ideations by examining past history of self-harm, current ideation, substance abuse, and the level of social supports.

In elevated and mixed states, the possibility of risk taking, impulsive behaviours, irritability, violence and misadventure must be considered. Where risks are deemed high, the patient needs more assertive care, and referral to psychiatric inpatient services is appropriate. Application of the relevant state mental health act may be required. Manic episodes cannot be contained in a general practice or community setting.

Given the diagnostic and management challenges of bipolar disorder, psychiatric confirmation of diagnosis and management advice is advisable. For patients with low to moderate risk, their initial care will usually be provided by their general practitioner, who has a pivotal role in assessment, diagnosis, referral and ongoing care.

Treatment

The goal of treatment in bipolar disorder is to stabilise mood. Symptomatic and specific maintenance medications are available for the acute treatment of bipolar disorders. However, maintenance medication remains the cornerstone of management – both for acute episodes and maintenance treatment.[7]

In recent years several new drugs have shown efficacy for the control of manic symptoms and prevention of relapse, but not all are approved for use in bipolar disorders.[8] Trialling medications in the acute phase of the illness – depressed, mixed, hypomanic and manic episodes – helps to find the most effective and tolerable drug or drugs necessary to achieve and maintain euthymic mood in individual patients.

In Australia, several effective drugs for bipolar disorders are

subsidised by the Pharmaceutical Benefits Scheme, but some drugs require private prescriptions for use (see Table 1).

Manic episodes

Drugs recommended for the treatment of manic episodes are listed in Table 1.[8,9] Lithium, certain anticonvulsants[10] and several antipsychotics have mood stabilising properties. They treat and prevent mood elevations and, to a lesser extent, help control and prevent depressive episodes.

Episodes of mania typically require inpatient management. Patients with mania require sedation to reduce psychomotor acceleration. So called 'manic exhaustion' had a very high mortality in the premedication era. Prompt restoration of the sleep-wake cycle assists recovery. Often adjunctive benzodiazepines are used for sedation, but it is preferable if the drug chosen to stabilise mood can also serve this function. Managing mania sometimes requires large doses of antimanic drugs in the acute phase, though lower doses may suffice in the maintenance phase. Tolerability is a key factor for subsequent compliance with medications and long-term illness control.

Resolution of the acute episode takes weeks to months. Approximately 50% of patients with mania will respond to monotherapy with any antimanic drug, and around 70–75% will respond to combination therapy. The longer-term evidence on such combination therapy remains limited, and while monotherapy is preferable from compliance, tolerability and cost perspectives, only a third of patients achieve longer-term mood stability on monotherapy.[11] Combination therapy is pragmatically the norm. In rare treatment-resistant cases of mania, where even multiple medications fail to control mania, electroconvulsive therapy and in some cases clozapine may need to be trialled.[12] Acute treatment is generally the start of maintenance therapy.

Table 1

Drugs for the acute management of manic episodes

First-line	– lithium – valproate – carbamazepine – second generation antipsychotics (olanzapine*, risperidone, quetiapine, aripiprazole*, ziprasidone*)
Second-line	– second generation antipsychotic plus lithium or valproate – lithium plus valproate
Third-line	– electroconvulsive therapy – clozapine†

This list is a composite of recent evidence-based reviews and consensus management guidelines for bipolar mania[8,9]

* indicates no Pharmaceutical Benefits Scheme subsidy for acute mania at time of writing

† the efficacy of clozapine is decreased with smoking

Hypomanic episodes

Due to the shorter duration of hypomanic episodes, and the lack of marked impairment, hypomania is less frequently the presenting symptom of the illness. Patients with hypomania may feel energetic and creative, and may not need much sleep. They are unlikely to present complaining of feeling 'too well'.

In clinical practice, treatments for manic states are effective in hypomania. Importantly, patients with only hypomanic but no manic episodes (bipolar II pattern) do not tend to progress to bipolar I manic states. Nonetheless, hypomanic episodes are a core precipitant of downward mood destabilisations into major depressive episodes, and thus warrant active treatment, even though depression is invariably the reason patients present for treatment in bipolar II disorder.

Mixed episodes

Mixed states are characterised by elevated and depressed mood mixed together and are among the most difficult mood conditions to identify. Elevated symptoms can be brief, and include racing and 'crowded' thoughts, lability of affect, insomnia and restlessness. Specific pharmacotherapy for mixed states is extrapolated from treatments for mania. One crucial factor is to avoid antidepressants during such mixed states, as they will exacerbate and sometimes trigger the episodes. This can be counterintuitive, when patients present with a dysphoric affect. Mixed states are the most under-recognised of the bipolar specific states, and it is likely that many mixed states are triggered by antidepressants. If a patient's agitated depressive symptoms seem to worsen with antidepressants, consider the possibility of a mixed state and bipolar diagnosis.

Depressive episodes

Drugs for the treatment of bipolar depressive episodes are listed in Table 2.[8,9] The best current evidence for efficacy in bipolar depression exists for lithium, quetiapine and lamotrigine.[8]

Antidepressants place patients at risk of switching to elevated phases of the disorder and rapid cycling patterns. Although the results of a recent study do not support the use of adjunctive antidepressant therapy in the acute treatment of bipolar depression[13], this topic remains very controversial. Many patients with bipolar depression will not respond to changes in mood stabilising medicines alone. They may need an antidepressant, but this must be taken with a mood stabilising drug. Frequent regular mental state review is necessary for any patient taking this combination to detect destabilisation, and non-response or loss of response to the antidepressant. Patients should not simply be left on the antidepressant long term without review.

Considerable controversy exists as to how long antidepressants should be continued, and there is no good evidence of efficacy in the maintenance phase. What is clear is the need for

monitoring of the patient's mental state and dose reduction or cessation of the antidepressant if elevated symptoms emerge.

Should an antidepressant be needed, low-dose selective serotonin reuptake inhibitors are usually adequate and may have less propensity to induce elevated phases of the disorder.[14] As fluoxetine has a five-week washout period it is best avoided in bipolar conditions in case a manic, mixed or hypomanic mood switch necessitates cessation.

Psychosocial care

Education, self-monitoring of mood, mood diaries and social rhythm training all assist with better longer-term patient outcomes. Psychosocial care is best implemented as early as possible in the course of illness to help patients with recovery and to cope with residual symptoms of illness. Including family and carers in the management plan is an important aspect of care. Continuity of care with good communication and rapport between doctor and patient is particularly important in fostering compliance with treatment and earlier presentation for acute care in the event of relapse.

Conclusion

Bipolar disorders can present in varying ways. Prompt recognition of the phase of illness and tailoring the patient's therapy accordingly will help optimise outcomes. Consider bipolar disorders in patients with treatment-resistant or recurrent depression. Newer anticonvulsants and antipsychotics offer further treatment options for these diverse and often disabling illnesses. Prescribers should carefully monitor patients with bipolar disorders who require antidepressants, given the risk of destabilising their mood. Integrating education, lifestyle modification and engagement of patients and carers in management augments therapeutic efficacy.

Table 2

Drugs for acute management of bipolar depressive episodes

Optimise current medications or initiate therapy	
First-line	– lithium, quetiapine or lamotrigine monotherapy – lithium or valproate with selective serotonin reuptake inhibitor or bupropion* – olanzapine with selective serotonin reuptake inhibitor – lithium with valproate
Second-line	– add-on or switch to a second mood stabiliser† and/or add a selective serotonin reuptake inhibitor (if patient is not already taking one)
Third-line	– mood stabiliser† with serotonin noradrenaline reuptake inhibitor or tricyclic antidepressant or monoamine oxidase inhibitor – electroconvulsive therapy

This list is a composite of recent evidence-based reviews and local consensus management guidelines for bipolar depression[8,9]

* an antidepressant re-patented in Australia for smoking cessation

† lithium, valproate, carbamazepine, lamotrigine, olanzapine or quetiapine. Keep patient on whichever mood stabilising drugs have worked during elevated phases of illness.

References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593-602.
2. Jamison KR. Suicide and bipolar disorder. J Clin Psychiatry 2000;61(Suppl 9):47-51.
3. Access Economics. Bipolar disorder: costs. An analysis of the burden of bipolar disorder and related suicide in Australia. Melbourne: Access Economics, for SANE Australia; 2003. http://www.accesseconomics.com.au/publicationsreports/reports.php [cited 2008 May 13]
4. Berk M, Dodd S, Callaly P, Berk L, Fitzgerald P, de Castella AR, et al. History of illness prior to a diagnosis of bipolar disorder or schizoaffective disorder. J Affect Disord 2007;103:181-6.
5. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530-7.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Text revision. Washington, DC: American Psychiatric Press; 2000.
7. Pyle DI, Mitchell PB. Maintenance treatments for bipolar disorders. Aust Prescr 2007;30:70-3.
8. Yatham LN, Kennedy SH, O'Donovan C, Parikh SV, MacQueen G, McIntyre RS, et al; CANMAT guidelines group. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord 2006;8:721-39.
9. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. Aust N Z J Psychiatry 2004;38:280-305.
10. Nasrallah HA, Ketter TA, Kalali AH. Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. J Affect Disord 2006;95:69-78.
11. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. Acta Psychiatr Scand 2007;115:12-20.
12. Gitlin M. Treatment-resistant bipolar disorder. Mol Psychiatry 2006;11:227-40.

13. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007;356:1711-22.
14. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006;163:232-9.

Professor Berk has received grant/research support from Stanley Medical Research Foundation, MBF, National Health and Medical Research Council, beyondblue, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma and Servier. He has been a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Pfizer. He has also been a speaker for Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Organon, Pfizer, Sanofi-Synthelabo, Solvay and Wyeth.

Self-test questions

The following statements are either true or false (answers on page 83)

7. Patients with mania are best managed in general practice.
8. In bipolar disorders, patients taking a mood stabilising drug combined with an antidepressant should be regularly reviewed for changes in their mental state.

Your questions to the PBAC

Methylphenidate

The management of adolescents who need stimulant medications is complicated by the restrictions of the Pharmaceutical Benefits Scheme (PBS). I have a patient who has benefited from using an extended-release formulation of methylphenidate. She is calmer and more relaxed than she was on intermittent doses of the immediate-release formulation. The problem is that my patient is now over 18 years old so cannot receive the extended-release formulation as a PBS prescription.

There are probably many adolescents with attention deficit hyperactivity disorder who are well managed with the extended-release formulation. Some of them will continue to need treatment after their eighteenth birthday, but the current PBS authority requirements prevent this. To continue treatment, patients will have to switch to another formulation or a different drug without an age restriction. How can this anomaly in the PBS be rectified?

George Blake
Paediatrician
Moana Medical Centre
Adelaide

PBAC response:

In assessing applications and making recommendations for PBS listing, the Pharmaceutical Benefits Advisory Committee (PBAC) is required to take into account a number of criteria, including the indication for which the medicine has been approved for use in Australia. The PBAC cannot make a recommendation on a medicine for use outside its approved indication as registered with the Therapeutic Goods Administration (TGA) as this would go against evidence-based decision making.

In the case of extended-release methylphenidate, the registered TGA indication is for the treatment of attention deficit hyperactivity disorder in children and adolescents aged 6–18 years. Consequently, when considering the application to list the drug on the PBS, the PBAC was limited to making a recommendation that covered the 6–18 year old population only.

For the PBS listing to be extended to include persons over 18 years of age, the drug's sponsor would first need to have the TGA indication changed. This would most likely involve submitting data to the TGA to demonstrate safety and efficacy in this age group. Following a revised indication, the next step would be to provide a submission to the PBAC that includes an evaluation of the cost-effectiveness of extended-release methylphenidate against immediate-release methylphenidate or another appropriate comparator in the treatment of adults.

Your questions to the PBAC

Australian Prescriber readers are invited to write in with their questions about decisions of the Pharmaceutical Benefits Advisory Committee. The segment 'Your questions to the PBAC' will publish selected questions from readers, and answers from the Committee itself. Questions may address issues such as regulatory decisions, pharmaceutical benefits listings, withdrawal of a drug from the market and Authority prescriptions.

It may not be possible to reply to all individual questions. Those letters and responses selected by the Editorial Executive Committee will be published in the journal, subject to the usual editorial controls.