The pharmacological treatment of bipolar disorder in primary care

Gin S Malhi, Danielle Adams and Michael Berk

ABSTRACT

Objective: To provide a practical overview of the pharmacological management of adults with bipolar disorder in primary care and the role of general practitioners in the pharmacotherapy of this complex disorder.

Data sources: Published guidelines for the treatment of bipolar disorder, plus Cochrane reviews, meta-analyses, review articles and reports from randomised controlled trials that were published up to May 2009.

Study selection: Over 500 articles on the treatment of bipolar disorder were reviewed, with an emphasis on meta-analyses and systematic reviews of randomised controlled trials. Where evidence was more limited, open trials and non-controlled data were also reviewed.

Data extraction: Key recommendations relevant to GPs were synthesised and rated according to National Health and Medical Research Council levels of evidence.

Data synthesis: Lithium, valproate and atypical antipsychotics are first-line treatment options for acute mania, and monotherapy is ideal if it produces an adequate response. For depressive episodes, recommendations are less definitive and the use of antidepressants is controversial. Most patients require maintenance treatment, during which pharmacotherapy should be used to prevent relapse, and psychological and social interventions should be considered.

Conclusions: Bipolar disorder is a lifelong episodic illness that affects 1%–2% of the population, many of whom are principally managed by their GPs. Pharmacological treatment with mood-stabilising agents is the primary form of management, although this is ideally provided in conjunction with psychosocial interventions.

MJA 2010; 193: S24–S30

Bipolar disorder is a common illness that affects 1%–2% of the general population;[1] it is therefore often first assessed, and frequently managed, by general practitioners. It usually presents with symptoms of depression, but a diagnosis of bipolar disorder is contingent on the occurrence of an episode of mania or hypomania.[2] Consequently, many cases of bipolar disorder remain undetected or are misdiagnosed as major (unipolar) depression. Further, individuals with hypomania rarely seek help, and those with comorbid anxiety or symptoms of depression that do not respond to treatment often resort to self-medication with alcohol or illicit substances. Equally, bipolar disorder is thought to be overdiagnosed in some populations such as adolescents and young adults.[3]

Suffice to say the clinical picture of bipolar disorder is complex and its treatment is necessarily sophisticated. In recent years, the importance of psychological and social interventions in the successful management of bipolar disorder has been increasingly recognised; however, pharmacotherapy remains the mainstay of treatment for most patients.

Traditionally, bipolar disorder is partitioned according to its phases of illness — depression, mania and euthymia (normal mood stated) — and its treatment is considered in corresponding stages. Here, we summarise the pharmacological management of adults with bipolar disorder in primary care in relation to its phases of illness. We do not discuss complex presentations, treatment non-response and comorbidities, as these are normally managed by psychiatrists, but we do briefly mention mixed states and rapid cycling.

METHODS

We synthesised recommendations from recently published guidelines for the treatment of bipolar disorder.[4-6] Treatment recommendations are therefore divided into sections on acute bipolar mania, acute bipolar depression and maintenance.

We also conducted a literature search of articles on pharmacological treatment of bipolar disorder that were published up to May 2009 — using electronic databases (MEDLINE, PubMed, PsycINFO), book chapters and articles known to the authors — to identify Cochrane reviews, meta-analyses, review articles and reports from randomised controlled trials. The search terms bipolar disorder, mania, pharmacotherapy, general practice, manic–depressive illness and depression were used. Key recommendations relevant to GPs were synthesised and rated according to National Health and Medical Research Council (NHMRC) levels of evidence.[7]

Over 500 articles were reviewed, with an emphasis on meta-analyses and systematic reviews of randomised controlled trials. Where evidence was more limited, open trials and non-controlled data were also reviewed. We distilled the key recommendations and clinical messages relevant to the pharmacological management of bipolar disorder in primary care. However, the majority of the available evidence did not satisfy NHMRC levels I or II; consequently, much of the advice is based on lower levels of evidence than would normally be ideal.

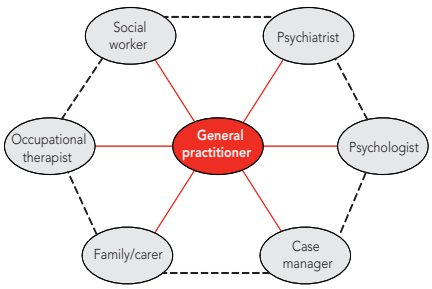
RESULTS

The role of the GP

GPs are integral to the management of bipolar disorder, often with involvement from the initial detection and assessment of the illness through to longer-term management. The GP is usually the first health professional from whom the patient will seek assistance. Alternatively, in instances where the illness emerges insidiously, it may be the GP's long-term knowledge of the patient that assists in detecting subtle changes in mood and behaviour.

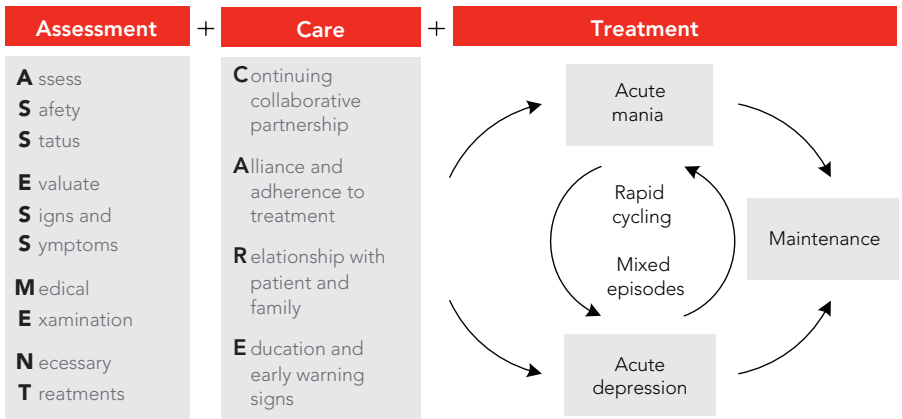
The GP's role in managing bipolar disorder will vary according to the patient, the severity of the illness and the level of available support. The GP may take on the primary role of treating the patient, with the option of referral to specialist services if and when required. Alternatively, the patient may be primarily managed by an external team, such as a community mental health service, but with links to the GP maintained. Further, multiple professionals are typically

1 The integral role of the general practitioner in the management of bipolar disorder



All health care professionals should be aware of the important role that GPs play in integrating care. It is therefore imperative that GPs are copied on all correspondence and kept informed about decisions. ◆

2 Overview of the management of bipolar disorder[4]



Reproduced with permission from: Malhi GS, Adams D, Lampe L, et al. Clinical practice recommendations for bipolar disorder. *Acta Psychiatr Scand Suppl* 2009; (439): 27-46. ◆

involved in working with patients who have a mental illness, including professionals who primarily target clinical interventions and those who target more broad aspects of life affected by the illness, such as social and occupational functioning. While many of the professionals who work with these patients should also communicate with one another, the GP often serves as the focal point around which the other services are provided, including contact with family and carers (Box 1). With respect to pharmacological management, the main priorities for the GP are to assess efficacy, encourage adherence to treatment and monitor for potential side effects. Ideally, treatment plans are developed and initiated following consultation with a psychiatrist, particularly in complex cases, and with referral back to the psychiatrist during periods of increased severity of illness or risk.

Models of treatment

If a diagnosis of bipolar disorder is suspected, the first imperative is to *act*. Action involves careful *assessment* so as to provide individualised *care* and effective *treatment*. Box 2 provides an overview of the management of bipolar disorder, adapted from previously published recommendations.[4] In all cases, management should begin with a detailed clinical assessment that includes diagnostic formulation, assessment of safety and risk, a brief medical examination (including baseline investigations and screening for medical illnesses), and implementation of any necessary action such as facilitating an emergency assessment for hospitalisation. Guidelines for baseline and ongoing monitoring in bipolar disorder have been reviewed in detail recently and are summarised in Box 3. The care principles outlined in Box 2 are applicable throughout all stages of treatment and are essential for effective long-term management. An effective collaborative alliance is important for increasing the likelihood that the patient remains engaged in treatment; this can be fostered by providing emotional support and education to the patient and his or her family. Much of this can be initiated by a GP, but prompt transition to joint involvement of a psychiatrist is recommended, especially when affirming diagnosis and planning future management.

Treatment involves implementing strategies to achieve remission of symptoms of acute manic episodes and/or depressive episodes, as well as longer-term maintenance treatment to optimise social and occupational functioning and prevent relapse. In addition, ensuring safety and specifically reducing the risk of suicide is an ongoing consideration throughout all stages of treatment. Pharmacotherapy remains the primary treatment modality, but ideally it is supplemented with psychological interventions; in some instances, specialist physical measures such as electroconvulsive therapy may also be useful. Box 4 provides a detailed overview of side effects and recommended therapeutic dosing for agents commonly used in bipolar disorder.

Acute bipolar mania

During acute mania, an assessment of risk including personal safety, reputation and the safety of others should be undertaken. Steps may need to be taken to manage acute mania — for example, hospitalisation or referral for specialist mental health services is often necessary during this phase of illness. Treatments for acute bipolar mania should aim to treat the acute symptoms of mania and to manage any accompanying behavioural disturbance (Box 5).

What are the first-line treatment options for acute mania?

Where possible, any mania-inducing agents that the patient is already taking (eg, antidepressants and stimulants) should be tapered and ceased. The patient should also be advised to institute general measures to reduce stimulation and maintain a routine, and to delay making important decisions. Restoration of sleep is also important.

With regard to pharmacological treatments, lithium, valproate, atypical antipsychotics, haloperidol and, to a lesser extent, carbamazepine all have indications for acute mania.[4-6,9] The choice of agent depends on episode severity, patient preference and likely side effects. While haloperidol is effective in acute mania, it is not a first-line option because of a high risk of extrapyramidal side effects and its inability to prevent depression. If a rapid response is required, valproate or the atypical antipsychotics are preferable to lithium.

If possible, monotherapy should be trialled to reduce the likelihood of adverse effects. However, when there is marked risk or greater severity of illness, or the response to an initial monotherapy trial has not been adequate, combinations such as lithium or valproate combined with an atypical antipsychotic add efficacy.[11,12] In

3 International Society for Bipolar Disorders guidelines for baseline and ongoing monitoring in bipolar disorder[8]

All agents

Obtain patient history: medical comorbidities (including cardiovascular disease risk factors), smoking status, alcohol use, pregnancy status, and family history of cardiovascular disease risk factors

Undertake baseline investigations: waist circumference and/or body mass index, blood pressure, full blood count, electrolytes, urea and creatinine, liver function tests, fasting glucose, and fasting lipid profile

Agent	Specific baseline investigations	Specific ongoing monitoring
Lithium	Thyroid-stimulating hormone and serum calcium	• Urea and creatinine: every 3–6 months • Thyroid-stimulating hormone, serum calcium, and weight: at 6 months, then annually
Valproate	Identify any history of haematological or hepatic disease	• Weight, full blood count, liver function tests, and menstrual changes (for women of reproductive age): every 3 months for 1 year, then annually • Provide advice on bone health
Carbamazepine	Identify any history of haematological or hepatic disease	• Full blood count: monthly • Liver function tests, and electrolytes, urea and creatinine: monthly for 3 months, then annually • Review oral contraceptive efficacy • Inform patients of potential dermatological reactions: if rash occurs, cease medication immediately and seek emergency medical attention • Provide advice on bone health
Lamotrigine	None	• Inform patients of potential dermatological reactions: if rash occurs, cease medication immediately and seek emergency medical attention
Atypical antipsychotics	Identify any family history of cardiac problems, including congenital long QT syndrome	• Weight: monthly for 3 months, then every 3 months • Blood pressure and fasting glucose: every 3 months for 1 year, then annually • Fasting lipid profile: at 3 months, then annually • Electrocardiogram and prolactin levels where clinically indicated

general, about 50% of individuals with mania respond to monotherapy with an antimanic agent, and 75% respond to a combination of an atypical antipsychotic and either lithium or valproate.

Psychotic symptoms frequently occur in acute mania and symptoms are often mood congruent (eg, grandiose delusions). If antipsychotics are not already being used, short-term administration of atypical antipsychotics may be necessary.

How should behavioural disturbance in acute mania be managed?

The adjunctive short-term use of benzodiazepines (eg, lorazepam) may help manage additional behavioural disturbance. However, these are usually tapered within days and gradually withdrawn as symptoms start to abate. If the patient is being treated with an antipsychotic for mania, this may also provide an additional settling effect.

Acute bipolar depression

Depression is the predominant phase of bipolar disorder and, as such, it confers substantive risks in terms of morbidity and suicide.[13] In comparison to acute mania, the pharmacotherapy for bipolar depression is more complicated and based on data that are less clear. This is reflected in recommendations that are generally less definitive and vary across guidelines (Box 6).

What are the first-line treatment options for bipolar depression?

First-line monotherapy options include lithium, valproate, quetiapine and lamotrigine.[9] Lithium is particularly noted for its antisuicidal properties, but is disadvantaged by a delay in effect of 2–3 weeks. First-line medication combinations include olanzapine plus fluoxetine,[14] and lithium combined with valproate or lamotrigine.[15,16] Each agent, or combination of agents, has unique advantages and disadvantages in relation to clinical effectiveness, speed of antidepressant action, tolerability and prophylactic properties.

Are the conventional antidepressants effective in bipolar depression?

Unlike the use of antidepressants in unipolar depression, antidepressant use in bipolar disorder is a controversial issue. The effectiveness of conventional antidepressants in bipolar depression is unclear, and three recent large studies have reported no additional benefit from the adjunctive use of antidepressants in bipolar depression.[17-20] Further, in some patients, the use of conventional antidepressants is associated with an increased risk of a switch to mania.[17,21,22] Nonetheless, antidepressants may benefit a small cohort of patients with bipolar depression but, if used, should be prescribed in combination with a mood-stabilising agent to minimise the risk of affective instability. In this regard, selective serotonin reuptake inhibitors are preferable because they are less likely to induce a switch to mania than other antidepressant classes and are less dangerous in cases of overdose.[23]

Maintenance treatment

Maintenance treatment (Box 7) is likely to be necessary in most patients with an established diagnosis of bipolar disorder. Following an acute episode, conservative indications for maintenance treatment include instances where there has been at least one other prior mood episode in the past 5 years or two prior episodes across the lifetime, the acute episode was severe and included suicide risk or psychotic features, or there is ongoing functional disability.

What are the key considerations in the long-term management of bipolar disorder?

Bipolar disorder is a lifelong illness with episodes that can cause marked disruption and stress not only to patients but also their families. When patients present with severe illness or experience frequent relapse, the demands on the treating physician can also be significant. It may be necessary for the GP to broaden the management and include referrals to external health care providers

4 Side effects and therapeutic dosing for agents commonly used in bipolar disorder*[8-10]

Side effects		Therapeutic dosing	
Common (incidence ⩾ 1%)	Uncommon or rare (incidence < 1%)†	Dose range and serum levels	Dosing considerations
Lithium			
GIT: nausea, vomiting, epigastric discomfort, dry mouth, metallic taste, diarrhoea, weight gain CNS: fatigue, headache, difficulty concentrating, vertigo, fine tremor Skin: dry skin, exacerbation of psoriasis or acne, rash Metabolic: hypermagnesaemia, hypercalcaemia, hypothyroidism Other: benign electrocardiogram changes, leukocytosis	Nephrogenic diabetes insipidus, hyperparathyroidism, memory impairment, hair loss, arrhythmias, hyperthyroidism	Acute mania: 400–1200 mg/day Maintenance: reduce dose to maintain serum level within therapeutic range Therapeutic levels: 0.6–0.8 mmol/L (lower end of range recommended for maintenance) Risk of toxicity increases markedly at > 1.5 mmol/L (> 3.5 mmol/L is potentially lethal), toxicity can also occur within the therapeutic range (particularly in older patients) Abrupt reduction of > 0.2 mmol/L increases risk of relapse	Lithium concentration can be affected by other medications (eg, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs) and sodium depletion (eg, gastrointestinal disturbance) There can be a delay of 6–8 weeks for an antidepressant effect
Lithium toxicity: signs include loss of balance, increasing diarrhoea, vomiting, anorexia, weakness, ataxia, blurred vision, tinnitus, polyuria, coarse tremor, muscle twitching, irritability and agitation. Drowsiness, psychosis, disorientation, seizures, coma and renal failure may also occur.			
Valproate			
GIT: nausea, vomiting, abdominal cramps, anorexia, diarrhoea, indigestion (especially preparations without enteric coating), increased appetite and weight gain CNS: sedation, tremor Skin: transient hair loss Other: thrombocytopenia, elevated liver transaminase levels, asymptomatic elevations of ammonia	Severe hepatic dysfunction, pancreatitis, extrapyramidal syndrome, hyperammonaemic encephalopathy	Acute mania: can consider rapid titration Maintenance: usually 1000–2000 mg/day, divided doses, titrated gradually Therapeutic levels: 350–700 mmol/L (guide only)‡	
Carbamazepine			
GIT: dry mouth, vomiting, diarrhoea, anorexia, constipation, abdominal pain CNS: dizziness, headache, ataxia, drowsiness, blurred vision, diplopia Skin: rash	Agranulocytosis, aplastic anaemia, severe skin reactions (including Stevens–Johnson syndrome), SIADH, arrhythmias, orofacial dyskinesias, hepatitis	Acute mania: 400–1200 mg/day, titrated gradually Maintenance: 200–400 mg/day Therapeutic levels: 20–50 mmol/L (guide only)	Carbamazepine impacts on the cytochrome p450 system and can affect other drugs that are metabolised by this system (eg, antidepressants, anticonvulsants, risperidone, haloperidol)

GIT = gastrointestinal tract. CNS = central nervous system. SIADH = syndrome of inappropriate antidiuretic hormone secretion. * This table is not exhaustive and specific product information and recognised sources of information should be consulted before prescribing. † In addition, every medication has the potential to cause a hypersensitivity syndrome (fever, severe skin reactions, lymphadenopathy, hepatitis, haematological abnormalities, facial oedema). ‡ Routine monitoring is not necessary and only recommended when initiating therapy or altering doses. ◆

such as psychiatrists, psychologists, social workers and case managers working within community mental health teams.

Treatment non-adherence is a major risk factor for relapse. The maintenance phase is therefore an important time to re-evaluate the treatment plan, work with the patient to maintain engagement in treatment and develop a collaborative approach to care. Engagement of family members may also be particularly beneficial. The long-term nature of primary care lends itself to monitoring and supporting adherence. In particular, it is important to assess for comorbidities (such as anxiety, and drug and alcohol misuse); monitor for subsyndromal depressive symptoms; monitor side effects of medications (including cardiometabolic health risk); identify and check for early warning signs; provide education about the illness; promote a healthy lifestyle which includes good sleep, hygiene, regular exercise and routines; and foster the development of problem-solving skills. The maintenance phase is therefore the optimum time to consider incorporating adjunctive psychological and social interventions into the treatment plan.

Which treatments are recommended in the long-term management of bipolar disorder?

Following an acute episode, it is important to taper and withdraw any agents (such as benzodiazepines or antipsychotics) that were used to manage temporary behavioural or cognitive disturbance. The goal of pharmacotherapy in maintenance is to prevent

4 Side effects and therapeutic dosing for agents commonly used in bipolar disorder (continued)*[8-10]

Side effects		Therapeutic dosing	
Common (incidence ⩾ 1%)	Uncommon or rare (incidence < 1%)†	Dose range and serum levels	Dosing considerations
Lamotrigine			
GIT: dry mouth, nausea, vomiting CNS: diplopia, dizziness, ataxia, blurred vision, headache, irritability, somnolence, tremor, asthenia, insomnia Skin: maculopapular rash, Stevens–Johnson syndrome (0.3–2.0% in children)‡ Other: arthralgia	Hepatic failure, blood dyscrasias, lupus-like reaction, severe skin reactions including Stevens–Johnson syndrome and Lyell syndrome	Acute bipolar depression: 100–200 mg/day titrated upwards slowly No demonstrated benefits in measuring serum lamotrigine	To prevent serious skin reaction, initiate at a low dose and increase slowly Dosage may need to be adjusted if combining with other medications, particularly valproate and carbamazepine
Atypical antipsychotics			
Metabolic: weight gain, dyslipidaemia, hyperglycaemia, hyperprolactinaemia Extrapyramidal symptoms: tremor, akathisia, rigidity, slowing, dystonia Anticholinergic reactions: constipation, dry mouth, blurred vision, urinary retention Other: sedation, increased appetite, sexual dysfunction, gastrointestinal upset, peripheral oedema, nausea, cerebrovascular events such as stroke and TIA (especially in older patients), orthostatic hypotension, tachycardia	Jaundice, neuroleptic malignant syndrome, seizures, tardive dyskinesia, electrocardiogram changes (increased QT interval), SIADH, temperature irregularity, blood dyscrasias, arrhythmias, cardiac arrest, seizures, hepatic fibrosis, lupus Clozapine: agranulocytosis (1%), myocarditis, cardiomyopathy, seizures	Olanzapine: acute mania, 5–20 mg/day; maintenance, continue at dose used for acute episode Risperidone: acute mania, usual dose 2–6 mg/day Quetiapine: acute mania, usual dose 200–800 mg/day titrated to average of 600 mg/day; depression, usual dose 300–600 mg/day Ziprasidone: acute mania, 80–160 mg/day	
SSRI antidepressants			
GIT: nausea, diarrhoea CNS: dizziness, headache, tremor, agitation, insomnia, drowsiness Anticholinergic reactions: dry mouth Other: myalgia, sweating, weakness, anxiety, weight gain or loss, sexual dysfunction, rhinitis	Extrapyramidal reactions: including tardive dyskinesia and dystonia Other: sedation, confusion, palpitations, tachycardia, hypotension, hyponatraemia (as part of SIADH), abnormal platelet aggregation or haemorrhagic complications (eg, bruising, epistaxis, gastrointestinal and vaginal bleeding), elevated liver enzymes, hepatitis, hepatic failure, galactorrhoea, blood dyscrasias, seizures, akathisia, paraesthesia, taste disturbance	Equivalent doses used in treating major depression	Serotonin toxicity is a potentially life-threatening adverse drug reaction with cognitive, autonomic and somatic effects Some combinations with other drugs are contraindicated (especially MAOIs or within 14 days of stopping a MAOI, and moclobemide or within 2 days of stopping moclobemide) should be avoided

GIT = gastrointestinal tract. CNS = central nervous system. TIA = transient ischaemic attack. SSRI = selective serotonin reuptake inhibitor. SIADH = syndrome of inappropriate antidiuretic hormone secretion. MAOI = monoamine oxidase inhibitor. * This table is not exhaustive and specific product information and recognised sources of information should be consulted before prescribing. † In addition, every medication has the potential to cause a hypersensitivity syndrome (fever, severe skin reactions, lymphadenopathy, hepatitis, haematological abnormalities, facial oedema). ‡ Risk is greatest with high initial doses or when combined with valproate. ◆

relapse. In this regard, lithium is still considered the gold-standard treatment, although it appears to be more effective at preventing manic relapse than depression. Lamotrigine and valproate also have prophylactic properties, with lamotrigine being more efficacious at preventing depressive relapse compared with manic relapse.[24,25] Other anticonvulsants (eg, carbamazepine) have been less impressive and are not consistently recommended as first-line treatment options.[4,9]

There is growing interest in the use of atypical antipsychotics for maintenance treatment, and quetiapine, olanzapine and aripiprazole have been shown to have benefits. Quetiapine appears to be equally effective at preventing both manic and depressive episodes, whereas all other atypical antipsychotics are more effective at preventing manic episodes. While some longer-term evidence is beginning to emerge,[26-28] the long-term prophylactic properties of atypical antipsychotics are yet to be reliably established and further research is needed before such agents can be confidently recommended for long-term use in bipolar disorder; there is no clear class effect in this regard.

Again, monotherapy is considered ideal and trials of medications may take several months before effectiveness becomes clear. Nonetheless, a significant proportion of patients will not respond adequately and

5 Summary of treatments for acute mania

- *Focus of treatment:* treat acute symptoms of mania and manage any behavioural disturbance.
- *First-line treatments:* lithium, valproate and atypical antipsychotics.
- *Behavioural disturbance:* short-term benzodiazepine or antipsychotic therapy (if not already prescribed for mania). ◆

6 Summary of treatment for bipolar depression

- *First-line monotherapy options:* lithium, valproate, quetiapine and lamotrigine.
- *First-line combination options:* olanzapine plus fluoxetine, and lithium combined with valproate or lamotrigine.
- *Antidepressants:* the efficacy of antidepressants is not established in bipolar depression. If prescribing antidepressants, always do so in combination with an agent that has antimanic properties to limit the risk of affective instability or a switch to mania. ◆

7 Summary of maintenance treatments

- *Considerations:* facilitate engagement in treatment, assess for comorbidities, monitor side effects, provide education about illness, identify and check for early warning signs.
- *First-line treatments:* lithium, lamotrigine, valproate and quetiapine.
- *Second-line treatments:* olanzapine, aripiprazole and carbamazepine.
- *Inadequate response to treatment:* seek consultation with a psychiatrist. ◆

combination regimens are the rule rather than the exception; this may require further consultation with psychiatrists. Treatment options for patients who experience rapid cycling and mixed episodes are summarised in Box 8.

Novel and emerging treatments

There are a number of novel agents that have shown promise in initial clinical trials in treating bipolar disorder. While further trials are needed before specific recommendations can be made, such agents include *N*-acetylcysteine,[29] omega-3 fatty acids,[30] tamoxifen,[31,32] asenapine,[33] antiglucocorticoids,[34] celecoxib,[35] modafinil[36] and pramipexole.[37]

8 Rapid cycling and mixed episodes

During rapid cycling, individuals with bipolar disorder experience four or more mood episodes over a 12-month period, and some of these may be mixed episodes. A mixed episode is a period that lasts a week or more and satisfies criteria for both a manic and major depressive episode (except duration).

Rapid cycling

Rapid cycling is associated with poorer long-term response to treatment, higher rates of morbidity and increased suicide risk. Factors that may precipitate or exacerbate rapid cycling, such as antidepressants, substance misuse, medications and medical illness should be excluded. The evidence base for management of rapid cycling is limited and treatments appear to be less effective in treating depressive symptoms than manic symptoms.

Treatment options include:

- Pharmacological monotherapy: valproate, lithium, olanzapine, lamotrigine and quetiapine
- Pharmacological combinations: lithium plus valproate, and lithium plus carbamazepine or lamotrigine
- Adjunctive psychological interventions.

Mixed episodes

Mixed episodes can be difficult to diagnose. Initially, taper and cease all substances with a potential to elevate mood (eg, antidepressants, stimulants).

Treatment options include:

- Pharmacological monotherapy: olanzapine, quetiapine and valproate
- Pharmacological combinations: olanzapine plus fluoxetine, and valproate plus olanzapine. ◆

CONCLUSION

Bipolar disorder is a complex illness but, in most cases, it can be managed effectively once it is detected and the necessary supports and treatments are instituted. The role of the primary care physician is pivotal in the identification of bipolar disorder and its subsequent lifelong management. Suitable treatments are increasingly available but require sophisticated administration. Hence, it is important that health professionals in all areas of medicine are familiar with the management of this common psychiatric illness.

ACKNOWLEDGEMENTS

Financial support for this research was provided by the NHMRC (Program Grant 510135).

COMPETING INTERESTS

Gin Malhi has served on international and national pharmaceutical advisory boards, received funding for research and has been in receipt of honoraria for talks at sponsored meetings worldwide involving AstraZeneca, Eli Lilly, Janssen-Cilag, Organon, Pfizer and Wyeth. Danielle Adams has received an honorarium from Eli Lilly for a speaking engagement. Michael Berk has received funding for research from Stanley Medical Research Foundation, MBF, NHMRC, beyondblue, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma and Servier, and honoraria for speaking engagements from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Pfizer, Sanofi-Synthelabo, Servier, Solvay and Wyeth, and has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Servier.

AUTHOR DETAILS

Gin S Malhi, FRCPsych, FRANZCP, MD, Professor of Psychiatry,[1,2] and Head[3]
Danielle Adams, BSc(Psych)(Hons), MPsych(Clin), Clinical Psychologist[1,2]
Michael Berk, MB BCh, FRANZCP, PhD, Professor of Psychiatry and Professorial Research Fellow,[4,5,6] and Head, First Episode Bipolar Unit[7]

1 CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, Sydney, NSW.
2 Northern Sydney Central Coast Mental Health Drug and Alcohol Services, Northern Sydney Central Coast Area Health Service, Sydney, NSW.
3 Discipline of Psychiatry, University of Sydney, Sydney, NSW.
4 Department of Clinical and Biomedical Sciences — Barwon Health, University of Melbourne, Melbourne, VIC.
5 The Geelong Clinic, Healthscope, Geelong, VIC.
6 Mental Health Research Institute, Melbourne, VIC.
7 Orygen Youth Health Research Centre, Melbourne, VIC.

Correspondence: gin.malhi@sydney.edu.au

REFERENCES

1 Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007; 64: 543-552.
2 American Psychiatric Association. Diagnostic and statistical manual for mental disorders. 4th ed. Washington, DC: APA, 1994.
3 Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? *J Clin Psychiatry* 2008; 69: 935-940.

4 Malhi GS, Adams D, Lampe L, et al. Clinical practice recommendations for bipolar disorder. *Acta Psychiatr Scand Suppl* 2009; (439): 27-46.

5 National Institute for Health and Clinical Excellence. Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Clinical Guideline 38. London: National Health Service, 2006.

6 Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord* 2009; 11: 225-255.

7 National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: Commonwealth of Australia, 1999.

8 Ng F, Mammen OK, Wilting I, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar Disord* 2009; 11: 559-595.

9 Malhi GS, Adams D, Cahill CM, et al. The management of individuals with bipolar disorder: a review of the evidence and its integration into clinical practice. *Drugs* 2009; 69: 2063-2101.

10 Malhi GS, Berk M. How to treat bipolar disorder. *Aust Doctor* 2008; 13 Jun: 25-32. http://www.australiandoctor.com.au/HTT/PDF/ad_025_032__jun13_08.pdf (accessed Jul 2010).

11 Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry* 2007; 64: 442-455.

12 Smith LA, Cornelius V, Warnock A, et al. Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. *Acta Psychiatr Scand* 2007; 115: 12-20.

13 Mitchell PB, Malhi GS. Bipolar depression: phenomenological overview and clinical characteristics. *Bipolar Disord* 2004; 6: 530-539.

14 Tohen M, Vieta E, Calabrese J. Efficacy of olanzapine and olanzapine/fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003; 60: 1079-1088.

15 van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; 70: 223-231.

16 Young LT, Joffe RT, Robb JC, et al. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. *Am J Psychiatry* 2000; 157: 124-126.

17 Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004; 161: 1537-1547.

18 Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 2007; 356: 1711-1722.

19 Ghaemi SN. Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression. *Bipolar Disord* 2008; 10: 957-968.

20 Malhi GS. Seeking definition. *Bipolar Disord* 2008; 10: 853-855.

21 Leverich GS, Altshuler LL, Frye MA, 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: 232-239.

22 Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 2006; 189: 124-131.

23 Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. *Br J Psychiatry* 1994; 164: 549-550.

24 Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003; 60: 392-400.

25 Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; 64: 1013-1024.

26 Vieta E, Eggens I, Persson I, et al. Efficacy and safety of quetiapine in combination with lithium/divalproex as maintenance treatment for bipolar I disorder (international trial D1447C00126). *Eur Psychiatry* 2008; 23 Suppl 2: S237-S238.

27 Suppes T, Liu S, Brecher M, et al. Maintenance treatment in bipolar I disorder with quetiapine concomitant with lithium or divalproex: a placebo-controlled, randomized multicenter trial: Abstracts from the 3rd Biennial Conference of the International Society for Bipolar Disorders 2008. *Bipolar Disord* 2008; 10 Suppl 1: 40.

28 Brecher M, Anderssen H, Paulsson B. Quetiapine in the maintenance treatment of bipolar I disorder: combined data from two long-term phase III studies. *Eur Psychiatry* 2008; 23 Suppl 2: S225-S226.

29 Berk M, Copolov DL, Dean O, et al. *N*-acetyl cysteine for depressive symptoms in bipolar disorder — a double-blind randomized placebo-controlled trial. *Biol Psychiatry* 2008; 64: 468-475.

30 Montgomery P, Richardson AJ. Omega-3 fatty acids for bipolar disorder. *Cochrane Database Syst Rev* 2008; (2): CD005169. doi: 10.1002/14651858.

31 Palmer JT, Payne JL. Stabilization of hypomania following initiation of tamoxifen. *Am J Psychiatry* 2008; 165: 650-651.

32 Mathew SJ, Manji HK, Charney DS. Novel drugs and therapeutic targets for severe mood disorders. *Neuropsychopharmacology* 2008; 33: 2080-2092.

33 Calabrese J, Cohen M, Zhao J, Panagides J. Efficacy and safety of asenapine as adjunctive treatment for acute mania associated with bipolar disorder [Abstract NR3-061]. New Research Abstracts, Annual Meeting of the American Psychiatric Association. Washington, DC: American Psychiatric Association, 2008

34 Gallagher P, Malik N, Newham J, et al. Antiglucocorticoid treatments for mood disorders. *Cochrane Database Syst Rev* 2008; (1): CD005168.

35 Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol* 2008; 23: 87-94.

36 Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 2007; 164: 1242-1249.

37 Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 2004; 161: 564-566.

(Received 14 Feb 2010, accepted 27 May 2010) ❑