

## Clinical overview

# Clinical practice recommendations for bipolar disorder

Malhi GS, Adams D, Lampe L, Paton M, O'Connor N, Newton LA, Walter G, Taylor A, Porter R, Mulder RT, Berk M. Clinical practice recommendations for bipolar disorder.

**Objective:** To provide clinically relevant evidence-based recommendations for the management of bipolar disorder in adults that are informative, easy to assimilate and facilitate clinical decision-making.

**Method:** A comprehensive literature review of over 500 articles was undertaken using electronic database search engines (e.g. MEDLINE, PsychINFO and Cochrane reviews). In addition articles, book chapters and other literature known to the authors were reviewed. The findings were then formulated into a set of recommendations that were developed by a multidisciplinary team of clinicians who routinely deal with mood disorders. These preliminary recommendations underwent extensive consultative review by a broader advisory panel that included experts in the field, clinical staff and patient representatives.

**Results:** The clinical practice recommendations for bipolar disorder (bipolar CPR) summarise evidence-based treatments and provide a synopsis of recommendations relating to each phase of the illness. They are designed for clinical use and have therefore been presented succinctly in an innovative and engaging manner that is clear and informative.

**Conclusion:** These up-to-date recommendations provide an evidence-based framework that incorporates clinical wisdom and consideration of individual factors in the management of bipolar disorder. Further, the novel style and practical approach should promote their uptake and implementation.

**G. S. Malhi<sup>1,2,3</sup>, D. Adams<sup>1,2</sup>,  
L. Lampe<sup>1,2,3</sup>, M. Paton<sup>2</sup>,  
N. O'Connor<sup>3,4</sup>, L. A. Newton<sup>2</sup>,  
G. Walter<sup>3,5</sup>, A. Taylor<sup>2</sup>, R. Porter<sup>6</sup>,  
R. T. Mulder<sup>6</sup>, M. Berk<sup>7,8,9</sup>**

<sup>1</sup>CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, St Leonards, NSW, Australia, <sup>2</sup>Northern Sydney Central Coast Mental Health Drug and Alcohol, Northern Sydney Central Coast Area Health Service, Sydney, NSW, Australia, <sup>3</sup>Discipline of Psychological Medicine, University of Sydney, Sydney, NSW, Australia, <sup>4</sup>Sydney South West Area Health Service, Sydney, NSW, Australia, <sup>5</sup>Child and Adolescent Mental Health Services, NSCCAHS, Sydney, NSW, Australia, <sup>6</sup>Department of Psychological Medicine, University of Otago, Christchurch, New Zealand, <sup>7</sup>Melbourne University, Barwon Health and the Geelong Clinic, Geelong, Victoria, Australia, <sup>8</sup>Orygen Research Centre, University of Melbourne, Melbourne, Victoria, Australia and <sup>9</sup>Mental Health Research Institute, Melbourne, Victoria, Australia

Key words: bipolar disorder; treatment recommendations; clinical practice guidelines; evidence-based review

Professor Gin S Malhi, CADE Clinic, Level 5, Building 36, Royal North Shore Hospital, St Leonards, Sydney, NSW 2065, Australia.  
E-mail: gmalhi@med.usyd.edu.au

### Clinical recommendations

- The management of bipolar disorder should be based on an integration of evidence-based data and clinical experience.
- Once a diagnosis of bipolar disorder is suspected it is important to *ACT* promptly. Action involves careful '*assessment*' so as to provide individual '*care*' and effective '*treatment*'.
- The management of bipolar disorder should be based upon a robust therapeutic relationship.
- Psychological strategies are effective and should be regarded alongside pharmacological treatments as integral to the management of bipolar disorder.

### Additional comments

- The clinical practice recommendations (CPR) for bipolar disorders should be used in conjunction with other recognised sources to guide the management of bipolar disorder.
- Practice recommendations or treatment guidelines cannot fully capture the myriad of variables unique to each individual and thus need to be used flexibly alongside consideration of the person, their sociocultural context and availability of resources.
- The bipolar CPR focus on the management of bipolar disorder in adults. Special populations, comorbidities and novel treatments have not been reviewed in detail.

## Introduction

Bipolar disorder, formerly known as manic-depressive illness, is a common, chronic, episodic mood disorder that is one of the leading causes of disability worldwide (1). In addition to lengthy periods of illness, it is associated with marked inter-episode dysfunction and consequently, individuals spend a significant proportion of their lives unwell (2). Further, the illness confers a high risk of self-harm and suicide (3) and yet, in practice, the diagnosis is often delayed, resulting in widespread suboptimal management of the disorder. High rates of comorbidity with anxiety disorders and a propensity towards substance misuse further limit detection and effective treatment.

Fortunately, in recent years, there has been a marked increase in the number of studies examining bipolar disorder. Researchers worldwide have attempted to better define the illness and understand its nature, and develop more effective treatments and management strategies.

## Facts and figures

The aetiology and pathogenesis of bipolar disorder is not known, however, a number of likely factors including psychological, social and biological determinants have been identified. Environmental factors and lifestyle issues are thought to impact on the severity and trajectory of the illness (4, 5). In particular, stressful life events and substance misuse may adversely affect treatment response and time to recovery (6, 7). Further, bipolar disorder has been shown to be a strongly heritable illness (8, 9) that results in higher rates of mood disorder in first-degree relatives (10).

The statistics pertaining to bipolar disorder vary somewhat according to its diagnosis and definition; however, some key facts and figures are summarised in Box 1. Estimates of bipolar disorder differ considerably across epidemiological studies of community samples with recent research suggesting, that together, bipolar I and bipolar II affect nearly 4% of adults (11). However, even this figure, which is twice that of other studies (see Box 1), is considered by some to be conservative because it does not include individuals within the bipolar spectrum (12).

An early age of onset of bipolar disorder appears to be associated with greater severity and poorer outcome (13, 14). However, in practice, there is a significant delay in the assignment of a correct diagnosis and institution of appropriate treatment (15).

In part, this occurs because bipolar disorder most often begins with a depressive episode that naturally

leads to a diagnosis of depression (16, 17), and usually, several depressive episodes precede the first episode of mania or hypomania (18, 19). Further, mania and especially hypomania are routinely under-reported and in practice fail to prompt clinical consultation (20, 21). In fact, symptoms of hypomania are often not regarded as problematic and can be difficult to identify if they occur amongst depressive symptoms as in mixed hypomania (22).

Recent research has identified subtle neuropsychological deficits even in the euthymic phase of bipolar disorder (23–25), and it is likely that these impact upon social and executive functioning. Clinically, bipolar disorder is marked by significant interpersonal and occupational difficulties (17, 26, 27) that perhaps stem from cognitive impairment and result in functional disability.

### Box 1. Facts and figures of bipolar disorder

#### Epidemiological statistics

- Lifetime prevalence of bipolar I is 1%; mean reported age of first mood episode is 18.2 years (28).
- Lifetime prevalence of bipolar II is 1.1%; mean reported age of first mood episode is 20.3 years (28).
- Bipolar I affects both genders equally; bipolar II is more common in women (29, 30).

#### Illness characteristics

- Age at which first symptoms of bipolar disorder emerge peaks 15–19 years.
- First mood episode is most likely to be depression; this is also the predominant phase of the illness (2, 20).
- Bipolar disorder confers a significant risk of suicide (15 times more likely than in general population); 7–15% of bipolar individuals commit suicide (30); suicide is most likely to occur during mixed or depressive episodes (31).

#### Treatment responsiveness

- A significant number of individuals with bipolar disorder achieve high levels of functioning; however, many remain chronically ill despite robust management.
- Rapid cycling and psychotic features are associated with greater treatment resistance.
- Medication, especially lithium may significantly reduce the risk of suicide (32).

## Phases and phenomenology

Bipolar disorder is a recurrent episodic illness that comprises periods of depression, mania, hypomania and mixed states. The signs and symptoms of bipolar depression are generally similar, but not identical, to those of unipolar depression. For instance, in comparison with unipolar depression, atypical features, particularly hypersomnia,

Table 1. Common signs and symptoms associated with mania and bipolar depression

Signs/symptoms*	Mania	Bipolar depression
Appearance	Unusual, garish or strange attire	Diminished attention to physical appearance, grooming or personal hygiene
Behaviour	Increased sociability Sustained goal-directed activity (although often ineffective) Increased impulsivity and risk-taking behaviours and increased sexual drive	Reduced interest or pleasure in most activities Less likely to initiate activities Reduced appetite/weight loss
Cognition	Distractible or heightened focus on irrelevant details Difficulties with planning and reasoning Diminished capacity to make decisions	Diminished concentration Problems with short-term memory Difficulty in decision-making
Energy	Marked increase in energy	Diminished energy, lethargy
Mood	Abnormal and sustained elation/euphoria or irritability	Depressed mood, sadness or flatness, feelings of worthlessness, diurnal variation in mood
Psychomotor changes	Restlessness, agitation	Retardation (slowed speech, thoughts, movements)
Sleep	Reduced need for sleep	Impaired sleep: insomnia, early morning awakening or hypersomnia with daytime napping
Speech	Loud, accelerated, pressured Talkative and difficult to interrupt	Slowed, decreased volume Reduced variation in tone Reduced content
Thought content	Inflated self-esteem Grandiose ideation (may be delusional)	Diminished self-esteem. Ideas of hopelessness and helplessness Recurrent thoughts of death or suicidal ideation (with plans or attempts) Excessive or inappropriate guilt, self-blame (may become delusional)
Thought form	Flight of ideas, racing thoughts Circumstantiality/tangentiality	Impoverished, slowed thinking Negative ruminations

Source: adapted from Malhi and Berk (34).

\*Refer to DSM-IV-TR (33) for detailed descriptions and additional criteria and specifiers.

melancholia, psychotic symptoms and psychomotor changes are more likely to feature in bipolar depression (19, 21). In contrast, the signs and symptoms of mania are quite markedly different and often completely reversed (Table 1).

Admixtures of symptoms of varying severity and duration produce a variety of symptom profiles that constitute differing mood episodes. The latter, along with course specifiers, are described in Table 2. Clinically, mania, hypomania and mixed states characterise bipolar disorder and differentiate it from unipolar depression. Bipolar disorder is further categorised into subtypes that include bipolar I and bipolar II (see Table 3). However, the thresholds for defining mood episodes, and hence these subtypes, remain under discussion (35).

Consequently, in addition to a categorical approach, some researchers have proposed a dimensional perspective in which bipolar illness is viewed as a spectrum of disorders (bipolar spectrum disorder) (12, 36). However, to date, the majority of findings stem from research conducted in bipolar I disorder and therefore these recommendations deal predominantly with the subtypes defined in DSM-IV-TR (33) (see Table 3). The management of bipolar I disorder is considered according to its phases of illness; however, the recommendations also comment upon complex presentations such as rapid cycling, mixed states and partial or no treatment response.

Table 2. DSM-IV-TR phenomenology of bipolar episodes

Bipolar disorder episodes	
Manic episode	A distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week duration (or any duration if hospitalised) that causes significant functional impairment
Major depressive episode	Includes at least five of the depressive symptom criteria (see Table 2 in Malhi et al. (37)) over a 2-week period causing impairment in functioning
Mixed episode	Criteria for both a manic and major depressive episode (except for duration) are satisfied nearly every day during a period of 1 week or more
Hypomanic episode	A distinct period of persistently elevated, expansive or irritable mood, lasting throughout at least 4 days. There are no psychotic features and the episode does not cause marked impairment in social or occupational functioning, or necessitate hospitalisation
Rapid cycling	The occurrence of four or more mood episodes during a period of 12 months. Episodes can occur in any combination and order, but are demarcated by partial or full remission for at least 2 months or by a switch to an episode of opposite polarity

Source: for detailed diagnostic criteria consult DSM-IV-TR (33).

Specific terminology has been used in the bipolar clinical practice recommendations (CPR) to categorise the pharmacological agents available for the treatment of bipolar disorder. The terms have been chosen on the basis of the intended *therapeutic action* rather than the traditional *class* of the medication (see Fig. 1). For example, *antimanic*

Table 3. DSM-IV-TR classification of bipolar subtypes

DSM-IV-TR classification of bipolar disorder	
Bipolar I disorder	One or more episode of mania with or without major depressive episodes
Bipolar II disorder	One or more episode of hypomania as well as at least one major depressive episode with no psychotic features
Cyclothymic disorder	Low grade cycling of mood with the presence or history of hypomanic episodes and periods of depression that do not meet criteria for major depressive episodes
Bipolar disorder NOS	Bipolar symptoms that do not meet the criteria for previous subtypes

Source: for detailed diagnostic criteria consult DSM-IV-TR (33). NOS, not otherwise specified

*agents* are medications efficacious in the treatment of mania or hypomania and *maintenance agents* are those administered in the euthymic phase of bipolar disorder with proven prophylactic efficacy, namely, the maintenance of well-being. A third term, *bipolar depression agent*, has been coined to describe medications with efficacy in the treatment of bipolar depression. It is not to be confused or used interchangeably with antidepressants. Some medications may belong to more than one category, depending on their indication or use but the term *mood stabiliser* has deliberately been omitted from the recommendations to reduce confusion. For instance, many agents are effective maintenance treatments but are not as effective acutely, and the converse also applies. The use of specific terms also allows recognition of the increasing role of agents such as the atypical antipsychotic medications, which along with many other medications, do not qualify fully as mood stabilisers on the grounds they are untested long-term (38, 39). The application of these terms as they are applied to each phase of bipolar illness is illustrated in Fig. 1.

The terms response, remission, recovery and relapse are defined in the accompanying depression CPR [see Fig. 1 of Malhi et al. (37)]. The defini-

tions of these terms have been adapted for use in bipolar disorder and are detailed in a recent set of bipolar guidelines (40).

Aims of the recommendations

The clinical practice recommendations for bipolar disorders have been devised to assist the management of bipolar disorder. The recommendations aim to reflect both evidence-based practice and real-world experience. To achieve widespread uptake and implementation, a deliberate effort has been made to make the recommendations appealing and easy to assimilate.

Material and methods

The bipolar CPR have been developed by a team of clinicians and researchers that routinely treat bipolar disorder in a variety of clinical settings [for a detailed description of the methods see Malhi and Adams (41)]. The primary aim of the bipolar CPR was to provide a practical overview of managing bipolar disorder in adults, from clinical assessment through to treatment. The treatment sections are divided into acute mania, acute bipolar depression, complex presentations, maintenance and the management of partial or non-response.

The strength of the recommendations contained within the bipolar CPR reflects the National Health and Medical Research Council Levels of Evidence criteria as listed in Table 4 [see Malhi and Adams for further discussion (41)].

Results

The management of bipolar disorder: ‘ACT’

Bipolar disorder is a complex illness that requires sophisticated management and this is best achieved

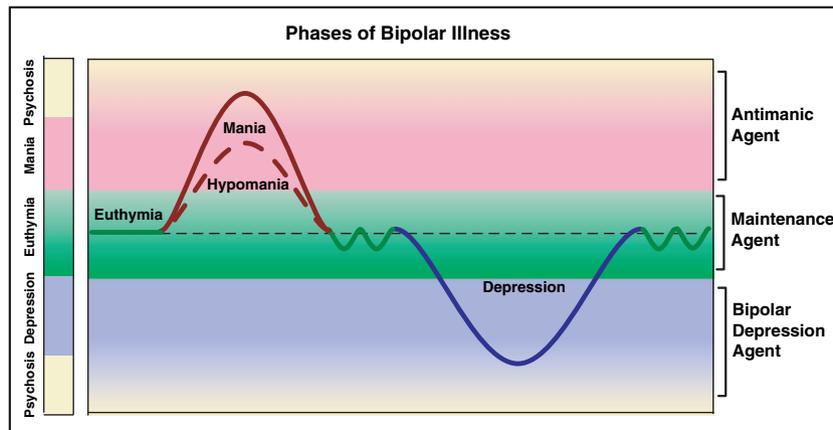


Fig. 1. The phases of bipolar illness with corresponding treatment terminology.

Table 4. Definition of levels of evidence criteria used in bipolar recommendations

Level	NHMRC level of evidence (42)
I	Systematic review of all relevant randomised controlled trials
II	One or more properly designed randomised controlled trial
III	Well-designed prospective trial (non-randomised controlled trial); comparative studies with concurrent controls and allocation not randomised; case-controlled or interrupted time series with a control group
IV	Case series, either post-test or pretest/post-test
V	Expert opinion

NHMRC, National Health and Medical Research Council.

using a multidisciplinary approach. Successful long-term management usually involves family members, mental health specialists and a primary care physician.

Clinically, once a diagnosis of bipolar disorder is suspected the first imperative is to ‘act’ (see Figure 2). Action involves careful ‘assessment’ so as to provide individualised ‘care’ and effective ‘treatment’.

Assessment

In all cases, the management of bipolar disorder should begin with a detailed clinical ‘assessment’ (see Box 2) performed by a mental health professional. The aim of assessment is to formulate a diagnosis and institute any necessary measures. A brief medical evaluation that includes a number of baseline investigations should also be conducted to screen for medical illnesses (see Table 5).

Table 5. Recommended baseline investigations for bipolar disorder

Recommended baseline investigations for bipolar disorder
<b>Obtain</b>
Personal and family medical history (screen for metabolic and cardiac disease)
<b>Examine</b>
Extrapyramidal side-effects: clinical assessment of abnormal involuntary movements
Cataracts: ocular examination (quetiapine only)
Metabolic syndrome:
Waist circumference
Body mass index
Blood pressure
Fasting lipid profile (triglycerides, HDL, LDL)
Fasting blood sugar
<b>Screen/Test</b>
Full blood count
Blood chemistry
Electrolytes
Serum creatinine (including 24 h creatinine clearance)
Thyroid stimulating hormone – liver function tests
Urinalysis
Hyperprolactinaemia
Prolactin levels (if indicated)
Substance use
Urine toxicology (if indicated)
Polycystic ovarian syndrome
Reproductive endocrine abnormalities (if prescribing valproate to females of child-bearing potential)
Pregnancy test (if indicated, especially if prescribing valproate or carbamazepine)
Test for infectious diseases (if indicated)
<b>Perform</b>
ECG (if prescribing lithium and age > 40 years)
EEG (if indicated)
If indicated, MRI (preferred)/CT

Source: from references (48–51).

HDL, high-density lipoproteins; LDL, low-density lipoproteins; ECG, electrocardiogram; EEG, electroencephalograph; MRI, magnetic resonance imaging; CT, computerised tomography.

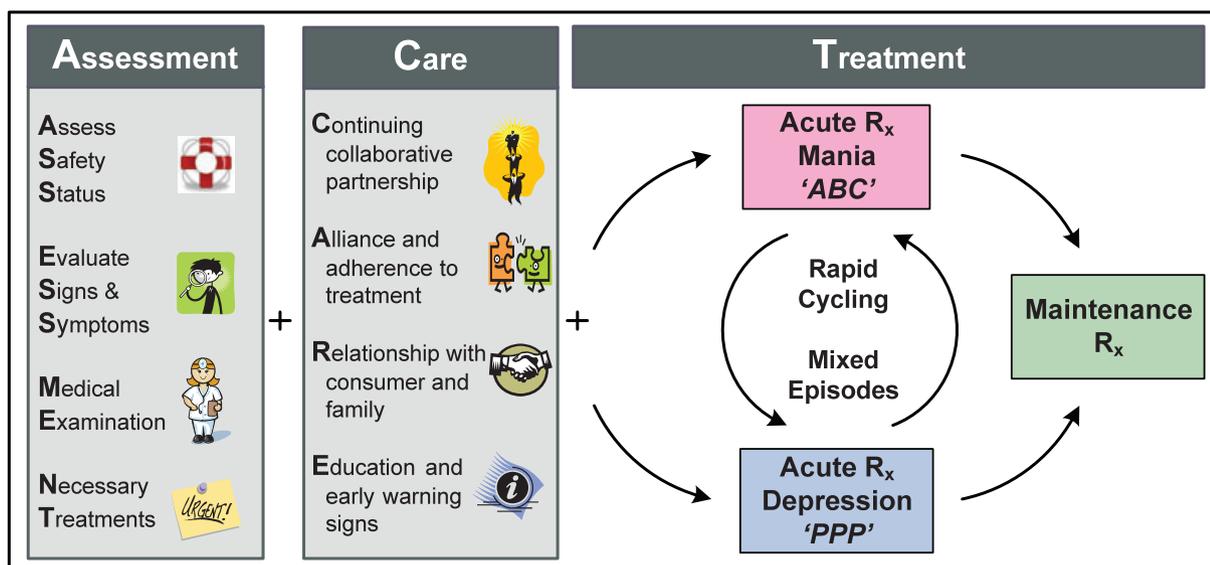


Fig. 2. Overview of the management of bipolar disorder: ‘ACT’: Rx, treatment; ‘ABC’: A, acute mania; B, behavioural disturbance; C, cognitive disturbance/psychosis; ‘PPP’, psychological interventions, pharmacotherapy and physical treatments.

### Box 2. Assessment

**Assess Safety and Status**



**Evaluate Signs and Symptoms**



**Medical Examination**



**Necessary Treatments**



Ensure a comprehensive risk **assessment** is completed and ongoing throughout treatment. It is important to ensure the **safety** of the individual and those around them and to consider their **status** (e.g. in-patient/out-patient, voluntary/involuntary).

- In acute mania, there is increased risk of aggression, excessive spending and disinhibited behaviour. Judgement and insight are often impaired.
- Suicide risk is thought to increase immediately after admission to, and immediately following discharge from, hospital (43).
- Consider risk to others, including risk to children or other family members.
- Where risk is identified a management plan should be developed and reviewed regularly throughout treatment. Clinical **evaluation** of the **signs** and **symptoms** of the illness remains the definitive means for achieving diagnosis.
  - Diagnostic formulation should specify episode type and duration of illness.
  - Rating scales serve as a valuable clinical tool that informs assessment, assists monitoring and quantifies treatment response. Consider:
    - **Bipolar Inventory of Symptoms Scale (BISS)** (44)
    - **Structured Clinical Interview for Mood Spectrum (SCI-MOODS)** (45).
    - **Young Mania Rating Scale (YMRS)** (46) for mania
    - **Bipolar Depression Rating Scale (BDRS)** (47) for bipolar depression
  - Where possible, obtain corroborative history and track time course of illness.
  - Assess medical (see below) and psychiatric comorbidities.
  - Consideration should be given to social, occupational and cognitive functioning.
  - Seek further specialised assessment if diagnosis remains unclear.

A **medical examination** at the time of psychiatric assessment is important to identify comorbidities and differential diagnoses.

- See Table 5 for recommended baseline investigations.
- Some medications used for bipolar disorder can have significant adverse effects and require ongoing medical monitoring.

Behavioural disturbance may warrant immediate administration of **necessary treatments** to ensure safety.

- Treatment may be necessary before a comprehensive psychiatric assessment can be undertaken.
- Involuntary admission may be required during an acute phase of illness.
- If treated in the community, consult with family/carer to assist in taking steps to minimise risks and document these measures in a risk plan.

Care

In the management of bipolar disorder, ‘*care*’ should begin immediately and remain ongoing throughout treatment (see Box 3). The components of ‘*care*’ are essential for the long-term management

of bipolar disorder and it is therefore important to quickly establish a trusting collaborative partnership that facilitates close monitoring of symptoms and encourages treatment adherence. A robust therapeutic alliance can also be used to provide psychoeducation and emotional support.

### Box 3. Care

**Continuing collaborative partnership**



**Alliance and adherence to treatment**



It is important to establish a **continuing collaborative partnership** from the outset of treatment and engage the individual, and where appropriate their family/carer, in their own recovery.

- A sound therapeutic alliance and collaborative approach will set the foundations for optimal treatment outcome.
- In the majority of cases, bipolar disorder is a recurrent illness that will require long-term ongoing care.
- Address any issues of grief and/or adjustment that may arise when coming to terms with the need for ongoing long-term treatment.
- Ensure communication is maintained with all key parties involved in providing care (including in particular the GP and family).

Establishing a therapeutic **alliance** encourages engagement and **adherence to treatment**. The greatest risk of relapse is treatment non-compliance.

- To ensure treatment adherence, it is important to maintain a therapeutic relationship and monitor satisfaction with treatment.
- Continuity of care contributes to close monitoring of early warning signs.
- Consider the psychosocial context and the factors contributing to the illness (e.g. stressful life events, unemployment and interpersonal relationship issues).
- Identify adaptive factors such as personal strengths, support network, coping styles and willingness to engage in treatment.
- Develop a collaborative relapse prevention plan.

<p><b>Roles and responsibilities of relatives</b></p> 	<p>Family involvement is associated with improved outcomes (level II) and therefore <b>relatives</b> play a pivotal <b>role</b> and can undertake important <b>responsibilities</b>.</p> <ul style="list-style-type: none"> <li>• Where possible, include family/carers in collaborative management plan.</li> <li>• Working with families can include providing emotional support, coping strategies, psychoeducation (e.g. coping strategies), obtaining feedback on treatment progress, monitoring changes in mental state and direct involvement in psychological interventions.</li> </ul>
<p><b>Education and early warning signs</b></p> 	<p>Information and <b>education</b> about the illness, available treatment options and possible consequences of treatment should be routinely provided.</p> <ul style="list-style-type: none"> <li>• Interventions that identify <b>early warning</b> signs should be provided routinely and can help reduce risk of relapse and improve functioning (level I) (52).</li> <li>• Encourage structured routines and sleep. Lower stimulation during manic episodes.</li> <li>• Encourage the use of a mood diary and life-event charting to monitor mood patterns and effectiveness of interventions.</li> </ul>

GP, general practitioner/primary care physician.

Treatment

The general aim of treatment is to reduce the morbidity associated with bipolar disorder and limit the disability it confers. This entails the prompt and effective treatment of acute episodes and the prevention of relapse and/or recurrence, so as to achieve optimal mental well-being and functioning. Treatment options for bipolar disorder range from psychological interventions and pharmacotherapy, to physical measures that may require specialist expertise.

The treatment of bipolar disorder is logically divided into the management of acute episodes and the inter-episode administration of maintenance treatment. The two phases of treatment differ in terms of their respective therapeutic goals and approaches to management but in practice distinguishing these phases of treatment can be difficult. However, for the purposes of clarity, acute and

maintenance treatments have been dealt with separately in these recommendations.

Acute treatment is further divided into the treatment of mania and bipolar depression and the management of these mood episodes is described in detail in Boxes 4 and 5 respectively (along with Figs 3–6). Recommendations specific to the complex presentations of rapid cycling and mixed episodes are described separately in Box 6 and Figure 7.

However, it is important to note that it is maintenance treatment that determines success in the lifelong management of bipolar disorder (see Box 7 and Figure 8). The primary aim of maintenance treatment is to prevent the recurrence of mood episodes whilst maintaining optimal functioning and treating inter-episode subsyndromal symptoms. It is therefore important to closely monitor clinical symptoms and side-effects and the potential general health consequences of long-term treatment (see Box 7 and Table 7).

**Box 4. Acute treatment: bipolar mania**

Treatment Focus	Treatment Recommendations
<b>A</b> cute symptoms of mania	Antimanic agent (I)
<b>B</b> ehavioural disturbance	Short-term benzodiazepine      Antipsychotic (I) <sup>†</sup>
<b>C</b> ognitive disturbance (psychosis)	Antipsychotic (I) <sup>†</sup>

ECT(III)  
Consider if severe or high risk

<sup>†</sup> Antipsychotic may also serve as antimanic agent. Avoid using two antipsychotics concurrently.

*Fig. 3. Treatment recommendations for acute bipolar mania: 'ABC'.*

**'A': Acute symptoms of mania**

Taper and cease any antidepressants or agents with mood-elevating properties (e.g. stimulants) and institute general measures where possible: reduce stimulation, lower activity level, delay individual from making important decisions and maintain a structured routine.

R<sub>x</sub>

- Commence treatment with an *antimanic agent* (level I). In selection, consider antimanic efficacy and tolerability (see Fig. 4), and also factor the likelihood of continuing acute treatment into maintenance phase.
  - *Monotherapy*: Antimanic agents with evidence for the treatment of acute mania include lithium, valproate, olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone, paliperidone, haloperidol and, to a lesser extent, carbamazepine (53–59).
  - *Combination*: Recent studies have shown superior efficacy of lithium or valproate combined with short-term administration of an atypical antipsychotic compared with monotherapy with either lithium or valproate alone (54, 60, 61).
- If symptoms and/or behavioural disturbance are severe or protracted, consider electroconvulsive therapy (ECT) (level III) (62).

Notes

- Haloperidol is efficacious but longer-term use carries an increased risk of extrapyramidal side-effects (e.g. tardive dyskinesia). As it lacks maintenance efficacy, and acute treatments are often continued, it is not recommended unless other options have failed.
- Gabapentin (63, 64), lamotrigine (64), topiramate (65), phenytoin (66) and oxcarbazepine (67) are not recommended for the treatment of acute mania.
- The speed of action for valproate can be accelerated using dose-loading (68).

**‘B’: Behavioural disturbance**

R<sub>x</sub>

- Short-term use of a benzodiazepine (e.g. lorazepam) or an antipsychotic may be required to manage acute behavioural disturbance (note that the use of two antipsychotics concurrently is not recommended).
- Oral administration is preferable; however, if intramuscular administration is necessary, an injectable atypical or a combination of an injectable typical antipsychotic and benzodiazepine are recommended (48).

Notes

- Intramuscular (IM) aripiprazole (9.75 mg and 15 mg) is superior to placebo and comparable with IM lorazepam (2 mg) (69).
- In a double-blind RCT, IM olanzapine 10 mg was superior to placebo and showed a trend toward greater improvement than IM lorazepam 2 mg (70).

**‘C’: Cognitive disturbance (ie psychosis)**

Psychosis occurs in approximately 60% of episodes of acute mania.

R<sub>x</sub>

- Antipsychotics may be used as an adjunctive treatment for acute psychotic symptoms if not already being administered as an antimanic agent.
- Atypical antipsychotics are preferred to typical antipsychotics because of better tolerability (54, 60).

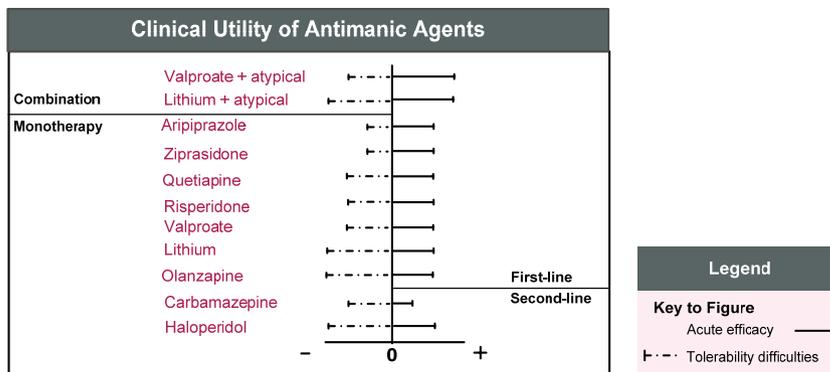


Fig. 4. The clinical utility of antimanic agents according to efficacy and tolerability.

ECT = electro convulsive therapy, Rx = treatment, RCT = randomised controlled trial.

**Box 5. Acute treatment: bipolar depression**

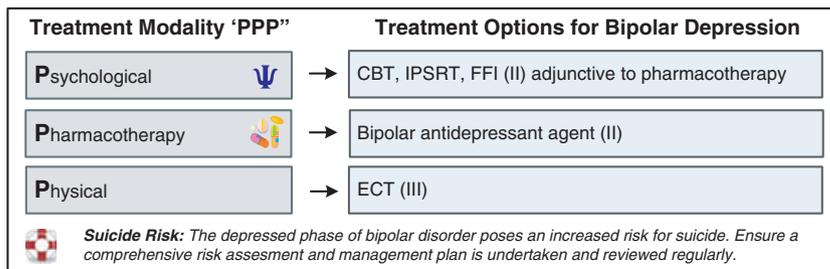


Fig. 5. Treatment options for acute bipolar depression: ‘PPP’, psychological interventions, pharmacotherapy and physical treatments; IPSRT, interpersonal and social rhythm therapy; FFT, family focused therapy; CBT, cognitive behavioural therapy; ECT, electroconvulsive therapy.

**Psychological interventions (adjunctive) Ψ**

There are no definitive studies of psychotherapies as monotherapy in bipolar disorder and therefore psychological interventions should be administered in conjunction with pharmacotherapy. Further, the evidence for psychological treatments in bipolar depression is limited as compared with maintenance.

R<sub>x</sub>

- Intensive psychosocial interventions such as interpersonal and social rhythm therapy (IPSRT), family focused therapy (FFT) and in particular cognitive behavioural therapy (CBT), have shown superior clinical outcomes as compared with brief psychoeducation in the treatment of bipolar depression (71–73) (Level II). See Table 6 for a list of evidence-based psychological interventions used in bipolar disorder.

Notes

- Psychological treatments are not recommended during the acute phase if the individual has severe psychomotor impairment or psychotic features.

**Pharmacotherapy** 

Where practical, screen for and cease any agents that may exacerbate depression (e.g. typical antipsychotics such as chlorpromazine, antihypertensive agents and corticosteroids).

R<sub>x</sub>

- Initiate and/or optimise a *bipolar depression agent* (level II) (see Fig. 6).
  - *First-line monotherapy* treatment options include: quetiapine (74–76), lamotrigine (64, 77), olanzapine (78), lithium (79, 80) and valproate (81, 82).
  - *Second-line* options for bipolar depression include adjunctive/combination therapies: adjunctive risperidone (83), lithium augmentation of antidepressants (84, 85), olanzapine and fluoxetine combination (78), valproate and lithium (48), or lamotrigine as add-on to lithium (86).
- If concurrent psychotic symptoms are present: augment with atypical antipsychotic (level II). However, avoid combining two antipsychotic medications.

Conventional antidepressants

- Research that has examined the efficacy of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) in the treatment of bipolar depression suggests that the benefits of antidepressants remain unclear (87–90).
- If a conventional antidepressant is to be used to treat bipolar depression, it should be administered in combination with an antimanic/maintenance agent so as to diminish the likelihood of switching and then gradually tapered after 2–3 months of sustained recovery.
- Antidepressants should not be prescribed in rapid-cycling bipolar disorder.

Notes

- TCAs (7–11%) and venlafaxine (13–15%) are associated with a relatively higher risk of inducing a switch to mania than SSRIs (0–4%) (87, 91–96); other agents can also precipitate switching (e.g. psychostimulants).

**Physical treatments**

- ECT is an effective treatment (level III) (97, 98) and should be considered if: risk to self or others is high, psychotic features present or there has been a previous response to ECT.

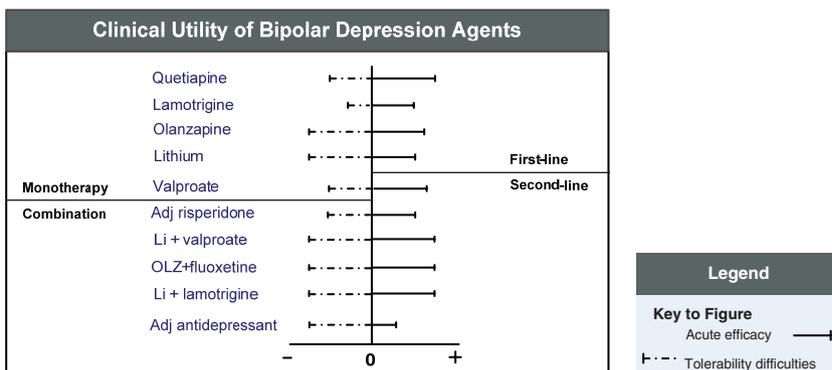


Fig. 6. The clinical utility of agents used for bipolar depression according to efficacy and tolerability ratings OLZ, olanzapine; Li, lithium; Adj, adjunctive.

IPSRT = Interpersonal and Social Rhythm Therapy, FFT = Family-Focused Therapy, CBT = Cognitive Behavioural Therapy, ECT = electroconvulsive therapy, Rx = treatment, TCA = tricyclic antidepressant, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin and noradrenaline reuptake inhibitor.

**Box 6. Complex bipolar presentations**

**Rapid cycling**

Rapid cycling is associated with poorer long-term response to treatment, higher rates of morbidity and increased suicide risk (99–101).

- Screen for and, where possible, exclude factors that may precipitate or exacerbate rapid cycling: antidepressants, substance misuse, medications and medical illness such as hypothyroidism (101).

R<sub>x</sub> options.

The evidence-base for rapid-cycling is limited and treatments appear to be less effective in countering depressive symptoms than manic symptoms (101, 102).

- *Pharmacological monotherapy*: Consider valproate (level II), lithium (level II), olanzapine (level II), lamotrigine (level II) (primarily for bipolar II patients) (99, 100, 103–108), quetiapine (level III) (109).

- **Combination therapies:**
  - Consider adjunctive psychological interventions (level V) as outlined in ‘maintenance’ section.
  - **Pharmacological combinations:** There is limited evidence to support combination treatment, but clinical needs may warrant a trial of combinations, e.g. lithium + valproate (level III) (110), lithium + carbamazepine (level III) (111), adjunctive lamotrigine (level V) (104).
- **Physical treatments:** ECT (level III) (112, 113).

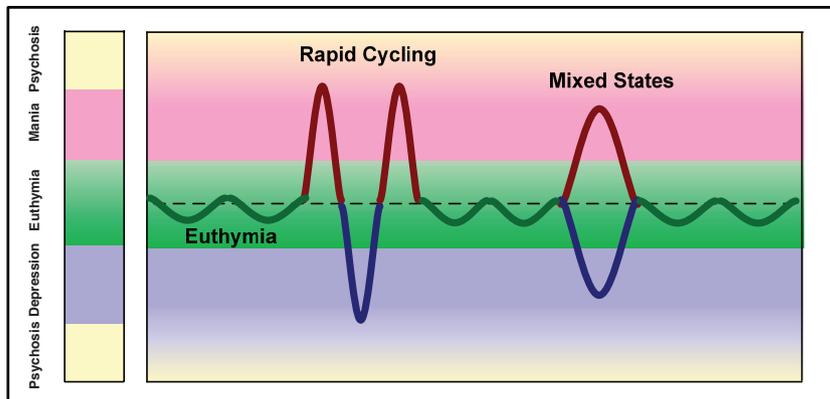


Fig. 7. Schematic representation of rapid cycling and mixed states in bipolar disorder.

### Mixed states

Mixed states are notoriously difficult to diagnose and distinguish from both mania and agitated depression (22). Few treatment studies have specifically examined mixed states, with most including patients with mixed states in studies of acute mania and acute bipolar depression. Therefore, treatment recommendations for mixed states also overlap with those for acute episodes.

- Initially, taper and cease substances with a mood-elevating effect or those that induce inter-episode switching (e.g. antidepressants, stimulants).

#### R<sub>x</sub> options

- Consider olanzapine (level II), quetiapine, or valproate as monotherapy, or olanzapine and fluoxetine in combination (114) or valproate in combination with olanzapine (level II) (115–118).
- **Adjunctive treatments:** There is an overall paucity of evidence for mixed states. Lamotrigine adjunctive to an antimanic agent may be a useful option for mixed states to treat depressive symptoms (116, 119). However, treatment effect is likely to be delayed as this requires slow titration, especially in conjunction with valproate.
- If symptoms and/or behavioural disturbance is severe or protracted, consider ECT (level III) (120).

#### Notes

- Lithium may have reduced efficacy for treating mixed states (115, 119).
- Antidepressants are not recommended as they can worsen or induce rapid cycling.

ECT = electroconvulsive therapy, Rx = treatment.

## Box 7. Maintenance treatment

### General principles

Once a diagnosis of bipolar disorder has been established ongoing treatment is likely to be necessary. Indications include: prior mood episode in past 5 years or two previous mood episodes over any time period, severe acute episode with suicide risk or psychotic features; ongoing functional disability (level V).

It is important to re-evaluate the treatment plan and ensure consideration of comorbid conditions, psychosocial stressors and other factors that may increase risk of relapse. Maintenance treatment should provide a collaborative approach to continued care and in this regard the principles outlined in ‘CARE’ (see Box 3) are of paramount importance.

Pharmacological and psychological treatment strategies should be used to achieve the following:

- **Minimise:** subsyndromal depressive symptoms because disability is closely related to the depressive component of the illness (20).
- **Modify:** address psychosocial stressors; develop problem-solving skills, develop social support/networks (especially with chronic depressive symptoms); and encourage a healthy lifestyle (good sleep hygiene, exercise, regular routine).
- **Manage:** comorbidities, particularly substance misuse.
- **Monitor:** safety/risk; early warnings signs; physical health, long-term treatment confers risks of metabolic syndrome.
- **Maintain:** stable mental state, review and monitor clinical response to medications, adherence and side-effects.
- **Maximise:** engagement, social and occupational functioning, psychoeducation family/carer support.

### Psychological interventions adjunctive to medication $\Psi$

- Psychosocial interventions adjunctive to medications appear to have greatest benefit in reducing risk of relapse and can improve functioning (71, 121, 122). Therapeutic effect can be optimised by targeting euthymic patients in maintenance phase of illness, however, likely to be less effective in those with a high number of prior mood episodes (> 12 episodes) (122, 123).

- Strong evidence exists for interventions focused on the recognition of early warning signs (level I) (52). Evidence for specific therapies includes CBT (level II) (72, 124–126), FFT (level II) (127–129), IPSRT (level II) (130) and group psychoeducation (level II) (126, 131). See Table 6 for a brief description of these interventions.

### Pharmacotherapy

Initially, it is important to withdraw any adjunctive agents that have been used to manage behavioural or cognitive disturbance associated with an acute mood episode. In practice, maintenance agents are often used in combination; however, there is a paucity of evidence for this strategy and, where possible, monotherapy is preferable.

#### Rx

- Medications that have been shown to be effective maintenance agents include (see also Fig. 8):
  - lithium (level I) (132), particularly at preventing manic episodes (133, 134);
  - lamotrigine (level II), particularly for preventing depressive episodes (102, 135);
  - valproate (level II) (110, 136, 137);
  - atypical antipsychotics: olanzapine (level II) (136, 138–140), aripiprazole (level II) (141, 142) and quetiapine adjunctive to lithium or valproate (level II) (143, 144).
- Other atypical antipsychotics have a limited evidence base, restricted to small trials or retrospective data: ziprasidone (level III) (145), risperidone (level III) (146, 147), adjunctive depot risperidone (level III) (148) and adjunctive clozapine (level III) (149).

#### Notes

- Maintenance agents are likely to be required ongoing and should be selected following consideration of efficacy and tolerability profiles (see Fig. 8 and Table 7), along with individual patient factors including preference, past response and safety factors. In this regard, lithium needs to be monitored regularly to maintain therapeutic blood levels (0.4–1.0 mmol/l).
- Carbamazepine has a mixed evidence base as a maintenance treatment (150).
- The efficacy of conventional antidepressants (e.g. TCAs, SSRIs and SNRIs) in the maintenance of bipolar disorder is not established (151). However, if depressive episodes are recurrent, antidepressant treatment in combination with a bipolar maintenance agent may be considered only after weighing up the benefits of prevention vs. the risk of precipitating mania/rapid cycling.

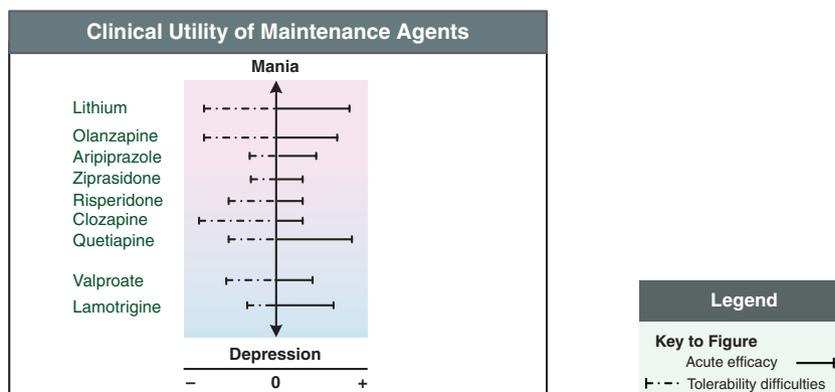


Fig. 8. The clinical utility of bipolar maintenance agents rated according to efficacy of preventing mania and/or depression and tolerability.

Key: CBT = Cognitive Behavioural Therapy, FFT = Family-Focused Therapy, IPSRT = Interpersonal and Social Rhythm Therapy, Rx = treatment, TCA = tricyclic antidepressant, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin and noradrenaline reuptake inhibitor.

#### Treatment response

Both in the acute treatment of mood episodes and during maintenance treatment, it is important to monitor treatment response. This is particularly important in bipolar disorder as insight is often compromised during acute episodes and individuals may not appreciate their treatment needs. Further, monitoring of signs and symptoms is essential during maintenance treatment to ensure full recovery is achieved and maintained, and that

early indications of relapse/recurrence are promptly detected.

Treatment response is judged clinically and should involve consideration of the time in treatment, the response to medication, the severity of the illness and ongoing risk. If acute symptoms worsen, or if after a suitable period (e.g. 7 days for mania, 4–6 weeks for depression) there is no significant improvement, then it is reasonable to consider alternative treatment options (see Box 8 and Figure 9).

**Box 8. Partial or no treatment response**

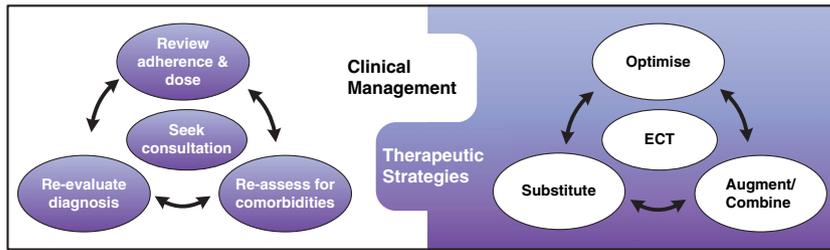


Fig. 9. Clinical management and therapeutic strategies in partial or no treatment response. ECT, electroconvulsive therapy.

**Clinical management**

Structured rating scales (see ‘Assessment’), along with clinical assessment, assist in gauging treatment response and quantifying change in clinical profile.

- *Review adherence and dosage*: Reassess adherence and satisfaction with treatment plan. If taking an antidepressant, ensure a therapeutic dose is prescribed and that adequate blood levels of medications are attained.
- *Re-evaluate diagnosis*: Reassess for psychosocial stressors maintaining symptoms, consider alternative causes (e.g. organic causes).
- *Re-assess for comorbidities*: especially anxiety, drug and alcohol, or personality disorders. Assess for medical comorbidities.
- *Seek consultation*: Consultation should be considered when prescribing novel treatments, in complex cases, or where there has been partial or no response to multiple treatment trials. Consider specialist consultation or referral to a specialist clinic.

**Therapeutic strategies**

Mania: non-response.

- *Optimise* antimanic agent: check levels, adjust dose, and/or
- *Augment and/or combine* with another antimanic agent. Clinically, where there is an inadequate treatment response to monotherapy trials, combination therapy is often used. Data on comparable efficacy of different combinations are limited. Combinations trialled include:
  - lithium + valproate (level II) (152, 153)
  - lithium and carbamazepine (level II) (111, 154)
  - lithium or valproate + olanzapine (level II) (140)
  - adjunctive clozapine or risperidone (level III) (148, 149, 155)
- *Substitute* antimanic agent (see Fig. 4), and/or
- *ECT* (level III): consider if high severity or posing significant risk.

Bipolar depression: non-response.

- *Optimise* dose (check levels and/or adjust dose) of existing agent used for treating bipolar depression and/or
- *Substitute* to alternative bipolar depression agent, and/or
- *Augment and/or combine*
  - See Fig. 7 for second-line combination options.
  - Consider adjunctive psychological therapy targeting depressive symptoms (e.g. CBT, IPSRT, FFT) (121).
  - Consider use of conventional antidepressants (87) (see Box 5), and/or
- *ECT* (Level III): Consider if high severity/treatment resistance, or posing significant risk.

Note: If using antidepressants, monitor closely for switch to mania.

Maintenance: treatment non-adherence. This is a common problem in bipolar disorder, particularly during maintenance (refer to principles of ‘CARE’). In cases of ongoing persistent disengagement from treatment, after failure of appropriate psychosocial interventions and legally appropriate involuntary treatment, consider depot treatment: injectable atypical antipsychotics (level III) (e.g. risperidone) (156, 157) or first generation antipsychotics (level III) (158). However, the latter is not recommended where there is a predominantly depressive course.

Key: ECT = electroconvulsive therapy, CBT = Cognitive Behavioural Therapy, IPSRT = Interpersonal and Social Rhythm Therapy, FFT = Family-Focused Therapy.

**Discussion**

The management of bipolar disorder is complicated and reflects the innate complexity of the illness. The bipolar CPR provide suggestions for management based on an amalgamation of evidence and experience. Alongside pharmacological and psychological treatment recommendations,

importance has been attached to contextual considerations such as individual preferences and social factors. By design, the bipolar CPR focus on the treatment of adults; however, the illness often emerges prior to adulthood and can also manifest in older age groups. The management of bipolar disorder in these particular populations and other special circumstances is beyond the

Table 6. Glossary of psychosocial interventions with level I or II evidence as adjunctive treatment in bipolar depression or maintenance

Therapy	Evidence*	Basic principles
EWS interventions	Level I (52)	EWS interventions apply a mixture of cognitive behavioural strategies and psychoeducation strategies to help patients identify and manage early symptoms of a relapse
CBT	Level II (72, 121, 124–126)	CBT employs a combination of cognitive and behavioural techniques to target maladaptive thinking, deficits and factors predisposing to and perpetuating depressed mood
IPSRT	Level II (121, 130)	IPSRT focuses on the links between mood symptoms and quality of social relationships and social roles, the importance of maintaining regularity in daily routines, and the identification and management of potential precipitants of rhythm disruption
FFT	Level II (121, 127)	FFT includes a combination of psychoeducation and skills-based training including communication enhancement training and problem-solving skills provided to the patient and family
Group psychoeducation	Level II (126, 131)	Psychoeducation interventions aim to provide information and emotional support, help patients adjust to living with a chronic illness, and enhance adherence to treatment

EWS, early warning signs; CBT, cognitive behavioural therapy; IPSRT, interpersonal and social rhythm therapy; FFT, family focused therapy.

\*Evidence for psychological treatments is greatest in maintenance phase compared with bipolar depression.

Table 7. Side-effects for medications routinely used in bipolar disorder

Medication	Side-effects	
	Common (incidence $\geq 1\%$ )	Uncommon or rare (incidence $< 1\%$ )†
Lithium	<p><i>GIT:</i> nausea, vomiting, epigastric discomfort, dry mouth, metallic taste, diarrhoea, weight gain</p> <p><i>CNS:</i> fatigue, headache, difficulty concentrating, vertigo, fine tremor</p> <p><i>Skin:</i> dry skin, exacerbation of psoriasis or acne, rash</p> <p><i>Metabolic:</i> hypermagnesaemia, hypercalcaemia, hypothyroidism</p> <p><i>Other:</i> benign ECG changes, leucocytosis</p> <p><i>Lithium toxicity:</i> 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 occur</p>	Nephrogenic diabetes insipidus, hyperparathyroidism, memory impairment, hair loss, arrhythmias, hyperthyroidism
Valproate	<p><i>GIT:</i> nausea, vomiting, abdominal cramp, anorexia, diarrhoea, indigestion (especially with non-enteric coated preparations), increased appetite and weight gain</p> <p><i>CNS:</i> sedation, tremor</p> <p><i>Skin:</i> transient hair loss</p> <p><i>Other:</i> thrombocytopenia, elevated liver transaminases, asymptomatic elevations of ammonia</p>	Severe hepatic dysfunction, pancreatitis, extrapyramidal syndrome, hyperammonaemic encephalopathy
Carbamazepine	<p><i>GIT:</i> dry mouth, vomiting, diarrhoea, anorexia, constipation, abdominal pain</p> <p><i>CNS:</i> dizziness, headache, ataxia, drowsiness, blurred vision, diplopia</p> <p><i>Skin:</i> rash</p>	Agranulocytosis, aplastic anaemia, severe skin reactions (including Stevens-Johnson syndrome), SIADH, arrhythmias, orofacial dyskinesias, hepatitis
Lamotrigine	<p><i>GIT:</i> dry mouth, nausea, vomiting</p> <p><i>CNS:</i> diplopia, dizziness, ataxia, blurred vision, headache, irritability, somnolence, tremor, asthenia, insomnia</p> <p><i>Skin:</i> maculopapular rash, Stevens-Johnson syndrome (0.3–2.0% in children)*</p> <p><i>Other:</i> arthralgia</p>	Hepatic failure, blood dyscrasias, lupus-like reaction. Severe skin reactions including Stevens-Johnson syndrome and Lyell syndrome
Atypical antipsychotics	<p><i>Metabolic:</i> weight gain, dyslipidaemia, hyperglycaemia, hyperprolactinaemia</p> <p><i>Extrapyramidal symptoms:</i> tremor, akathisia, rigidity, slowing, dystonia</p> <p><i>Anticholinergic reactions:</i> constipation, dry mouth, blurred vision, urinary retention</p> <p><i>Other:</i> sedation, increased appetite, sexual dysfunction, GI upset, peripheral oedema, nausea, cerebrovascular events, especially in the elderly (stroke, TIA), orthostatic hypotension, tachycardia</p>	Jaundice, neuroleptic malignant syndrome, seizures, tardive dyskinesia, ECG changes (increased QT interval), SIADH, temperature irregularity, blood dyscrasias, arrhythmias, cardiac arrest, seizures, hepatic fibrosis, lupus <i>Clozapine:</i> agranulocytosis (1%), myocarditis, cardiomyopathy, seizures

Source: MIMS (180), Australian Medicines Handbook (181).

GIT, gastrointestinal tract; CNS, central nervous system; TIA, transient ischaemic attack; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

\*Risk is greatest with high initial doses or when combined with valproate.

†In addition, many medications have the potential to cause a hypersensitivity syndrome (fever, severe skin reactions, lymphadenopathy, hepatitis, haematological abnormalities, facial oedema).

scope of this paper; however, along with an overview of the side-effects of medications, these are briefly mentioned.

#### Special populations and comorbidities

The current bipolar CPR focus on the management of bipolar disorder in adults. A review of the evidence-base for other populations was beyond the scope of this paper and for treatment advice publications that provide specific guidance in managing bipolar disorder in **young people (51, 159)**, the elderly (160) and during the perinatal period (161–163) should be consulted.

In practice, bipolar disorder rarely manifests without significant comorbidities and often necessitates polypharmacy. However, detailed recommendations as regards such presentations are not yet possible, principally because instructive research findings are lacking and a meaningful understanding of the disorder is yet to be achieved. When managing bipolar disorder with comorbidities, the current recommendations should be considered only in conjunction with existing reviews of concurrent psychiatric comorbidities (164, 165), substance misuse **(166)** or medical problems (167, 168).

#### Medication side-effects and novel treatments

A summary of the potential side-effects of the medications routinely used in bipolar disorder is provided in Table 7. This list is not exhaustive and before initiating treatment specific product information and recognised sources of pharmaceutical data should be consulted.

Novel treatments that are commonly used for the management of bipolar disorder have not been discussed, either because of a lack of sufficient data and clinical usage or a lack of widespread availability of the treatment. Such treatments include novel pharmacological agents [*N*-acetyl-cysteine (169), omega-3 fatty acids (170), tamoxifen (171, 172), asenapine, antihypertensives (173), celecoxib (174), modafinil (175) and pramipexole (176)] and innovative physical treatments such as TMS (177–179).

To conclude, bipolar disorder is a difficult illness to manage because of its intrinsic complexity and variability. In essence, the bipolar CPR are derived from both evidence and clinical experience and have been developed to provide basic practical guidance for the management of bipolar disorder. They cannot take into account the myriad of clinical variables that are invariably present, and are thus not prescriptive, and need to be used

flexibly. Recommendations, like guidelines, are practical clinical tools, derived from an incomplete and evolving database. They need to be interpreted taking into account the person's clinical circumstances, sociocultural context, comorbidities and local health resources. Therefore, they do not represent a reference standard of care in medico-legal proceedings. They nevertheless provide a useful framework and should be used in conjunction with recognised sources of information and the application of clinical wisdom.

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#### Declaration of interest

In the past 3 years, Professor Gin Malhi has served on a number of international and national pharmaceutical advisory boards, received funding for research and has been in receipt of honoraria for talks at sponsored meetings worldwide involving the following companies: AstraZeneca, Eli Lilly, Jansen-Cilag, Organon, Pfizer and Wyeth. Professor Garry Walter has received educational grants from Eli Lilly, Janssen-Cilag and Pfizer, a research grant from AstraZeneca, and travel assistance and an honorarium for a talk from Eli Lilly. Dr Lisa Lampe has received honoraria for lectures, workshops, advisory boards and educational material in the past 5 years from the following companies: Wyeth, Lundbeck, Pfizer, Sanofi, Janssen Cilag and AstraZeneca. She has received travel assistance from Wyeth and sits on the Pristiq Advisory Board (Wyeth). In the last 5 years, Professor Richard Porter has received honoraria for speaking engagements from Janssen-Cilag and Sanofi-Aventis. During the past 3 years, Professor Roger Mulder received honoraria for speaking and travel assistance from Douglas Pharmaceuticals, Janssen-Cilag and AstraZeneca. Professor Michael Berk has received funding for research from Stanley Medical Research Foundation,

MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier, AstraZeneca, has received honoraria for speaking engagements from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay, Wyeth, and served as a consultant to AstraZeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Pfizer. Danielle Adams, Andrea Taylor, Dr Nick O'Connor, Dr Michael Paton and Dr Liz Newton have no competing interests.

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