

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: bipolar disorder summary

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Bipolar disorder is a capricious and chronic illness marked by significant fluctuations in mood and energy.^{1,2} Patients have the highest suicide risk (30–60 times that of the general population) and usually experience recurrence of an episode within 2 years of remission.³ For clinicians, ensuring the successful long term management of patients with bipolar disorder is imperative.

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Practice Guidelines for Mood Disorders,³ published in December 2015, highlight important developments in the assessment, diagnosis and treatment of mood disorders (ie, depression and bipolar disorder) that have occurred since publication of the previous guidelines in 2004.⁴ The updated guidelines aim to inform the real world practice of physicians and are an amalgamation of current evidence-based knowledge and clinical wisdom.

This guideline summary is an abstracted version of the more comprehensive guidelines and accompanies our guideline summary for the treatment for major depression.⁵ It overviews the long term management of bipolar disorder within the community, where the general practitioner plays a central role as part of a treatment team that usually consists of a psychiatrist, psychologist and other mental health care professionals. It is therefore important that all physicians are aware of bipolar symptoms and are able to collaboratively implement successful long term management.

Background

Bipolar disorder is a chronic lifelong illness characterised by acute exacerbations of mania and depression that, in contrast to major depression, affects males and females equally.^{6,7} It typically commences in late adolescence and first manifests with depressive symptoms (Box 1, A), which creates a diagnostic challenge because there are no clinical features that reliably distinguish bipolar depression from major depression.⁸ Typically, individuals who develop bipolar disorder experience several episodes of depression before eventually manifesting symptoms of mania.⁹ The early detection of symptoms suggestive of mania is therefore critical (Box 1, B). Elevated or irritable mood and increased goal-directed activity are notable symptoms, along with a decreased need for sleep, increased self-esteem, and cognitive changes such as distractibility.⁷ Risk taking and suicidal ideation are also key indicators of possible bipolar disorder and, if severe, may necessitate hospitalisation.^{1,10} In practice, the symptoms of bipolar disorder are often confounded by those of common comorbid illnesses, such as those listed in Box 1, E, making identification and diagnosis even more challenging.

Abstract

Introduction: In December 2015, the Royal Australian and New Zealand College of Psychiatrists published a comprehensive set of mood disorder clinical practice guidelines for psychiatrists, psychologists and mental health professionals. This guideline summary, directed broadly at primary care physicians, is an abridged version that focuses on bipolar disorder. It is intended as an aid to the management of this complex disorder for primary care physicians working in collaboration with psychiatrists to implement successful long term management.

Main recommendations: The guidelines address the main phases of bipolar disorder with a particular emphasis on long term management, and provide specific clinical recommendations.

Mania:

- All physicians should be able to detect its early signs so that treatment can be initiated promptly.
- At the outset, taper and cease medications with mood-elevating properties and institute measures to reduce stimulation, and transfer the patient to specialist care.

Bipolar depression:

- Treatment is complicated and may require trialling treatment combinations.
- Monotherapy with mood-stabilising agents or second generation antipsychotics has demonstrated efficacy but using combinations of these agents along with antidepressants is sometimes necessary to achieve remission. Commencing adjunctive structured psychosocial treatments in this phase is benign and likely effective.

Long term management:

- Physicians should adjust treatment to prevent the recurrence of manic and/or depressive symptoms and optimise functional recovery.
- Closely monitor the efficacy of pharmacological and psychological treatments, adverse effects and compliance.

Changes in management as a result of the guidelines: The guidelines position bipolar disorder as part of a spectrum of mood disorders and provide a longitudinal perspective for assessment and treatment. They provide new management algorithms for the maintenance phase of treatment that underscore the importance of ongoing monitoring to achieve prophylaxis. As a first line treatment, lithium remains the most effective medication for the prevention of relapse and potential suicide, but requires nuanced management from both general practitioners and specialists. The guidelines provide clarity and simplicity for the long term management of bipolar disorder, incorporating the use of new medications and therapies alongside established treatments.

1 An overview of bipolar disorder and its treatment*

A. Epidemiology

- Lifetime prevalence is 0.6%
- Affects females and males equally
- Mean age of onset is late teens, whereas mean age of diagnosis is late 20s (differential diagnosis of depression is crucial)
- Ratio of manic episodes to depressive episodes is 1:3
- Nearly half of patients experience recurrence within 2 years
- Highest suicidal risk (30-60 times than in the general population)

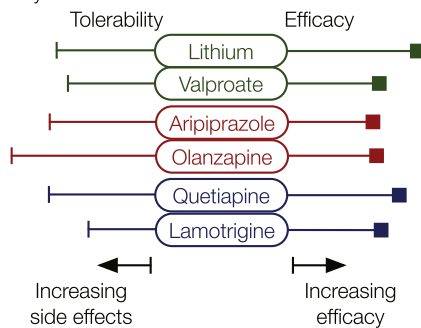
B. Diagnosis

- Occurrence of manic episode (at least 1 week)
- Elevated mood, increased goal-directed and/or risky activity, increased energy with
 - Decreased need for sleep
 - Pressured speech, racing thoughts
 - Distractibility
 - Inflated self-esteem
- Rating Scales: YMRS, BDRS

C. Management

Goal: Maintaining mood stability and providing long term prophylaxis

Key medications for maintenance



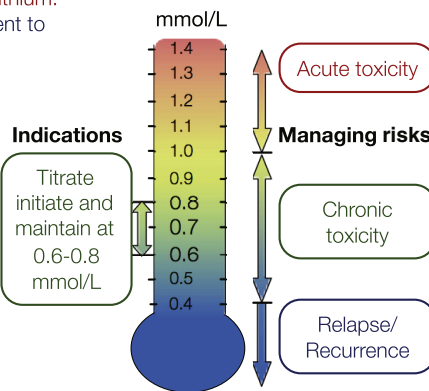
Determining treatment based on episode dominance:
Typically, trial lithium first. Add valproate in combination if necessary.

Mania predominates: add one red agent to lithium.

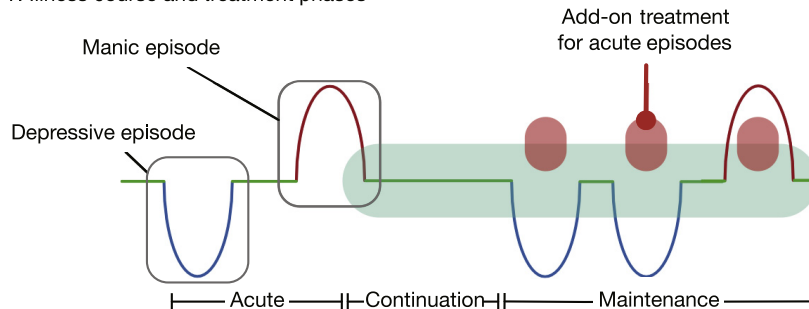
Depression predominates: add one blue agent to lithium.

D. Lithium maintenance

- Most effective long term agent for prevention of relapse and suicide
- Optimal management involves both GPs and specialists
- Use Lithiumeter 2.0 (right)



F. Illness course and treatment phases



A: Epidemiology: among psychiatric illnesses, bipolar disorder confers the greatest risk of suicide. Its treatment is distinct from that of major depressive disorder and therefore it is important to differentiate the two illnesses. **B:** Diagnosis: the diagnosis of bipolar disorder rests on the occurrence of a manic episode. Current symptoms can be quantified using the Young Mania Rating Scale (YMRS)¹¹ and the Bipolar Depression Rating Scale (BDRS).¹²

C: Management: bipolar disorder is a recurrent lifelong illness and the primary goal of management is to maintain mood stability and prevent future episodes. Bipolar disorder is primarily managed with medications (Pharm) such as lithium (Li), neuroleptics (Neurolep.) and anticonvulsants (AC), along with psychological therapies (Psych). Severe or unremitting episodes may require electroconvulsive therapy (ECT). Key medications are presented according to tolerability and efficacy, as well as their relative utility for prophylaxis. **D:** Lithium maintenance: in order to maintain appropriate lithium levels across phases of bipolar disorder (depression, mania, maintenance), an easily accessible tool has been created (Lithiumeter 2.0)³⁷ to guide clinicians. **E:** Key comorbidities: patients with bipolar disorder often have comorbidities that require additional management. These can be psychiatric or medical. **F:** Illness course and treatment phases: although bipolar disorder is characterised diagnostically by acute episodes of illness, in terms of treatment, long term management is the critical treatment phase. Therefore, continuation and maintenance of treatment is essential and long term monitoring is necessary. Over the course of the illness, recurrences/acute episodes require additional treatment strategies that can be added to ongoing prophylactic treatment. * Adapted with permission from Malhi et al.³ ♦

This abridged version of the clinical practice guidelines for mood disorders contains an overview of the recommendations for managing the three main phases of bipolar disorder: mania, bipolar depression and euthymia. The full guidelines are available on the RANZCP website (<https://www.ranzcp.org/Files/Resources/Publications/CPG/Clinician/Mood-Disorders-CPG.aspx>). They contain additional recommendations in the areas of classifying and diagnosing mood disorders; distinguishing major depression and bipolar disorder; models and formulation for the assessment of mood disorders; side effect profiles of common medications used for treating mood disorders; treating patients with suboptimal response to initial treatment; treating patients with bipolar II disorder; bipolar disorder in children and adolescents; treating patients with complex presentations (such as mixed states and rapid cycling); and managing bipolar disorder in special populations.

Method

To develop the clinical practice guidelines, the RANZCP appointed a Mood Disorders Committee, which comprised specialists with academic and clinical expertise and was independent of any pharmaceutical companies. The introduction to the full guidelines outlines the scope and methodology of the guideline development process.³ The Committee systematically synthesised clinician and research evidence from existing depression and bipolar disorder guidelines and searched the literature using recognised search engines.

The guidelines make two types of recommendations that reflect the reasoning used to formulate advice. First, evidence-based recommendations (EBRs) were formulated using the NHMRC levels of evidence (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf) for intervention studies, graded accordingly in recommendation boxes (eg, EBR I, etc). Information for these recommendations was gathered from existing published bipolar guidelines, along with literature known to the Committee and articles obtained from various databases. A second type of recommendation was also employed, derived through discussion and agreement within the Committee and termed a consensus-based recommendation (CBR). CBRs were formulated when the existing intervention evidence base was absent, ambiguous or of doubtful clinical impact in the Australian and New Zealand context, and the Committee (based on collective clinical and research knowledge and experience) reached consensus on the clinical utility of the recommendations.

Before submission for publication, the Committee developed draft guidelines that underwent extensive consultation and external review involving expert and clinical advisers, the public, consumer groups, professional bodies and mood disorder specialist groups. Following review, the guidelines were published in the *Australian and New Zealand Journal of Psychiatry*.³

Recommendations

Typically, the treatment of bipolar disorder is determined by the phase of illness in which the patient presents. There are three main phases that define the course of the illness — depression, mania and euthymia — and each requires distinct management (Box 1, F).

Clinical recommendations for the management of mania

It is important that community clinicians identify the early signs of mania so that management can be initiated promptly. Undetected, the symptoms of mania (Box 1, B) — reckless

spending, inappropriate sexual behaviour and other high risk goal-oriented actions — can damage the patient's relationships and reputation. Acute mania is a medical emergency that is best managed by specialists and often requires hospitalisation.¹³ Individuals suffering an episode of mania can be persuasive, push limits and rationalise their impulsive or reckless behaviour to make a case for not being admitted. However, insight is often compromised during mania, and if hospitalisation becomes necessary, it is usually achieved by involuntary means, entailing the use of mental health legislation. It is therefore important to include family members and carers and provide informative counselling from the outset.¹⁴

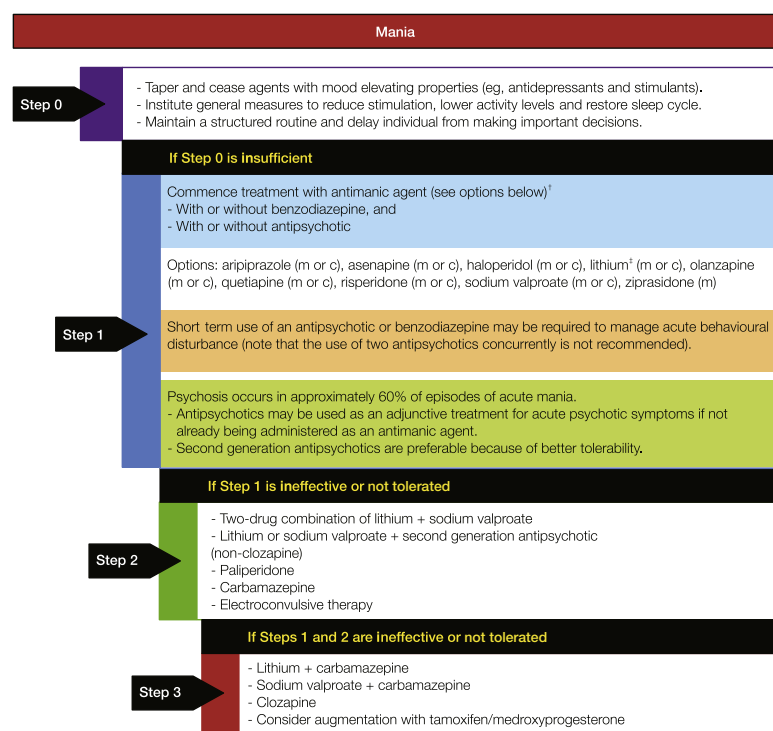
When a patient is experiencing manic symptoms, it is crucial to taper and cease any agents with mood-elevating properties (eg, antidepressants, stimulants) and institute general measures, such as reducing stimulation, lowering activity levels, delaying the individual from making important decisions, and containing risk-taking behaviours (CBR). Medications are essential to manage the biological symptoms of mania and counter heightened arousal,^{2,15-19} and prescribing a hypnotic can be useful to reinstate a regular pattern of sleep²⁰ (CBR). For a detailed step-by-step approach to medication choices, see Box 2 and Tables 19 and 20 in the full guidelines.³ Less severe mood elevations and heightened activity are indicative of bio-behavioural dysregulation that may in the first instance simply require careful monitoring.²¹ These periods of moderated mania, sometimes referred to as highs, are termed hypomania and by definition do not require hospitalisation.³

Clinical recommendations for the management of bipolar depression

The treatment of bipolar depression is generally more difficult and complicated in comparison with major depressive disorder, and outcomes are usually poorer.²² This is partly because no medications have been specifically developed to treat this phase of bipolar disorder, but also because successful management requires careful consideration of complex issues, such as the risk of treatment-emergent affective switching into mania or hypomania (CBR), possible cycle acceleration (CBR), and the precipitation of mixed symptoms (CBR).^{2,23,24} As a result, bipolar depression is best managed by a different approach from that used to treat major depressive disorder.³ Of note, the use of adjunctive antidepressants to treat bipolar depression remains contentious, as does the long term efficacy of this strategy.^{3,24,25} There is strong clinical consensus that, where feasible, patients should be offered adjunctive evidence-based psychological therapy (EBR level I) — for example, cognitive behaviour therapy (EBR level I), interpersonal and social rhythm therapy (EBR level III) or family-focused therapy (EBR level II) — as part of a comprehensive biopsychosocial and lifestyle approach to managing this highly impairing phase of bipolar disorder.^{3,26}

As shown in Box 3, monotherapy with second generation antipsychotics or mood-stabilising agents has demonstrated efficacy in the treatment of bipolar depression. Second generation antipsychotics include quetiapine, lurasidone and olanzapine (rank order) and mood-stabilising agents include lithium, lamotrigine and valproate, creating a total of six possible monotherapy options. In practice, a trial of monotherapy is often necessary to identify patients who can be managed with a single agent, but while monotherapy is preferable, frequently patients require combinations of medications including antidepressants alongside mood-stabilising agents and second generation antipsychotics²⁷ (CBR).

2 Stepwise management of mania*



c = combination; m = monotherapy. † Oral risperidone, olanzapine, quetiapine or asenapine immediately OR intramuscular haloperidol, olanzapine immediately; choice determined by the patient's capacity to cooperate with oral medication. With olanzapine, benzodiazepines need to be administered with caution because of potential for over-sedation, whereas, in conjunction with haloperidol, a benzodiazepine is useful because of the risk of acute dystonia. Plan to change to oral medications as soon as possible and supplement oral medications with haloperidol if required by the patient's mental state. If oral medications cannot be used after 2–3 injections of short acting intramuscular antipsychotics, zuclopenthixol acetate 50–100 mg may be used intramuscularly to provide parenteral medication without the need for frequent injections. ‡ Add lithium slow release 450 mg (or immediate release 500 mg) at night OR add valproate 500 mg twice daily, if concerned about use of lithium (or patient refuses). Use non-teratogenic agents (second generation antipsychotics) if patient is pregnant. Check the blood level of lithium or valproate after 5 days. For lithium, check full blood count, renal function, thyroid function and calcium level before starting lithium or as soon as possible following introduction and screen for pregnancy using beta human chorionic gonadotropin.

* Reproduced with permission from Malhi et al.³ ♦

If several trials of combinations of medications prove to be ineffective, then electroconvulsive therapy and adjunctive treatments may be trialled^{3,28} (CBR).

Clinical recommendations for the long term management of bipolar disorder

The primary aims of long term treatment are to maintain euthymia and prevent relapse or recurrence of manic and depressive symptoms and to optimise functional recovery and quality of life. Usually this requires both psychotherapeutic and pharmacological approaches.²⁹ Once an acute episode has resolved, the focus of management shifts to continuation and then maintenance treatment.³

Continuation treatment. Management moves from acute to continuation treatment as the acute symptoms of a depressive or manic phase of illness remit.³⁰ At this point, adjunctive agents (eg, benzodiazepines) that may have been used to manage acute behavioural and cognitive disturbance associated with a mood episode should be withdrawn.³¹ It is especially important to monitor the patient's compliance with medication and ensure adequate adherence to treatment instructions. This can be achieved

through active engagement and regular therapeutic monitoring alongside reappraisal of the benefits and risks of ongoing therapy.³⁰

Continuation therapy aims to achieve optimal mood stability and prevent recurrence (Box 4, A). Monotherapy is desirable but very much dependent on the pattern of illness. Combination strategies are often necessary; suitable strategies include a mood stabiliser (eg, lithium or valproate) in combination with olanzapine (EBR level I), quetiapine (EBR level I), lamotrigine (EBR level I) or aripiprazole (EBR level II). These combinations are useful in treating bipolar disorder in which depression dominates or depression and mania occur equally.

It is important to reassess patients regularly for recurrence of episodes, adverse side effects and overall functioning (Box 4, B). Once a patient has achieved a period of at least 6 months mood stability with continuation treatment, long term management transitions to maintenance therapy.

Maintenance treatment. The principal aims of maintenance treatment are to:

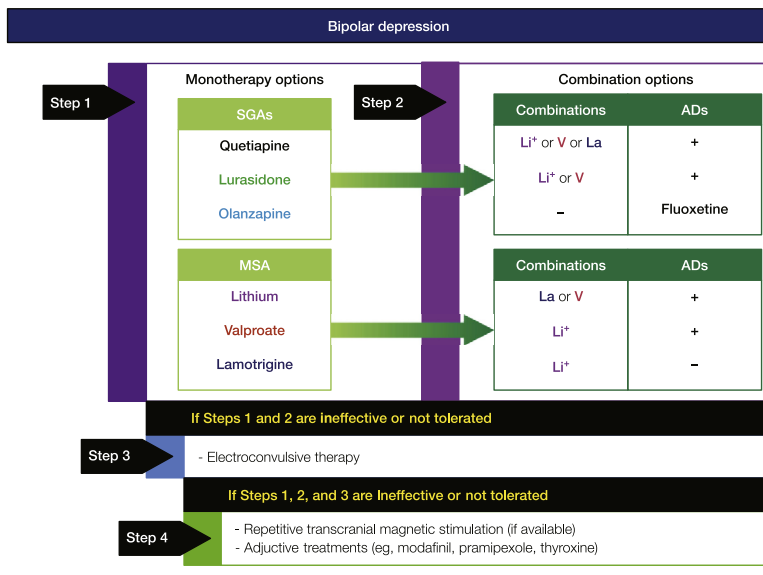
- encourage patients to closely monitor their mood, recognise early warning signs and promptly seek assistance if necessary;
- maintain mood stability;
- increase regularity of sleep/wake cycles;
- achieve complete functional recovery;
- provide long term prophylaxis; and
- build biological, psychological and social resilience, thus improving quality of life.

When planning maintenance treatment, the first step is to review the treatments that have been used during the continuation phase of management. Medications necessary for treating acute symptoms may have been tapered or completely withdrawn during the continuation phase, and long term maintenance may require the initiation of new medications.^{30,32} The choice of

medication in maintenance is governed by factors different from those relevant to continuation treatment (Box 4, C), and the cost–benefit ratio of side effects to efficacy may require further consideration.^{27,33} If a clear pattern of illness is evident, it is useful to gauge the predominant polarity as this will inform decisions regarding the most effective prophylactic agent for mania or depression.^{34,35}

Patients with bipolar disorder are advised to use mood-stabilising and prophylactic medication indefinitely to prevent future episodes of illness³⁰ (CBR) (Box 1, C and D). Lithium remains the gold standard in achieving mood stability and long term prophylaxis.^{34–36} As a first line treatment, lithium provides excellent efficacy in terms of relapse prevention and protection against suicide.^{35–38} It may also reduce the severity and frequency of episodes should relapses occur. Other maintenance treatments such as valproate or lamotrigine may be added to lithium if necessary, and lithium is generally well tolerated.^{37,39,40} However, initial management is often highly involved, with a need for frequent monitoring of lithium plasma levels and adjustment of doses in order to ensure tolerability and limit the risk of toxicity.³⁶ Weekly, monthly, then quarterly appointments with a doctor involving blood tests are recommended in order to monitor the efficacy and side effects

3 Stepwise management of bipolar depression*



+ = agent can be added; - = agent should not be added. The diagram illustrates the potential binary combinations between second generation antipsychotics (SGAs), mood-stabilising agents (MSAs) and antidepressants (ADs) when considered appropriate. Lithium (Li⁺) and ADs can be added to all agents but each has one exception: olanzapine and lamotrigine (La) respectively. The combination of SGAs with each other has no confirmed benefits in efficacy but MSAs may usefully be combined, provided one is lithium. The combination of lithium and lamotrigine carries the complication of increased blood levels of both medications, making close monitoring critically important. * Reproduced with permission from Malhi et al.³ ♦

To ensure successful long term management, it is imperative that physicians work with patients to develop a strategy for medication adherence while minimising any adverse effects. The discontinuation of long term treatment risks relapse or recurrence, but equally, the long term use of medications may lead to significant adverse effects.^{3,33,42} Therefore, a collaborative discussion of the benefits and negative consequences with both the individual and their carers is necessary at the outset of treatment and whenever a significant change to management is being considered.¹³ Medication adherence is a goal of adjunctive psychological interventions, which also reduce relapse, ameliorate residual symptoms and improve quality of life²⁸ (EBR level I). The full guidelines provide an overview of psychological treatments known to be efficacious for bipolar disorder maintenance treatment.³

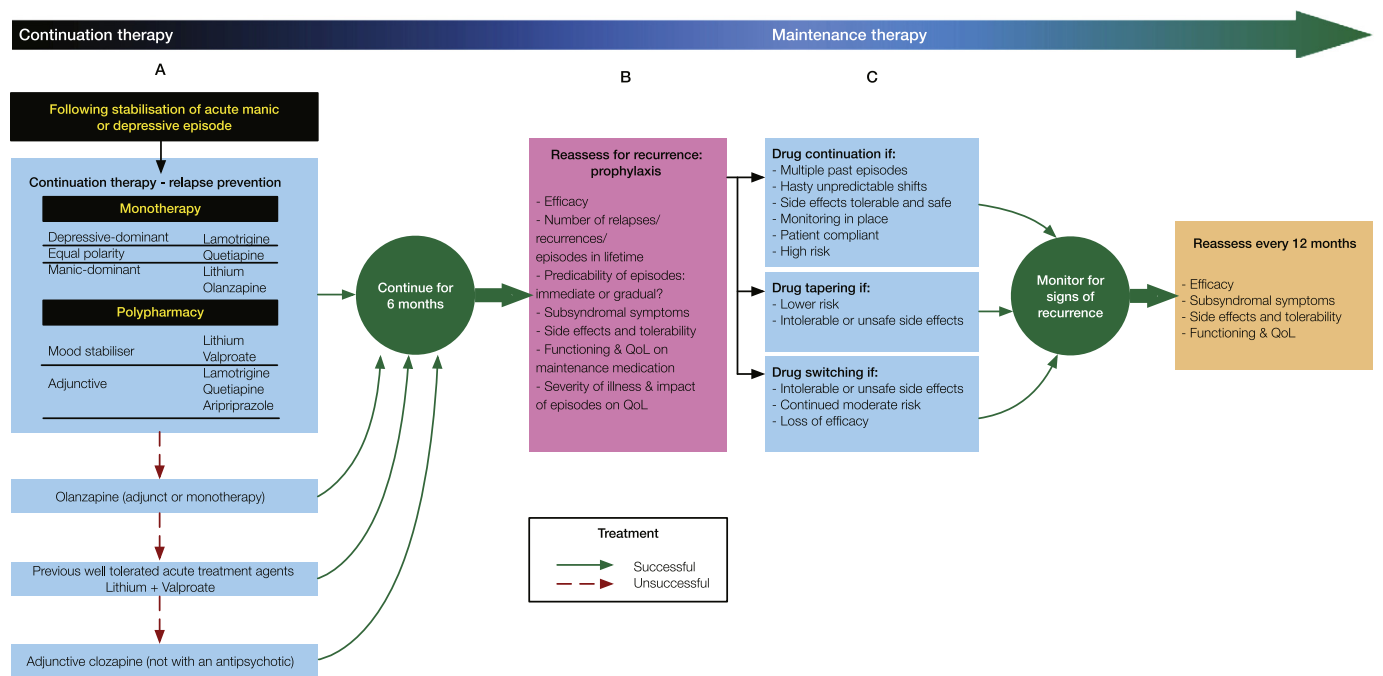
Continued monitoring is an essential aspect of long term management. Once long term stability is achieved, patients should be assessed at least biannually to determine functional capacity and symptom recurrence while re-evaluating the tolerability of treatment³ (CBR). To monitor the onset of relapse, it is useful to assess the extent to which the onset of episodes is predictable; for example, whether they are insidious, abrupt, related to life stresses or contain a seasonal component.⁴³ Typically, the emergence of symptoms is gradual and they increase in number and severity over a period of days. It is therefore

important that both patients and physicians are able to detect these early warning signs, anticipate the onset of episodes of illness and adjust treatment accordingly.^{44,45} Maintenance treatment recommendations are set out in Box 5.

of lithium therapy (CBR). During lithium therapy, physicians can refer to the Lithiummeter³⁷ to adjust medication dosages and may also consider applying a Lithium Battery – Clinical⁴¹ to assess potential cognitive side effects.

important that both patients and physicians are able to detect these early warning signs, anticipate the onset of episodes of illness and adjust treatment accordingly.^{44,45} Maintenance treatment recommendations are set out in Box 5.

4 Continuation and maintenance therapy for bipolar disorder: decision-making diagram*



QoL = quality of life. * Adapted with permission from Malhi et al.³ ♦

5 Treatment recommendations for bipolar disorder*

Stage	Treatment recommendation	Grade
Mania	Detect early signs and symptoms of mania and refer to a specialist	CBR
	Promptly taper and cease any agents with potential mood-elevating properties and reduce stimulation and activity	CBR
	Institute measures to limit impulsive and risk-taking behaviours (eg, hospitalisation)	CBR
Bipolar depression	Monotherapy with a second generation antipsychotic or a mood-stabilising agent may have efficacy in managing bipolar depression	CBR
	Combinations of a second generation antipsychotic with a mood-stabilising agent or antidepressant can assist in achieving remission	CBR
	Antidepressant monotherapy should be avoided in: bipolar I disorder; episodes that feature psychomotor agitation; in a mixed mood state	EBR level III
	On commencing antidepressants, patients should be monitored closely for symptoms of mania, and if these emerge, antidepressant therapy should be discontinued	CBR
Maintenance and prophylaxis	Adjust treatment to achieve mood stability (eg, tapering medications for acute episodes, initiating new maintenance medications)	CBR
	Monitor medication compliance and ensure adequate adherence to treatment	CBR
	Regularly re-evaluate to assess the effectiveness of treatment, side effects, overall functioning and quality of life	CBR
	Educate patients on detection of early warning signs that anticipate illness onset	CBR
	Offer adjunctive psychosocial interventions to ameliorate residual symptoms, reduce risk of relapse and improve quality of life	EBR level I

CBR = consensus-based recommendation; EBR = evidence-based recommendation (based on National Health and Medical Research Council levels of evidence; https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf). * Adapted with permission from Malhi et al.³ ♦

Special considerations

Illness patterns. The illness course of bipolar disorder is varied and may require nuanced management strategies.^{46,47} Complex presentations such as mixed features, rapid cycling and seasonal patterns are addressed in the full guidelines.³ For discussion on the diagnosis and assessment of mixed states, see Malhi et al.⁴⁸

Comorbidities. Bipolar disorder is associated with psychiatric or medical comorbidities such as anxiety, substance misuse and personality disorders.⁴⁹⁻⁵¹ Managing bipolar disorder in these contexts is discussed in the full guidelines.³ For advice on differentiating bipolar disorder from confounding borderline personality disorder, see Bassett et al.⁵²

Women of childbearing age. Special care should be taken for women of childbearing age as they have a high risk of relapse following childbirth and mood-stabilising medications may adversely affect the developing fetus.³ Contraceptive advice should be considered (CBR), especially as disinhibition can be a feature of mania. The full guidelines provide guidance regarding the management of bipolar disorder in women of childbearing age, and women who are pregnant and/or breastfeeding.³

Conclusion

The clinical practice guidelines for mood disorders provide updated and relevant information for GPs and physicians

regarding the management of bipolar disorder as part of the spectrum of mood disorders. The guidelines contain updated clinical algorithms concerning the acute, continuation and maintenance phases of treatment and provide clear guidance to ensure the optimal management of lithium. The advice provided in the guidelines should equip clinicians to navigate the complexities of managing all phases of bipolar disorder.

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