Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Definitions and diagnosis

**GPP** When diagnosing bipolar disorder, a careful clinical assessment that includes a longitudinal history, as well as obtaining a history of mania and hypomania in patients with a first presentation of depression, should be performed (pg 15).

**Grade C, Level 2+**

The use of screening instruments in day-to-day practice in primary and tertiary settings is not recommended (pg 15).

Acute treatment

**A** Haloperidol may be used for the treatment of acute mania (pg 16).

**Grade A, Level 1+**

**A** Aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone may be used for the treatment of acute mania (pg 17).

**Grade A, Level 1+**
Combination pharmacotherapy with an antipsychotic and a mood stabiliser may be used for patients showing inadequate response to mood stabiliser monotherapy (pg 17).

Lithium monotherapy may be used for the treatment of acute mania (pg 17).

Sodium valproate monotherapy may be used for the treatment of acute mania (pg 18).

Carbamazepine monotherapy may be used for the treatment of acute mania (pg 18).

Lamotrigine should not be used for the treatment of acute mania as it lacks efficacy in this area (pg 18).

Clonazepam or lorazepam (IM or oral) may be used in the acute treatment of agitation in mania (pg 19).

Haloperidol (IM or oral), olanzapine (IM or oral), quetiapine (oral) or aripiprazole (IM) may be used in the acute treatment of agitation in mania (pg 19).

If antidepressants are to be used in combination with mood stabilisers as first-line treatment for the acute treatment of bipolar depression, they should be used cautiously due to conflicting evidence of efficacy (pg 20).

The lowest therapeutic dosage of antidepressants, for the shortest required period of time, should be used for patients who continue to be depressed despite the optimal use of mood stabilisers (pg 21).
Quetiapine monotherapy, olanzapine monotherapy or olanzapine-fluoxetine combination may be used in the treatment of bipolar depression (pg 21).

Grade A, Level 1+

Monotherapy with sodium valproate or carbamazepine is not recommended in the treatment of bipolar depression due to conflicting evidence regarding efficacy (pg 21).

Grade A, Level 1+

There is insufficient evidence to recommend lamotrigine monotherapy in the treatment of bipolar depression. However, it is recommended as an add-on for patients already on lithium for treatment of bipolar depression (pg 21).

Grade A, Level 1+

Lithium may be used in the treatment of bipolar depression (pg 21).

Grade A, Level 1+

Consider using sodium valproate or quetiapine as first-line treatment in patients with rapid cycling. This may be combined with lithium (pg 22).

Grade A, Level 1+

A combination of lithium and lamotrigine may be considered as an alternative treatment for rapid cycling (pg 22).

Grade A, Level 1+

Non-pharmacological treatments should not be used for patients with rapid cycling bipolar disorder due to insufficient evidence (pg 22).

GPP

Mood stabilisers may be used when treating mixed states. Of these, valproate and carbamazepine should be preferred over lithium as there is more evidence for the efficacy of valproate and carbamazepine than for lithium (pg 22).

Grade A, Level 1+
Electroconvulsive therapy can be considered for manic and depressive episodes which are severe or which fail to respond to pharmacological interventions, or when pharmacological interventions are not possible (pg 23).

Grade B, Level 2++

Consider the use of electroconvulsive therapy as anti-manic and anti-depressive treatment in mixed states that are severe or fail to respond to pharmacological interventions, or when pharmacological interventions are not possible (pg 23).

Grade C, Level 2+

Maintenance

Lamotrigine can be used for prophylaxis in patients who have initially stabilised with lamotrigine (pg 24).

Grade A, Level 1+

Lithium, valproate, or olanzapine may be used as maintenance therapy in preventing relapse to either pole of illness in patients with bipolar disorder (pg 25).

Grade A, Level 1+

Aripiprazole may be used as maintenance therapy in bipolar patients with recent manic or mixed episode (pg 25).

Grade A, Level 1+

Quetiapine, in combination with lithium or valproate, may be used as maintenance therapy in patients with bipolar I disorder (pg 25).

Grade A, Level 1+

To minimize the risk of manic switching and/or rapid cycling, patients whose depressive symptoms have remitted for at least 8 weeks from an acute depressive episode may have their antidepressant medication gradually discontinued over several weeks, whilst maintaining them on their mood stabiliser medication (pg 26).

Grade A, Level 1+
Patients should not be routinely continued on their antidepressant treatment for long-term as they offer minimal to no significant continuing benefits or effects on depressive episode prevention or enhanced remission rates (pg 26).

Grade A, Level 1+

Maintenance medications for bipolar disorder should not be discontinued, in view of the high risk of relapse (pg 26).

Grade A, Level 1+

If discontinuation of maintenance medications is planned, it should be performed by gradual tapering of the dosage over several weeks (pg 26).

Grade A, Level 1+

Lithium and valproate may be used as maintenance therapy for patients with rapid cycling bipolar disorder (pg 27).

Grade A, Level 1+

Patients with rapid cycling bipolar disorder should not be routinely continued on antidepressant therapy after achieving remission as it does not offer significant clinical benefit in preventing relapse (pg 27).

Grade B, Level 2++

Psychological interventions

Whenever possible, health professionals should provide psychoeducation to patients with bipolar disorder, and their families/caregivers (pg 28).

GPP

Upon identification of early warning signs/relapse signatures by individuals or family members/caregivers, individuals can use the plan of action that they developed based on these early warning signs. This plan of action should be a collaborative effort between the patient, family members/caregivers and healthcare professionals (pg 29).

Grade A, Level 1+
Cognitive behavioural therapy, family therapy or interpersonal social rhythms therapy may be considered as part of the treatment plan for bipolar depression (pg 31).

**Grade A, Level 1+**

**Reproductive health issues**

A Women on combined oral contraceptive pills who are concurrently taking carbamazepine and/or lamotrigine should be advised of the risk of decreased contraceptive effect as a result of drug interactions (pg 32).

**Grade A, Level 1+**

B Use of sodium valproate in women of childbearing age should be balanced against the risk of decreased fertility, foetal malformations and perinatal complications (pg 33).

**Grade B, Level 1+**

A Periconceptional folate supplementation should be prescribed to protect against neural tube defects (pg 34).

**Grade A, Level 1+**

D Abrupt discontinuation (i.e. less than 2 weeks) of mood stabilisers should be avoided if possible, in order to lessen the chance of relapse (pg 34).

**Grade D, Level 3**

GPP Consider switching to antipsychotic treatment, or gradual decrement (over 15–30 days) of monotherapy mood stabiliser to the lowest effective amount in divided doses during pregnancy; concurrent careful foetal monitoring is recommended (pg 34).

GPP Consider resuming mood stabiliser treatment immediately postpartum as this is a period of vulnerability to relapse (pg 34).
Sodium valproate and carbamazepine are preferable to lithium and lamotrigine during breastfeeding; mothers who require the latter two medications may be advised to consider abstinence from breastfeeding for the infant’s safety (pg 34).* 

In the event of breastfeeding, while taking mood stabilisers, consider administering feeds before taking medication and discarding the first post-dose batch of expressed milk, so as to minimise the infant’s consumption of medication via breast milk (pg 34).

First-trimester paroxetine use should be avoided as it is associated with increased risk of serious congenital (particularly cardiac) defects (pg 35).

Selective serotonin reuptake inhibitors should be used judiciously in late pregnancy because of associations with persistent pulmonary hypertension of the newborn and neonatal behavioural syndrome (pg 35).

While there is no evidence for routine monitoring for congenital malformations during antenatal use of antidepressants, careful foetal monitoring is recommended nonetheless (pg 35).

Women who are planning conception should be advised that antipsychotics are associated with hyperprolactinemia and amenorrhea, which may affect fertility (and predispose toward premature bone loss) (pg 37).
D Typical antipsychotics, such as chlorpromazine and haloperidol, may be considered for treatment of pregnant women with bipolar disorder, as they appear less likely than atypical antipsychotics to cause metabolic complications and other serious adverse effects (pg 37).

Grade D, Level 3

GPP When considering antipsychotics for pregnant women, the clinical presentation and side effect profile should also be considered. For instance, previous poor response or side effects to typical antipsychotics should merit consideration of an atypical antipsychotic (pg 37).

GPP Weight, blood sugar and blood pressure should be monitored in pregnant women on atypical antipsychotics (pg 37).

GPP When antipsychotics are used in pregnant women, close and careful foetal monitoring via regular visits and scans is recommended (pg 37).

GPP In the event of breastfeeding while taking antipsychotics, consider administering feeds before taking medication and discarding the first post-dose batch of expressed milk to minimise the infant’s consumption of medication via breast milk (pg 37).

C Benzodiazepines should be avoided in pregnancy (pg 38).

Grade C, Level 2+

D Electroconvulsive therapy may be considered as a treatment option in pregnancy for the same indications as in nonpregnant patients (pg 38).

Grade D, Level 3
Substance misuse

A Addiction disorders in patients with bipolar disorder should be treated (pg 39).

Grade A, Level 1+

GPP Patients with dual diagnosis of bipolar disorder and addiction disorders should be treated in an integrated specialist treatment centre (pg 39).

Suicide prevention

C Clinicians should routinely assess risk of suicide in all patients with bipolar disorder (pg 40).

Grade C, Level 2+

Monitoring

B During each review, clinical assessment of cardiovascular risk factors (e.g. obesity, smoking) should be performed for all patients with bipolar disorders (pg 41).

Grade B, Level 2++

GPP Prior to starting treatment, doctors should obtain a patient’s personal and family history of obesity, diabetes, dyslipidaemia, hypertension and cardiovascular disease (pg 41).

GPP A patient’s alcohol and smoking history, height, weight (including the calculation of body mass index) and blood pressure measurements, together with fasting blood (plasma) glucose level and lipid profile assessment should be obtained at baseline. This clinical monitoring should also be repeated at regular planned intervals (pg 42).

GPP
Consider using the Clinical Global Impression scales (both severity and improvement component scales) to measure illness severity and treatment progress during consultations (pg 43).
### Levels of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td><strong>1</strong>+ +</td>
<td>High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias</td>
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<tr>
<td><strong>1</strong>+</td>
<td>Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
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<tr>
<td><strong>1</strong>-</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
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<tr>
<td><strong>2</strong>+ +</td>
<td>High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
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<tr>
<td><strong>2</strong>+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
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<tr>
<td><strong>2</strong>-</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
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<tr>
<td><strong>3</strong></td>
<td>Non-analytic studies, e.g. case reports, case series</td>
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<td><strong>4</strong></td>
<td>Expert opinion</td>
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### Grades of recommendation

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<tr>
<td><strong>A</strong></td>
<td>At least one meta-analysis, systematic review of RCTs, or RCT rated as <strong>1</strong>+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as <strong>1</strong>+ , directly applicable to the target population, and demonstrating overall consistency of results</td>
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<td><strong>B</strong></td>
<td>A body of evidence including studies rated as <strong>2</strong>+ +, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as <strong>1</strong>++ or <strong>1</strong>+</td>
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<td><strong>C</strong></td>
<td>A body of evidence including studies rated as <strong>2</strong>+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as <strong>2</strong>++</td>
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<tr>
<td><strong>D</strong></td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as <strong>2</strong>+</td>
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<tr>
<td><strong>GPP</strong> (good practice points)</td>
<td>Recommended best practice based on the clinical experience of the guideline development group</td>
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