

# Bipolar disorder

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## 1. Introduction

Bipolar disorder (BD) presents in different phases over time and is often complicated by comorbid conditions such as substance-use disorders and anxiety disorders. Treatment usually involves pharmacotherapy with combinations of different classes of medications and frequent medication revisions.

Since practice recommendations or treatment guidelines cannot fully summarise the myriad of presentations, they need to be used flexibly, taking into account the individual patient, the sociocultural context and the availability of treatment resources. The Medicines Control Council (MCC) in South Africa often lags behind other international regulatory agencies regarding the registration of medications with confirmed efficacy for indications in BD and therefore clinicians have to prescribe certain drugs off-label in the treatment of routine, difficult and treatment-resistant cases of BD.

In this guideline, levels of evidence derived from studies will be explored.<sup>[1]</sup> Evidence criteria include:

- Level 1: meta-analysis or replicated double-blind (DB), randomised controlled trial (RCT) with a placebo condition
- Level 2: at least one DB-RCT with active comparison condition or placebo
- Level 3: prospective uncontrolled trial with at least  $\geq 10$  participants
- Level 4: anecdotal reports or expert opinion.

This guideline makes treatment recommendations:<sup>[1]</sup>

- First line: level 1 or level 2 evidence plus clinical support for safety and efficacy
- Second line: level 3 evidence or higher plus clinical support for safety and efficacy
- Third line: level 4 evidence or higher plus clinical support for safety and efficacy
- Not recommended: level 1 or level 2 evidence for lack of efficacy.

### 1.1 Epidemiology of bipolar disorder pertinent to the treatment guideline<sup>[2-5]</sup>

#### 1.1.1 Epidemiological statistics

For bipolar I disorder, the mean reported age of the first mood episode is 18.2 years, while the lifetime prevalence is 1%. For bipolar II disorder, the mean reported age of first mood episode is 20.3 years, while the lifetime prevalence is 1.1%. Bipolar I disorder affects men and women equally, while bipolar II disorder is more common in women.<sup>[3,4]</sup>

#### 1.1.2 Illness characteristics

The first symptoms of BD often present at 15 - 19 years of age. The most likely first episode, and also predominant phase in the later stages of the illness, is depression. Suicide is 15 times more likely in BD patients compared to the general population, with as many as 7 - 15% of all bipolar sufferers committing suicide. Suicide is most likely to occur during mixed or depressive episodes.<sup>[5]</sup>

## 2. Diagnosis and clinical characteristics

The diagnosis should be made with rigour. As the full spectrum of the disorder does not present itself at one point in time only, the diagnosis should be made over time. Table 1 summarises the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*<sup>[6]</sup> classification of bipolar subtypes.<sup>[7,8]</sup>

The International Society for Bipolar Disorders (ISBD) Diagnostic Guidelines Task Force made the following recommendations for the *DSM-V* and *International Classification of Diseases 11th Revision (ICD-11)* for BD.<sup>[1]</sup> For BD I, the *DSM-V* criteria for mania should remain similar, but for bipolar depression, the criteria should include a probabilistic approach acknowledging the presence of: (i) atypical depressive symptoms (hyperphagia, hypersomnia, or leaden paralysis); (ii) psychomotor disturbance; (iii) pathological guilt or psychotic features; and (iv) a positive family history of BD. It was suggested that the rapid-cycling specifier for BD I should be extended to BD II and BD not otherwise specified (NOS)(now known as Other Specified Bipolar and Related Disorder in the *DSM-V*. The Task Force also suggested modifications to the diagnostic criteria for BD II and BD NOS to improve the identification of bipolar spectrum disorders to include the following: (i) subthreshold hypomanic episodes, and (ii) other signs of bipolarity without manic or hypomanic episodes (also known as bipolar spectrum disorder). These include:

- Family history (BD, alcohol and substance use, mental illnesses, suicides)
- Depressive symptoms (atypical, psychomotor slowing, psychosis, seasonal)
- Course of illness (early age of onset, short duration of episodes, greater number of episodes).

Separating major depressive disorder (MDD) and BD, particularly BD II, can be a challenge.<sup>[2]</sup> Several reports have found that BD, in contrast to MDD, is associated with:

- A significantly earlier age of onset
- More recurrences

**Table 1. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) classification of bipolar subtypes<sup>[6,7,11]</sup>**

Bipolar I disorder is characterised by one or more episodes of mania with or without major depressive episodes.

Bipolar II disorder is characterised by one or more episode of hypomania as well as at least one major depressive episode with no psychotic features.

Cyclothymic disorder is characterised by a low grade cycling of mood with the presence or history of hypomanic episodes and periods of depression that do not meet the criteria for major depressive episodes.

Bipolar disorder not otherwise specified is characterised by bipolar symptoms that do not meet the criteria for previous subtypes.

- Atypical and mixed depressions
- A family history of BD or completed suicide.

A BD diagnosis is highly predicted by mixed states, especially BD II, which has been linked with an increased lifetime risk for comorbid psychiatric disorders, more mood episodes, higher rates of treatment contacts, and lower rates of full-time employment compared to pure states.

Once a BD diagnosis has been made, the diagnostic formulation should identify the episode type and the longitudinal course of illness. Valuable clinical tools that inform assessment and assist in monitoring and quantifying treatment response include the following rating scales:

- Bipolar Inventory of Symptoms Scale (BISS)
- Structured Clinical Interview for Mood Spectrum (SCI-MOOD)
- Young Mania Rating Scale (YMRS) for mania
- Bipolar Depression Rating Scale (BDRS) for bipolar depression
- Mood Disorders questionnaire.

Once the diagnosis of BD has been confirmed, a comprehensive risk assessment should be completed on an ongoing basis throughout treatment. Ensuring the safety of patients with acute mania is essential, since there is an increased risk of aggression, excessive spending and disinhibited behaviour, decreased judgement and insight, and an increased risk of suicidal thoughts immediately after admission to, and immediately following discharge from, hospital. The risk to others, including to children or other family members, should also be considered. The appropriate venue for treatment, i.e. inpatient or outpatient, voluntary or involuntary, should then be determined.

### 3. Recommended baseline investigations for BD<sup>[2]</sup>

The recommended investigations should assist clinicians in management and are not diagnostic in nature. The list below represents a list of possibilities to be considered where clinically appropriate and does not represent an exhaustive list of tests to be performed in every patient with suspected BD.

Baseline investigations:

- 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, high-density lipoprotein (HDL), low-density lipoprotein (LDL))
  - Fasting blood sugar
- Screen/test:
  - Full blood count
  - Blood chemistry:
    - (i) Electrolytes
    - (ii) Serum creatinine
    - (iii) Thyroid-stimulating hormone
    - (iv) Liver function tests
  - 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)
- Perform:
  - Electrocardiogram (ECG) (if prescribing lithium and age >40 years)
  - Electro-encephalograph (EEG) (if indicated)
  - Magnetic resonance imaging (MRI) (preferred)/computed tomography (CT) – indicated in suspected organic aetiology.

## 4. Treatment

### 4.1 Pharmacological treatment

Malhi and co-authors<sup>[2]</sup> have used specific terminology to categorise the pharmaco-

logical agents for BD treatment. As illustrated in Fig. 1 these terms have been chosen based on the intended therapeutic action rather than on the traditional medication class.<sup>[2]</sup>

Medications efficacious in the treatment of mania or hypomania include antimanic agents. Maintenance agents include those administered in the euthymic phase of BD with proven prophylactic efficacy. Bipolar depression agents, which should not be confused or used interchangeably with the term antidepressants, include effective medications for the treatment of bipolar depression.

Some medications have indications for multiple phases of the illness. Since there are very few drugs that truly meet the full definition of a mood stabiliser (i.e. effective for all phases of the illness), the term mood stabiliser has largely fallen into dis favour. While some antibipolar agents are efficient in the acute phase, others are more efficient in the maintenance phase.

The treatment of BD can be divided into the following components:

- Acute treatment of mania and hypomania
- Acute treatment of depression
- Maintenance treatment
- Bipolar II disorder
- Treatment of complex bipolar presentations (i.e. rapid cycling and mixed states)
- Partial or no treatment response
- Treatment of comorbidities (i.e. anxiety disorders and substance-use disorders (not included in this guideline)).

### 4.2 Acute treatment: bipolar mania

For acute symptoms of mania, taper and cease any antidepressants or agents with mood-elevating properties (e.g. stimulants) and introduce general measures where possible:

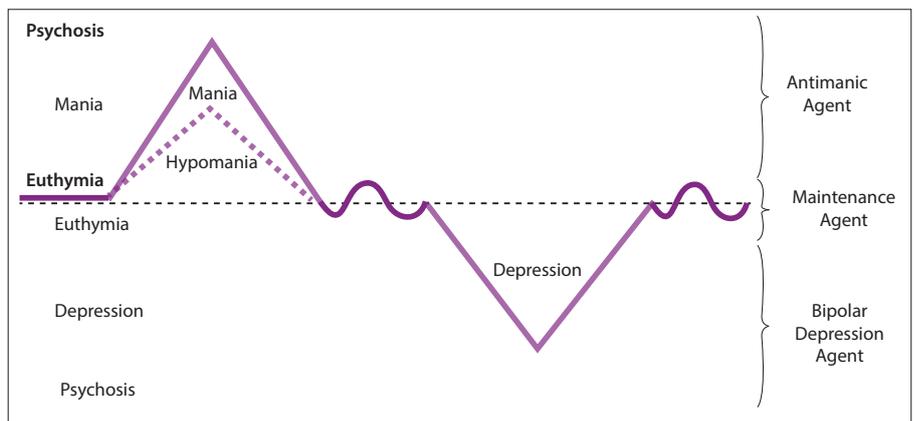


Fig. 1. Phases of bipolar illness with matching treatment terminology.<sup>[2]</sup>

- Reduce stimulation
- Lower activity level
- Delay individual from making important decisions
- Maintain a structured routine.

Commence treatment with an antimanic agent (level 1). When selecting an agent, its antimanic efficacy and tolerability, as well as the likelihood of continuing acute treatment into maintenance phase, should be considered. Recommendations for the pharmacological treatment of acute mania are summarised in Table 2.<sup>[3]</sup>

#### 4.2.1 Monotherapy<sup>[2]</sup>

Antimanic agents with evidence for efficacy in acute mania include:

- Lithium
- Valproate – the speed of action for valproate can be accelerated using dose-loading
- Olanzapine
- Aripiprazole
- Quetiapine
- Risperidone
- Ziprasidone
- Paliperidone
- Haloperidol – haloperidol is efficacious but longer-term use carries an increased risk of extrapyramidal side-effects (e.g. tardive dyskinesia). Haloperidol is not recommended unless other options have failed, as it lacks efficacy in maintenance treatment.
- To a lesser extent, carbamazepine.

#### 4.2.2 Combination treatment<sup>[2]</sup>

In comparison to monotherapy with either lithium or valproate alone, recent studies have shown superior efficacy of lithium or valproate in combination with the short-term administration of an atypical antipsychotic. If symptoms and/or behavioural disturbances are severe or protracted, electroconvulsive therapy (ECT) (level 3) should be considered. During ECT, discontinue lithium and anticonvulsants. Although recent studies have indicated that anticonvulsants may be continued during ECT without losing therapeutic efficacy of ECT, it is advisable to discontinue anticonvulsants during ECT.

Gabapentin, lamotrigine, topiramate, phenytoin and oxcarbamazepine are not recommended for the treatment of acute mania.

#### Behavioural disturbance:<sup>[2]</sup>

- Acute behavioural disturbance can be managed by either the short-term use of a benzodiazepine (e.g. lorazepam) or an antipsychotic; the concurrent use of two antipsychotics is not recommended.
- Oral administration is preferable.
- It is advisable to use an injectable atypical or a combination of an injectable typical antipsychotic and a benzodiazepine if intramuscular (IM) administration is necessary. RCT data support the use of IM aripiprazole or IM olanzapine (level 2) in the treatment of acute agitation.<sup>[1]</sup>
- IM aripiprazole (9.75 mg and 15 mg) (not available in South Africa) is superior to placebo and comparable with IM lorazepam (2 mg).<sup>[10]</sup> In a DBRCT, IM olanzapine 10 mg was superior to placebo and has shown a trend toward greater improvement than IM lorazepam 2 mg.<sup>[11]</sup>
- In view of the risk of respiratory failure, olanzapine should not be used in combination with benzodiazepines.

#### Psychotic mania:

- Psychosis is common and occurs in approximately 60% of acute manic episodes.
- For acute psychotic symptoms, an antipsychotic may be employed as adjunctive treatment, if not already being administered as an antimanic agent.
- Atypical antipsychotics are preferred to typical antipsychotics since they have enhanced tolerability.

#### 4.2.3 Psychotherapy for mania

Psycho-education (PE) and family-focused therapy (FFT) are efficacious in the prevention of mania/hypomania (and possibly depression).<sup>[11]</sup> To prevent bipolar episodes, interpersonal social rhythm therapy (IPSRT) and cognitive-behavioural therapy (CBT) are probably efficacious.<sup>[11]</sup>

### 4.3 Acute treatment: bipolar depression

#### 4.3.1 Pharmacotherapy for bipolar depression

In patients with bipolar depression, any agents that could exacerbate depressive symptomatology (e.g. typical antipsychotics such as chlorpromazine, antihypertensive agents and corticosteroids) should be ceased.<sup>[2]</sup>

**Table 2. Recommendations for pharmacological treatment of acute bipolar II depression<sup>[1]</sup>**

First line	Quetiapine*
Second line	Lithium Lamotrigine Divalproex* Lithium or divalproex + antidepressants Lithium + divalproex Atypical antipsychotics + antidepressants
Third line	Antidepressant monotherapy (particularly for those with infrequent hypomanias), switch to alternate antidepressant Ziprasidone*
Not recommended	Risk-benefit ratio for antidepressant use in BD II is still an unresolved issue Switch rates with antidepressants are lower in patients with BD II compared with those with BD I

\*New

First-line monotherapy treatment options for bipolar depression include:<sup>[2]</sup>

- Quetiapine 300 - 600 mg/day
- Lamotrigine 200 - 500 mg/day
- Olanzapine 5 - 15 mg/day
- Lithium
- Valproate.

Second-line options for bipolar depression include the following adjunctive or combination therapies:

- Adjunctive risperidone 2 - 4 mg/day
- Lithium and antidepressant combinations
- Olanzapine and fluoxetine combination
- Valproate and lithium
- Lamotrigine as an add-on to lithium.

For concurrent psychotic symptoms, atypical antipsychotics can be used as augmentation (level 2),<sup>[2]</sup> but combining two antipsychotic medications should best be avoided.

The benefits of conventional antidepressants such as the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and noradrenaline reuptake inhibitors (SNRIs) in the treatment of bipolar depression is currently unclear.<sup>[2]</sup> If a conventional antidepressant is employed for bipolar depression, it should be concurrently administered with an antimanic maintenance agent to diminish the possibility of switching. The antidepressant should then gradually be tapered after 2 - 3 months of sustained recovery.<sup>[2]</sup> In addition, antidepressants should not be prescribed in rapid-cycling BD. Also, venlafaxine (13 - 15%) and the TCAs (7 - 11%) are associated with a relatively higher risk of inducing a manic switch than SSRIs (0 - 4%),<sup>[11]</sup> while other agents can also precipitate switching (e.g. psychostimulants).<sup>[2]</sup>

ECT should be considered if the risk to self or others is high, if psychotic features are present, or if there has been a previous response to ECT (level 3).<sup>[2]</sup>

#### 4.3.2 Psychotherapy for bipolar depression

As there is no definitive evidence for the efficacy of psychological therapies as BD monotherapy, these therapies are best administered as adjunctive treatments to pharmacotherapy. There is also limited evidence for psychological treatments in acute bipolar depression compared to evidence for their use as maintenance-phase treatments.

CBT and FFT are efficacious, with IPSRT possibly efficacious, as adjuncts to medication, in the treatment of bipolar depression.<sup>[11]</sup>

If a patient has severe psychomotor impairment or psychotic features, psychological treatments are not recommended during the acute phase.<sup>[2]</sup>

#### 4.4 Maintenance treatment

Maintenance treatment is important once a diagnosis of BD has been made. Indications for maintenance treatment include:<sup>[2]</sup>

- A mood episode in the past 5 years
- Two previous mood episodes over any time period
- Severe acute episodes with psychotic features, or a suicide risk
- Ongoing functional disability (level 5).

The treatment plan should be re-evaluated and attention should be paid to factors that may increase the risk of relapse, including comorbid conditions and psychosocial stressors. A collaborative

approach to maintenance care should be adopted. Furthermore, both pharmacological and psychological treatment strategies should be used to eliminate subsyndromal depressive symptoms, since disability is closely related to the depressive component of the illness. Psychosocial stressors should be addressed; address problem-solving skills and the development of social support networks (especially with chronic depressive symptoms); encourage a healthy lifestyle (good sleep hygiene, exercise, regular routine); treat comorbidities, particularly substance misuse; monitor clinical response to medications, adherence and side-effects; monitor social and occupational functioning; provide PE for the family; and address caregiver support.<sup>[2]</sup>

#### 4.4.1 Psychological interventions as an adjunct to medication

These appear to have the greatest benefit in reducing the risk of relapse and can improve functioning. By targeting euthymic patients in the maintenance phase of illness, therapeutic effects can be optimised, but are likely to be less effective in those with a high number of prior mood episodes (>12 episodes). There is strong evidence for interventions that focus on the recognition of early warning signs (level 1) and this includes:

- CBT (level 2)
- FFT (level 2)
- IPSRT (level 2)
- Group PE (level 2)

#### 4.4.2 Maintenance pharmacotherapy<sup>[2]</sup>

As a first step, any adjunctive agents that have been used to manage behavioural disturbance associated with an acute mood episode should be withdrawn. As little evidence currently exists for combining treatments, monotherapy is preferred. Medications shown to be effective maintenance agents include:

- Lithium (level 1), mainly for preventing manic episodes
- Lamotrigine (level 2), mainly for preventing depressive episodes
- Valproate (level 2)
- Atypical antipsychotics: olanzapine (level 2)
- Aripiprazole (level 2)
- Quetiapine adjunctive to lithium or valproate (level 2).

Other atypical antipsychotics that have a limited evidence base (restricted to small trials or retrospective data) include:

- Ziprasidone (level 3)
- Risperidone (level 3)
- Adjunctive depot risperidone (level 3)
- Adjunctive clozapine (level 3).

Selection of maintenance agents should be based on their efficacy and tolerability profiles. In addition, consideration needs to be given to individual patient factors (preference, past response, safety). In this regard and to maintain therapeutic blood levels, lithium needs to be monitored regularly (0.6 - 1.2 mmol/l). The evidence for carbamazepine as a maintenance treatment is mixed, while there is no evidence for the efficacy of conventional antidepressants (e.g. TCAs, SSRIs and SNRIs) in maintenance. That said, if depressive episodes are recurrent, an antidepressant may be considered as an adjunctive to a maintenance agent, after carefully weighing up the benefits of prevention versus the risk of precipitating mania or rapid cycling.<sup>[2]</sup> The recommendations for maintenance pharmacotherapy of BD are summarised in Table 3.

**Table 3. Recommendations for maintenance pharmacotherapy of bipolar disorder<sup>[1]</sup>**

First line	Lithium	
	Lamotrigine monotherapy (limited efficacy in preventing mania)	
	Divalproex	
	Olanzapine	
	Quetiapine*	
	Lithium or divalproex + quetiapine*	
	Risperidone LAI*	
	Adjunctive risperidone LAI*	
	Aripiprazole (mainly for preventing mania)*	
	Adjunctive ziprasidone*	
Second line	Carbamazepine	
	Lithium + divalproex	
	Lithium + carbamazepine	
	Lithium or divalproex + olanzapine, lithium + risperidone	
	Lithium + lamotrigine	
	Olanzapine + fluoxetine	
Third line	Adjunctive phenytoin	
	Adjunctive clozapine	
	Adjunctive ECT	
	Adjunctive topiramate	
	Adjunctive omega-3-fatty acids	
	Adjunctive oxcarbazepine	
	Adjunctive gabapentin	
	Not recommended	Adjunctive flupenthixol
		Monotherapy with:
		Gabapentin
Topiramate		
Antidepressants		

LAI = long acting injection; ECT = electroconvulsive therapy.

\*New

**Table 4. Strength of evidence for monotherapy treatments of acute bipolar II depression<sup>[1]</sup>**

Agent	Level of evidence*
Lithium	3
Anticonvulsants	
Divalproex	3
Lamotrigine	3
Gabapentin	3 (-ve)
Atypical antipsychotics	
Olanzapine	No data
Risperidone	No data
Quetiapine	1
Ziprasidone	3
Aripiprazole	No data
Clozapine	No data
Antidepressants	
Antidepressant monotherapy	4
Fluoxetine	3
Venlafaxine	3
Tranylcypromine	2
Combination therapy	
Lithium or divalproex + pramipexole	2
Lithium or divalproex + SSRI or bupropion	2 (-ve)
Lithium or divalproex + topiramate	Limited evidence
Atypical antipsychotic + antidepressant	3
Lamotrigine + bupropion	4

\* Level of evidence:

Level 1. Meta-analysis or replicated double-blind (DB), randomised controlled trial (RCT) with a placebo condition.

Level 2. At least one DB-RCT with active comparison condition or placebo.

Level 3. Prospective uncontrolled trial with at least ≥ 10 participants.

Level 4. Anecdotal reports or expert opinion.

SSRI = selective serotonin reuptake inhibitor.

#### 4.4.3 How long to treat

Treatment of BD is often lifelong, and a minimum of 6-monthly reviews is recommended.

The strength of evidence for monotherapy treatments for acute bipolar II depression, and for maintenance of BD II are summarised in Tables 4 and 5, respectively.

### 4.5 Complex bipolar presentations

#### 4.5.1 Rapid cycling<sup>[2]</sup>

This presentation is associated with higher rates of morbidity, increased suicide risk, and poorer long-term treatment response.

It is important to screen for and, where possible, exclude factors that may precipitate or exacerbate rapid cycling:

- Antidepressants
- Substance misuse
- Medications
- Medical illness, e.g. hypothyroidism.

Treatment options for rapid cycling:<sup>[2]</sup>

- There is a limited evidence base of effective treatments for rapid cycling.
- Current treatments appear to be less effective in countering depressive symptoms than manic symptoms.  
Pharmacological monotherapy:
  - Consider valproate (level 2)
  - Lithium (level 2)
  - Olanzapine (level 2)
  - Lamotrigine (level 2) (primarily for BD II patients)
  - Quetiapine (level 3).
- Combination therapies:
  - Consider adjunctive psychological interventions (level 5) as outlined under maintenance treatments.
  - There is limited evidence to support combination pharmacological treatments and this should be decided according to clinical need, e.g.:
    - Lithium + valproate (level 3)

**Table 5. Strength of evidence for the maintenance therapy of bipolar II disorder<sup>[1]</sup>**

Agent	Level of evidence <sup>*</sup>
Lithium	2
Anticonvulsants	
Divalproex	3
Lamotrigine	2
Carbamazepine	3
Gabapentin	4
Atypical antipsychotics	
Adjunctive risperidone	3
Antidepressants	
Fluoxetine	3
Imipramine	2 (-)
Combination therapy	
Lithium + imipramine	2 (-)
Lithium + SSRI, venlafaxine or bupropion	4
Electroconvulsive therapy	4

\* Level of evidence:

Level 1. Meta-analysis or replicated double-blind (DB), randomised controlled trial (RCT) with a placebo condition.

Level 2. At least one DB-RCT with active comparison condition or placebo.

Level 3. Prospective uncontrolled trial with at least ≥10 participants.

Level 4. Anecdotal reports or expert opinion.

SSRI = selective serotonin reuptake inhibitor

- Lithium + carbamazepine (level 3)
- Adjunctive lamotrigine (level 5).
- Physical treatments: ECT (level 3).

#### 4.5.2 Mixed states

Distinguish mixed states from both mania and agitated depression.<sup>[2]</sup> Studies focusing on monotherapy and adjunctive treatment options for mixed states are scant, although patients with mixed states have been included in trials of acute mania and acute bipolar depression. As a start, it is important to taper and cease medications with mood-elevating properties, especially those that may induce inter-episode switching.<sup>[2]</sup> Antidepressants can worsen or induce rapid cycling and are thus not recommended. Lithium may have reduced efficacy for treating mixed states.<sup>[2]</sup> Treatment options include:<sup>[2]</sup>

- Olanzapine (level 2)
- Quetiapine or valproate as monotherapy
- Olanzapine and fluoxetine in combination
- Valproate in combination with olanzapine (level 2).

Lamotrigine may be a useful adjunctive treatment to an antimanic agent for depressive symptoms in mixed states, although treatment effect is likely to be delayed as this requires slow titration, especially when used in conjunction with valproate.<sup>[2]</sup>

ECT (level 3) may be considered if symptoms and/or behavioural disturbances are severe or protracted.

#### 4.6 Partial or no treatment response

Structured rating scales employed in combination with clinical assessment can be valuable in assessing treatment response and in quantifying symptom change.

- Re-evaluate the diagnosis. Reassess for psychosocial stressors that may maintain symptoms and consider alternative causes (e.g. organic causes).
- Reassess for medical comorbidities and psychiatric comorbidities (e.g. anxiety disorders, drug and alcohol use disorders, personality disorders).
- Review adherence and dosage. Reassess adherence and satisfaction with treatment plan. Ensure a therapeutic dose is prescribed and that adequate blood levels of medication are attained when taking an antidepressant.

Therapeutic strategies for non-response in mania:<sup>[2]</sup>

- Optimise antimanic agent:
    - Check levels
    - Adjust dose
    - And/or augment
    - And/or combine with another antimanic agent.
  - Consider combination therapy. This is often used in clinical settings where response to monotherapy has been inadequate. Head-to-head comparison studies of different combinations are scant. Combinations that have been assessed in clinical trials include:<sup>[2]</sup>
    - Lithium and valproate (level 2)
    - Lithium and carbamazepine (level 2)
    - Lithium or valproate and olanzapine (level 2)
    - Adjunctive clozapine or risperidone (level 3).
  - Substitute antimanic agent with another and/or consider ECT (level 3) if episode is very severe or there is a high suicide risk.<sup>[2]</sup>
- Bipolar depression: non-response:<sup>[2]</sup>
- Optimise dose (check blood levels and/or adjust dose) of medication being used and/or
  - Switch to alternative bipolar depression agent and/or
  - Augment and/or combine agents
  - Consider adjunctive psychological therapy that will target depressive symptoms (e.g. CBT, IPSRT, FFT).
  - Consider using conventional antidepressants, but closely monitor for switch to mania.
  - Consider ECT (level 3) if episode is very severe, or there is marked or significant risk for treatment resistance.

Treatment non-adherence is common in BD.<sup>[2]</sup> Depot treatment of either an injectable atypical antipsychotics (level 3) (e.g. risperidone) or an injectable first-generation antipsychotic (level 3) should be considered in cases of ongoing persistent non-compliance, and after failure of other appropriate interventions.<sup>[2]</sup> A first-generation depot antipsychotic is not recommended where the course of BD is characterised predominantly by depression.<sup>[2]</sup>

#### 4.7 Algorithm

Fig. 2 outlines the treatment algorithm. Please refer to Appendix A for other aspects of treatment and management.

## 5. Summary points

- For acute symptoms of mania, commence treatment with an antimanic agent. Antimanic agents with evidence for efficacy in acute mania include lithium, valproate, olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone, paliperidone, haloperidol and to a lesser extent carbamazepine.
- Recent studies have shown superior efficacy of lithium or valproate in combination with the short-term administration of an atypical antipsychotic.
- Gabapentin, lamotrigine, topiramate, phenytoin and oxcarbamazepine are not recommended for the treatment of acute mania.
- If IM administration is required for acute agitation/behavioural control, it is advisable to use an injectable atypical or a combination of an injectable typical antipsychotic and a benzodiazepine. RCT data support the use of IM aripiprazole or IM olanzapine for acute agitation.
- First-line monotherapy treatment options for bipolar depression include quetiapine, lamotrigine, olanzapine, lithium, and valproate.
- For concurrent psychotic symptoms, both in bipolar mania and depression, atypical antipsychotics can be used as augmentation.
- In bipolar depression, an antidepressant should be administered concurrently with an anti-manic maintenance agent to reduce the possibility of switching. The antidepressant should then gradually be tapered after 2 - 3 months of sustained recovery.
- Antidepressants should not be prescribed in rapid-cycling BD.
- For rapid cycling, consider valproate, lithium, olanzapine, lamotrigine (for BD II), or quetiapine.
- Psychotherapies are best used as adjuncts to medication in bipolar depression. CBT (cognitive-behaviour therapy) and family-focused therapy (FFT) are efficacious, with interpersonal social rhythm therapy (IPSRT) possibly efficacious, as adjuncts to medication, in the treatment of bipolar depression. Adjunctive psychotherapy can reduce the risk of relapse and improve functioning.
- Maintenance treatment must be considered if there has been a mood episode in the past 5 years, if there have been 2 previous mood

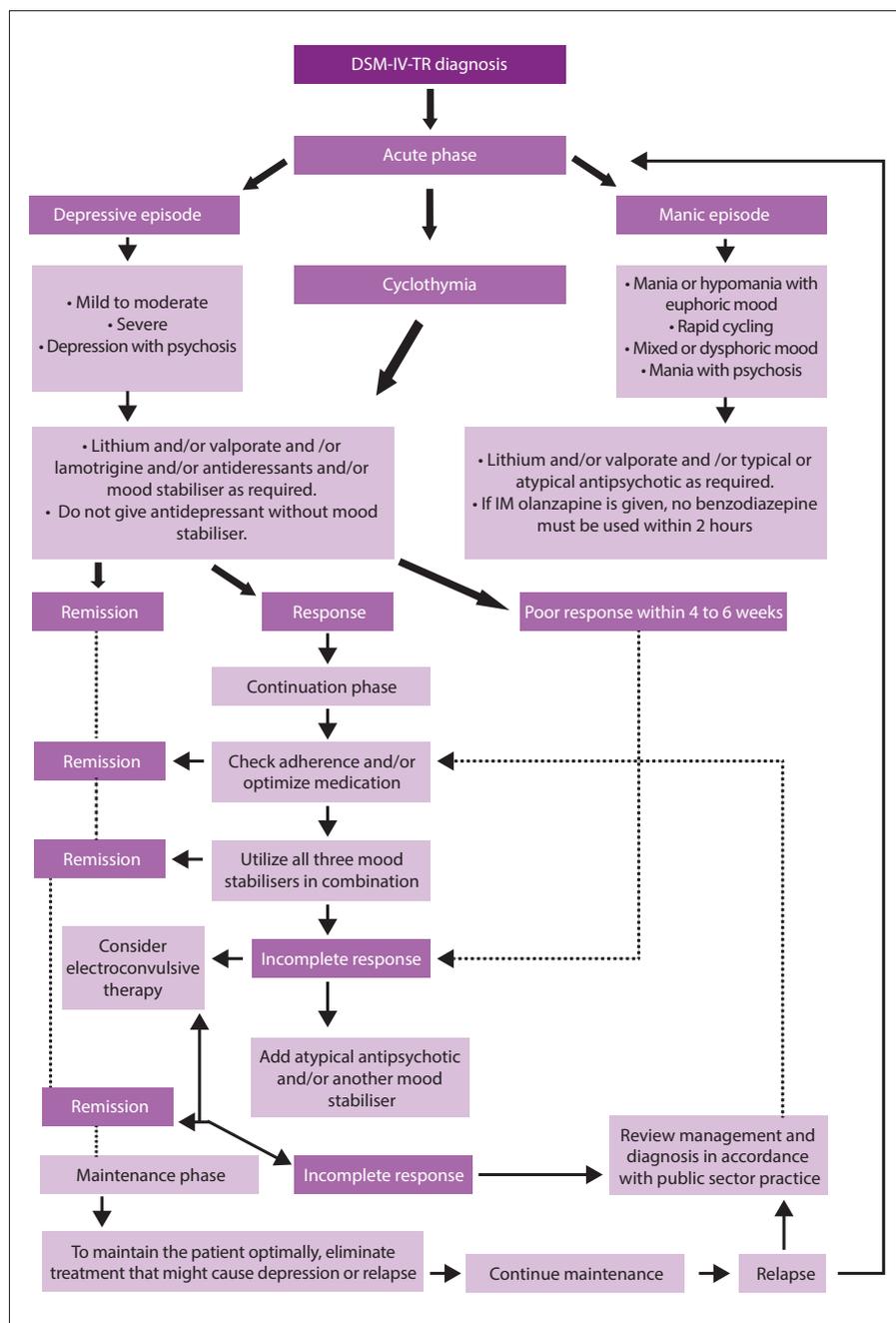


Fig. 2. Bipolar disorder algorithm.<sup>[1,2]</sup>

episodes over any time period, if acute episodes are severe with psychotic features or if there is a suicide risk, or if there is ongoing functional disability.

- Medications shown to be effective maintenance agents include lithium (mainly for preventing manic episodes), lamotrigine (mainly for preventing depressive episodes), valproate, atypical antipsychotics (olanzapine, aripiprazole, and quetiapine adjunctive to lithium or valproate).

- For non-response in bipolar mania, consider combining 2 mood stabilisers (e.g. lithium + valproate, lithium + carbamazepine, lithium or valproate + olanzapine) or combining a mood stabiliser with an atypical antipsychotic; for non-response in bipolar depression consider switching to another bipolar depression agent or augmenting with another bipolar depression agent or with psychotherapy.

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## Appendix A: Other aspects of treatment and management

### 1. Definition of the bipolar disorder prescribed minimum benefit as defined in the Medical Schemes Act

The chronic disease list (CDL) specifies medication and treatment for the 25 chronic medical conditions that are covered in the section on prescribed minimum benefits. Bipolar disorder (BD) is one of the 25 conditions. The section on these conditions stipulates the following:

‘To manage risk and ensure appropriate standards of healthcare, so-called treatment algorithms were developed for the CDL conditions. The algorithms, which have been published in the *Government Gazette*, can be regarded as benchmarks, or minimum standards, for treatment. This means that the treatment your medical scheme must provide for may not be inferior to the algorithms. If you have one of the 25 listed chronic diseases, your medical scheme not only has to cover medication, but also doctors’ consultations and tests related to your condition. The scheme may make use of protocols, formularies (lists of specified medicines) and designated service providers (DSPs) to manage this benefit.’

### 2. Indications for hospital admission

Consider hospitalisation in patients who:

- Pose a serious threat of suicide or harm to others
- Are severely ill
- Are ill and lack social support outside of a hospital
- Demonstrate significantly impaired judgment
- Have complicating general medical or psychiatric conditions
- Have not responded adequately to outpatient psychiatric treatment
- Need urgent revisions of medication treatment requiring constant supervision in hospital.

### 3. Guidelines for intravenous treatment

Intravenous (IV) drug treatment is rarely appropriate in the treatment of BD and may only be indicated in the following cases:

- Where taking of oral medication is not possible, as in intensive care settings
- As part of treatment of secondary syndromes related to treatment side-effects, i.e. acute dystonia
- For IV sedation of acutely agitated/manic patients
- IIV sodium valproate has been described for the initial treatment of acute mania but is not deemed a routine treatment. It may be considered when a manic presentation poses a life-threatening risk to patient or others.