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SINGAPORE

Bipolar Disorder

MOH Clinical Practice Guidelines 5/2011



College of Family
Physicians, Singapore



Academy of Medicine,
Singapore



Singapore Medical
Association

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Levels of evidence and grades of recommendation

Levels of evidence

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

Grades of recommendation

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

CLINICAL PRACTICE GUIDELINES

Bipolar Disorder

MOH Clinical Practice Guidelines 5/2011

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

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Foreword

Bipolar disorder is a chronic relapsing illness, and, if left untreated, may pose significant morbidity and suicide risks. Global estimates suggest that between 1-2% of people may suffer from bipolar disorder over their lifetimes¹ with 10-19% of individuals with bipolar disorder attempting suicide.

People with bipolar disorder also suffer from markedly poorer quality of life. As most cases commence when individuals are aged between 15-19 years followed by 20-24 years, bipolar disorder has also been shown to result in significant costs in terms of lost productivity.

There is good evidence for effective treatment of bipolar disorder, and studies show that people with bipolar disorder who are symptom free have a higher quality of life compared with those who are not fully stabilised.

Bipolar disorder will be the third mental illness to be incorporated into the national chronic disease management programme in Nov 2011 (after depression and schizophrenia). This set of guidelines has been developed to support this initiative. I hope that this set of guidelines will assist healthcare professionals in this field to provide better care for people with bipolar disorder.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

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).

GPP

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

Grade C, Level 2+

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+

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

Grade A, Level 1+

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

Grade A, Level 1+

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

Grade A, Level 1+

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

Grade A, Level 1+

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

Grade A, Level 1+

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

Grade A, Level 1+

A 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).

Grade A, Level 1+

A 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).

Grade A, Level 1+

GPP 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).

GPP

A Quetiapine monotherapy, olanzapine monotherapy or olanzapine-fluoxetine combination may be used in the treatment of bipolar depression (pg 21).

Grade A, Level 1+

A 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+

A 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+

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

Grade A, Level 1+

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

Grade A, Level 1+

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

GPP

A 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+

B 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++

C 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

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

Grade A, Level 1+

A 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+

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

Grade A, Level 1+

A 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+

A 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+

A 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+

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

Grade A, Level 1+

A 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+

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

Grade A, Level 1+

B 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

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

GPP

A 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+

A 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

GPP Consider resuming mood stabiliser treatment immediately postpartum as this is a period of vulnerability to relapse (pg 34).

GPP

B&GPP 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).[†]

***Grade B, Level 2++**

†GPP

GPP 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).

GPP

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

Grade B, Level 2++

B 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).

Grade B, Level 2++

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

GPP

D 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).

Grade D, Level 3

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

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

GPP

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

GPP

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).

GPP

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).

GPP

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

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

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).

GPP

1 Introduction

Bipolar disorder is a chronic relapsing illness, and, if left untreated, may pose significant morbidity and suicide risks.

Global estimates suggest that between 1-2% of people may suffer from bipolar disorder over their lifetimes.¹

The age of onset for bipolar disorder ranges between childhood to 50 years of age, with a mean age of approximately 21 years. Most cases commence when individuals are aged between 15-19 years. The second most frequent age range of onset is between 20-24 years.¹

Bipolar disorder has significant morbidity and mortality rates. The cost of lost productivity resulting from this illness in the United States during the early 1990s was estimated at \$15.5 billion annually.²

Many studies show that sufferers of bipolar disorder who are not fully stabilised (i.e. adequately treated) have a lower quality of life compared to those who are generally considered symptom free. Studies have also shown that even the patients who are considered symptom free and in remission, continue to have a poorer quality of life compared with the general population.³⁻⁴

1.1 Objectives and scope of guideline

These guidelines are not to be viewed as a protocol, but provide a framework to:

- Diagnose and initiate treatment for adult patients with bipolar disorder
- Continue maintenance treatment

Although bipolar disorder can present in children, there is still ongoing debate on the diagnostic criteria for classifying bipolar disorder in children and adolescents.

The treatment of children and adolescents with bipolar disorder presents many challenges. There is understandably limited evidence regarding the use of medications in this population. The treatment and follow-up should be by a specialist in this field.

1.2 Target group

The target group of the guidelines are general practitioners, and clinicians involved in the diagnosis and treatment of patients with bipolar disorder.

1.3 Guideline development

These guidelines were compiled by a committee comprising a family physician, pharmacists, psychologists, psychiatrists and a patient representative appointed by the Ministry of Health. They were developed based on best available current evidence and expert opinion.

1.4 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence may supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review 3 years after publication, or if new evidence appears that requires substantive changes to its recommendations.

2 Definitions and diagnosis

2.1 Definitions

Bipolar disorder is defined in two main diagnostic schemes: the International Classification of Diseases from the World Health Organisation (10th edition ICD-10), and the Diagnostic and Statistical Manual (4th edition text revised DSM-IV TR) from the American Psychiatric Association. Both these schemes are broadly similar, although the DSM-IV-TR differentiates between bipolar I and bipolar II disorders (see Annex A for more details):⁵⁻⁶

- Bipolar I Disorder 296.xx -- One or more manic episodes or mixed episodes. Individuals often have one or more major depressive episodes.
- Bipolar II disorder 296.89 -- One or more major depressive episodes accompanied by at least one hypomanic episode.

Bipolar disorder is an episodic illness. During acute episodes, the patient's mood, behaviour and activity levels are significantly disrupted. Episodes may be characterised by either an elevation of mood with increased energy and activity (i.e. mania or hypomania), or a lowering of mood with decreased energy and activity (i.e. depression). In rare cases, patients may have had manic episodes in the absence of depressive episodes; such patients are still classified as having bipolar disorder.

Manic episodes can begin abruptly and last between two weeks and five months (with median duration of approximately four months). Depressive episodes may last longer. The first episode may occur at any age. The frequency of episodes and pattern of remissions and relapses are highly variable and differ among individuals. Periods of remissions tend to get shorter as the illness progresses.

In Singapore, the DSM-IV-TR is commonly used for both diagnostic and research purposes.

2.1.1 Signs and symptoms of mania and hypomania

Signs and symptoms of mania include:

- A distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week (or any duration if hospitalisation is necessary)
- During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
 - Inflated self-esteem or grandiosity
 - Decreased need for sleep
 - More talkative than usual or pressure to keep talking
 - Flight of ideas or subjective experience that thoughts are racing
 - Distractibility
 - Increase in goal-directed activity or psychomotor agitation
 - Excessive involvement in pleasurable activities that have a high potential for painful consequences.

2.1.2 Signs and symptoms of depression

Signs and symptoms of depression include:

- Five (or more) of the following symptoms that have been present during the same 2-week period and represent a change from the previous functioning; at least one of the symptoms is either depressed mood or a loss of interest or pleasure.
 - Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation by others.
 - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
 - Significant weight loss when not dieting or weight gain (e.g. a change or more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
 - Insomnia or hypersomnia nearly every day.
 - Psychomotor agitation or retardation nearly every day
 - Fatigue or loss of energy nearly every day.
 - Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.
 - Diminished ability to think or concentrate, or indecisiveness, nearly every day.
 - Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

2.1.3 Mixed episode

Symptoms of both mania and depression can occur together. Both the criteria for a manic episode as well as for a major depressive episode are met and for nearly every day during at least a 1-week period.

The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationship with others, or to necessitate hospitalisation to prevent harm to self or others, or there are psychotic features.

2.1.4 Psychotic symptoms

Severe episodes of mania and depression can include psychotic symptoms. These may comprise either or both hallucinations or delusions. These can be mood congruent (e.g. delusions of grandiosity in a manic episode) or mood incongruent.

2.1.5 Rapid cycling

Some patients with bipolar disorder may have four or more episodes of a mood disturbance in the previous 12 months that meet criteria for a major depressive episode, manic, mixed or hypomanic episode.

2.2 Diagnosis

The diagnosis of bipolar disorder is based on the criteria listed in ICD-10 or DSM-IV-TR (See section 2.1).

2.2.1 Early diagnosis and intervention

Little evidence was identified regarding the prodromal symptoms of bipolar illness that allow predictions of illness to be made.⁷⁻⁹ Early symptoms have been mainly examined in nonrepresentative communities, making it difficult to extrapolate these results to local adult patients with bipolar affective disorder.¹⁰⁻¹⁵ No specific evidence was identified on the impact of pre-symptomatic treatment on outcome.

There is evidence that early and accurate identification and diagnosis of first episode bipolar disorder and timely intervention may improve long term outcomes. Also, delays in getting the correct diagnosis and treatment make a person more likely to experience personal, social, and work-related problems.¹⁶⁻¹⁸

However, differentiating major depressive disorder (MDD) and bipolar disorder, particularly bipolar II disorder, can be a challenge. Several studies suggest the temporal instability of a bipolar diagnosis and the need for multiple visits to confirm the diagnosis in some patients.¹⁹⁻²⁰

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.

GPP

2.2.2 Screening instruments (questionnaires)

The use of screening instruments to differentiate bipolar disorder from major depressive disorder in a tertiary setting where patients present with an episode of depression is supported only by weak evidence.

Similarly, there is little evidence to suggest that the use of screening instruments is useful in screening for bipolar disorder in the general public or in a primary care setting.²¹⁻²⁴

C The use of screening instruments in day-to-day practice in primary and tertiary settings is not recommended.

Grade C, Level 2+

2.2.3 Diagnostic instability

Accurately diagnosing bipolar disorder may take many years because of the instability of its presentation. There may be symptom overlap with other psychiatric disorders in addition to the presence of confounding co-morbidities. Diagnostic delay may also be due to the late presentation of a manic or hypomanic episode in the context of a depressive illness. **Diagnostic instability may be present in patients with affective disorders.**

3 Acute treatment

The majority of treatment studies focus on bipolar I disorder. This is, in part, due to the diagnostic difficulties inherent to bipolar II disorder. As little evidence exists regarding the specific treatment of bipolar II disorder, recommendations have been extrapolated from evidence relating to patients with bipolar I disorder or a mixture of bipolar I and bipolar II disorders.

3.1 Mania

3.1.1 Antipsychotic drugs

Antipsychotic drugs include typical antipsychotics, such as haloperidol, as well as atypical antipsychotics, such as olanzapine and quetiapine. As their name suggests, they are used in the treatment of psychosis. However, they have other indications as well.

Unfortunately, they may have side effects. Typical antipsychotics, such as haloperidol, are associated with extra-pyramidal side effects. Atypical antipsychotics, such as olanzapine, are associated with weight gain, hyperglycaemia and hypercholesterolemia.

Olanzapine and risperidone have also been associated with increased morbidity and mortality risk in the elderly.²⁵

Haloperidol

Haloperidol is used in the treatment of psychosis and agitated behaviour, in addition to severe nausea and hiccups. In a Cochrane systematic review,²⁶ haloperidol was more effective in reducing manic symptoms as compared to placebo, both as monotherapy and as adjunctive treatment to lithium or valproate.

A Haloperidol may be used for the treatment of acute mania.

Grade A, Level 1+

Atypical antipsychotics

In a meta-analysis of 24 studies,²⁷ aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone have been found to be effective in the acute treatment of mania as monotherapy. In the same study, it was also reported that olanzapine, quetiapine and risperidone, when added to mood stabilisers, significantly improved manic symptoms compared to mood stabilisers alone. This finding is consistent with the results of another meta-analysis,²⁸ which reported that the addition of antipsychotics for patients not responding adequately to mood stabilisers improved the treatment outcome.

A Aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone may be used for the treatment of acute mania.

Grade A, Level 1+

A Combination pharmacotherapy with an antipsychotic and a mood stabiliser may be used for patients showing inadequate response to mood stabiliser monotherapy.

Grade A, Level 1+

3.1.2 Lithium

Although lithium salts have been in use for various conditions since the 1800s, the use of lithium in the treatment of bipolar disorder was discovered in 1949. However, the United States Food and Drug Administration (FDA) only approved it for the treatment of mania in 1970. Lithium has been found to be superior to placebo in the treatment of acute mania in a meta-analysis of 12 trials.²⁹ In this study, it was also found to be superior to chlorpromazine.

A Lithium monotherapy may be used for the treatment of acute mania.

Grade A, Level 1+

3.1.3 Antiepileptics

Antiepileptics are used as mood stabilisers in the treatment of bipolar disorder. However, it has been reported by the US FDA that patients taking antiepileptic drugs have about twice the risk of suicidal thoughts and behaviours (0.43%) compared with patients receiving placebo (0.22%). It is recommended by the FDA that clinicians explain the benefits and risks of antiepileptic use.

Sodium valproate

Sodium valproate has been found to be superior to placebo in the treatment of acute mania in two randomised controlled trials³⁰⁻³¹ and in a systematic review. There is no difference in efficacy among sodium valproate, lithium and carbamazepine in the treatment of acute mania.

A Sodium valproate monotherapy may be used for the treatment of acute mania.

Grade A, Level 1+

Carbamazepine

Two randomised controlled trials³²⁻³³ found carbamazepine to be more effective than placebo in the treatment of acute mania.

A Carbamazepine monotherapy may be used for the treatment of acute mania.

Grade A, Level 1+

Lamotrigine

Two unpublished placebo controlled trials by GlaxoSmithKline, GW609 and GW610 showed that lamotrigine is not effective in the treatment of acute mania.³⁴

A Lamotrigine should not be used for the treatment of acute mania as it lacks efficacy in this area.

Grade A, Level 1+

3.1.4 Benzodiazepines

Benzodiazepines are useful in treating anxiety, insomnia, agitation, seizures, muscle spasms and alcohol withdrawal. They are also useful in preparation for medical and dental procedures. Long-term use is discouraged due to possible adverse psychological and physical effects, including tolerance, physical dependence and withdrawal symptoms upon cessation of use.

A meta-analysis of seven randomised controlled trials³⁵ found that clonazepam is effective in diminishing the symptoms of acute mania. The same meta-analysis demonstrated that lorazepam showed potential, but not definitive, efficacy in this area.

3.1.5 Acute management of bipolar agitation and aggression

Haloperidol,²⁶ olanzapine³⁶ and quetiapine³⁷ were found to be effective in reducing agitation and aggression as shown in randomised controlled trials.

Intramuscular (IM) antipsychotics are useful for managing uncooperative and highly agitated patients. Intramuscular haloperidol²⁶, olanzapine³⁸, and aripiprazole³⁹ has been shown to be effective.

In a meta-analysis, clonazepam and lorazepam, in both oral and intramuscular forms, have been shown to be effective in the acute treatment of agitation in mania.³⁵

There was no evidence supporting the use of intramuscular zuclopenthixol acetate (Clopixol Acuphase).

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

Grade A, Level 1+

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

Grade A, Level 1+

3.2 Depression

Bipolar depression is less studied than mania. However, studies have shown that patients spend longer periods in depressive relapse compared to manic episodes.

There is conflicting evidence with regards to the use of antidepressants in the treatment of bipolar depression. A meta-analysis⁴⁰ found that they are effective in the short-term treatment of bipolar depression.

However, two reviews⁴¹⁻⁴² revealed that antidepressants added to mood stabilisers did not improve outcome compared with mood stabiliser alone. It suggests that there is little support for the first-line use of antidepressants in the treatment of bipolar depression.

Similarly, there are conflicting reviews and meta-analysis regarding the efficacy of sodium valproate,⁴¹ and carbamazepine⁴¹⁻⁴² in the treatment of bipolar depression.

There were several small studies done in the 1960s and 1970s looking at the use of lithium in the treatment of bipolar depression which suggests that it is superior to placebo. However a randomised controlled trial in 2010 found no difference between lithium and placebo in alleviating the symptoms of bipolar depression.⁴³

Nonetheless, a systematic review⁴⁴ found that patients on lithium were less likely to die by suicide and less likely to deliberately self-harm. There were also fewer deaths overall in patients who received lithium.

Several studies found quetiapine,⁴¹⁻⁴³ olanzapine,^{41-42, 45} and olanzapine with fluoxetine^{41, 46} to be effective in the treatment of bipolar depression.

Lamotrigine monotherapy did not demonstrate efficacy in the acute treatment of bipolar depression in four out of five randomised controlled trials.^{41, 47} However, in another randomised controlled trial, it was found to be effective as an add-on treatment to lithium in bipolar depression.⁴⁸

A 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).

Grade A, Level 1+

However, it is recognised that some patients continue to be depressed despite the optimal use of mood stabilisers, and antidepressants may be required.

GPP 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.

GPP

A Quetiapine monotherapy, olanzapine monotherapy or olanzapine-fluoxetine combination may be used in the treatment of bipolar depression.

Grade A, Level 1+

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

Grade A, Level 1+

A 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.

Grade A, Level 1+

A Lithium may be used in the treatment of bipolar depression.

Grade A, Level 1+

3.3 Rapid cycling and mixed states

Bipolar disorder with rapid cycling is defined by the occurrence of four or more episodes of mood disturbances in a year. It occurs in up to 20% of patients with bipolar disorder.

Mixed affective states are characterized by combinations of manic and depressive symptoms in one episode and may occur in up to 40% of patients with bipolar disorder.

There are very few randomised controlled trials examining the pharmacological treatment of rapid cycling and mixed states. These studies also tend to be of small sample size.

Randomised controlled trials showed that both lithium and valproate are effective at preventing relapse in rapid cycling.⁴⁹⁻⁵⁰

There is no benefit in continuing antidepressants after remission is achieved, in patients with rapid cycling.

There is evidence that quetiapine and lamotrigine may be effective in the acute treatment of rapid cycling bipolar disorder.⁵⁰⁻⁵¹

There are few studies examining pure mixed episode samples. Available evidence suggests using mood stabilisers to treat mixed states, of which sodium valproate and carbamazepine are preferred over lithium.^{31, 52}

There is limited data on the use of non-pharmacological treatments for patients with rapid cycling.

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

Grade A, Level 1+

A A combination of lithium and lamotrigine may be considered as an alternative treatment for rapid cycling.⁵⁰

Grade A, Level 1+

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

GPP

A 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.

Grade A, Level 1+

3.4 Electroconvulsive therapy (ECT)

Studies examining the use of electroconvulsive therapy (ECT) in bipolar disorder are limited. Ethical concerns make it hard to randomise patients and control against placebo.

Available evidence indicates that electroconvulsive therapy results in remission or marked improvement of symptoms in a large proportion of patients with acute mania.⁵³ It is also associated with symptom improvement in bipolar depression.⁵⁴ However, side-effects such as cognitive impairments as well as the stigma of undergoing ECT have to be taken into account.

There is also limited – albeit positive – data examining the use of ECT in the acute treatment of mixed episodes.⁵⁵ However, these studies tend to have small sample sizes.

B 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.

Grade B, Level 2++

C 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.

Grade C, Level 2+

4 Maintenance

4.1.1 Lithium

Three systematic reviews indicated that lithium therapy is effective at reducing relapse in patients with bipolar disorder. The effect of lithium is greater for prevention of manic and hypomanic episodes and marginal with respect to depressive episodes. Lithium is associated with an increased risk of manic relapse on discontinuation after less than 2 years on treatment.⁵⁶⁻⁵⁷

A randomised controlled trial with bipolar I patients found that after stabilisation, continued prophylaxis with lithium delayed the onset of the next manic or mixed episode.⁵⁸

4.1.2 Sodium Valproate

A Cochrane systematic review of valproate showed no significant difference in preventing relapse as compared to lithium.⁵⁹

4.1.3 Lamotrigine

A systematic review showed that lamotrigine significantly reduced depressive relapses.²⁸ A randomised controlled trial with bipolar I patients found that after stabilization, continuation with lamotrigine delayed the onset of the next depressive episode.⁶⁰

A Lamotrigine can be used for prophylaxis in patients who have initially stabilised with lamotrigine.

Grade A, Level 1+

4.1.4 Antipsychotics

Recent randomised controlled trials have showed that olanzapine is effective at preventing relapse.^{58,61} A randomised controlled trial showed that aripiprazole is effective as maintenance therapy in bipolar patients with a recent manic or mixed episode.⁶² A randomised controlled trial also showed that quetiapine in combination with lithium or valproate is effective at preventing relapse in patients with bipolar I disorder.⁶³⁻⁶⁴

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

Grade A, Level 1+

A Aripiprazole may be used as maintenance therapy in bipolar patients with recent manic or mixed episode.

Grade A, Level 1+

A Quetiapine, in combination with lithium or valproate, may be used as maintenance therapy in patients with bipolar I disorder.

Grade A, Level 1+

4.1.5 Antidepressant drugs

Recent randomised controlled trials have shown that antidepressants offer minimal to no significant continuing clinical benefits to patients who have had 8-week post bipolar depressive episode remission. There are no robust effects on depressive episode prevention or enhanced remission rates with continued antidepressant use.⁶⁵

Rapid cycling patients have worsened outcomes with selective serotonin reuptake inhibitors (SSRIs) or the other newer antidepressants.⁶⁵

Newer antidepressants such as SSRIs show a mild tendency to delay the onset of subsequent new depressive episodes without increasing manic switching morbidities.⁶⁶

Patients with bipolar II disorder have not shown any benefit with antidepressant usage. Antidepressant medication alone without a mood stabiliser carries larger risks of manic or hypomanic relapses.⁶⁷

However, abrupt or rapid discontinuation of clinically effective antidepressant treatment was associated with a significantly shorter time to first new episode of major depression.⁶⁸

A 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.

Grade A, Level 1+

A 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.

Grade A, Level 1+

4.1.6 Medication discontinuation

Current evidence does not advocate the discontinuation of maintenance medications for bipolar disorder. The risk of illness relapse/recurrence remains high even for patients who have remained stable for long periods of time while on medications.⁶⁹⁻⁷⁰

A Maintenance medications for bipolar disorder should not be discontinued, in view of the high risk of relapse.

Grade A, Level 1+

If maintenance medications are to be stopped, gradual dose tapering till discontinuation have shown to minimize relapse of illness or risk of new illness.⁷⁰

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

Grade A, Level 1+

4.1.7 Rapid cycling

A randomised controlled trial showed that lithium and valproate were equally effective at preventing relapse.⁷¹

A Lithium and valproate may be used as maintenance therapy for patients with rapid cycling bipolar disorder.

Grade A, Level 1+

An open randomised trial on modern antidepressants (i.e. non tricyclic antidepressants) showed no statistically significant benefit with antidepressant continuation after achieving remission. In fact, the study showed that rapid cycling course predicted three times more depressive episodes with antidepressant continuation.⁶⁵

B 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.

Grade B, Level 2++

5 Psychological interventions

Psychological interventions can help to improve the condition of a patient with bipolar disorder and the course of the illness, and maintain psychosocial functioning. In the studies evaluating the use of psychological interventions in patients with bipolar disorder, the majority has to do with treatment during the depressive episodes⁷² and as part of the maintenance treatments.⁷³⁻⁷⁴ Due to the nature of a patient in a manic phase, it is difficult to do psychological intervention during such times.

5.1 Psychoeducation

The aim of psychoeducational interventions is to provide patients (and sometimes family members and/or caregivers) with information about their illness and its treatment. Oftentimes, psychoeducation for people with bipolar disorder focuses on encouraging the use of traditional treatment in general, and pharmacotherapy in particular.⁷⁵ Psychoeducational interventions can vary from brief lecture-style presentations to prolonged interventions. Extended interventions not only provide information, they also facilitate discussion on issues relevant to bipolar disorder. Commonly discussed issues include adherence to taking medication, avoidance of drug abuse, and identification of relapse and stress and anxiety management.

GPP Whenever possible, health professionals should provide psychoeducation to patients with bipolar disorder, and their families/caregivers.

GPP

5.2 Early warning signs

Studies have demonstrated that psychological interventions were effective in helping people to detect early warning signs of bipolar disorder, and cope effectively with such prodromes, thus preventing relapses.⁷⁶⁻⁷⁷

Psychological intervention should include training in recognizing early warning signs of relapse of depression or mania, in order to prevent recurrence of illness. Such early warning signs of depression or mania are often different for different people, suggesting that individuals have distinctive “relapse signatures”.

Nevertheless, some common mania prodromes include:

- being more sociable
- increased self-worth
- racing thoughts
- increased optimism
- irritability
- increased activities
- decreased need for sleep
- sharper senses

Common depression prodromes include:

- loss of interest in activities or people
- not being able to put worries aside
- feeling sad
- wanting to cry
- interrupted sleep

A 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.

Grade A, Level 1+

5.3 Other forms of psychotherapy

There is evidence for the effectiveness of the following forms of psychotherapy for bipolar depression:

- Family-focused therapy
- Interpersonal and social rhythm therapy
- Cognitive behaviour therapy
- Psychoeducation

According to Miklowitz (2007)⁷², patients receiving intensive psychotherapy (up to 30 sessions of 1 of 3 forms, mean=14.3 sessions – family-focused therapy, interpersonal and social rhythm therapy, and cognitive behaviour therapy) had significantly higher year-end recovery rates and shorter times to recovery than patients in collaborative care up to 5 sessions of (a brief psychoeducational intervention, mean=2.2 sessions). There were no statistically significant differences among the

3 intensive psychotherapies. However, they were also much less cost-effective than patients receiving the brief intervention.

It is interesting to note that brief psychotherapy also had a good 1-year recovery rate (51.5%), although it was significantly less than the recovery rate in intensive psychotherapy (64.4%).

Cognitive behavioural therapy (CBT)

Cognitive behavioural therapy aims to change dysfunctional cognitive styles and behaviour in order to improve emotional states. When used with people with bipolar disorder, the diathesis-stress model is sometimes used to emphasize the need for combined medication and psychological therapies.⁷⁸

Cognitive behavioural therapy focuses on helping patients detect early warning signs of depression and mania, and using cognitive behavioural strategies to improve mood when low, and reduce highs when manic, in order to keep mood within a previously agreed range (e.g., -1 to +1, where -5= depressed and 5= manic).

Some cognitive behavioural therapists promote the importance of sleep and routine to avoid sleeplessness triggering an episode. Others also look out for behaviour that compensates for “loss of time” due to previous illness, and attempt to deal with such extreme striving attitudes.

Family therapy

As effective family functioning can maintain a person’s psychological balance, family interventions may help relatives and caregivers to care for and support patients with bipolar disorder. Family therapy can include very different kinds of interventions from diverse theoretical backgrounds.⁷⁹

Some use direct psychoeducational methods with the aim of instructing patients and relatives or carers about how to manage the illness. Others utilise behavioural therapy models with educational purposes, often including communication and problem-solving training. Yet others focus on modifying the functioning of the whole family group, treating them as a system where each owns some part of the illness so no one is isolated, as in the case of systemic family therapy models.

Interpersonal Social Rhythms Therapy (IPSRT)

Interpersonal social rhythms therapy was designed specifically for treating individuals with bipolar disorder.⁸⁰ This approach evolved from Interpersonal Therapy (IPT). As with IPT, treatment focuses on four interpersonal problem areas (grief, interpersonal role transition, role dispute and interpersonal deficits). Issues in these areas are addressed by various strategies, which include eliciting and defining the salient problem area, followed by supported grieving/emotional processing and problem solving.

In addition to these traditional aspects of interpersonal therapy, interpersonal social rhythms therapy focuses on the regularity of daily activities. It prioritises the maintenance of structure and routine in these daily activities in spite of fluctuations in mood, for example, those caused by life events.

Interpersonal social rhythms therapy utilizes a chronobiological model of bipolar disorder. According to this model, life events (both negative and positive) may cause disruptions in patients' social rhythms that subsequently activate patients' vulnerabilities in circadian rhythms and sleep-wake cycles which then lead to the development of bipolar symptoms. Interpersonal social rhythms therapy helps patients to keep regular daily routines, reduce interpersonal problems, and take medication according to regimen. By modulating both biological and psychosocial factors, it aims to mitigate patients' circadian and sleep-wake cycle vulnerabilities, to help them better manage the potential chaos of the symptoms of bipolar disorder, and improve their overall functioning.

A Cognitive behavioural therapy, family therapy or interpersonal social rhythms therapy may be considered as part of the treatment plan for bipolar depression.

Grade A, Level 1+

6 Reproductive health issues

The management of bipolar disorder requires the use of long-term maintenance medications. This has implications for women who wish to bear children.

Psychotropic medication taken during pregnancy may increase the risk of neonatal toxicity, post-delivery withdrawal syndrome and possible long-term impact on the infant's development. Similar concerns exist for psychotropic medication taken during breastfeeding. Careful consideration should therefore be given to the risks and benefits of prescribing psychotropic medication at such times.

However, pregnancy is not protective against relapse. 52% of pregnant women and 58% of nonpregnant women relapsed when taken off medication, there being no statistical difference between the two groups.⁸¹ Pregnant women who stopped mood stabiliser treatment had 2.3 times higher recurrence risk compared to pregnant women who continued medication (85.5% vs. 37.0%).⁸² Furthermore, the postpartum period is a time of particular vulnerability to relapse – stopping medication during this period causes a 70% relapse rate.⁸¹⁻⁸²

6.1 Fertility

There is no evidence linking bipolar medications with changes in male fertility. However, antipsychotics and some antidepressants reduce female fertility by increasing prolactin levels and the relative risk of oligomenorrhoea with hyperandrogenism on valproate was 7.5 times compared to other mood stabilisers.⁸³

6.2 Contraception

Carbamazepine and lamotrigine may inhibit the desired effect of oral contraceptives via drug interactions.⁸⁴

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.

Grade A, Level 1+

6.3 Drugs in pregnancy and breastfeeding

6.3.1 Mood stabilisers

There are multiple studies examining the use of mood stabilisers in pregnant and breastfeeding women. This population includes women with epilepsy and other mood disorders.

Use of sodium valproate, lithium carbonate, lamotrigine and carbamazepine in pregnancy is associated with increased risk of foetal malformations and perinatal complications. In particular, children exposed to sodium valproate or polypharmacy *in utero* are more prone to poor long-term neurodevelopmental outcomes.⁸⁵

Periconceptual folate supplementation protects against neural tube defects (RR 0.28, 95% CI 0.15 – 0.52) but has no clear effect on other birth defects.⁸⁶

Gradual discontinuation of mood stabiliser delays time to relapse (time to 25% recurrence was 8 weeks when medications were stopped over 1 – 14 days vs. 20 weeks when medications were stopped over 15 – 30 days).⁸¹⁻⁸²

Regarding lactation:⁸⁷

- Milk/plasma drug concentration ratio for lithium is low (0.2–0.7) but it has a long half-life; a case report describes toxicity in an infant who became hypotonic and cyanotic
- Carbamazepine (<0.7) and valproate (<0.1) have low milk/plasma ratios:
 - Several case reports describe healthy outcomes
 - However, isolated case reports of foetal adverse events exist (hepatic dysfunction after carbamazepine use and bicytopenia after valproate use)
- No evidence exists for lamotrigine either way

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

Grade B, Level 1+

A Periconceptional folate supplementation should be prescribed to protect against neural tube defects.

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.

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.

GPP

GPP Consider resuming mood stabiliser treatment immediately postpartum as this is a period of vulnerability to relapse.

GPP

B&GPP 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.†

***Grade B, Level 2++**

†GPP

GPP 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.

GPP

6.3.2 Antidepressants

Studies that examine the use of antidepressants in pregnancy and lactation are few. Standard clinical definitions of certain terms (e.g. neonatal behavioural syndrome) are also lacking. Many of the existing studies examine risk instead of benefit.

First-trimester use of paroxetine is associated with odds ratios of 1.46 (95% CI 1.17 – 1.82) for cardiac defects and 1.24 (95% CI 1.08 – 1.43) for aggregated congenital defects.⁸⁸

Selective serotonin reuptake inhibitors use in late gestation may be associated with increased risk of persistent pulmonary hypertension of the newborn and neonatal behavioural syndrome. However, the association between selective serotonin reuptake inhibitors (including paroxetine) and major foetal malformations is equivocal and there are no strong associations between antidepressants and miscarriage, neurobehavioural problems, bleeding and QTc-interval prolongation.⁸⁹

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

Grade B, Level 2++

B 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.

Grade B, Level 2++

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

GPP

6.3.3 Antipsychotics

The majority of available evidence comes from case reports and case series. Some studies feature pregnant women with schizophrenia, other psychiatric disorders and hyperemesis. It is not known if these differences in diagnoses impact generalisability to patients with bipolar disorder.

Antipsychotics, as an entirety, are associated with increased prolactin up to 10 times normal and amenorrhea in 17–78% of female users. Atypical antipsychotics, as a group, may be associated with increased risk of gestational metabolic complications and large gestational weight, as well as foetal malformations (especially with clozapine).

On the other hand, typical antipsychotics, as a group, may be associated with limb defects, other foetal anomalies and perinatal complications, but appear to show less association with gestational metabolic complications.⁹⁰

Reviews of small studies and case reports yield the following information:^{88, 90-91}

- Three case reports describe no lasting adverse effects with the use of aripiprazole.
- Multiple case reports describe major malformations, gestational metabolic complications and foetal death following overdose of clozapine.
- A manufacturer database describes gestational diabetes, spontaneous abortions and other perinatal complications following the use of olanzapine. An observational study describes high placental passage (mean 72.1%, SD 42.0) and higher incidence of low birth weight. However, other case reports and series describe healthy outcomes with olanzapine.
- An observational study found that quetiapine caused the lowest placental passage (mean 23.8%, SD 11.0) among atypical antipsychotics. Other cases reports describe healthy outcomes on quetiapine. A case-control study found no association between its use and teratogenicity.
- A postmarketing review of risperidone found no association with spontaneous abortions and teratogenicity.
- Three case reports describe limb defects with haloperidol use but one small prospective cohort shows no increased risk of malformations above baseline.
- There were case reports of birth defects and gestational metabolic complications with use of flupenthixol and zuclopenthixol.
- An observational study describes increased risk of neonatal jaundice but no neurodevelopmental anomalies with chlorpromazine. A prospective cohort described no increase of malformations, mortality, abnormal birth weight and IQ. There were case reports and series describing foetal EPSE and perinatal complications, especially in late pregnancy. Other case reports and case series described no association with foetal malformations.
- There were case reports and database findings equivocally linking trifluoperazine use and limb defects.
- Case reports and casenote reviews suggest no increase in adverse foetal outcomes with fluphenazine.
- A few case reports describe healthy outcomes of breastfeeding mothers taking olanzapine and risperidone.
- There is no/minimal data on amisulpride, sertindole, ziprasidone and anticholinergics.

D 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).

Grade D, Level 3

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.

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.

GPP

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

GPP

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

GPP

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.

GPP

6.4 Benzodiazepines

Pooled data from case-control studies show that exposure to benzodiazepines in early pregnancy may increase the risk of major malformations and oral cleft.⁹²

C Benzodiazepines should be avoided in pregnancy.

Grade C, Level 2+

6.5 Electroconvulsive therapy

The use of electroconvulsive therapy (ECT) in pregnant patients has relatively few side effects and has not been implicated as a causal factor of congenital malformations. Measures may be employed to reduce the risk of adverse events during ECT, such as avoiding atropine administration, ensuring adequate oxygenation and elevating the right hip.⁹¹

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

Grade D, Level 3

7 Substance misuse

Bipolar disorder is associated with co-morbid conditions such as drug and alcohol abuse. However this is a poorly researched aspect as most of previous studies usually exclude such co-morbidities.

7.1 Alcohol and substance misuse

A 5-year follow-up study noted that alcoholism was more frequent in bipolar patients than in comparison subjects. It was often a secondary complication.⁹³

Substance abuse in patients with bipolar disorder is associated with an earlier onset, increased suicidality, mixed states, rapid cycling, more frequent episodes, more visits to the emergency department and hospitalisations, poor compliance, slower remission as well as a suboptimal response to lithium.⁹⁴

The use of naltrexone in alcohol dependence was associated with improvements in mood, days of alcohol use and cravings, compared with placebo.⁹⁵⁻⁹⁶

Patients on sodium valproate had decreased heavy drinking compared with placebo.⁹⁷

A Cochrane review did not find any clear evidence supporting any substance misuse programme for those with serious mental illness over standard care.⁹⁸

A Addiction disorders in patients with bipolar disorder should be treated.

Grade A, Level 1+

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

GPP

8 Suicide prevention

Rates of completed suicide in people with bipolar disorder remain unacceptably high, at between 10% and 19%, 15 times that of the general population. At least a quarter will attempt suicide, a rate higher than that seen in unipolar depression. The depressed phase of bipolar disorder is linked to about 80% of suicide attempts and completed suicides.⁹⁹⁻¹⁰⁰

Risk factors associated with completed suicide in bipolar disorder include:¹⁰¹

- History of attempted suicide
- Co-morbid anxiety disorder
- Hopelessness
- Male

Risk factors associated with attempted suicide in bipolar disorder include:

- History of attempted suicide
- Co-morbid anxiety or eating disorder
- Family history of suicide
- Personal history of abuse
- Early onset of bipolar disorder
- Mixed state
- Rapid cycling
- Depression (negatively associated with mania)
- Increasing severity of depressive or manic episodes
- Alcohol and/or drug abuse
- Single

C Clinicians should routinely assess risk of suicide in all patients with bipolar disorder.¹⁰¹

Grade C, Level 2+

9 Monitoring

9.1 Metabolic disease

Medical disease is common in patients with bipolar disorder and can lead to increased morbidity and mortality.¹⁰²⁻¹⁰³ Conditions that often occur among the bipolar population include obesity, endocrine and cardiovascular disorders. Compared with that of the general population, the prevalence of obesity in patients with bipolar disorder is higher.¹⁰⁴⁻¹⁰⁷

Systematic reviews of epidemiological data stress the importance of monitoring and screening bipolar patients for metabolic disorders prior to commencement and during medication treatment, in view of the nature of the illness as well as adverse metabolic effects associated with bipolar medications.¹⁰⁸⁻¹¹²

Several cross sectional studies from various countries, including one done in an Asian population, found an increased prevalence of metabolic syndromes in patients with bipolar disorder compared with the general population.^{111, 113-114}

Given the established morbidity and mortality associated with metabolic syndrome and the high prevalence amongst patients with bipolar disorders (most studies show a prevalence of 20 to over 30 percent), the inferred potential impact of early detection and intervention is significant. However, there is currently insufficient direct evidence on the impact of early intervention on clinical outcomes specifically amongst patients with bipolar disorders and metabolic syndrome.

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

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.

GPP

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.

GPP

9.2 Monitoring of treatment and medication

There are several guidelines describing largely similar parameters for monitoring each type of medication. However, there are subtle differences that vary from one guideline to another.

These monitoring guidelines serve to help identify those at risk of developing adverse events from the medications used to treat their bipolar disorder and to manage those risks accordingly.

A comparison of recommended monitoring guidelines by various agencies is provided for information in Annex B.

The Clinical Global Impression (CGI) rating scales are commonly used measures of symptom severity, treatment response and treatment efficacy in studies of patients with mental disorders. The scales are quick to administer and helps clinicians to monitor patient progress in a consistent, systematic manner.

The scales have two components: the Clinical Global Impression - Severity scale (CGI-S) and the Clinical Global Impression - Improvement scale (CGI-I).

The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.

The Clinical Global Impression - Improvement scale (CGI-I) is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state (i.e. at initiation of treatment).

GPP Consider using the Clinical Global Impression scales (both severity and improvement component scales) to measure illness severity and treatment progress during consultations.

GPP

10 Novel therapies

There is insufficient evidence to make recommendations for the use of many novel therapies in the treatment of bipolar disorder. The novel therapies discussed in this chapter are therapies that are currently being studied.

10.1 Omega 3 fatty acids

The evidence for the efficacy of omega 3 fatty acids as monotherapy or adjunct therapy for bipolar disorder is still limited. Only one randomised trial showed positive benefits of omega 3 fatty acids as an adjunctive treatment for depressive symptoms but not for manic symptoms in bipolar disorder. There is still a need for more well-designed and executed trials on which to base clear recommendations on the role of omega 3 fatty acids in bipolar disorder.¹¹⁵

10.2 Repetitive transcranial magnetic stimulation (rTMS)

There has been conflicting evidence in the use of rTMS in the treatment of bipolar disorder. Some studies have demonstrated efficacy of rTMS in depression, whilst others have shown rTMS carrying a slight risk of treatment emergent mania. rTMS still requires further investigation and more research is needed.¹¹⁶⁻¹¹⁷

10.3 Tamoxifen

There have been promising placebo-controlled studies that have shown robust improvements in manic symptoms with tamoxifen. However, more conclusive studies are needed on which to base clear recommendations on the role and use of tamoxifen in bipolar disorder.¹¹⁸⁻¹¹⁹

There is currently insufficient evidence on which to base any clear recommendations on the roles of novel therapies such as omega 3 fatty acids, repetitive transcranial magnetic stimulation (rTMS) and tamoxifen in the treatment of bipolar disorder.

11 Clinical quality improvement

The following clinical quality improvement parameters, based on the recommendations in this guideline, are proposed:

- 1) Percent of patients with bipolar disorder who are assessed using the clinical global impression scales (severity, improvement) during consultations.
- 2) Percent of patients with bipolar disorder with at least two consultations for Chronic Disease Management Programme (CDMP) Mental Health in a year.

12 Cost-effectiveness issues

No specific economic studies on the cost-effectiveness of the various treatments for bipolar disorder in Singapore were found.

Studies have been done in other healthcare settings but there are limitations in applying such studies to the Singaporean healthcare system.

12.1 Economics of acute treatment

A NICE technology appraisal¹²⁰ examining the use of olanzapine and semisodium valproate for acute mania concluded that no distinction could be made between the two drugs on cost-effectiveness grounds.

In another technology assessment from the United Kingdom,¹²¹ comparing quetiapine, olanzapine or valproate against placebo, no definitive conclusions could be made due to limitations in the studies reviewed.

A cost-consequence study from the United States¹²² found that over a 12-week period, treatment with valproate or olanzapine produced similar clinical outcomes but showed no differences in total costs of care.

No cost-effectiveness studies were found relating to the treatment of acute bipolar depression.

12.2 Economics of maintenance treatment

A systematic review in 2007¹²³ found that for patients with a recent depressive episode, valproate, lithium monotherapy and the combination of lithium and imipramine are potentially cost-effective. It also found that for patients with a recent manic episode, olanzapine and lithium monotherapy are potentially cost-effective.

A separate cost-effectiveness study¹²⁴ found that prevention of mood episodes with lithium and lamotrigine is cost-effective in patients with a recent manic, mixed or hypomanic episode.

A cost-effectiveness study¹²⁵ examining quetiapine added to lithium or valproate for the maintenance treatment of patients with bipolar I disorder concluded that the addition of quetiapine improved the clinical outcomes and reduced the healthcare costs compared with lithium or valproate alone.

There have not been any economic studies examining psychosocial interventions to prevent relapse.

Annex A Comparison of ICD-10 and DSM-IV-TR

ICD-10	DSM-IV TR
<p>F30.0 Hypomania</p> <p>There is a persistent mild elevation of mood (for at least several days on end), increased energy and activity, and usually marked feelings of well-being and both physical and mental efficiency. Increased sociability, talkativeness, overfamiliarity, increased sexual energy, and a decreased need for sleep are often present but not to the extent that they lead to severe disruption of work or result in social rejection.</p> <p>Irritability, conceit, and boorish behaviour may take the place of the more usual euphoric sociability.</p> <p>Concentration and attention may be impaired.</p> <p>There are no hallucinations or delusions.</p>	<p>296.40 Hypomanic episode</p> <p>For at least four days sustained elevated, expansive or irritable mood different from the patient's usual non-depressed mood and persistence of at least three symptoms (at least four if the only abnormality of mood is irritability). Grandiosity or exaggerated self-esteem, reduced need for sleep, increased talkativeness, flight of ideas or racing thoughts, easy distractibility, psychomotor agitation or increased goal-directed activity (social, sexual, work or school), poor judgement (as shown by spending sprees, sexual adventures, foolish investments).</p> <p>There are no features of psychosis (delusions, hallucinations, bizarre behaviour or speech). The episode does not require hospitalisation or markedly impair work, social or personal functioning.</p>

ICD-10	DSM-IV TR
<p>F30.1 Mania without psychotic symptoms</p> <p>For at least one week (less if hospitalised): Mood elevated, expansive or irritable out of keeping with the patient's circumstances. Elation is accompanied by increased energy, resulting in overactivity, pressure of speech, and a decreased need for sleep. Normal social inhibitions are lost, attention cannot be sustained, and there is often marked distractibility. Self-esteem is inflated, and grandiose or over-optimistic ideas are freely expressed.</p> <p>F30.2 Mania with psychotic symptoms</p> <p>In addition to F30.1, delusions (usually grandiose) or hallucinations (usually auditory) are present, or the excitement, excessive motor activity, and flight of ideas are so extreme that the subject is incomprehensible or inaccessible to ordinary communication.</p>	<p>296.4x Manic episode</p> <p>For at least one week (or less if hospitalised) the patient's mood is abnormally and persistently high, irritable or expansive. To a material degree during this time, the patient has persistently had three or more of these symptoms (four or more if the only abnormality of mood is irritability): grandiosity or exaggerated self esteem, reduced need for sleep, increased talkativeness, flight of ideas or racing thoughts, easy distractibility, psychomotor agitation or increased goal-directed activity (social, sexual, work or school), poor judgement (as shown by spending sprees, sexual adventures, foolish investments).</p> <p>Symptoms severity results in (at least one) material distress, psychotic features, hospitalisation to prevent harm to self or others, and impairment in functioning.</p> <p>Further subgroups:</p> <ol style="list-style-type: none"> (1) Mild. Symptoms barely meet criteria for an episode of mania. (2) Moderate. There is an extreme increase in either activity or impaired judgement. (3) Severe without psychotic features. The patient requires nearly continuous supervision to prevent physical harm to self or to others (4) Severe with psychotic features. The patient has delusions or hallucinations, which may be mood-congruent or mood-incongruent.
<p>F31 Bipolar affective disorder</p> <p>Multiple episodes of mania/hypomania or both depression and mania/hypomania; current episode as defined.</p>	<p>296.xx Bipolar I disorder</p> <p>One or more manic episodes or mixed episodes. Individuals often have one or more major depressive episodes.</p> <p>296.89 Bipolar II disorder</p> <p>One or more major depressive episodes accompanied by at least one hypomanic episode.</p>

ICD-10	DSM-IV TR
<p>F31.6 Bipolar affective disorder, current episode mixed</p> <p>The patient has had at least one authenticated hypomanic, manic, depressive, or mixed affective episode in the past, and currently exhibits either a mixture or rapid alteration of manic and depressive symptoms.</p>	<p>296.6x Mixed episode</p> <p>Fulfilled symptom criteria for both major depressive and manic episodes nearly every day for a week or more. The symptoms are severe enough that they include one of the following: psychotic features, hospitalisation to prevent harm to self or others, and impairment in work, social or personal functioning.</p>
<p>F32 Depressive episode</p> <p>Patient suffers from two week of low mood, decreased energy levels, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self esteem and self-confidence are almost always reduced and, even in the mild form, ideas of guilt or worthlessness are often present. Low mood varies little from day to day, is unresponsive to circumstances and may be accompanied by anhedonia, early morning awakening, diurnal mood variation (worse in the morning), marked psychomotor retardation, agitation, loss of appetite, weight loss and loss of libido.</p> <p>Depressive episodes may be specified as mild (at least four symptoms), moderate (at least six and difficultly continuing with ordinary activities) or sever (at least eight symptoms which are marked and distressing)</p>	<p>296.5x Major depressive episode</p> <p>Two weeks of more then four symptoms/signs which must include either depressed mood and/or anhedonia. Other symptoms include: marked loss or gain of weight or appetite, excessive or difficult sleep, Psychomotor agitation or retardation. Fatigue or loss of energy, feelings of worthless or excessive guilt, indecisions or difficult concentrating; repeated thought of death or of suicide.</p> <p>These symptoms cause clinically important distress or impair work, social or personal functioning.</p> <p>The episode did not start within two months of the loss of a loved one (unless the symptoms are severe enough to include severely impaired functioning, severe preoccupation with worthlessness, ideas of suicide, delusions or hallucinations or psychomotor retardation).</p>

Annex B Comparison of recommended monitoring guidelines by various agencies

	UK National Institute for Health and Clinical Excellence monitoring guidelines	International Society for Bipolar Disorders monitoring guidelines	Institute of Mental Health monitoring guidelines (For Atypical Antipsychotics)
Antipsychotics			
Electrocardiogram	Nil	As and when needed basis	As and when needed basis
Weight	Every 3 months (1 st year)	Every month (first 3 months), then every 3 months	Baseline, every 3 months & then yearly
Waist circumference	nil	Nil	Baseline and every year
Fasting blood glucose	3 months after starting (1 month for olanzapine)	Every 3 months (1 st year); then yearly	Baseline, then after 3-6 months & every year
Lipids	3 months after starting (1 month for olanzapine)	At 3 months after initiation; then yearly	Baseline, then after 3-6 months & every year
Blood pressure	Nil	Every 3 months (1 st year); then yearly	Baseline, then after 3-6 months & every year
Prolactin levels (For Risperidone)	As needed when hyperprolactin symptoms appear	As needed when hyperprolactin symptoms appear	nil
Lithium			
Serum lithium levels	1 week after starting AND after every dose changes (range 0.6 - 0.8mmol/L) AND every 3 months	At least 5 days after initiation, dosage changes or adding interacting drug, till 2 consecutive levels that lie within therapeutic range is attained; thereafter every 3-6 months	5-7 days after starting AND after every dose change or interacting drugs added; Every 2 weeks (acute stage); then every 3-6 months.
Weight	At start and when needed if the patient gains weight rapidly	Baseline; then after 6 months; thereafter every yearly.	Nil
Full blood count	Nil	Baseline only	Baseline
Electrolytes	Nil	Nil	Baseline and yearly
Thyroid	Every 6 months	Baseline (Thyroid-stimulating hormone and Calcium); then after 6 months; thereafter every yearly.	Baseline, and every 3 months (first 6 months); then 6-12 monthly or when needed basis
Renal	Every 6 months	Baseline (Urea and Creatinine); then every 3-6 months	Baseline, and every 3 months (first 6 months); then 6-12 monthly or when needed basis
Electrocardiogram	Nil	Nil	Baseline and periodically
Pregnancy testing	Nil	Nil	Baseline only
Signs of lithium toxicity	As needed when toxicity symptoms emerge	As needed toxicity symptoms emerge	As needed toxicity symptoms emerge

UK National Institute for Health and Clinical Excellence monitoring guidelines	International Society for Bipolar Disorders monitoring guidelines	Institute of Mental Health monitoring guidelines
Valproate		
Valproate levels	Two levels to establish therapeutic dose	After at least 2-3 days after starting or dosage changes
Liver function tests	Every 3 months (1 st year); thereafter yearly	Baseline and 1 st month; then every 3-24 months
Full blood count	Every 3 months (1 st year); thereafter yearly	Baseline and 1 st month; then every 3-24 months
Renal	Baseline only	Baseline only
Pregnancy testing	Baseline and monitor menstrual changes (for females of reproductive age)	Baseline only
Weight	As needed who gain weight rapidly	Nil
Lamotrigine		
Blood monitoring	Routine blood level monitoring NOT required	Nil
Carbamazepine		
Plasma levels	Two levels to establish therapeutic dose, separated by 4 weeks	2-4 weeks post initiation, then every 3-4 days after dosage changes
Electrolytes	Nil	Baseline only
Full blood count	Every 1 month (first 3 months), thereafter yearly	Baseline and after first 2 months; then every 3-6 months
Liver function tests	Every 6 months	Baseline and after first 2 months; then every 3-6 months
Blood urea nitrogen/Renal	Every 6 months	Baseline and periodically (ECG & eye testing)
Electrocardiogram	Nil	Baseline only
Pregnancy testing	Nil	Baseline only
Physical Health		
Lipid panel	At baseline and annually for over 40s	Nil
Full blood count	At baseline	Nil
Weight	At baseline and annually	Nil
Blood pressure	At baseline and annually	Nil
Weight Gain management		
Counselling – Diet	Yes	As and when needed
Counselling – Exercise	Yes	As and when needed
Referral to dietitian	Yes, if medical co-morbidities present	As and when needed

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: <http://smj.sma.org.sg/cme/smj/index.html> (*the link will only be available once the December 2011 issue of the SMJ becomes available*). The answers will be published in the SMJ February 2012 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Indicate whether each statement is true or false.

	True	False
1. Based on current knowledge, bipolar disorder:		
A) Is a chronic, relapsing illness.	<input type="checkbox"/>	<input type="checkbox"/>
B) Only begins in adolescence.	<input type="checkbox"/>	<input type="checkbox"/>
C) If severe, may present with psychotic symptoms.	<input type="checkbox"/>	<input type="checkbox"/>
D) Is easily diagnosed at first presentation.	<input type="checkbox"/>	<input type="checkbox"/>
2. Appropriate acute treatment options for bipolar disorder include:		
A) Intramuscular lorazepam for agitation.	<input type="checkbox"/>	<input type="checkbox"/>
B) Combination of an antipsychotic and a mood stabiliser for patients showing inadequate response to mood stabiliser monotherapy.	<input type="checkbox"/>	<input type="checkbox"/>
C) Lamotrigine monotherapy for mania.	<input type="checkbox"/>	<input type="checkbox"/>
D) Lithium for bipolar depression.	<input type="checkbox"/>	<input type="checkbox"/>

	True	False
3. With regards to the prevention of relapse in patients with bipolar disorder:		
A) Lithium, valproate and olanzapine may be used as maintenance therapy in preventing relapse.	<input type="checkbox"/>	<input type="checkbox"/>
B) Quetiapine may be used alone as maintenance therapy in patients with bipolar I disorder.	<input type="checkbox"/>	<input type="checkbox"/>
C) Bipolar patients whose depressive symptoms have remitted for at least 8 weeks may have their antidepressant medications stopped.	<input type="checkbox"/>	<input type="checkbox"/>
D) Maintenance medication should not be discontinued in view of the high risk of relapse.	<input type="checkbox"/>	<input type="checkbox"/>
4. A 28-year old, married female patient with bipolar disorder is currently on lamotrigine only as maintenance therapy. She is now interested in family planning. Evaluate the following statements:		
A) Combined oral contraceptive pills will be more effective in her case.	<input type="checkbox"/>	<input type="checkbox"/>
B) Peri-conceptual folate supplementation is contra-indicated.	<input type="checkbox"/>	<input type="checkbox"/>
C) Breastfeeding is not advised.	<input type="checkbox"/>	<input type="checkbox"/>
D) If she is pregnant and suffers a major depressive episode, there are no antidepressants that she can use.	<input type="checkbox"/>	<input type="checkbox"/>

- | | True | False |
|---|--------------------------|--------------------------|
| 5. A 21-year old male bipolar patient is on follow-up with you. Evaluate the following statements: | | |
| A) If he presents with co-morbid alcohol addiction, he should be treated for substance abuse. | <input type="checkbox"/> | <input type="checkbox"/> |
| B) Suicide risk assessment should be done only if patient expressed suicide ideology. | <input type="checkbox"/> | <input type="checkbox"/> |
| C) Cognitive behavioural therapy can be considered as part of the treatment plan for bipolar depression. | <input type="checkbox"/> | <input type="checkbox"/> |
| D) Clinical assessment of cardiovascular risk factors should be done only when he is at least 45 years old. | <input type="checkbox"/> | <input type="checkbox"/> |

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