BAP GUIDELINES FOR THE MANAGEMENT OF BIPOLAR DISORDERS

1st Edition, 2022

বাংলাদেশ এসোসিয়েশন অব সাইকিয়াট্রিস্টস (বিএপি)
BANGLADESH ASSOCIATION OF PSYCHIATRISTS (BAP)

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BANGLADESH ASSOCIATION OF PSYCHIATRISTS (BAP)

BAP Guidelines for the Management of Bipolar Disorders

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Preface to the first edition

Bipolar disorders are a group of mood disorders characterized by periods of depression and periods of abnormally elevated mood that last from days to weeks each. They negatively impact quality of life and functioning and associated with significant morbidity and mortality. The Bangladesh Association of Psychiatrists (BAP) felt the need to develop a management guideline for psychiatrists and also for physicians working in non-specialized settings to improve clinical practice while recognizing, assessing, diagnosing and treating bipolar disorders.

This guideline is based on available evidence on epidemiology, diagnosis and treatment of bipolar disorders and obtained mainly through desk review of established guidelines. The suggestions in this guideline represent the view of BAP, arrived at after careful consideration of different evidence. However, we expect that the users will exercise their judgement, alongside with the individual needs, preferences and values of the patients.

I want to thank the experts who worked rigorously during this guideline development process. I believe this guideline will greatly help to improve health care practices in Bangladesh and consequently our patients' lives.

Md. Waziul Alam Chowdhury
President
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Acknowledgement

We would like to express our gratitude towards the BAP members for their continued support and encouragement; the psychiatrists, general physicians, patients and their caregivers who participated in the focus group discussion and gave their time and valuable feedback; the health care professionals involved in the management of bipolar disorders. A heartfelt thanks to Sanofi Bangladesh Ltd., a subsidiary of Beximco Pharmaceutical Ltd. for their contribution as the scientific partner. They offered only logistic and financial support and was not involved in formulating any of the contents of this guideline.

Contents

Symbols and abbreviations

Adj	Adjunct therapy
b.i.d.	Twice a day
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBC	Complete blood count
CBT	Cognitive behavioral therapy
ECT	Electroconvulsive therapy
HbA1c	Hemoglobin A1c
IPSRT	Interpersonal and social rhythm therapy
LFTs	Liver function tests
MAOI	Monoamine oxidase inhibitor
NICE	National Institute for Health and Care Excellence
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants
t.i.d.	Three times a day

Part 1
Background

1.1 Introduction

Bipolar disorders are a group of chronic and complex disorders of mood characterized by a combination of manic, hypomanic and depressive episodes usually with interepisodic recovery. Persons with bipolar disorders experience mood episodes and also changing energy and activity levels. Moods range from periods of elated, irritable or energized behavior (known as manic or hypomanic episodes) to very sad, indifferent, or hopeless periods (known as depressive episodes). They face difficulties in their daily functioning in workplaces and academic activities, lose interpersonal harmony, encounter psychosocial dysfunction, marital discords, suicidal attempts, completed suicide and are vulnerable to substance misuse and medication side effects.

Bipolar Disorders

1. Bipolar I Disorder
2. Bipolar II Disorder
3. Cyclothymic Disorder

Bipolar disorders have multifactorial origin with involvement of genetic, biochemical, psychological and social factors. The hereditary factors may account for 85% of the cause of bipolar disorder. There is evidence that severity of bipolar disorders is related to family history of bipolar disorder, childhood emotional abuse, substance misuse and psychological stressors.

Bipolar disorders as a category include three different diagnoses: bipolar I, bipolar II, and cyclothymic disorder. The necessary diagnostic feature of bipolar I disorder involves the occurrence of at least one lifetime manic episode, although depressive episodes are common. Bipolar II disorder needs the occurrence of at least one hypomanic episode and one major depressive episode. Cyclothymic disorder (also called cyclothymia)— defined by numerous periods of hypomanic symptoms as well as periods of depressive symptoms lasting for at least 2 years (1 year in children and adolescents) not severe enough to meet the criteria for manic episode or major depressive episode respectively.

1.2 Epidemiology

Evidence suggests that prevalence of bipolar disorders in the community varies considerably due to geographical, gender, age, racial differences and also due to methods of estimation.

Lifetime prevalence of bipolar I disorder is 1% and mean age of onset is 18.2 years. This is nearly same for bipolar II disorder, which is 1.1% and mean age of onset is little bit higher, reported as 20.3 years. Besides, recent evidence revealed that community prevalence of bipolar I and II is around 4% in adult population. But this estimation is higher than other study findings.

In Bangladesh, National Survey on Mental Health (2018-19) revealed that community prevalence of bipolar and related disorders among adult population is 0.4% and 0.1% in children and adolescents. Gender-wise prevalence found was 0.5% in men and 0.3% in women.

1.3 Rationale

The National Mental Health Survey, Bangladesh 2018-19 revealed that 0.4% adults are suffering from bipolar disorders. As per health bulletin of DGHS, persons with bipolar disorders were the 2nd highest number of admitted patients (38.2%) in 2020 at NIMH and the 3rd highest number of admitted patients (19.4%) at Pabna Mental Hospital. The disorder is disabling because of its early onset, severity and chronicity, and has negative impact on almost every aspect of a patient's life and well-being. Again, bipolar depression is the underrecognized and undermanaged aspect of the disorder and accounts for much of the morbidity and mortality related with the disorder.

Stigma related to mental illness is a widespread issue in Bangladesh which is a major impediment towards help-seeking for mental disorders; however, the treatment gap is small for severe mental disorders. Patients and family members often experience fear, loss, lowered family esteem, shame, distrust, anger, inability to cope, hopelessness, and helplessness and could be directly blamed for causing the illness. Patients also feel guilt, shame, inferiority and wish for secrecy. Stigma leads to discriminations where individuals with mental disorders and their family members may be excluded from interpersonal relationships and public life and legal, economic, social and institutional rights and responsibilities may be denied.

It has emerged from focus group discussions that general physicians are not trained and skilled enough to diagnose and manage bipolar disorders. Also, patients delay in seeking help and there is no clear referral system at work in Bangladesh. Psychiatrists have to consider patients' socioeconomic conditions, follow up and laboratory facilities before prescribing, that can result in prescribing drugs that are lower in hierarchical ranks. Till date there is no single uniform management guideline for bipolar disorders in Bangladesh. Bangladesh Association of Psychiatrists (BAP) felt the extreme need to develop a national clinical management guideline for the psychiatrists and other physicians.

Features of this guideline:

1. Diagnosis can be confirmed by psychiatrists as well as by other physicians working in a setting with low resources.
2. The concepts, assessment, management and referral pathways are clearly described here.

3. The clinical features, ranging from mild to severe illness and special population with bipolar disorders (children and adolescent, pregnant and lactating mother, elderly, persons with physical comorbidity, etc.) are considered in this guideline.
4. A nationwide 5W service mapping (Who's doing What, Where, When and for Whom) for management for bipolar disorders is included in this guideline that makes it more usable for psychiatrists and other physicians, which develop a basis for rational liaison psychiatric service.
5. The evidence-based principal of management was developed here after considering country context, cultural compatibility and available resources.
6. This guideline comprises information to be used in both inpatient and outpatient settings.
7. A comprehensive management plan including follow up and compliance issues are also discussed here.
8. This guideline will be updated periodically.

All those things have made this guideline unique and uniform and very much compatible with the context of Bangladesh.

1.4 Objectives

The objectives of this guideline are to provide clear, concise, comprehensive and uniform information to all psychiatrists and other physicians on the current concept in the management of bipolar disorders considering the context of our country. Since bipolar disorders are mostly managed by psychiatrists, here this guideline provides necessary directives and primary management algorithm along the referral pathways for the general practitioners and physicians other than psychiatrists. Particular attention was given to make this guideline user friendly for psychiatrists and primary care physicians working in settings with limited resources to ensure advanced and updated management of bipolar disorders.

1.5 Target users

This guideline is made by BAP to provide a uniform protocol for the physicians. Psychiatrists are the key target users of this clinical management guideline; however, a brief but comprehensive portion is also added for the physicians working in non-specialized settings (general practitioners, specialists other than psychiatrists) to guide them through initial management and referral issues. Allied mental health professionals like psychologists, counselors, clinical social workers, mental health nurses can also read the guideline to get a good understanding of clinical practices involved at different stages of bipolar disorders' management.

Part 2
Methodology

Methodology

This guideline has been developed after considering the desk review of updated clinical practice guidelines from several authorities like American Psychiatric Association (APA), National Institute for Health and Care Excellence (NICE guidelines), Bipolar management guidelines of Indian Psychiatric Associations, The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, etc., expert consensus, clinical experience and the findings from the focus group discussions with the psychiatrists, general practitioners and persons with living experience of bipolar disorders in Bangladesh.

Hierarchical ranking of treatment recommendations is used in this guideline. They were created by considering the efficacy of each treatment modalities across various phases of illness as well as safety, tolerability and risk of treatment emergent switch, obtained from levels of evidence from various types of studies. We recommend that drugs listed top in the hierarchy be tried first, unless there are patient specific reasons for choosing a drug lower in the hierarchy.

Table 1: Definition of levels of evidence criteria used in bipolar recommendations

Level	Evidence	BAP evidence gathering
I	Systematic review/meta-analysis of all relevant randomized controlled trials	Obtained from desk review
II	One or more properly designed randomized controlled trial	
III	Well-designed prospective trial (non-randomized controlled trial); comparative studies with concurrent controls and allocation not randomized; case-controlled or interrupted time series with a control group	
IV	Case series, either post-test or pretest/post-test	
V	Expert opinion	Consensus among experts, focus group discussion with experts

Part 3
Management

3.1 Diagnostic convention

For the diagnosis of bipolar I disorder, patients have to meet criteria for at least one episode of mania. Some patients might have had previous depressive episodes and most patients will have subsequent episodes that can be either manic or depressive. Hypomanic episode, mixed episode and interepisodic subthreshold symptoms can also occur.

For diagnosis of bipolar II disorder, patients have to meet criteria for at least one hypomanic episode and one major depressive episode.

For diagnosis of cyclothymic disorder, patients have to experience numerous periods of depressive symptoms and hypomanic symptoms for at least 2 years (1 year in children) in the absence of any manic, mixed or major depressive episode.

Manic episode or mania is a period of at least 1 week or more in which the patient experiences a change in behavior that markedly affects their functioning. The characteristic features of mania are elevated, expansive or irritable mood, increased goal-directed activity, talkativeness, rapid speech, decreased need for sleep, grandiosity, etc.

Hypomanic episodes are distinct period of 4 or more days, with elevated, expansive or irritable mood with other features like increased activity, talkativeness, rapid speech, decreased need for sleep, grandiosity, etc. Symptom severity and functional impairment help to distinguish between mania and hypomania.

Major depressive episode or simply depressive episode is diagnosed when a patient has a persistently low or depressed mood, anhedonia or decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts.

For detailed information about diagnostic conventions readers are advised to consult DSM-5 or ICD-11.

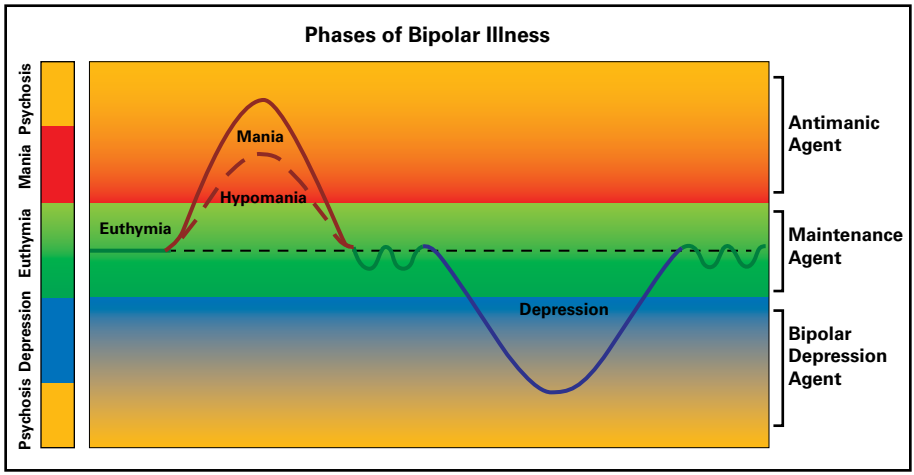


Figure 1: Phases of bipolar illness

Episodes and bipolar disorders are further subdivided according to their clinical features, onset pattern, course, severity, remission state, etc. They have important implications in choosing drug and managing the patient.

Table 2: Assessing bipolar disorder – clinical subtypes and specifiers according to DSM-5

Specifier	Severity	Course	Onset	Remission state
Anxious distress Mixed feature Melancholic Atypical Catatonic Psychotic	Mild Moderate Severe	Single episode Recurrent episode Rapid cycling Seasonal	Early Late Peripartum	Partial remission Full remission Resistant

3.2 Principles of management

The aims of treatment are to rapidly remit the acute episodes, prevent recurrence and readmission, improve functioning between episodes and provide support for the patient and his family members. Physicians are encouraged to ensure the following steps during management.

a. Confirm the diagnosis

Careful and thorough attention to history and exclusion of other psychiatric, physical or substance related conditions are required to reach the diagnosis. Bipolar disorder often starts with depression and careful attention needs to pay to differentiate between unipolar and bipolar depression. Detail assessment should include information about clinical features, duration and number of episodes, suicidal risk, risk of violence, comorbidities, family history, substance use, past treatment, pregnancy state, social support, assessment of caregivers, etc.

b. Determine the treatment setting

Treatment can be given on either outpatient or inpatient basis depending on patient's condition. Possible indications for hospitalization may be

- Patients who are considered to pose a serious threat to harm themselves or others or have strong suicidal intents
- Inadequate food and fluid intake
- Reckless behavior
- Presence of medical illness
- Substance misuse
- Lack of social support
- Failure to engage or respond to outpatient treatment
- Need for ECT

When patients refuse, they can be hospitalized involuntarily if they meet the criteria of involuntary admission in The Mental Health Act, Bangladesh 2018.

c. Good therapeutic relationship and compliance

It is a long-term illness and establishing and maintaining a supportive and therapeutic relationship is critical to the proper understanding and management of an individual patient. Factors like male sex, younger age, being single, poor insight, substance use, lack of social support, greater severity of illness, side effects of medications, inadequate efficacy, cost of medications, etc. can lead to partial or non-adherence to medications which need to be carefully addressed.

d. Educate the patient and the family

Patients benefit from education regarding their illness, prognosis and treatment. Education should be an ongoing process and printed material on different aspects of bipolar illness can be helpful. Patients and families need to educate about the role of psychosocial stressors and other disruptions in precipitating or exacerbating mood episodes. Patients may benefit from regular patterns of daily activities and psychiatrists should educate the patients and families about the early sign and symptoms of relapse into manic and depressive episodes.

e. Assess and manage functional impairments

Bipolar disorders patients often face emotional, social, familial, academic, occupational and financial problems and identified impairment in functioning should be addressed. Patient may require assistance in scheduling absence from work and other duties, may require encouragement to avoid major life changes while in an ongoing episode and set realistic goals in terms of levels of functioning.

3.3 Physical examination and investigations

Appropriate examination and investigation need to be conducted on an individual basis. The purpose of these are three folds. First, to exclude medical diagnoses that can produce manic or depressive features; second, to see whether the patient is fit for commencing psychotropic drugs and third, to establish a baseline parameter to compare with future examinations and investigations. In unusual and particularly refractory mood episodes, more detailed investigations including brain imaging may be necessary. Pulse, blood pressure, BMI and waist circumference measurements, physical examination for endocrine and neurological disorders, organ insufficiency, extra-pyramidal syndrome are commonly carried out.

Box 1: Suggested routine baseline investigations for patients with bipolar disorders

CBC
RBS
Serum creatinine, Urine R/M/E
SGPT
TSH
ECG (>40 years or if indicated)
Pregnancy test (if relevant)

Box 2: Investigations in indicated situations for patients presenting with bipolar disorders

HbA1c
Electrolytes and calcium
Blood urea, eGFR
Fasting lipid profile
Urine toxicology for substance use
Liver enzymes, serum bilirubin, HBsAg
Thyroid antibodies
Prolactin
Sexually Transmitted Disease (STD) testing (e.g., VDRL, HIV)
EEG (If indicated)
If indicated, Brain MRI (preferred)/CTscan

3.4 Management of bipolar disorders

Hierarchical ranking of treatment recommendations is used in this guideline. They were created by considering the efficacy of each treatment modalities across various phases of illness as well as safety, tolerability and risk of treatment emergent switch, obtained from levels of evidence from various types of studies. We recommend that drugs listed top in the hierarchy be tried first, unless there are patient specific reasons for choosing a drug lower in the hierarchy.

Table 3: Hierarchical ranking of treatment recommendations

First-line agents	Level 1 or Level 2 evidence for efficacy Good safety/tolerability profile No risk for treatment emergent switch
Second-line agents	Level 3 or higher evidence for efficacy Good safety/tolerability profile Low risk of treatment emergent switch
Third-line agents	Level 4 or higher evidence for efficacy Concern for safety/tolerability and/or Significant risk of treatment emergent switch

Evidence does not support the use of psychological treatment during the acute phases of bipolar disorders. Different modalities of psychotherapies can be used as monotherapy and adjunctive therapies during the maintenance phases of treatment.

3.4.1 Management of bipolar I disorder

a. Management of acutely disturbed or violent behavior

Violent and aggressive behavior can occur in bipolar disorder specially during manic episodes. Risk is elevated when patient has comorbid physical illness, delirium, substance abuse or preexisting personality disorder. Before commencing drug treatment exclude physical illness and delirium, and use de-escalation techniques.

Step 1 – Oral treatment

- If the patient is on regular antipsychotic, offer oral treatment with - Lorazepam 1-2 mg/Midazolam 7.5-15 mg/Promethazine 50 mg.
- If the patient is not taking antipsychotic, offer oral treatment with - Olanzapine 10mg/Quetiapine 100 mg/Risperidone 1-2 mg/Haloperidol 5 mg.
- If necessary, repeat after 45-60 minutes.
- Consider combining sedatives and antipsychotics.
- If it fails or the patient put himself or others at risk, consider IM or IV treatment.

Step 2 – Intramuscular (IM) treatment

- Lorazepam 2-4 mg/Promethazine 50 mg/Haloperidol 5 mg.
- Considering combining drugs if single drug fails – Haloperidol + Lorazepam / Haloperidol + Promethazine.
- Repeat after 30-60 minutes, if necessary.

Step 3 – Intravenous (IV) treatment

- Diazepam 10 mg over at least 2 minutes.
- Repeat after 10 minutes, if necessary, up to 3 times.
- IV treatment may be used over IM when very rapid effect is required.

Monitor temperature, pulse, blood pressure and respiratory rate after commencing treatment. Initially every 15 minutes for 1 hour. ECG is recommended when parenteral antipsychotic therapy is given.

Zuclopenthixol acetate (50/100 mg), although not a rapid tranquillizing agent, can be used in patients who required repeated injections of short acting antipsychotic drugs like haloperidol or sedative drugs like diazepam or lorazepam. It should not be used in patients who accept oral medication, are neuroleptic naïve and have hepatic, renal or cardiac disease.

Seek expert advice if these steps don't work.

b. Management of acute bipolar mania

i. Pharmacological treatment of manic episodes

Lithium, valproate and other anticonvulsants, typical and atypical antipsychotics, and some other drugs and therapies have been effectively used in the treatment of mania/ hypomania. The hierarchical list of drug choice in mania based on their efficacy, safety, tolerability and possibility of treatment emergent side effect is given below (Table 4).

Table 4: Biological treatment recommended for mania and hypomania

Line of recommendation	Monotherapy	Combination therapy
First-line (Listed hierarchically)	Valproate Lithium Haloperidol Risperidone Quetiapine Aripiprazole Paliperidone	Haloperidol + Valproate/Lithium Risperidone + Lithium/Valproate Quetiapine + Lithium/Valproate Aripiprazole + Lithium/Valproate
Second-line (Listed hierarchically)	Olanzapine Carbamazepine ECT	Olanzapine + Lithium/Valproate Lithium + Valproate
Third-line	Chlorpromazine Clonazepam Clozapine	Carbamazepine + Lithium/ Valproate

Detail assessment should include information about clinical features, duration and number of episodes, suicidal risk, risk of violence, comorbidities, family history, substance use, past treatment, pregnancy state, social support, assessment of caregivers, etc. The assessment and management strategies should follow the general principle of management.

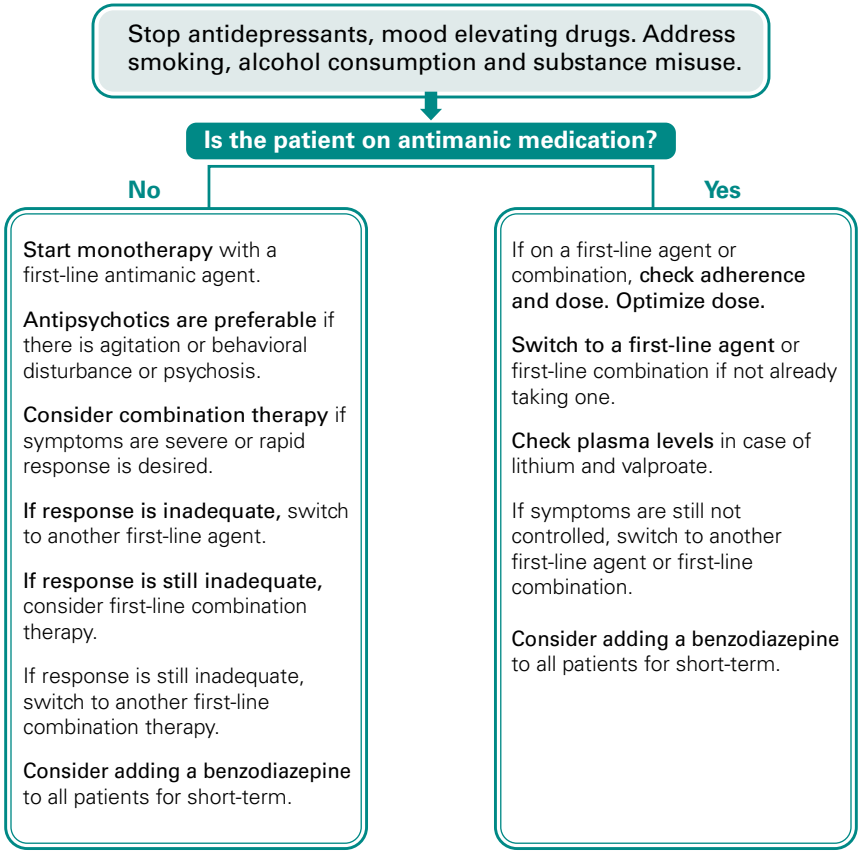


Figure 2: Treatment algorithm for acute mania and hypomania

ii. Initiation and optimization of treatment

- For all patients, previously treated with 1st or 2nd line agents or untreated, treatment should be started with one of the available first-line agents or combinations.
- At least two first-line agents and two first-line combinations should be tried before switching to second-line treatment.
- Some therapeutic response with antimanic drugs is expected within 1-2 weeks. If no response is observed within 2 weeks with optimum therapeutic dose of antimanic drugs and other contributing factor for non-response are excluded, then switch or combination strategies should be considered.
- Third-line agents should be tried last, and rarely be necessary.
- Consider adding short-term benzodiazepine for all patients (e.g., clonazepam up to 8 mg/day, lorazepam up to 4 mg/day).

Table 5: Treatment options for bipolar mania according to clinical presentations

Clinical presentation	Preferred agent
Classical euphoric grandiose mania Classical/dysphoric mania, substance abuse Severe symptoms, behavioral disturbance	Lithium Valproate Atypical antipsychotics Combination therapy
Anxious distress	Valproate Quetiapine Olanzapine
Mixed features	Valproate + Atypical antipsychotics Quetiapine Aripiprazole
Psychotic features	Lithium/Valproate + Atypical antipsychotics
Rapid cycling	Lithium + Valproate Lithium + Lamotrigine Lithium/Valproate + Quetiapine/ Aripiprazole/Olanzapine

c. Management of acute bipolar depression

i. Pharmacological treatment for acute bipolar depression

Lithium, anticonvulsants, atypical antipsychotics, and some other drugs such as antidepressants have been effectively used in managing bipolar depression. The assessment and management strategies should follow the general principle of management mentioned previously. The hierarchical list of drug choice in bipolar depression is given below (Table 6).

Table 6: Biological treatment recommended for bipolar I depression

Line of recommendation	Monotherapy	Combination therapy
First-line (Listed hierarchically)	Quetiapine Lithium Lamotrigine Lurasidone	Lurasidone + Lithium/Valproate Lamotrigine (adj)
Second-line (Listed hierarchically)	Valproate ECT	Olanzapine + Fluoxetine SSRI (adj)
Third-line	Olanzapine	Aripiprazole (adj) Armodafinil (adj) Carbamazepine Levothyroxine (adj) Olanzapine

adj-Adjunctive

ii. Initiation and optimization of treatment

- For all patients, pharmacotherapy should be started with one or more of the available first-line agents. Patient's preference, assessment findings, prior response, safety and tolerability as well as clinical features should guide choice of medication.
- Lack of early improvement (i.e., two-three weeks) is a predictor for non-response. In case of non-response, dosing should be optimized and issues of non-response and non-adherence should be assessed.
- After following the above strategies, in case of inadequate or non-response add on (combination) therapy or switching should be considered, within the first-line recommendations.
- Monotherapy with anti-depressant is discouraged, as there is risk of treatment emergent mania.
- Patients who are inadequately responsive to first-line drugs, monotherapy with valproate or combination of lithium/valproate/antipsychotic with an SSRI is recommended.
- TCAs, MAOIs and venlafaxine are frequently associated with manic/hypomanic switch; so, their use is not recommended.

Table 7: Treatment options for bipolar depression according to clinical presentations

Clinical presentation	Biological therapy
Anxious distress	Quetiapine, Olanzapine + Fluoxetine Lurasidone
Mixed features	Olanzapine + Fluoxetine Lurasidone
Melancholic features	ECT Venlafaxine
Psychotic features	ECT Atypical antipsychotics
Rapid cycling	Lithium Valproate Quetiapine Olanzapine
Atypical features	Fluoxetine/Sertraline + Lithium/Valproate

d. Maintenance therapy for bipolar I disorder

- The term relapse refers to worsening of symptoms after an initial improvement during the treatment of a single episode of mood disorder, whereas recurrence refers to a new episode after a period of complete recovery.
- Treatment to prevent relapse is called continuation treatment; treatment to prevent recurrence is called maintenance treatment.
- Following the first ever manic episode, drug treatment (continuation treatment) should be continued for 3 to 6 months after remission. Gradually withdrawing the drug at the end of treatment reduces the risk of relapse.
- Almost all individuals with bipolar I disorder require maintenance treatment to prevent subsequent episodes, reduce residual symptoms, and restore premorbid functionality and quality of life.
- Maintenance treatment, early in the course of illness, has been shown to reverse cognitive impairment and to improve prognosis.
- Generally, medications that have been found to be effective in the acute phase should be continued during the maintenance phase.
- Long-term antidepressant use is not recommended, especially in light of the concerns about potential risk of manic/hypomanic switch and mood instability.
- Ongoing clinical monitoring is also a crucial part of maintenance treatment that should be used to enhance adherence, detection of relapse, adjustment of the therapeutic dosage and monitoring of side effects.
- Adjunctive psychosocial interventions are an important component of management of bipolar I disorder and should be offered for all patients (see psychological intervention part for a list of psychosocial therapies).
- The choice of agent or agents used in maintenance treatment should be discussed with the patients and their caregivers (as appropriate) after considering the current and prior medication use and response, safety and tolerability of each agent, predominant episode polarity and clinical features that may influence prognosis.
- With regard to treatment options, the evidence suggests that monotherapy with a single mood agent is often ineffective and patients may require a combination of antimanic agents to achieve mood stability.
- There is no clear consensus about the duration, maintenance treatment should be reviewed yearly.
- Discontinuation of maintenance treatment may be considered if the patient has made a full recovery from the last episode, was free of episodes in the preceding 4 years, has no history of severe consequences from mania or bipolar depression and no history of cycling with multiple mood episodes.

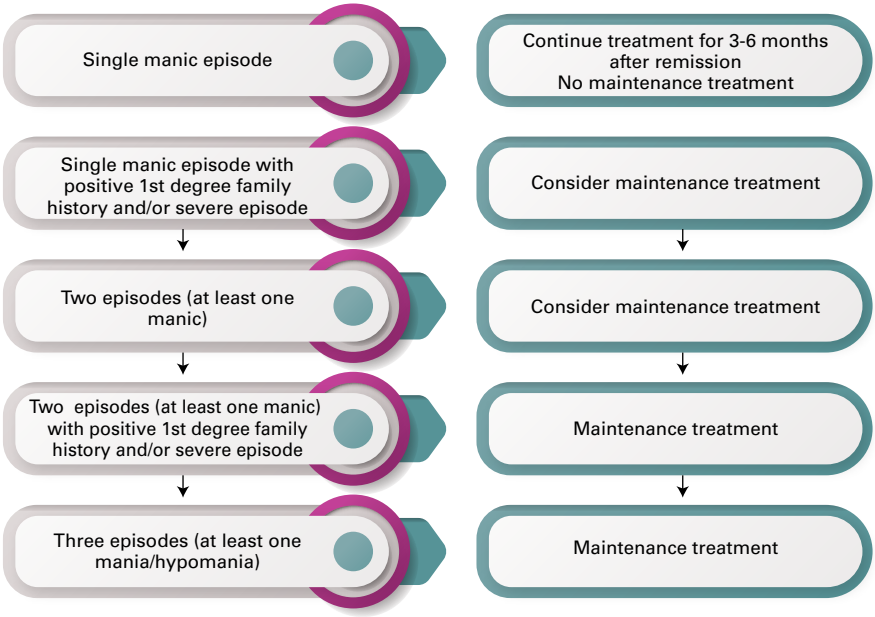


Figure 3: Algorithm for maintenance treatment in bipolar disorders

Table 8: Maintenance treatment recommended for bipolar I disorder

Line of recommendation	Monotherapy	Combination therapy
First-line (Listed hierarchically)	Valproate Lithium Quetiapine Lamotrigine Aripiprazole	Quetiapine + Lithium/Valproate Aripiprazole + Lithium/Valproate
Second-line (Listed hierarchically)	Olanzapine Risperidone LAI Carbamazepine	Lurasidone + Lithium/Valproate
Third-line		Aripiprazole + Lamotrigine Clozapine (adj) Olanzapine + Fluoxetine

adj-Adjunctive

3.4.2 Management of bipolar II disorder

a. Management of hypomania

- Drugs used in the treatment of hypomania are similar to those used in bipolar I mania.
- Stopping the antidepressant or stimulating drug is recommended before initiating the treatment for hypomania like the mania.
- Antidepressants are not as problematic in bipolar II as in bipolar I disorder (i.e., less chance of treatment emergent hypomania)

b. Management of bipolar II depression

- The patient should be assessed as per bipolar I depression.
- There is evidence that bipolar II depression has higher risk of suicide than bipolar I depression.

Table 9: Biological treatment recommended for bipolar II depression

Line of recommendation	Biological therapy
First-line	Quetiapine
Second-line	Lithium Lamotrigine ECT Sertraline (for pure depression) Venlafaxine (for pure depression)
Third-line	Agomelatine (adj) Valproate Fluoxetine (for pure depression) T3/T4 thyroid hormones (adj)

adj-Adjunctive

c. Maintenance treatment

- Maintenance treatment prevents relapse, reduce sub-syndromal symptoms and improve quality of life.
- As with bipolar I disorder, selection of an agent should be guided by acute phase treatment.

Table 10: Maintenance treatment recommended for bipolar II disorder

Line of recommendation	Drug
First-line	Quetiapine Lithium Lamotrigine
Second-line	Venlafaxine
Third-line	Carbamazepine Valproate Escitalopram Fluoxetine Risperidone (prevention of hypomania)

3.4.3 Cyclothymic disorder

- Much of the clinical management of cyclothymic disorder is extrapolated from the management guidelines for bipolar I disorder.
- Conservative non-pharmacological approaches can be considered initially to manage cyclothymic disorder if severity is mild, causing tolerable distress and minimal functional impairment.
- Although there is little strong quality evidence but following table could guide physicians in the treatment of cyclothymic disorder.
- Augmented CBT was found to be effective for depressive and hypomanic symptoms.
- Cyclothymia may be a precursor to bipolar I or II disorder, therefore, longitudinal assessment and psychoeducation of patients as to when to seek help are advisable.

Table 11: Recommended pharmacotherapy for cyclothymic disorder

Monotherapy	Combination therapy
Lithium – if significant affective intensity	Lithium + Lamotrigine
Valproate – if anxiety is predominant	Monotherapy agent + Atypical antipsychotic
Lamotrigine – if anxious-depressed polarity is prominent	

3.5 Special population

a. Children and adolescents

- Between one-third (community samples) and two-thirds (clinical samples) of patients with bipolar disorder experience their first mood episode during childhood or adolescence and often such an earlier onset is related to a more severe illness characterized by increased symptom burden and comorbidity. The prevalence of bipolar disorder in a community sample of children and adolescents found was 1%.
- Multidisciplinary service, family involvement and family intervention, structured psychological interventions like emotion regulation skills, problem solving, CBT and vocational and educational interventions should be considered.
- Try to avoid valproate in girls or young women of childbearing age.
- The use of ECT in adolescents is rare, but numerous case reports support its efficacy and safety in the treatment of severe affective, psychotic and catatonic conditions.
- Youths with bipolar disorder are at greater risk for substance use disorders, short-term treatment with lithium and valproate may be useful in these conditions.
- Stimulants (adjunctive amphetamine/methylphenidate) may also be used for comorbid ADHD in stable/euthymic youth taking optimal doses of anti-manic medications.
- Treatment with a maintenance agent should continue for a minimum of 18 months after stabilization of a manic episode.

Table 12: Treatment recommendations for children and adolescents with bipolar I disorder

	Acute mania	Bipolar depression	Maintenance therapy
First-line	Risperidone Haloperidol Aripiprazole, (not longer than 12 weeks) Olanzapine Quetiapine	Lurasidone	Aripiprazole Lithium Valproate Lamotrigine- more than 13 years of age group
Second-line	Quetiapine (adjunctive therapy)	Lithium Lamotrigine	Quetiapine Risperidone
Third-line	Valproate	Olanzapine-Fluoxetine combination, 6/25-12/50 mg Quetiapine, up to 300 mg Antidepressant (Escitalopram/Sertraline) + Mood stabilizer – cautiously	

Dose should be adjusted according to age, body weight and clinical manifestation

b. Women of childbearing age

Many medications used to treat bipolar disorder are associated with a higher risk of birth defects, thus psychiatrists should encourage effective pre-conception counselling including contraceptive practices and planned pregnancy for all female patients of childbearing age who are receiving pharmacological treatment.

c. Pregnancy

- The management of bipolar disorder over the perinatal period is intrinsically complicated because it is a time of high risk for relapse and mood stabilizers can have a deleterious effect on the developing fetus.
- For women with pre-existing bipolar disorder who wish to conceive, a careful risk-benefit analysis for remaining on mood stabilizing medication needs to be done.
- It is better to include family members and caregivers regarding taking decision to start psychotropic medications during pregnancy.

Specific options include:

a. Continuing medication throughout pregnancy

b. Discontinuing medications at the beginning of pregnancy or before conception

c. Discontinuing the medication only for the first trimester

- Wherever possible, psychosocial strategies should be preferred over medications in the first trimester as this period holds the highest risk for teratogenicity.
- The administration of psychotropic during pregnancy should involve close liaison between a treating psychiatrist, obstetrician and neonatologist.
- When medications are deemed necessary, preference should be given to monotherapy using the lowest effective dose.

Pregnant women should have:

a. Folate supplementation

b. Ultrasound (high resolution ultrasound examination at 16–18 weeks gestation to detect abnormalities in the fetus)

c. Maternal serum α-fetoprotein screening

d. Breastfeeding women

- All medications used in the treatment of bipolar disorder are secreted in breast milk in varying degrees.
- Quetiapine, olanzapine and sertraline are preferred choices in breastfeeding, considering their relatively lower concentration in breast milk.
- A pragmatic alternative to breastfeeding is bottle feeding. Although there are many benefits to breastfeeding, associated sleep disruption may increase the risk of mood episodes in women with bipolar disorder. If possible, bottle feeding at night by the woman's partner or a support can be beneficial to allow the woman to maintain a better sleeping schedule.
- In women with postpartum psychosis or mania, breastfeeding may be riskier, and therefore may not be indicated, as the mother may be too disorganized to safely breastfeed the baby.

Table 13: Treatment recommendations for women with bipolar disorder

Women of child bearing age	Pregnancy	Breastfeeding
Avoid valproate and carbamazepine if planned pregnancy not possible	Consider stopping valproate or carbamazepine if already receiving. For manic episode olanzapine, quetiapine and other antipsychotics appeared safe in pregnancy. Use lithium in severe bipolar disorder. CBT – for moderate bipolar depression. SSRI/lamotrigine – for severe bipolar depression. ECT – for severe mania or depression.	Quetiapine Olanzapine Sertraline

e. Elderly population

- Among the older people lifetime prevalence of bipolar disorder and data supporting efficacy of medications in various mood states in this population are limited.
- Use drugs only when necessary but do not undertreat.
- Start with a low dose and increase slowly.

Table 14: Treatment recommendations for bipolar disorders in elderly

	Acute mania	Bipolar depression	Maintenance therapy
First-line	Valproate Lithium	Quetiapine Lurasidone	Lithium Lamotrigine
Second-line	Quetiapine	-	Valproate
Third-line	Aripiprazole Risperidone Carbamazepine For treatment-resistant episodes, consider clozapine and ECT.	Lithium Lamotrigine Valproate Aripiprazole Carbamazepine ECT in treatment resistant and strong risk of self-harm cases Mood stabilizer + SSRI	

3.6 Comorbidities

a. Comorbid medical conditions

i. Metabolic syndrome

- Metabolic syndrome in particular is a highly prevalent comorbidity, present in 20-65% of patients with bipolar disorder.
- It greatly increases an individual's risk for cardiovascular disease, diabetes mellitus, premature mortality and worsens bipolar clinical outcomes.
- Assessment should include a thorough physical and neurological examination and laboratory tests.
- More than >5% weight gain after 1 month of initiating treatment strongly predicts long term weight gain and should prompt preventive or remedial measures.
- Lifestyle interventions like improving diet, increasing physical activity, abstinence from smoking and alcohol should be tried first.
- Replacing high risk drugs (clozapine, olanzapine) with low-risk drugs like (aripiprazole, lurasidone) is an option.
- Another option is to add aripiprazole to existing treatment (5-15 mg/day).
- Metformin (500-2000 mg/day), topiramate (up to 300 mg/day) or orlistat can also be used to prevent or treat weight gain.

ii. Hepatic impairment

General guideline of prescribing in hepatic impairment

- Use lower starting doses.
- Be cautious with drugs that are extensively metabolized in liver.
- Avoid drugs with long half-lives, that are very sedative and very constipating.
- Choose a low-risk drug and initially (first six weeks) monitor liver function tests weekly.

Box 3: Recommended medications in hepatic impairment

Lithium
Antipsychotics - Haloperidol, Aripiprazole, Quetiapine, Risperidone, Paliperidone
Sertraline
Lorazepam

Note:

Lithium – dosage reduction not required as long as renal function is normal.

Aripiprazole, paliperidone – No dosage reduction in mild to moderate impairment.

Haloperidol, quetiapine, risperidone, sertraline - Start at half of the recommended dosage in mild to moderate impairment.

Severe impairment - more caution required (e.g., 75% dose reduction).

iii. Renal impairment

General guideline of prescribing in renal impairment

- Avoid drugs that are extensively renally cleared.
- Start at a low dose, increase gradually.
- Avoid long-acting drugs, drugs with anticholinergic effects (urinary retention), drugs that prolog QTc interval.
- Use creatinine clearance and ACR (albumin-to-creatinine ratio) to decide about dose range and titration frequency.
- Usual dosing: GFR 10-50ml/min - use normal dose; GFR <10ml/min – use1/4 to 1/2 of normal dose.

Box 4: Recommended medications in renal impairment

Valproate, Lamotrigine
Haloperidol, Olanzapine
Sertraline
Lorazepam

iv. Cardiovascular disease

- Some antipsychotics are associated with serious ventricular arrhythmia and sudden cardiac death.
- Perform ECG for all patients at baseline and then yearly. Monitor high risk patients more closely.
- Use QTc interval and T wave morphology for making clinical decisions.
- If QTc>440 ms (male) and >470 ms (female) but <500 ms, then reduce drug dose or switch to 1st line drugs.
- If QTc>500 ms or abnormal T wave morphology, then stop the drug and refer to cardiologist.
- At usual dose range 1st line antipsychotics have no effect on QT interval.
- Lithium can be safely prescribed, although T-wave depressions and sinus node dysfunction are most commonly reported.
- Sertraline interacts with warfarin and other anticoagulants.

Box 5: Recommended antipsychotics and other medications in patients with cardiovascular diseases

First-line antipsychotic - Aripiprazole, Lurasidone
Second-line antipsychotic - Risperidone, Paliperidone, Olanzapine
Third-line antipsychotic - Haloperidol, Quetiapine
Valproate
Lithium
Carbamazepine
Sertraline

b. Comorbid psychiatric disorders

- Unusual or atypical presentations may reflect concomitant psychopathology because of comorbid psychiatric or medical illness.
- Acute mood episodes, psychosis, suicidal ideation should be managed first, once mood is stabilized, additional comorbidities should be addressed.
- Majority patients with bipolar disorder have at least one comorbid psychiatric diagnosis, most common being substance use disorders, anxiety disorders, personality disorders and impulse control disorders.
- Comorbidity worsens prognosis, increases likelihood of treatment resistance and suicide risk.
- Substance use disorder should be addressed concurrently or sequentially, depending on patient's condition.

i. Substance use

- Comorbid substance use should be treated concurrently to mood symptoms, consideration can be given for inpatient treatment.
- A full assessment and diagnosis followed by detoxification is necessary.
- Lithium, valproate or a combination of lithium and valproate should be considered as first-line options.
- Quetiapine, risperidone alone or in combination with other drugs have shown efficacy in cocaine, amphetamine and methamphetamine use. Olanzapine is effective in opioid use disorder.
- SSRIs have shown minimal efficacy in bipolar depressive episode with substance use disorder; TCAs have shown some efficacy in improving depression but there is risk of switching to mania.
- Involvement of family members in the treatment process and Family Focus Therapy is recommended. It should be kept in mind that in many cases, patients might not be able to shift their substance usage until mood episode is improved.

ii. Anxiety disorders

- Bipolar disorder patients frequently experience symptoms of anxiety and comorbid anxiety disorders like generalized anxiety disorder, panic disorder, post-traumatic stress disorder, etc. are common. Anxiety can be a component of bipolar disorder itself.
- Mood stabilization is priority before specific anxiety treatments are considered.
- Benzodiazepines can rapidly alleviate anxiety symptoms but should be prescribed at the lowest possible dose for the shortest period possible, given the concerns about suicide risk, abuse and dependence.
- Pregabalin and agomelatine have shown efficacy in bipolar depression with anxiety. There is evidence for efficacy of quetiapine, olanzapine and olanzapine-fluoxetine combination.
- CBT is also an appropriate therapy for anxiety.

iii. Obsessive compulsive disorder

- OCD is a comorbid condition in 10%-20% of patients with bipolar disorder and may be more common in children and adolescents.
- Comorbid OCD has been associated with a higher number of previous mood episodes, rapid cycling, seasonality, substance misuse, and lower overall functioning.
- Symptoms of OCD may precede or follow mood symptoms and the severity of OCD symptoms tends to fluctuate with mood changes.
- Lithium, anticonvulsants alone or with atypical antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole) may be adequate to resolve comorbid symptoms of OCD.
- Antidepressants might not be necessary for the majority of patients; if used, SSRIs are preferred over other antidepressants.

iv. Personality disorders

- Borderline and cluster C personality disorders (avoidant, dependent, obsessive compulsive personality disorder) are commonly comorbid with bipolar depression.
- Concurrent treatment of both borderline personality disorder and mood disorders offer a better probability of improvement in both sets of illness symptoms and in function.
- Atypical antipsychotics have shown best efficacy in comorbid borderline personality disorder. Lithium, valproate and lamotrigine may provide some symptomatic relief for comorbid borderline personality disorder.
- Cognitive Behavioral Therapy (CBT) and Dialectical Behavior Therapy (DBT) are of particular value in personality disorders.

v. Attention-deficit/hyperactivity disorder (ADHD)

- Approximately 10%-20% of patients with bipolar disorder meet the criteria for adult ADHD and up to 20% of adults with ADHD also meet the criteria for bipolar disorder.
- Recommendations are to treat bipolar symptoms first with mood stabilizers and/or atypical antipsychotics to stabilize mood before considering treatment for ADHD symptoms.
- Atomoxetine, methylphenidate add-ons to mood-stabilizing treatments have been reported to be efficacious in improving ADHD symptoms.

Table 15: Recommended treatment for bipolar disorder with comorbid psychiatric disorder

Substance use	Anxiety disorders	OCD	Personality disorder	ADHD
Lithium Valproate Lithium +Valproate Family focused therapy	Quetiapine Olanzapine Olanzapine + Fluoxetine Pregabalin Agomelatine Benzodiazepine CBT	Lithium Valproate Lithium/Valproate + Atypical antipsychotics	Atypical antipsychotic Lithium Valproate CBT DBT	Lithium Valproate Lithium/Valproate + Atypical antipsychotic Atomoxetine Methylphenidate

3.7 Managing poor and non-response

A significant number of patients with bipolar disorders will show suboptimal response or non-response to treatment. For instances, half of the patients with bipolar depression will show treatment response by 4 weeks and only one-third of the patients will remit by 24 weeks. Table 16 shows the strategies to manage suboptimal or non-response.

Table 16: Strategies to address suboptimal or non-response

Reason	Strategy
Reevaluate the diagnosis and formulation, review the dosage, exclude comorbidities	
Manic phase	
Poor adherence	Review medication administration
	Monitor blood level if available
	Give Psychoeducation regarding nature of illness, rational for treatment and its benefits
	Supervision of medication administration, changing formulation, deport preparation, involve carers
	Manage side effects
First line medication not working	Use maximum tolerable dose
	Switch to another first line drug
Single drug not working	Combination therapy (e.g., atypical antipsychotic + lithium/ valproate)
Treatment resistant mania	ECT
Depressive phase	
Poor adherence	Manage as above
Depression	Assess for thyroid function, rapid cycling, mixed features and manage accordingly
Treatment resistant	Quetiapine/Lithium alone Quetiapine + Lamotrigine or Lithium + Lamotrigine Olanzapine + Fluoxetine Lithium or Quetiapine + SSRI ECT

Part 4
Psychological interventions

4.1 Psychological interventions

- The primary goals of psychotherapeutic treatments are to reduce distress and improve the patient's functioning in bipolar disorder between episodes as well as decrease the likelihood and severity of future episodes.
- In acute mania psychological interventions are not suitable for patients but in maintenance phase and depressive phase they demonstrate efficacy.
- In general, psychological interventions appear to demonstrate efficacy most convincingly with patients early in their illness course.

Recommended psychotherapies in maintenance and depressive phases

- 1st line - Psychoeducation
- 2nd line - CBT and Family-focused therapy (FFT)
- 3rd line - Interpersonal and social rhythm therapy (IPSRT)

The **key ingredients** of all psychotherapies so far found useful for bipolar disorder (including psychoeducation) are as follows:

1. Monitor moods and early warning signs
2. Recognize and manage stress triggers, significant life changes and interpersonal conflicts
3. Develop relapse prevention plans
4. Stabilize sleep/wake rhythms and daily routines
5. Encourage medication adherence
6. Reduce self-stigmatization, identify and correct maladaptive thoughts and beliefs
7. Re-engage with social, familial and occupational roles
8. Reduce alcohol or drug use (including caffeine in sensitive individuals)

4.2 Psychoeducation (PE)

Psychoeducation is the preferred or first line psychological intervention. It can be delivered in individual and group programs by focusing on relevance of participants. Psychoeducation is a descriptive term referring to providing information about the nature of the illness, its treatments, and key coping strategies to the patient and family. It also provides information and emotional support, help patients adjust to living with a chronic illness, and emphasizing adherence to medication and stabilizing moods.

Group psychotherapy may help patients address such issues as adherence to a treatment plan, adaptation to a chronic illness, regulation of self-esteem, and management of marital and other psychosocial issues. Support groups, peer support provide useful information about bipolar disorder and its treatment.

4.3 Early Warning Signs (EWS) interventions

EWS interventions apply a mixture of cognitive behavioral strategies and psychoeducation strategies to help patients identify and manage early symptoms of a relapse. Patients and families are able to understand and predict the onset of episodes; for example, whether they are insidious, abrupt, related to life stresses or contain a seasonal component. They can also benefit from an understanding of the role of psychosocial stressors and other disruptions in precipitating or exacerbating mood episodes.

Table 17: Early warning signs of manic and depressive relapse in bipolar disorder

Mania	Depression
Not needing much sleep	Low in energy
Feeling emotionally high	Low motivation
Energetic or very active	Feeling tired
Ideas flowing too fast	Difficulty concentrating
Difficulty concentrating	Negative thoughts
Senses seem brighter	Feeling sad or wanting to cry
Spending money more freely	Less talkative
Irritable	Interrupted sleep

Adapted from Lobban et al. 2011, p. 416-417. Copyright 2011 by Elsevier B.V.

4.4 Cognitive behavioral therapy (CBT)

CBT employs a combination of cognitive and behavioral techniques to target maladaptive thinking, deficits and factors predisposing to and perpetuating depressed mood. It focuses on the reciprocal relationships between thinking, behavior and emotions to decrease symptoms and relapse risk. Bipolar patients share many of the common cognitive distortions and attitudes described in unipolar patients. CBT could speed recovery from depression and prevents the cascade of isolated manic symptoms into full-blown episodes.

4.5 Family-focused therapy (FFT)

The entire family is considered as 'the client' even a single member is diagnosed as bipolar disorder. FFT includes a combination of psychoeducation and skills-based training that improve communication and problem-solving skills to the patient and family. Thereby reduce family stress and interactions and moderate relapse.

4.6 Interpersonal and social rhythm therapy (IPSRT)

IPSRT was developed from amalgamation of interpersonal therapy addressing losses, role conflicts, quality of social relationships and social roles, and other interpersonal problems with the identification of behaviors and management of potential precipitants of rhythm disruption by stabilizing circadian rhythms via stabilizing social rhythms. The re-establishment of routine and regular activity for those behaviors that recur at least once per week is a primary goal in treatment.

4.7 Online interventions

Online and digital strategies are worldwide popular technique but in Bangladesh it was popularly introduced in COVID period. Internet and mobile health interventions have shown good adherence to validated psychological health principles, good acceptability to patients, ease of access and ease of use.

Table 18: Recommendations for adjunctive psychological treatments in bipolar disorders

First-line	Psychoeducation (PE), individual or group format EWS interventions
Second-line	Cognitive behavioral therapy (CBT) Family-focused therapy (FFT), Family/caregiver interventions
Third- line	Interpersonal and social rhythm therapy (IPSRT) Peer support
Others	Dialectical behavioral therapy (DBT) Online interventions

Part 5
Other issues

5.1 Prognosis of bipolar disorder

More than 90% of individuals who have a single manic episode go on to have recurrent mood episodes. Within 2 years of first manic episode 40-50% of patients experience another manic episode. The average length of manic episode is about 6 months. Over a 25-year-follow-up, on average bipolar patients experience about 10 further episodes of mood disturbance.

Morbidity and mortality rates are quite high in terms of lost work, lost productivity, effect on marriage and approximately 25-50% patients attempt suicide and completed suicide rate is 10%. In bipolar II disorder depressive episodes are more enduring and disabling and suicide rate may be higher than individuals with bipolar I disorder.

Good prognostic factors include, episodes of short duration, later age of onset, few psychotic symptoms, few comorbid physical problems, good treatment response, compliance, social support, absence of substance abuse, etc.

5.2 Focus Group Discussion (FGD) findings

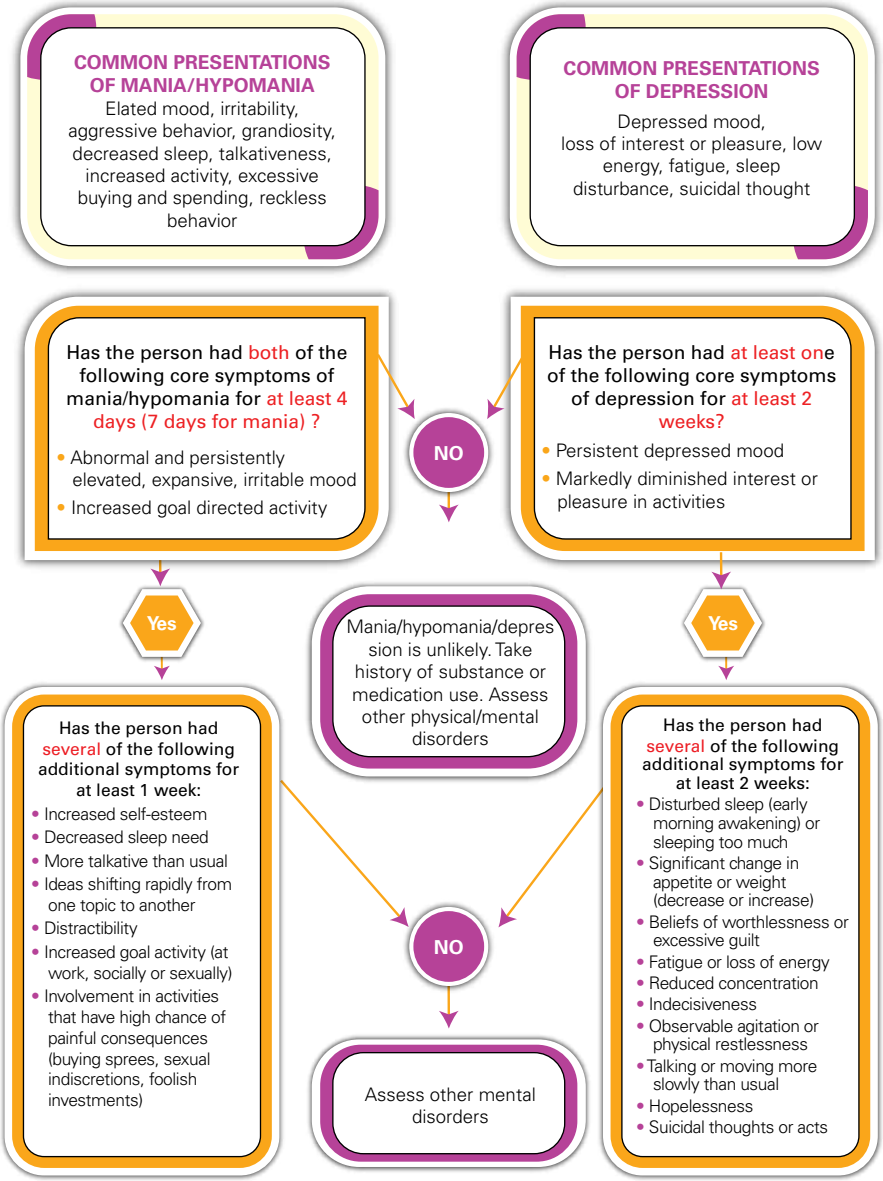
Although there is limited evidence to suggest antipsychotic long-acting injections (LAIs) in the treatment of bipolar disorders, it has emerged from the FGDs that psychiatrists use them occasionally. LAIs should only be used when there is considerable chance of non-compliance or the patient lacks social support. LAIs effectively prevent recurrence of manic episodes but not depressive episodes and may increase risk of depression. Also, there is no added benefit of LAIs over oral treatment in bipolar disorders.

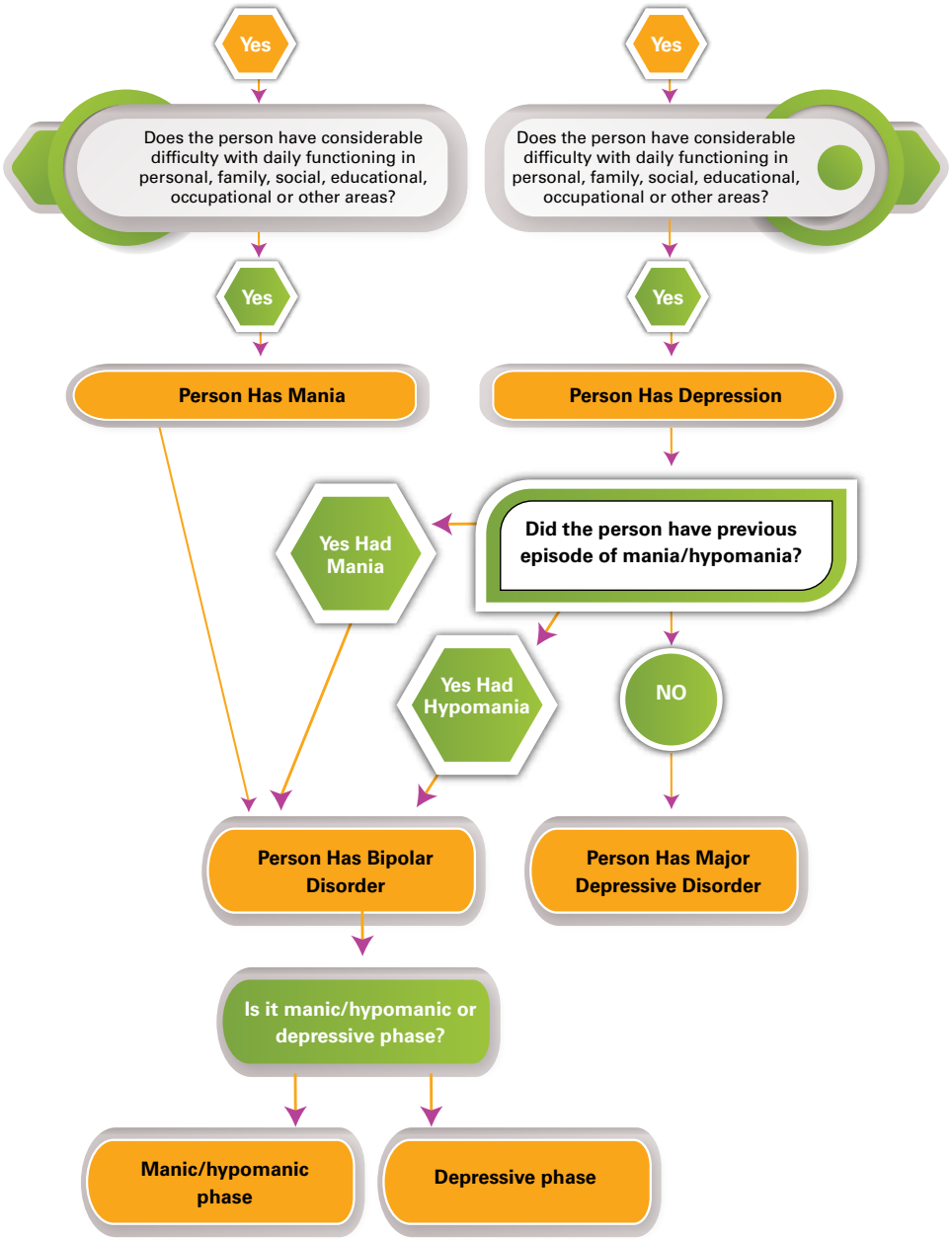
Most guidelines do not recommend haloperidol as a first-line agent in the treatment of bipolar disorders because of its side-effects profile and risk of depression. However, in Bangladesh the drug is widely available at low price. We suggest judicious use of haloperidol when cost and availability of other drugs and laboratory facilities could be an issue.

Prophylactic use of anticholinergic drugs to prevent EPS while on antipsychotic is recommended in situations where continuity of care is at stake.

5.3 Management in non-specialized setting

Bipolar disorder management in Primary Health Care:




Yes
Does the person have considerable difficulty with daily functioning in personal, family, social, educational, occupational or other areas?
Yes
Person Has Mania
Yes
Does the person have considerable difficulty with daily functioning in personal, family, social, educational, occupational or other areas?
Yes
Person Has Depression
Did the person have previous episode of mania/hypomania?
Yes Had Mania
Yes Had Hypomania
NO
Person Has Bipolar Disorder
Person Has Major Depressive Disorder
Is it manic/hypomanic or depressive phase?
Manic/hypomanic phase
Depressive phase

Management of manic/hypomanic phase:

Assessment: Thorough history taking with mental state examination. Stop antidepressant drugs, if patient is receiving any.

Mania: Have several of the following symptoms occurred simultaneously, lasting for at least 1 week:

Elevation of mood and/or irritability; Decreased need for sleep; Increased activity; Feeling of increased energy; Increased talkativeness or rapid speech; Impulsive or reckless behaviours such as excessive spending; Making important decisions without planning and sexual indiscretion; Loss of normal social inhibitions resulting in inappropriate behaviors; Being easily distracted; Unrealistically inflated self-esteem

Treatment for mania/hypomania:

Non-pharmacological:

- Psychoeducation to the person and their carers about treatment options and medications.
- Ensure fluid and nutrition.
- Reduce provocation for aggressive behavior and strengthen social supports.

Pharmacological:

- Valproate/Haloperidol:Use either valproate or haloperidol in adequate dose and for adequate duration **(see management chapter)**
- Add clonazepam – if sleep problem, restlessness, aggression.
- DO NOT manage the symptoms with ineffective treatments.
- Offer regular follow-up.
- Refer to a psychiatrist, if doesn't improve after 4-6 weeks of starting treatment.

Valproate/Haloperidol

Valproate: Start at 600-1000 mg at bedtime. Maximum dose 60 mg/kg body weight.

Haloperidol:Start at 10-15 mg once or twice daily. If no response in two weeks refer to psychiatrists. Add procyclidine - 10 mg daily in divided dose (1+1+0) to prevent extrapyramidal side effects.

Clonazepam: Add clonazepam for short duration. Give up to 4 mg daily.

- Symptoms usually remit 2-4 weeks of starting treatment.
- Need to continue for at least 3-6 months after resolution of symptoms

Management of bipolar depression:

Assessment: Thorough history taking with mental state examination. (See assessment part, pg. 20)

Treatment for bipolar depression:

Non-pharmacological:

- Psychoeducation to the person and their carers about treatment options and medications
- Reduce stress and strengthen social supports.
- Promote functioning in daily activities and community life.
- Always assess suicide risk during visit, if significant – refer the patient to a psychiatrist.

Pharmacological:

- Quetiapine: Use quetiapine to treat bipolar depression **(see management part)**
- DO NOT manage the symptoms with ineffective treatments.
- Offer regular follow-up

5.4 Medicolegal issues

If a person with bipolar disorder (and some other mental disorders) faces discrimination at work because of his/her illness or if work conditions prevent recovering from illness (like night shift duty), he/she is entitled to get protection under the Bangladesh Rights and Protection of Persons with Disabilities Act 2013.

Person with bipolar disorder may invest unwisely, take financial loan, spend recklessly and get involved in extravagant charity activities during manic/hypomanic episodes. Family education is important in this aspect. Proper documentation of patient's illness can help the patient in future legal proceeding.

When a patient with mental disorder absconds from psychiatric hospitals, especially closed wards, the responsibility falls into the hands of hospital authorities under the existing laws. The absconder may not take care of self and may be at risk of harm to self, others, and property. Law enforcement agencies should be informed as early as possible in such case.

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Annexures

a. Drug dosage in bipolar disorder

Table 19: Drug doses in acute mania (per day)

Generic name	Initial dose	Usual maintenance dose	Maximum dose
Mood stabilizers			
Lithium	Start 400 mg at night (200 mg in the elderly)	Maintain serum trough level 0.8 to 1.2 mmol/L. Reduce to 0.6 to 0.8 mmol/L. once euthymia is achieved.	1.2 mmol/L
Valproate	Extended-release formulation 600-1000 mg once daily 20-30 mg/kg loading dose in inpatients	1000-2000 mg Serum level 50-125 mcg/ml	60 mg/kg
Carbamazepine	100-200 mg b.i.d. XL - 200 mg b.i.d.	400-500 mg b.i.d. XL - 400-600 mg b.i.d.	1600 mg
Antipsychotics			
Aripiprazole	15 mg	15-30 mg	30 mg
Chlorpromazine	25 mg t.i.d. or 75 mg o.d.	75-300 mg	1000 mg
Haloperidol	5-10 mg	5-10 mg	15 mg
Olanzapine	15 mg	5-20 mg	20 mg
Paliperidone	6 mg	3-12 mg	12 mg
Quetiapine	IR – 100 mg/day increasing to 800 mg as required XL – 300 mg day increasing to 600 mg on day two	400-800 mg	800 mg
Risperidone	2-3 mg	2-6 mg	6 mg
Clozapine	12.5 mg	12.5 – 400 mg	900 mg
Others			
Lorazepam			Up to 4 mg
Clonazepam			Up to 8 mg

Source: British National Formulary - BNF 81, March 2021

Table 20: Suggested doses for acute bipolar depression (per day)

Generic name	Initial dose	Usual maintenance dose	Maximum dose
Lithium	Start 400 mg at night (200 mg in the elderly)	S. lithium level - 0.6 to 0.8 mmol/L	1.2 mmol/L
Valproate	250 mg t.i.d. Extended-release formulation 600-1000 mg once daily	1000-2000 mg Serum level 50-125 mcg/ml	60 mg/kg
Quetiapine	100 mg increasing to 300 mg by day 2 or 3	300-600 mg	600 mg
Olanzapine	5-15 mg	5-20 mg	20 mg
Olanzapine/ fluoxetine	5/20 or 10/40 mg	5/20 or 10/40 mg	-
Lamotrigine	25 mg	50-200 mg	400 mg
Lurasidone	20 mg	20-60 mg	120 mg
Antidepressants (always use with an anti-manic agent)			
Sertraline	50 mg	50-150 mg	200 mg
Fluoxetine	20 mg	20-60 mg	80 mg
Venlafaxine	37.5 mg b.i.d.	75-225 mg	375 mg
Agomelatine	25 mg	25-50 mg	50 mg

Source: British National Formulary - BNF 81, March 2021

b. Side effects of drugs used in mania

Table 21: Side effects of drugs used in mania

	Common (incidence ‡1%)	Uncommon or rare (incidence <1%)
Lithium	GIT: nausea, vomiting, epigastric discomfort, dry mouth, metallic taste, diarrhea, weight gain CNS: fatigue, headache, difficulty concentrating, vertigo, fine tremor Skin: dry skin, exacerbation of psoriasis or acne, rash Metabolic: hypothyroidism hypermagnesemia, hypercalcemia Other: benign ECG changes, leukocytosis	Nephrogenic diabetes insipidus, hyperparathyroidism, memory impairment, hair loss, arrhythmias, hyperthyroidism
	Lithium toxicity: signs include loss of balance, increasing diarrhea, vomiting, anorexia, weakness, ataxia, blurred vision, tinnitus, polyuria, coarse tremor, muscle twitching, irritability and agitation. Drowsiness, psychosis, disorientation, seizures, coma and renal failure may occur	
Valproate	GIT: nausea, vomiting, abdominal cramp, anorexia, diarrhea, indigestion (especially with non-enteric coated preparations), increased appetite and weight gain CNS: sedation, tremor Skin: transient hair loss Other: thrombocytopenia, elevated liver transaminases, asymptomatic elevations of ammonia	Severe hepatic dysfunction, pancreatitis, extrapyramidal syndrome, hyperammonemia encephalopathy

	Common (incidence ‡1%)	Uncommon or rare (incidence <1%)
Carbamazepine	GIT: dry mouth, vomiting, diarrhea, anorexia, constipation, abdominal pain CNS: dizziness, headache, ataxia, drowsiness, blurred vision, diplopia Skin: rash	Agranulocytosis, aplastic anemia, severe skin reactions (Including Stevens-Johnson syndrome), SIADH, arrhythmias, orofacial dyskinesias, hepatitis
Lamotrigine	GIT: dry mouth, nausea, vomiting CNS: diplopia, dizziness, ataxia, blurred vision, headache, irritability, somnolence, tremor, asthenia, insomnia Skin: maculopapular rash, Stevens-Johnson syndrome (0.3–2.0% in children) * Other: arthralgia	Hepatic failure, blood dyscrasias, lupus-like reaction. Severe skin reactions including Stevens-Johnson syndrome and Lyell syndrome
Atypical antipsychotics	Metabolic: weight gain, dyslipidemia, hyperglycemia, hyperprolactinemia Extrapyramidal symptoms: tremor, akathisia, rigidity, slowing, dystonia Anticholinergic reactions: constipation, dry mouth, blurred vision, urinary retention Other: muscle cramps, sedation, increased appetite, sexual dysfunction, GI upset, peripheral oedema, nausea, cerebrovascular events, especially in the elderly (stroke, TIA), orthostatic hypotension, tachycardia	Jaundice, neuroleptic malignant syndrome, seizures, tardive dyskinesia, ECG changes (increased QT interval), SIADH, temperature irregularity, blood dyscrasias, arrhythmias, cardiac arrest, seizures, hepatic fibrosis, lupus Clozapine: agranulocytosis (1%), myocarditis, cardiomyopathy, seizures

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

*Risk is greatest with high initial doses or when combined with valproate.
In addition, many medications have the potential to cause a hypersensitivity syndrome (fever, severe skin reactions, lymphadenopathy, hepatitis, hematological abnormalities, facial oedema).

c. Monitoring drug therapy

i. Investigations prior to starting and while monitoring antipsychotic therapy

Pre-antipsychotic evaluation

- Complete blood count (CBC)
- Plasma glucose
- Liver function tests (LFTs)
- Renal function tests (s. creatinine, eGFR, s. electrolytes)
- Blood lipids (cholesterol, triglycerides)
- Prolactin
- ECG
- Pulse, BP, weight, BMI

Monitoring of antipsychotic therapy

- CBC – yearly as part of a routine physical health check and to detect bone marrow suppression
- Plasma glucose (and HbA1c) – at 4-6 months then yearly. For olanzapine, clozapine at 1 month, 4-6 months and yearly.
- LFTs – yearly.
- Blood lipids – at 3 months then yearly. For olanzapine, clozapine 3 monthly for first year.
- Prolactin – at 6 months then yearly. Haloperidol, risperidone particularly associated with hyperprolactinemia.
- ECG – yearly
- Creatinine phosphokinase (CPK) – if NMS is suspected.

Monitor and record the followings during dose titration and then regularly and systematically throughout treatment:

- Pulse and blood pressure
- Weight or BMI
- Response to treatment, including changes in symptoms and behavior
- Side effects and their impact on physical health and functioning
- Emergence of movement disorders
- Adherence

ii.Investigations prior to starting and while monitoring valproate therapy

Pre-valproate evaluation

- Complete blood count (CBC)
- Liver function tests (LFTs)
- Urine pregnancy test (in case of women)
- Plasma glucose
- Blood lipids (cholesterol, triglycerides)
- Pulse, BP, weight, BMI

Monitoring of valproate therapy

- Routine monitoring of CBC and liver function tests are not recommended. May be done every 6-12 monthly in patients receiving long term valproate therapy.
- The therapeutic range for serum valproic acid level is 50-100 µg/mL
- Serum valproate levels during initial titration are to be done after 5 days of a stable dose.
- When to collect the sample: sample may be collected after 12 hours in case patient is receiving immediate release formulation; however, if the patient is taking extended-release formulation, blood sample need to be collected 21-24 hours after the last dose to estimate the serum valproate levels

Adapted from Shah, Grover & Rao (2017), p. S55.

iii. Investigations prior to starting and while monitoring carbamazepine therapy

Pre-carbamazepine evaluation

- Complete blood count (CBC)
- Liver function tests (LFTs)
- Urine pregnancy test (in case of women)
- Renal function tests (RFTs)
- Serum electrolytes (in case of elderly)
- Plasma glucose
- Blood lipids (cholesterol, triglycerides)
- Pulse, BP, weight, BMI

Monitoring of carbamazepine therapy

- Monitoring of CBC including platelet counts and liver function test need to be done every 2 weekly during the initial 2 months of treatment
- After first 2 months: if no abnormalities are noted during the first 2 months, than the CBC and liver function tests may be done every three monthly.
- The therapeutic range for serum carbamazepine level is 4-12 µg/ml
- Serum carbamazepine levels during initial titration are to be done after 5 days of a stable dose.

When to collect the sample: sample may be collected after 12 hours of the last dose

Adapted from Shah, Grover & Rao (2017), p. S55.

iv. Investigations prior to starting and while monitoring lithium therapy

Pre-lithium evaluation

- Serum creatinine, eGFR
- Serum electrolytes
- Thyroid function tests
- Complete blood count (CBC)
- Urine pregnancy test (in case of women)
- ECG
- Plasma glucose
- Blood lipids (cholesterol, triglycerides)
- Pulse, BP, weight, BMI

Monitoring of lithium therapy

- During the initial phase of illness, serum lithium levels must be done after 5 days of a stable dose.
- Sample for serum lithium levels must be taken 12-14 hours after the last dose of lithium
- If the medication is being given as b.i.d. or t.i.d. dose, the morning dose need to be withheld prior to collection of blood sample for serum lithium level

Monitoring of side effects: at every visit enquire about polyuria/ polydipsia, gastrointestinal side effects; Check for tremor, dysarthria, ataxia

Monitoring of serum lithium levels: Once the dose of lithium has been stabilized the serum levels must be done once in every 6 months; more frequent monitoring (e.g., 3 monthly) may be done in elderly and those receiving with concurrent medications like diuretics and in those with renal impairment. Monitor lithium dose and plasma lithium levels more frequently if urea levels and creatinine levels become elevated, or eGFR falls over 2 or more tests, and assess the rate of deterioration of renal function.

Investigations to be repeated 6-12 monthly as indicated: 24-hour urine volume, urinary proteins, serum creatinine, thyroid function tests, eGFR, S. Calcium

Adapted from Shah, Grover & Rao (2017), p. S54.

Table 22: Summary of treatment options for bipolar disorders

Biological treatments	Psychological treatments	Social treatments	Lifestyle modifications
Mood stabilizers Antipsychotics Antidepressants ECT	Cognitive behavior therapy Interpersonal therapy Coping strategies and stress management therapy	Family education Supportive group Social welfare	Exercise Diet Smoking cessation Managing substance abuse Sleep pattern Social rhythm therapy

Table 23: Summary of biological treatments recommended for bipolar disorders

Bipolar I Disorder			
Phases of Illness	**First-line**	**Second-line**	**Third-line**
Acute Mania/ Hypomania	(Listed hierarchically) **Monotherapy** Valproate Lithium Haloperidol Risperidone Quetiapine Aripiprazole Paliperidone **Combination Therapy** Haloperidol + Valproate/Lithium Risperidone + Lithium/Valproate Quetiapine + Lithium/Valproate Aripiprazole + Lithium/Valproate	(Listed hierarchically) **Monotherapy** Olanzapine Carbamazepine ECT **Combination Therapy** Olanzapine + Lithium/Valproate Lithium + Valproate	**Monotherapy** Chlorpromazine Clonazepam Clozapine **Combination Therapy** Carbamazepine + Lithium/Valproate
Bipolar I Depression	(Listed hierarchically) **Monotherapy** Quetiapine Lithium Lamotrigine Lurasidone **Combination Therapy** Lurasidone + Lithium/Valproate Lamotrigine (adj)	(Listed hierarchically) **Monotherapy** Valproate ECT **Combination Therapy** Olanzapine + Fluoxetine SSRI (adj)	**Monotherapy** Olanzapine **Combination Therapy** Aripiprazole (adj) Armodafinil (adj) Carbamazepine Levothyroxine (adj) Olanzapine

Maintenance Phase	(Listed hierarchically) **Monotherapy** Valproate Lithium Quetiapine Lamotrigine Aripiprazole **Combination Therapy** Quetiapine + Lithium/Valproate Aripiprazole + Lithium/Valproate	(Listed hierarchically) **Monotherapy** Olanzapine Risperidone LAI Carbamazepine **Combination Therapy** Risperidone LAI (adj) Lurasidone + Lithium/Valproate	**Combination Therapy** Aripiprazole + Lamotrigine Clozapine (adj) Olanzapine + Fluoxetine
Bipolar II Disorder			
Bipolar II Depression	Quetiapine	Lithium Lamotrigine ECT Sertraline (for pure depression) Venlafaxine (for pure depression)	Agomelatine (adj) Valproate Fluoxetine (for pure depression) T3/T4 thyroid hormones (adj)
Maintenance Phase	Quetiapine Lithium Lamotrigine	Venlafaxine	Carbamazepine Valproate Escitalopram Fluoxetine Risperidone (prevention of hypomania)

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