

Clinical Practice Guidelines for Management of Bipolar Disorder

Nilesh Shah, Sandeep Grover¹, G. Prasad Rao²

Department of Psychiatry, L. T. M. Medical College and General Hospital, Sion, Mumbai, ¹Department of Psychiatry, Post Graduate Institute of Medical Education and Research, Chandigarh, ²Schizophrenia and Psychopharmacology Division, Asha Hospital., Banjara Hills, Hyderabad, India

Participants of expert group on CPG for Bipolar Affective Disorder

Vidhyadhar Watve, Mrugesh Vaishnav, Vivek Kirpekar, D.K. Sharma, Mahendra Jain, Asim Kumar Mallick, C.L. Narayan, Anup Bharti, Madhu Nijhawan.

INTRODUCTION

Bipolar disorder (BPAD) is a serious mental disorder characterized by episodes of depression, hypomania/mania and mixed episodes, with interepisodic recovery. However, many patients with BPAD continue to exhibit residual symptoms in the interepisodic period. The illness usually starts in adolescence or early adulthood and has significant negative impact on the life of the sufferer and their caregivers. Patients with BPAD encounter educational difficulties, job related problems, interpersonal difficulties, psychosocial dysfunction, disability, marital problems, multiple suicidal attempts, completed suicide and medication side effects. Additionally patients with BPAD have high rates of physical and psychiatric comorbidity. The prevalence rates of BPAD vary from country to country. A large multinational study suggests that lifetime prevalence of BPAD-I ranges from 0-1% with a mean of 0.6 (SD-0.4). The prevalence rate of BPAD-II ranges from 0 to 1.1% with a mean of 0.4 (SD-0.3). Additionally a significant proportion of patients have been

shown to have subthreshold BPAD with a range of 0.1 to 2.4% with a mean of 1.4 (SD-0.8). There is no nationwide study to evaluate the prevalence rates of BPAD in India. In a country like India, patients have limited resources, poor knowledge about the disorder and treatment; have inadequate access to the health care facilities, which makes treatment of BPAD a challenge. Indian Psychiatric Society (IPS) made first attempt to formulate Clinical Practice Guidelines (CPGs) for management of BPAD in 2005. Since then, over the last one decade there have been several developments, especially in the form of emergence of new evidence for some of the pharmacological agents. Accordingly, these new guidelines attempt to update the previous guidelines published by IPS. These guidelines should be read along with the earlier version of the CPGs, published by IPS in 2005.

ASSESSMENT AND EVALUATION [TABLE-1]

Assessment of patients is an ongoing process and comprehensive assessment of a patient involves the assessment of patients themselves and their caregivers. The role of taking a proper history from the patient and all the available resources cannot be over-emphasized. In addition to the history taking, proper attention must be paid to the mental status examination. Diagnosis of BPAD is to be made on the basis of current diagnostic criteria, because a diagnosis based on diagnostic criteria can be considered more reliable, facilitates communication among various clinicians and paves the way for management on the basis of evidence based recommendations. It is important to remember that especially during the initial part of the illness, the symptoms may be confusing and at times it may be difficult to distinguish symptoms of mania from other psychiatric syndromes like schizophrenia, acute

Address for correspondence:

Dr. Nilesh Shah, Department of Psychiatry, L. T. M. Medical College and General Hospital, Sion, Mumbai - 400 022, Maharashtra, India.

E-mail: drnilshah@hotmail.com,

Dr. Sandeep Grover, Additional Professor, Department of Psychiatry, PGIMER, Chandigarh, India.

E-mail: drsandeepg2002@yahoo.com

Access this article online

Website:

www.indianjpsychiatry.org

DOI:

10.4103/0019-5545.196974

Quick Response Code



This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Shah N, Grover S, Rao GP. Clinical Practice Guidelines for Management of Bipolar Disorder. Indian J Psychiatry 2017;59:51-66.

Table 1: Components of assessment and evaluation**Basic assessments**

- Comprehensive assessment of both patients and caregivers
- Complete history with information from all possible sources in terms of type of first episode in lifetime, predominant polarity of illness, duration and severity of episodes, inter-episodic recovery, presence or absence of suicidal behaviour, violence and agitation, seasonal variation in onset of symptoms, presence of rapid cycling and ultra-rapid cycling features
- History taking focusing on precipitating factors- psychosocial stressors, disturbances in biological rhythms
- Physical examination- record data such as blood pressure, weight and wherever indicated body mass index and waist circumference
- Mental state examination
- Establish diagnosis according to current diagnostic criteria
- Differential diagnosis by ruling out secondary affective disorder
- Proper assessment of the current polarity of the illness
- Evaluate the risk for suicidal behaviour- suicidal ideations, intent, plans; access to means for suicide, possible lethality in case patient uses the means, psychotic symptoms in the form of commanding hallucinations, severe anxiety, comorbid substance use, past history of suicidal attempts and non-suicidal self-harming, family history of self-harm and completed suicide
- Areas to be evaluated during the current episode: symptom-severity, symptom-dimensions, comorbid physical and psychiatric including substance use conditions, risk of harm to self and others, level of functioning and socio-cultural milieu of the patient
- Past treatment history: type of medications used, response to treatment, duration of use of treatment, side effects experienced and reasons for discontinuation
- Basic investigations: haemogram, blood sugar and lipid levels, liver functions, renal functions, electrocardiogram
- Assessments of caregivers: knowledge about illness, knowledge about treatment, their attitudes and beliefs regarding treatment, the impact of the illness on them and their personal and social resources in the form of burden, distress, stigma, personal and marital life
- Ongoing assessments: response to treatment, side effects, treatment adherence, issues of marriage and pregnancy, disability, other health-care needs, ease of access to treatment team, therapeutic alliance, etc.

Additional/Optional assessments

- Use of standardized rating scales to rate various aspects of the illness
- Psychological testing for cognitive functions
- Neuroimaging especially in those with atypical features, neurological signs, non-response to treatment, later age of onset and elderly patients

and transient psychosis and other psychiatric disorders. A possibility of substance induced disorder or disorder secondary to organic causes is to be considered, when the symptoms are atypical or there is evidence of the use of substance or underlying organic causes. Occasionally establishing the definite diagnosis of BPAD may require time.

The assessment may cover history of number of previous episodes, type of first episode in lifetime, predominant polarity of illness, duration and severity of episodes, inter-episodic recovery, presence or absence of suicidal behaviour, violence and agitation, seasonal variation in onset of symptoms, presence of rapid cycling and features of ultra-rapid cycling. Assessment of current episode may also focus on the issues of severity of symptoms, suicidality and agitation. Understanding the role of various psychosocial

stressors and biological rhythms in onset of illness, precipitation of relapse and continuation of symptoms need to be understood thoroughly.

A thorough assessment includes assessment of comorbid psychiatric and medical conditions. It is important to remember that many a times; comorbidity is not very evident during the acute episode of illness. The comorbid conditions become more evident when the patient has come out of the acute episode of the illness. Evaluation of comorbid substance abuse needs to consider the type and frequency of substance abuse. If the patient does not provide adequate information about the substance use pattern, but there is high index of suspicion, urine or blood screens (with prior consent) can be used to confirm the existence of comorbid substance use/dependence, wherever such facilities are available. Functional impairment in various domains of life including impact of the illness on the family functioning and psychosocial impact of the illness on the caregivers is not to be neglected. A thorough physical examination need to be done to rule out presence of any physical illness and also to rule out episodes secondary to physical illnesses. This may be supplemented by the judicious use of investigations. Depending on the feasibility, unstructured clinical assessments need to be supplemented by documentation of severity and extent of symptoms on appropriate standardized rating scales. Patients with bipolar disorders also have cognitive deficits. Accordingly, depending on the need, detailed cognitive testing may be undertaken. The use of neuroimaging may be indicated in those with atypical features, neurological signs, non-response to treatment and having first episode of illness at a later age and elderly. Caregiver's assessment may involve evaluation of their knowledge about illness, knowledge about treatment, their attitudes and beliefs regarding treatment, the impact of the illness on them and their personal and social resources in the form of burden, distress, stigma, personal and marital life etc.

In case patient has received treatment in the past, then it is important to record the type of medications used, response to treatment, duration of use of treatment, side effects experienced and reasons for discontinuation.

Importance of ongoing assessment cannot be underestimated. With progress in treatment, new issues like response to treatment, side effects, treatment adherence, marriage, pregnancy, disability, other health-care needs, ease of access to treatment team and therapeutic alliance may need to be assessed from time to time.

FORMULATING A TREATMENT PLAN [FIGURE 1]

Formulation of treatment plan will involve decision making about the treatment setting, treatments to be used and areas to be addressed. Treatment plan need to be formulated in

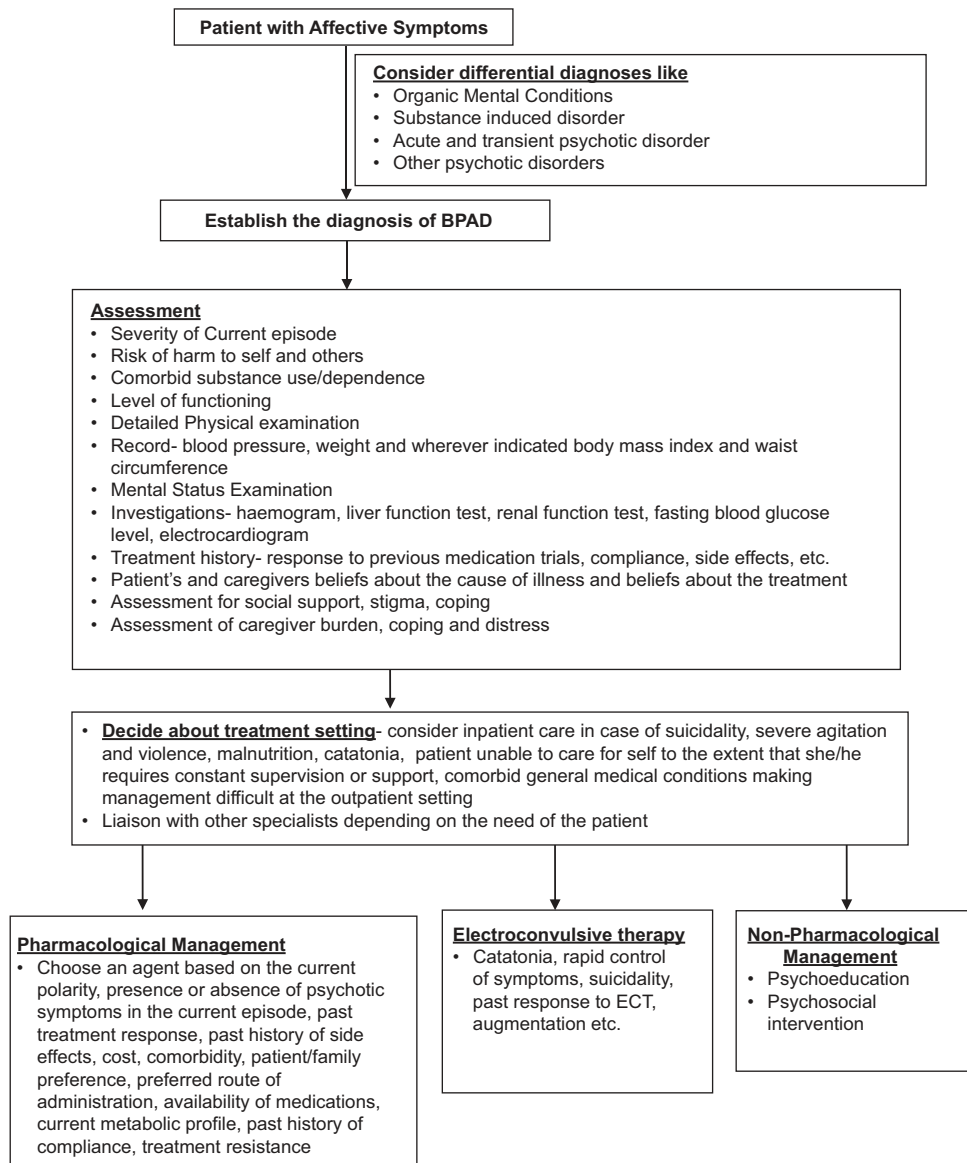


Figure 1: Initial evaluation and management plan for schizophrenia

consultation with patients, caregivers and other members involved in the treatment team. Treatment plans may be guided by the needs and be practical, feasible and flexible. Further, the treatment plan is to be re-evaluated from time to time and be modified as per the needs.

CHOICE OF TREATMENT SETTINGS

In general, most of the patients with BPAD are managed on the outpatient setting. However, some patients may require inpatient care. Whenever possible patient admitted to the inpatient setting should have accompanying family caregivers. In case inpatient care is required and such facilities are not available, then the patient and/or family need to be informed about the need for inpatient care and patient may be referred to the nearest available inpatient facility and admission may be facilitated.

OPTIONS FOR MANAGEMENT OF BIPOLAR DISORDER

Treatment options for management of BPAD can be broadly classified as mood stabilizers, antidepressants, antipsychotic medications, electroconvulsive therapy (ECT), adjunctive medications and psychosocial interventions [Table-2]. Use of various treatment options is guided by the phase of illness (mania/hypomania/depression/mixed) in which patient presents to the clinician and past treatment history.

PHARMACOLOGICAL MANAGEMENT OF BIPOLAR DISORDER

The mainstay of management of BPAD is mood stabilizers. The available mood stabilizers include lithium, valproate, lamotrigine, carbamazepine/oxcarbazepine and topiramate.

Lithium

Lithium is the oldest mood stabilizer used in the management of BPAD. It has been found to be efficacious in management of acute episode of either polarity and has been found to be efficacious in prevention or relapse of episodes of either polarity. Additionally, it has been shown to have a role in prevention of suicide in patients with BPAD.

Prior to starting lithium, history need to be reviewed for the presence of physical illnesses like renal dysfunction, thyroid dysfunction and cardiac conduction abnormalities. Additionally information needs to be reviewed for presence of dermatological diseases. In case of women, last menstrual period is to be ascertained and if required urine pregnancy test need to be done. Further, prior to starting lithium, patients need to be educated about the various side effects of lithium, use of salt-restricted diet and avoidance of medications (diuretics, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, etc.) which can increase serum lithium levels. Patients also need to be informed to avoid dehydration. Whenever lithium is started, it need to be started in low doses, preferably in divided doses and the dose need to be titrated upwards with monitoring of serum lithium levels. As steady state levels of lithium are achieved after about 5 days of starting lithium or dose increment, the levels are be done after 5 days of start of treatment or change in the dose. However, the levels may be checked earlier if patient manifests features of toxicity. The serum levels of lithium, which are usually required for management of acute episode, are in the range of 0.6 to 1.0

Table 2: Options for management for Bipolar disorder

Mood Stabilisers

- Lithium
- Divalproex/valproate
- Carbamazepine/Oxcarbazepine
- Lamotrigine
- Topiramate
- Gabapentin

Antidepressants

- Tricyclics, Selective serotonin reuptake inhibitors, Serotonin and nor-epinephrine reuptake inhibitors, bupropion, mirtazapine, etc.

Antipsychotic medications

- First-generation antipsychotic medications (Oral/parenteral/depot or long acting- preparations)
- Second-generation antipsychotic medications (Oral/parenteral/depot or long acting- preparations)

Somatic treatments

- Electroconvulsive therapy (ECT), transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS)

Adjunctive medications

- Anticholinergics, antidepressants, benzodiazepines, hypnotic-sedatives, anticonvulsants, lithium carbonate

Psychosocial interventions

- Social rhythm therapy, cognitive behavioural therapy, family intervention, cognitive remediation, individual therapy, group therapy, social skills training, vocational rehabilitation

Other measures

- Lifestyle and dietary modifications

meq/litre and for prophylaxis range from 0.6 to 0.8 meq/litre; however, few studies suggest that serum levels as low as 0.4 to 0.8 meq/litre may be sufficient for prophylaxis, albeit are associated with higher risk of relapse. Once the dose is stabilized, patient may be shifted to once a day dose to reduce the side effects and improve the medication compliance. Serum lithium levels may be monitored every 3-4 months. Renal function tests need to be monitored once in every 2-3 months during the initial 6 months of therapy and thyroid function tests need to be monitored once or twice during the first 6 months of treatment. Later, renal and thyroid function tests may be monitored once in 6 months to 1 year in clinically stable patients and more frequently if so indicated (see table-3). Lithium is usually preferred in patients who have classical mania, bipolar depression, predominant polarity of illness is that of depression, episodic course of illness, manic-depressive-euthymic course, non-rapid cycling course of illness, lack of mixed episode, older age of onset for BPAD, presence of family history of BPAD and presence of family history of lithium response.

Divalproex/valproate

Divalproex and its formulations (sodium valproate and valproic acid) have been found to be useful in the management of BPAD. It has been found to be efficacious

Table 3: Investigations prior to starting of lithium and while monitoring lithium therapy

Pre-lithium evaluation

- Serum Urea, Creatinine
- Serum electrolytes
- Thyroid function test
- May evaluate serum osmolality
- May evaluate 24 hour urine volume, proteins, creatinine, osmolality
- May calculate the eGFR
- Haemogram
- Urine Pregnancy test (in case of women)
- Electrocardiogram
- Fasting blood sugar
- Lipid Profile
- Anthropometry- height, weight, waist circumference

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 BD or TID 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 3-4 months; more frequent monitoring may be done in elderly and those receiving with concurrent medications like diuretics, and in those with renal impairment

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

in management of acute mania and mixed episodes. The evidence for its efficacy in acute depression is not as robust as that for lithium. It is also efficacious in prevention of mania and depression, when used during the maintenance phase. As with lithium, prior to starting valproate, clinicians need to review the medical history for presence of any hepatic, haematological and bleeding problems. Prior to starting of valproate, patient is to be educated about the side effects, especially about signs and symptoms of hepatic and haematological dysfunction. They need to be instructed to report to the clinicians at the earliest if these signs and symptoms emerge. Prior to starting valproate, it is important to investigate the patient for liver function test and haemogram. In young women, last menstrual periods need to be ascertained and if required urine pregnancy test need to be done to rule out pregnancy. As valproate is associated with weight gain and metabolic abnormalities, it may be a good practice to evaluate the lipid profile, fasting blood glucose levels and anthropometry (Table-4).

Usually valproate is started in low doses, i.e., 250 mg BD or 250 mg TID and titrated upwards with monitoring of side effects and serum levels. However, some of the studies have also evaluated rapid titration of valproate dose with initial dose of 20-30 mg/day and have shown that it is well tolerated. Maximum daily dose which is recommended is 60 mg/day but most patients do not require such high doses. The usual therapeutic serum levels which are considered to be efficacious vary from 50 to 100 µg/ml. Once the dose of valproate is stabilized, the dosing schedule need to be changed to OD or BD dosing to reduce the side effects and improve compliance. In case OD dosing is given, extended release formulation may be used. However, it is important to remember that the bioavailability of extended release formulations is about 15% less than the immediate release preparations and the dose is to be increased accordingly. Serum valproate levels are to be done after 5 days of starting or increase in the dose of valproate. The sample need to be collected after 12 hours in case patient is receiving immediate release formulation, however, if the patient is receiving extended release formulation, the sample may be collected after 21 to 24 hours (table-5). There is evidence to suggest that patients with BPAD-II, dysphoric or mixed mania, rapid cycling affective disorder, stable episode frequency, later age of onset of illness, shorter duration of illness, long and severe course of illness respond well to valproate. Other indicators for good response to valproate include presence of comorbid alcohol use disorder, mental retardation, anxiety and panic attacks, post-traumatic stress disorders, marked sleep disturbances, explosive dyscontrol and aggression and comorbid migraine.

Lamotrigine

The role of lamotrigine in management of BPAD has been well studied now and it has been shown to be efficacious in management of bipolar depression and prevention of

Table 4: Investigations prior to starting of valproate and while monitoring valproate therapy

Pre-valproate evaluation

- Haemogram
- Liver Function Test
- Urine Pregnancy test (in case of women)
- Fasting blood sugar
- Lipid Profile
- Anthropometry

Monitoring of valproate therapy

Routine monitoring of haemogram and liver function test is 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

Table 5: Investigations prior to starting of valproate and while monitoring valproate therapy

Pre-Carbamazepine evaluation

- Haemogram
- Liver Function Test
- Urine Pregnancy test (in case of women)
- Renal Function test
- Serum electrolytes (in case of elderly)
- Fasting blood sugar
- Lipid Profile
- Anthropometry

Monitoring of carbamazepine therapy

- Monitoring of haemogram 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 Haemogram 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

relapse of depression. However, the most dreaded side effect of lamotrigine includes skin rash, including Stevens - Johnson syndrome and toxic epidermal necrolysis. The skin lesions can occur any time during the therapy, but are more often reported during the initial phase of treatment and when used along with valproate. Evidence suggests that the risk of skin rash can be reduced by slow upward titration of the dose. Accordingly, while considering lamotrigine, patients need to be informed about the possibility of rash and told to contact the treating psychiatrist in case rash is seen. When the rash is more widespread, diffuse and associated with systemic symptoms like fever or sore throat, lamotrigine may be stopped. When initiated, lamotrigine may be started at the dose of 25 mg/day for initial 2 weeks, then it may be

given at the dose of 50 mg/day during the 3rd and 4th week. After that 50 mg/day can be increased per week depending on the therapeutic response.

Carbamazepine

Carbamazepine has been shown to be efficacious in the management of acute bipolar mania and prevention of relapse. Prior to starting carbamazepine, clinician needs to focus on the history of blood dyscrasias and hepatic dysfunction. When carbamazepine is considered, patients need to be informed about the signs and symptoms of hepatic dysfunction, haematological dysfunction and skin reactions and told to report to the psychiatrist if these symptoms emerge. Baseline investigation prior to starting of carbamazepine may include complete haemogram, liver function tests and renal function test (Table-5). When used in elderly serum electrolytes may also be done, in view of the risk of hyponatremia. Usual starting dose of carbamazepine is 200 mg/day given in divided doses and titrated upward slowly. Once the dose of 800-1000 mg/day is reached the increment of dose may be slower and the usual maintenance dose is about 1000 mg/day, but it can vary from patient to patient and may be 200 to 1600 mg/day. The carbamazepine therapeutic drug levels have not been established in patients with BPAD and the serum levels of 4-12 µg/ml, which is recommended for seizure disorders is commonly used. As with lithium and valproate the serum levels need to be done after 5 days of initiation of treatment or increment of dose.

Other anticonvulsants

There is lack of data in the form of double blind randomized controlled trials for Oxcarbazepine, but small open label studies suggests that it may be of some benefit as monotherapy or add-on therapy in patients with refractory mania. The data from open label studies suggest the usefulness of add-on therapy with topiramate in patients with bipolar depression. Studies which have evaluated the role of gabapentin in management of mania have yielded negative results.

Antipsychotics

Over the last decade or so, many large multicentric double blind placebo controlled and active comparator randomised controlled studies have evaluated the role of various atypical antipsychotics like olanzapine, quetiapine, aripiprazole, risperidone, paliperidone, amisulpiride, asenapine, ziprasidone and haloperidol etc. in the management of bipolar depression, bipolar mania and for maintenance phase treatment. Data from these studies suggest that antipsychotics like olanzapine, quetiapine, aripiprazole, risperidone, paliperidone and ziprasidone are effective in the management of acute mania. There is evidence for use of quetiapine monotherapy, and olanzapine and fluoxetine combination in the management of bipolar depression. There is evidence for lurasidone in the management of acute episode of bipolar depression. Olanzapine and quetiapine monotherapy or as adjunctive medications to lithium or

valproate have been shown to be efficacious in prevention of relapse of both depression and mania. Antipsychotics like long acting risperidone, ziprasidone have been shown to be beneficial in prevention of mania as monotherapy or as adjunctive medications to lithium or valproate.

Combination therapy

There is evidence to suggest that when lithium or valproate is combined with antipsychotics in the management of acute mania, the efficacy is higher and the onset of action is faster than that reported for single agent. Accordingly, depending on the severity of mania, combinations may be used.

Electroconvulsive Therapy (ECT)

There is evidence for use of ECT in the management of acute mania, mixed episode and bipolar depression. Indications for use of ECT are shown in Table-6.

Benzodiazepines

Studies have evaluated the efficacy of add-on benzodiazepines like clonazepam and lorazepam to lithium and current level of evidence suggests that the antimanic properties of these agents are difficult to distinguish from the sedative properties of these agents. Accordingly, these agents are considered to be adjunctive agents, which may be useful in management of acute episode. Further, there is evidence to suggest the beneficial role of lorazepam in the management of agitation and catatonia.

Other agents

Many other medications like calcium channel blockers, zonisamide, levetiracetam, acamprosate, omega-3 fatty acids, allopurinol etc, have been evaluated in small sample size trials as monotherapy or add on agents. However, available the evidence is not sufficient to recommend these medications as first line agents in management of bipolar mania and depression.

Antidepressants

Conventionally antidepressants have been used in the management of bipolar depression. However, over the last 2 decades or so, use of antidepressants in patients with bipolar

Table 6: Possible indications of use of ECT in patients of schizophrenia

- Bipolar depression not responding to adequate pharmacotherapy
- Bipolar mania not responding to adequate pharmacotherapy
- Catatonic symptoms
- Need for rapid control of symptoms
- Presence of suicidal behaviour which puts the life of the patient at risk
- Presence of severe agitation or violence which puts the life of others at risk
- Refusal to eat which puts the life of patient at risk
- History of good response in the past
- Augmentation of partial response to pharmacotherapy
- Not able to tolerate pharmacotherapy
- Treatment resistant illness
- Episodes of severe depression or mania during pregnancy

depression has emerged as a controversial topic in view of the risk of antidepressant-induced manic/hypomanic switch. Evidence from metaanalysis suggests that use of antidepressants along with mood stabilizers is superior to use of combination of a mood stabilizer and a placebo and is not associated with increased risk of manic switch. Most of the studies which have not found add-on antidepressants to be beneficial have involved paroxetine, hence, if one want to avoid use of an antidepressant, paroxetine is to be avoided. Among the various antidepressants, bupropion has been reported to be associated with lowest risk of antidepressant induced switch. However, it is important to remember that antidepressants should not be used as monotherapy, and in those with rapid cycling affective disorder and mixed episodes.

Adequate trial

The minimum recommended duration of treatment to consider it to be an effective trial for an acute manic episode is about 3-4 weeks. In case of bipolar depression, a 6 weeks trial is considered as an adequate trial.

NON-PHARMACOLOGICAL MANAGEMENT OF BIPOLAR DISORDER

Psychosocial management as an adjunct to pharmacotherapy has been shown to be of significant benefit during the management of acute phase of bipolar depression and maintenance phase of illness. Among the various psychosocial interventions, data supports the use of psychoeducation (individual and group), interpersonal and social rhythm therapy (IPSRT), cognitive behaviour therapy and family focused intervention. These psychosocial interventions have been shown to be associated with reduced risk of relapses, better functioning and better treatment adherence. The basic components of all these programs involve informing the patients about their illness, identifying the early signs of relapse, handling stress, maintaining social rhythms, addressing the interpersonal issues and expressed emotions, problem solving and enhancing medication and treatment adherence.

Psychoeducation for patients and or family (Table 7)

Psychoeducation may be considered both for the patient and family members (Table 7). The aim is to be to educate the patient and family about the illness. They may be provided simple explanations about the nature of the illness, treatment options, possible side effects of medications and likely length of treatment etc. Caregivers may also be provided with an opportunity to vent out their feelings and distress. Psychoeducation may also address the important issue of treatment adherence and identifying early signs of new episode. It is important to remember that psychoeducation is not a onetime event and prior to every session, feedback of the previous sessions may be taken and psychoeducation need to be tailored to the needs of the patient and the caregivers.

Table 7: Basic components of Psychoeducation

- Assessing the knowledge of the patient and caregivers about aetiology, treatment and prognosis
- Introduction of diagnosis
- Discussing the symptoms of depression, mania, hypomania and mixed episodes
- Providing information about aetiology
- Dealing with day today stress
- Providing information about the importance of stress management and regular habits
- Providing information about available treatment options, their efficacy/ effectiveness, side effects, duration of use
- Discussing about importance of medication and treatment compliance
- Providing information about possible course and long term outcome
- Discussing about problems of substance abuse, marriage and other issues
- How to detect early signs of relapse
- Discussing about Communication patterns, problem solving, disability benefits
- Discussing about relapse and how to identify the early signs of new episodes
- Improving insight into illness
- Handling expressed emotions and improving communication
- Enhancing adaptive coping to deal with persistent/residual symptoms
- Advise for lifestyle and dietary modifications

Interpersonal and social rhythm therapy (IPSRT)

This therapy is based on the theory that circadian rhythms in patients with BPAD are vulnerable to external factors and any disruption of circadian rhythms can precipitate an episode. Accordingly, it emphasizes on regularizing the social rhythms or routine of the patient and improving the interpersonal relationships of the patients so that they can derive more satisfaction in their social roles. The basic aim is to teach the patient as to how they can prevent the development of a new episode (Table-8). Patients are informed that new episodes can be precipitated by poor medication adherence, stressful life events and disruption of social rhythms. Patients are provided with skills as to how they can address interpersonal problems and issues in the social roles. They are also advised to maintain a regular daily routine and pay attention to the day to day stresses which can influence their daily routine and how they can minimize the impact of these day to day stressors on their daily routine.

Cognitive Behaviour therapy

Cognitive behaviour therapy (CBT) has been shown to be efficacious in the management of bipolar depression and during the maintenance phase of treatment. The basic goals of CBT is to educate the patient about the illness, teaching them cognitive behavioural skills for coping with their illness and psychosocial stressors and problems arising out of the same, enhance medication and treatment compliance, monitor the symptoms to prevent relapse.

Family focused interventions

Family forms an integral part of treatment in Indian setting. They are involved in treatment decision making, supervision of treatment and monitoring of treatment. However, family members can also contribute to relapse due to constant

criticism, poor supervision or over-involvement. High expressed emotion leads to increased risk of relapse and poor outcomes. Studies have shown that family focused interventions can reduce the chances of relapse, improve medication adherence and reduce the frequency of depressive episodes. Family focused interventions help the relatives and patients to integrate the experiences associated with mood episodes, acknowledging the vulnerability of having future episodes, accepting the need to continue with medications, educating the family about the difference in patients personality and BPAD, recognising and coping with stress and establishing a functional relationship (Table-9).

Advise for life style and dietary modifications

As it is well known that patients with BPAD are at increased risk for cardiovascular mortality and develop metabolic side effects due to use of psychotropic medications, all the patients need to be advised about life style and dietary measures to reduce the risk of metabolic side effects and cardiovascular morbidity and mortality. These include physical exercises, dietary modifications and abstinence from smoking, alcohol and other substances etc.

Rehabilitation

Rehabilitation programmes may be culturally moulded and adapted to the needs of patients and their families.

Treatment adherence

Mediation and treatment adherence is very important for management of patients with BPAD. Available evidence suggests that 20-60% of the patients with BPAD become non-compliant with medication and drop out of treatment. Hence, all efforts need to be made to enhance the medication compliance and treatment adherence. Measures which can help in improving the compliance are given in table-10.

MANAGEMENT OF DIFFERENT PHASES OF BIPOLAR DISORDER

Management of BPAD will depend on the phase of illness in which patient presents to the clinician, i.e., bipolar depression, bipolar hypomania/mania, first episode hypomania/mania, mixed episode or clinical remission. In addition to the phase of illness, factors which may help in deciding about the pharmacological agent include past history (number of episodes, type of episodes), comorbidity (comorbid psychiatric/physical disorders, substance dependence disorder), past treatment history (response, side effects) and clinical course (rapid cycling), associated symptoms (presence of psychotic symptoms) etc. In general based on the level of evidence, various pharmacological treatments are categorised as first line agents, second line agents and third line agents. Selection of an agent on the basis of current polarity and past history can be of

Table 8: Basic components of Interpersonal and social rhythm therapy (IPSRT)

Goals	<ul style="list-style-type: none"> Stabilize daily routines and sleep/wake cycles Understand the bi-directional relationship between moods and interpersonal events Minimize or remove the interpersonal problems related to grief, role transitions, role disputes, interpersonal deficits
Administered in 4 steps	
Step-1	<ul style="list-style-type: none"> Give rationale for IPSRT History taking with special focus on understanding the relationship of episodes with interpersonal problems and social routine Assess the patient's current and past interpersonal relationships Educating the patient about bipolar disorder Identify interpersonal problem areas to focus, for example grief, role transition, role dispute Agree on a topic to discuss Initiating the Social Rhythm Metric (i.e., quantify daily rhythms of life)
Step-2	<ul style="list-style-type: none"> Help the patient to establish a regular daily routine and resolve interpersonal problems Analyse the communication patterns, identify the problematic communication patterns, suggesting alternative communication methods, role play Maintaining social rhythms
Step-3	<ul style="list-style-type: none"> In the continuation or maintenance phase encourage the patient to use the skills learned in the previous phases of IPSRT
Step-4	<ul style="list-style-type: none"> Termination

Table 9: Basic components of Family focused interventions

<ul style="list-style-type: none"> Assessment of family Psychoeducation about symptoms, early recognition, etiology, treatment, adherence Communication skills training - behavioral rehearsal of effective speaking and listening strategies Accepting that patient is vulnerable for having future episodes Able to differentiate between patient's personality and bipolar disorder Recognising and coping with stress Problem-solving skills training Establishing and maintaining a functional relationship
--

Table 10: Measures which can improve medication compliance

<ul style="list-style-type: none"> Explain when and how often to take medicines Preferably give once a day dosing Prescribe minimum number of tablets and medications Always ask the patient about kind of formulation (e.g. tablet, capsule etc) which they would prefer to take Check the whole prescription to avoid duplication of medication Explain the patient/family that the beneficial effect will be seen only after days to weeks of intake of medications. Explain the patient the need to take medication even after feeling better Explanation of side effects- If patients ask about the side effects, explain the patient about the same. Explain the patient as to what to do- if they encounter side effects Encourage the patient to report side effects The need to consult with psychiatrist before discontinuing medications on their own

benefit, as in most cases, same agent is continued in the maintenance phase.

The basic principles of management in the acute phase are shown in Table-11. Clinicians may focus on carrying out a comprehensive assessment (psychiatric/medical/psychosocial), decide about the treatment goals, ensure safety of the patient and others, decide about the treatment setting, decide about the choice of medication in liaison with the patient and the family by taking into account the clinical and treatment related factors and institute psychosocial interventions at the earliest so as to provide comprehensive management. If patient is using alcohol or other illicit substance, all efforts are to be made to stop the same. Similarly, if a patient is on antidepressants and presents with hypomanic/manic or mixed symptoms, these need to be stopped immediately. Some of the indicators of inpatient care are shown in Table-12.

All treatment decisions need to be made in consultation with the patient and or family members and need to be documented. Whenever mood stabilizers are used, the required investigations need to be done prior to starting of mood stabilizers, patient's serum levels of medications are to be monitored and other investigations need to be repeated from time to time as indicated for various mood stabilizers.

The evidence for efficacy of various agents in management of different phases of illness (mania, depression, maintenance phase) vary and it is important to be aware of the same. Table-13, provides an update on the available level of evidence for different phases of illness.

MANAGEMENT OF HYPOMANIA/MANIA/MIXED EPISODE

The goal of management in mania/mixed episode is to control the aggression, agitation and disruptiveness of patients at the earliest. Depending of the severity of symptoms, inpatient care may be considered. If patient is on antidepressants then this is to be stopped immediately.

In terms of pharmacological management, first line agent for management of mania may involve use of lithium or valproate, olanzapine, haloperidol, quetiapine, aripiprazole, risperidone, paliperidone or ziprasidone as monotherapy. Typical antipsychotics like haloperidol, trifluoperazine and chlorpromazine have also been used in the Indian scenario. These are very useful in the management of irritability, aggression, impulsivity and psychotic features. However, these are associated with high incidence of extrapyramidal reactions. However, there is some evidence to suggest that combining lithium or valproate with an antipsychotic may be more effective than any of these agents when used alone.

Table 11: Management in the acute phase

- Comprehensive assessment (psychiatric (including alcohol and substance)/medical/psychosocial)
- Discontinue antidepressants if indicated (patient exhibiting hypomanic/manic/mixed symptoms)
- Deciding on goals of treatment
- Patients
 - Eliminate/reduce symptoms of phase of illness in which patient presents with and improve the level of functioning
 - Promote safety, reduce risk of harm, and reduce stress
- Caregivers
 - Minimise caregiver distress
 - Offer help to enable them to cope with the illness in their relative
- Both
 - Develop a therapeutic alliance and provide opportunities for patients and caregivers to actively engage in treatment
 - Offer basic information and support tailored to needs of patients and caregivers
- Choice of treatment setting
- Choice of medication
 - Type and severity of current episode
 - Type of past episode (s)
 - Predominant polarity
 - Past treatment history- response, side effects, compliance
- Use of adjunctive medications when indicated
- Use of ECT when indicated
- Psychosocial interventions
- Planning for further treatment- Pharmacoprophylaxis

Table 12: Some indications for inpatient care during acute episodes

Mania/mixed

- Presence of severe agitation or violence which puts the life of others at risk
- Presence of general medical or comorbid psychiatric conditions that make outpatient treatment unsafe or ineffective
- Patient not responding to a combination of first line agents
- Treatment-refractory mania/mixed episode

Depression

- Presence of suicidal behaviour which puts the life of the patient at risk
- Presence of severe agitation or violence which puts the life of others at risk
- Refusal to eat which puts the life of patient at risk
- Severe malnutrition
- Patient unable to care for self to the extent that she/he requires constant supervision or support
- Catatonia
- Presence of general medical or comorbid psychiatric conditions that make outpatient treatment unsafe or ineffective
- Patient not responding to a combination of medications

Among these agents, lithium is thought to have slower onset of action. Accordingly, it can be said that if the mania is less severe, monotherapy be considered. However, if mania is severe and associated with significant disruption than combination therapy need to be considered. Use of adjunctive benzodiazepines for short duration may be required. Patients who refuse medications and are unmanageable may be given depot antipsychotics like risperidone, paliperidone, olanzapine or a depot of typical antipsychotic medication.

Table 13: Comparison of several monotherapy and combination Pharmacotherapies for bipolar disorders

	Bipolar Mania	Bipolar Depression	Mixed episodes	Prevention of relapse of depression	Prevention of relapse of mania
Monotherapy					
Lithium (Li)	√	√	√	√	√
Valproate (V)	√	@	√	√	√
Lamotrigine (L)	X	√	NA	√	X
Carbamazepine (C)	@	?	X	@	@
Oxcarbazepine (O)	?	NA	NA	NA	NA
Topiramate (T)	X	X	NA	X	X
Gabapentin	X	NA	NA	X	X
Olanzapine (OLZ)	√	?	?	√	√
Quetiapine (Q)	√	√	NA	√	√
Asenapine (ASP)	√	NA	NA	NA	?
Aripiprazole (ARP)	√	X	?	X	√
Risperidone (R)	√	NA	√	NA	@
Paliperidone	√	NA	?	NA	@
Haloperidol	@	NA	NA	NA	
Ziprasidone	√	X	?	NA	@
Chlorpromazine	?	NA	NA	NA	NA
Clozapine	?	NA	NA	NA	NA
Cariprazine	NA	?	NA	NA	NA
Lurasidone	NA	@	NA	NA	NA
Combination					
Li + V	√	√	√	√	√
Li + OLZ	√	NA	NA	?	√
Li + R	√	NA	NA	NA	√
Li + L	NA	@	NA	NA	NA
Li + C	NA	?	NA	NA	NA
Li + SSRI	NA	√	NA	NA	NA
Li + Venlafaxine	NA	?	NA	NA	NA
(Li/V) + ARP	?	X	NA	NA	NA
(Li/V) + ASP	?	NA	NA	NA	NA
(Li/V) + (Q/ARP/Z)	NA	NA	NA	NA	√
V + OLZ	NA	NA	?	NA	NA
V + SSRI	NA	√	NA	NA	NA
OLZ + SSRI	NA	√	NA	√	NA
OLZ + C	X	NA	NA	NA	NA
R + C	X	NA	NA	NA	NA
L + Q	NA	?	NA	NA	NA

√ – Established efficacy; @ – Efficacy not Established clearly; X – Established that not useful; ? – Evidence limited to open label studies; NA – Evidence not available

If a patient comes with a 'breakthrough' hypomanic/manic episode, then the first step in the management involves optimization of the ongoing agent. The optimisation can be done by monitoring the serum levels of agents like lithium and valproate. If required, additional antipsychotics and benzodiazepines may be used, depending upon severity of the episode.

If the first-line agent used in optimal dose fails (lack of significant clinical benefit after 2 weeks of use), another first line agent need to be added to the ongoing treatment. Alternative strategies may include changing lithium to valproate or vice versa, changing to carbamazepine, adding antipsychotic medication if not used earlier, changing the antipsychotic if used earlier. ECT may be considered if patient is very disruptive, not responding to a trial of combination of medications, has history of good response to ECT in the past, pregnancy and those experiencing mixed episode. Psychosocial interventions like psychoeducation

of patient and family and family focused intervention be started at the earliest. Psychosocial interventions like CBT or IPSRT, focused specifically on the patient, should be considered when patient is cooperative.

MANAGEMENT OF BIPOLAR DEPRESSION

The main goal of management is to achieve euthymia, normal level of functioning and to avoid switching to hypomanic/manic episode. Among the various mood stabilizers, there is ample evidence to suggest that lithium and lamotrigine may be used as the first line medications in the management of bipolar depression.

If the patient presents with a breakthrough episode, the initial strategy is to check the medication compliance and ensure adequate compliance. If compliance is not an issue, initial strategy is to optimise the mood stabilizer which the patient is already getting.

If the patient is not on any mood stabilizer, than lithium or lamotrigine may be considered. Among the antipsychotics, data suggests that quetiapine monotherapy may also be beneficial. There is evidence for use of olanzapine and fluoxetine combination too. If the patient does not respond to monotherapy with mood stabiliser or antipsychotics, combination of these agents with antidepressants may be considered. Use of antidepressants without the use of concurrent mood stabilizer or an atypical antipsychotic is to be avoided. Benzodiazepines may be used as per the need. Psychosocial intervention in the form of CBT may also be considered when the depression is of mild to moderate severity. ECT may be considered, if depression is severe, in presence of suicidality, risk of harm to others, catatonic symptoms, psychotic symptoms, patient is pregnant, when use of various psychotropics is limited due to concurrent medical illnesses. There is preliminary evidence to suggest the beneficial effect of transcranial magnetic stimulation and direct cranial stimulation.

RAPID CYCLING AFFECTIVE DISORDER

Rapid cycling affective disorder (RCAD) is characterised by having 4 or more episodes (depression/mania/hypomania/mixed) in a single year. These episodes should be separated from each other by partial or full remission for at least 2 months or a switch to an episode of opposite polarity. Many risk factors (Table-14) have been identified for development of RCAD. Accordingly, the first step in the management of RCAD is to evaluate the patients for underlying medical conditions which may be contributing to the RCAD. Among medications, use of antidepressants has been shown to increase cycling.

In terms of psychotropics, there is evidence to suggest that lithium or valproate may be used as the first line agents. Other mood stabilizers which can be considered include lamotrigine. If patient does not respond to monotherapy, then combination of mood stabilizers or a combination of mood stabilizer and antipsychotic medication may be considered.

MAINTENANCE TREATMENT FOR BIPOLAR DISORDER

The primary goal of maintenance treatment is to prevent the recurrence of episode of either polarity, reduce/eliminate the residual symptoms and improve the overall functioning of the patient. In terms of pharmaco-therapeutic agents, best evidence for maintenance treatment is available for lithium and valproate. In recent years evidence has also emerged for use of olanzapine and quetiapine in prevention of recurrence of both depressive and manic episodes. However, these may be avoided because of associated higher risk of metabolic

Table 14: Risk factors for Rapid Cycling Affective Disorder

Risk factors for RCAD

- Hypothyroidism
- Long term aggressive use of antidepressants
- Comorbid substance use
- Minor tranquilizer/stimulant or caffeine abuse
- Cyclothymic and hyperthymic temperament
- Female gender
- Menopause
- Temporal lobe dysrhythmias
- Several episodes/stressors as an effect of kindling
- Onset of illness as depression
- Frequent and more depressive episodes
- ? COMT/BDNF gene abnormality
- ? Biological rhythm disturbances like wakefulness, light exposure

side effects. Long acting risperidone has been shown to be beneficial in prevention of recurrence. Lamotrigine has been shown to be efficacious in prevention of depressive episodes, but not for prevention of manic episodes. Olanzapine, aripiprazole, ziprasidone and asenapine has been shown to be of benefit in prevention of recurrence of manic episodes, but not for depressive episodes. Carbamazepine has also been shown to be effective in prevention of recurrence; however, it is less preferred compared to lithium and valproate because of its side effect profile and drug interactions. Studies have also evaluated the efficacy of lithium and valproate in combination with various antipsychotics. Besides use of pharmacotherapy, there is evidence to suggest the beneficial role of adjunctive psychosocial intervention in the management of BPAD. Maintenance ECT may also be considered in patients who have responded to ECT during their acute episodes.

The general principle of management during the maintenance phase of treatment is to continue the medication started during the acute phase of illness. Accordingly, while selecting the agent during the acute episode, clinicians may take into consideration the patient's preference, clinical factors which may influence the long term outcome, recurrence of episodes and side effects. If the patients have more manic episodes then one may prefer lithium, valproate or carbamazepine while for more depressive episodes one may consider Lithium, lamotrigine or quetiapine. In severe cases, combination of lithium and valproate may be considered.

It is important to note that patients with mood disorders are more vulnerable to extrapyramidal side effects like tardive dyskinesia with long term use of antipsychotics, especially typical antipsychotics. Patients who have been treated with a combination of lithium and antipsychotic or valproate and antipsychotic medication, the need for continued use of antipsychotic need to be reassessed on the basis of longitudinal course. Similarly, stoppage of antidepressants needs to be considered once bipolar depression remits. Combination

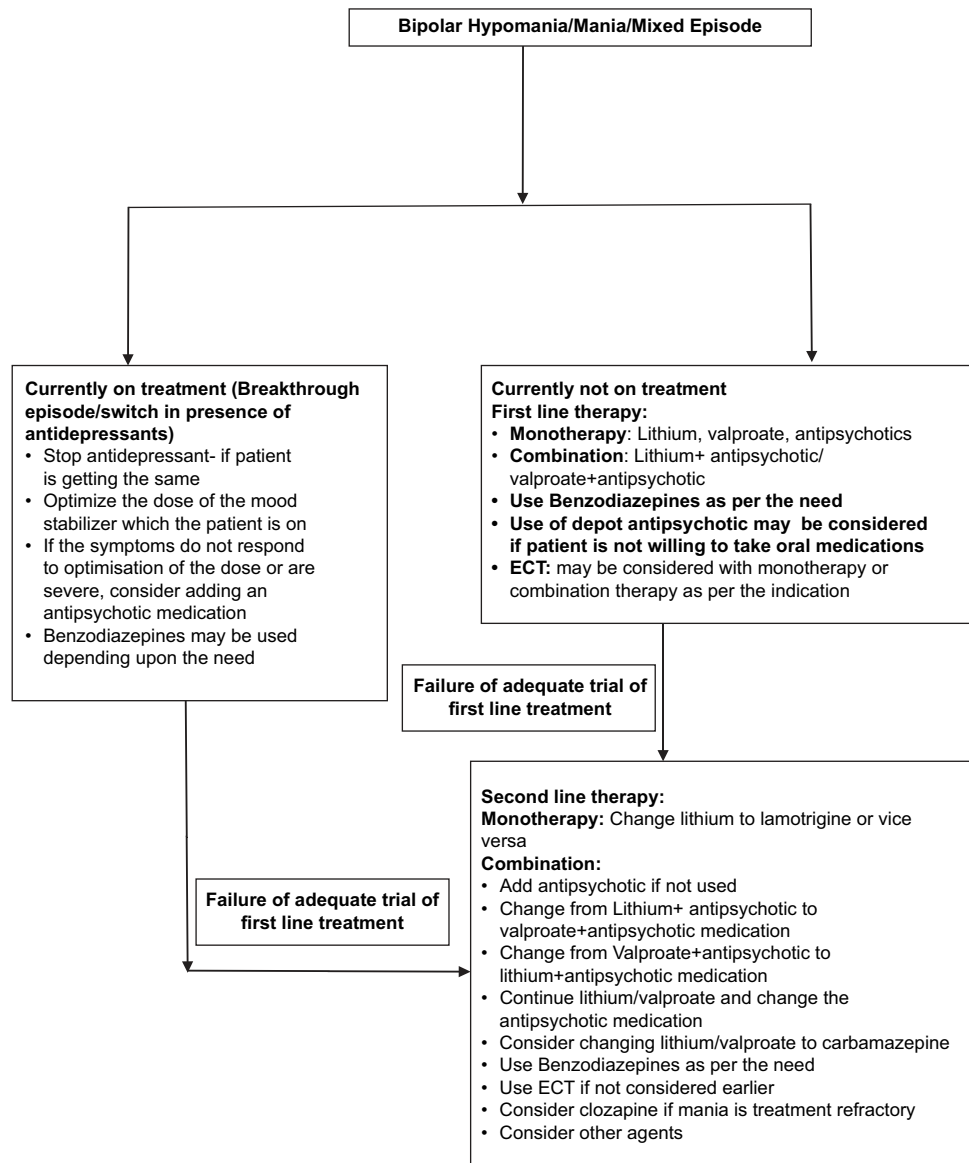


Figure 2: Management of Hypomania/ Mania/Mixed Episode

therapy during the maintenance phase is to be considered only for those who have not responded to the optimal dose of monotherapy during the maintenance phase of illness.

SPECIAL SITUATIONS

Clinicians often encounter certain clinical situations which either require special attention or can influence treatment decisions. Management of these situations is summarised in table-15.

SIDE EFFECTS AND THEIR MANAGEMENT

Various classes of psychotropic medications used for the management of BPAD are associated with many side effects, which require intervention. The side effects associated with antipsychotics are discussed in the clinical practice

guidelines for schizophrenia. The recommendations made for monitoring of metabolic side effects associated with various atypical antipsychotics may also be followed in patients with BPAD, if long term antipsychotic medications are considered.

Use of lithium is associated with multiple side effects. These side effects can be classified on the basis of occurrence (i.e., those occurring during the early or late phase of treatment) and frequency (Common, uncommon, rare and very rare) (Table-16). Most of these side effects can be managed with reduction in dose of medication or shifting to a sustained release preparation as the first line strategy.

The common management strategies for the side effects associated with lithium, valproate and carbamazepine are shown in Table-17.

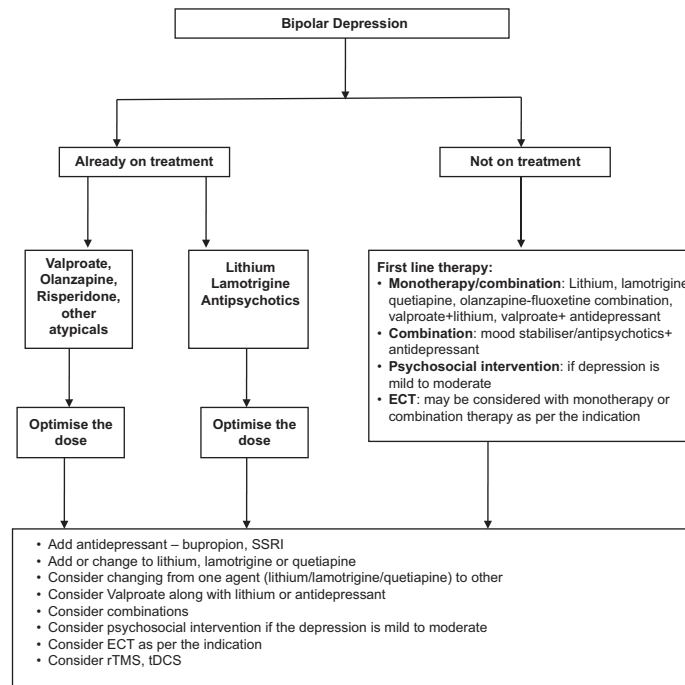


Figure 3: Management of Bipolar Depression

Table 15: Issues related to special situations

Special situation	Strategies
Suicidality	<ul style="list-style-type: none"> • Risk of suicide is high in patients with BPAD. • Suicidal behaviour is seen during the depressive episode, mixed episode and also in manic episode. Suicide have also been reported during the euthymic phase • Clinicians need to carefully evaluate the patients for suicidal ideations, plans, suicidal attempts at every follow-up. • High risk management be instituted and inpatient management may be considered if the patient is at high risk. • Psychoeducation of patient and family need to focus on discussing about warning signs of suicide. Patients experiencing severe distress due to a feeling of loss, stigma etc., are to be provided psychological support and monitored closely. • Use of lithium has been shown to lower the risk of suicide. • ECT is an important therapeutic option in patients at high risk of suicide during an acute episode.
Catatonia	<ul style="list-style-type: none"> • Catatonic features may be seen in both depressive and manic phase of illness. • Whenever a patient with BPAD presents with catatonia, all possible differential diagnosis for catatonia need to be considered. • Investigate to rule out organic cause (s). • Initial management may involve use of benzodiazepines, especially lorazepam, which leads to symptomatic relief in significant proportion of cases. • In case the catatonia does not respond to benzodiazepines or relapse after stopping benzodiazepines, ECT is to be considered.
Psychotic features	<ul style="list-style-type: none"> • Psychotic symptoms are seen in a significant proportion of patients with BPAD. • When present, use of antipsychotics is warranted.
Violence and Aggression	<ul style="list-style-type: none"> • All patients, especially those in mania need to be evaluated for violence and dangerousness during every assessment, especially during the acute phase of illness. • Whenever a patient is found to have serious threat for violence or exhibits violence, inpatient management may be considered. • Injectable antipsychotics like haloperidol or lorazepam can be used for management of violence and aggression.
Comorbid Alcohol and Substance use Disorders	<ul style="list-style-type: none"> • Substance use can precipitate an episode, increase the frequency of episode, may be associated with RCAD, higher risk for suicide, poor response to treatment, longer time to achieve remission, can influence the choice of medication, lead to higher vulnerability for side effects. • Both BPAD and substance use disorders need to be treated concurrently. • Efforts need to be made to keep the patient abstinent from alcohol and other substance(s), both during the acute episodes and during the maintenance phase of illness.
Comorbid Psychiatric disorders	<ul style="list-style-type: none"> • Patients of BPAD have high rate of comorbid anxiety disorders, ADHD etc. • Comorbid disorders, may not be evident during the acute episodes. Accordingly, patients need to be evaluated during the maintenance phase for any kind of comorbid psychiatric disorders. • Management of comorbid disorders need to be done along with concurrent management of BPAD.
Comorbid Physical illnesses	<ul style="list-style-type: none"> • Patients with bipolar disorder have high rate of physical comorbidities. • All patients need to receive thorough assessment for possible physical illnesses and depending on the feasibility may be investigated as per the requirement. • Those with comorbid physical illnesses are to be continuously monitored during all the phases of treatment. • Comorbid physical illnesses and concomitant medications also need to be taken into account while selecting the treatment setting and antipsychotic medication per se.

Contd...

Table 15: Contd...

Special situation	Strategies
Perioperative period	<ul style="list-style-type: none"> When used during the perioperative period, lithium can contribute to hemodynamic instabilities, interfere with sodium and potassium metabolism, and the renal excretion of lithium can be reduced in presence of renal complications. Therefore it is recommended that lithium need to be discontinued prior to surgery. Postoperatively, when the patient is hemodynamically stable, is able and allowed to drink, and is not on potentially interfering drugs, the medication may be restarted gradually.
Pregnancy	<ul style="list-style-type: none"> Mood stabilizers, including lithium are considered to be teratogenic and associated with higher rate of congenital malformations. Pregnancy is to be planned. Whenever feasible, exposure to lithium, valproate, carbamazepine, lamotrigine need to be avoided during pregnancy. Hence, attempt need to be made to discontinue these medications. If patient is not able to tolerate the discontinuation of medication, than the pros and cons of continuation of the medications during the first trimester need to be discussed and documented. If required, lithium may be used during second and third trimester of pregnancy; Use the minimal optimal dose. If required, antipsychotics, especially high potency typical antipsychotics may be considered. Use folic acid during pregnancy. If patient is receiving mood stabilizer during the pregnancy – monitor alpha fetoprotein levels at 20 weeks.
Post-partum & Breast feeding	<ul style="list-style-type: none"> There is high risk of relapse during the post-partum period. The new-born be evaluated thoroughly, if the mother was on psychotropics during pregnancy for malformations, drug overdose and withdrawal. Lithium need to be used with caution during the postpartum. When valproate is used during the post-partum, liver function tests and haemogram of the neonate need to be monitored adequately.
Elderly	<ul style="list-style-type: none"> Have high rates of comorbid medical illnesses and substance use disorders. More sensitive to side effects of medications, at risk for fall and fracture of hip. May develop cognitive deficits with use of lithium or benzodiazepines. Start low and go slow.
Children & Adolescents	<ul style="list-style-type: none"> Have high rates of comorbidity in the form of Attention-hyperkinetic disorder (ADHD), conduct disorder, substance use disorders. At times it may be difficult to distinguish between symptoms of mania and ADHD. Take longer time to stabilize. Data on use of lithium before 12 years of age is not available and use of lithium prior to this age is not recommended. Start at lower doses and titrate slowly.

MANAGEMENT OF TOXICITY

Among the lithium, valproate and carbamazepine, valproate has a wide therapeutic window. Lithium and carbamazepine toxicity may be fatal and are medical emergencies. The therapeutic range for serum lithium levels varies from 0.4 to 1.2 meq/litre. Toxic effects of lithium are usually seen when the serum levels of lithium rise above 1.5meq/litre. When the levels exceed 2meq/litre, life threatening side effects may emerge. Various signs and symptoms of toxicity with lithium, valproate and carbamazepine are shown in Table-18. Management of lithium toxicity is an acute emergency and involves stoppage of lithium, maintaining the airways, maintaining an intravenous line and use of haemodialysis if serum lithium levels are more than 2.5 mEq/Litre. However, in patients with end stage renal disease, haemodialysis may be considered in levels below 2.5mEq/litre as well.

Management of valproate toxicity also involve use of haemodialysis. However, there are no clear guidelines for the same. Management of carbamazepine intoxication involves gastric lavage, hemoperfusion and use of supportive measures.

Financial support and sponsorship

Nil.

Table 16: Side effects of lithium

<i>Early onset side effects</i>	<i>Common side effects</i>
Weight gain	<i>Short term dose related</i>
Tremor	Nausea, diarrhea, epigastric pain
Anorexia, Nausea, Diarrhea	Tremor
Aggravation of cutaneous conditions	Thirst, polyuria
Mild thirst	Metallic taste
Polyuria	<i>Long term side effects</i>
<i>Late onset side effects</i>	Weight gain
Nephrogenic diabetes insipidus	Hypothyroidism in women
Hypothyroidism	Reduction in eGFR
Thyroiditis	Tubular dysfunction
Hyperthyroidism	<i>Uncommon side effects</i>
Cognitive dulling	Fluid retention (oedema)
	Hypothyroidism
	<i>Rare side effects</i>
	Acne
	Psoriasis
	Hair loss
	Fatigue
	Arrhythmia
	Cognitive deficit
	Seizures
	Sexual side effects
	<i>Very Rare side effects</i>
	↑WBC count
	↑serum Ca ⁺⁺ , Mg ⁺⁺
	↑ parathyroid hormone
	↑blood sugar
	Benign intracranial hypertension
	Parkinsonism disease's like symptoms

Table 17: Management of side effects of mood stabilizers

Side effects	Management
Lithium	
Dose-related side effects: polyuria, polydipsia, weight gain, cognitive problems (e.g., dulling, impaired memory, poor concentration, confusion, mental slowness), tremor, sedation or lethargy, impaired coordination, gastrointestinal distress (e.g., nausea, vomiting, dyspepsia, diarrhoea), hair loss, benign leukocytosis, acne, and edema Electrocardiogram (ECG) Changes	Reduce the dose and/or shift to once a daily dose of medications, if the side effects still persist than use other medications: Tremors: beta-blockers Polyuria, polydipsia, edema: diuretics Acne: Topical antibiotics, retinoic acid Gastrointestinal side effects: give lithium after meals, change to lithium citrate Cardiac Side effects: Reduce the dose, if the abnormalities persist, may have to stop lithium in consultation with the cardiologist depending on the severity of the cardiac conduction abnormalities Renal side effects: Diuretics for impaired concentrating capacity- thiazides, amiloride
Renal Side effects: Impaired concentrating capacity, interstitial fibrosis, tubular atrophy Hypothyroidism	Hypothyroidism: Not an indication for stopping lithium, add levothyroxine Dermatological: Reduce the dose, appropriate dermatological treatment, if does not respond then may consider stopping lithium Inositol supplementation, TNF α inhibitors (Etanercept), Conventional treatment of Psoriasis (Topical corticosteroids, Keratolytics, Vitamin D analogues, Oral retinoids, Psoralen, Ultraviolet A (PUVA) therapy, Methotrexate) May have to consider stopping lithium in treatment resistant cases of psoriasis
Psoriasis	
Valproate	
Dose-related side effects: Gastrointestinal distress (nausea, vomiting, diarrhoea etc), tremor, sedation, benign hepatic transaminase elevations	Resolve with reduction in dose, if persist, then GI disturbances: change of preparation from Valproic acid to Divalproex, Proton-pump blockers, Histaminic blockers Tremors: beta-blockers Discontinuation of valproate Discontinuation of valproate Dietary restriction for increased appetite and weight gain May have to discontinue valproate if other options are available, metformin Discontinuation of valproate
Hepatotoxicity Leukopenia, Thrombocytopenia Hair loss, increased appetite, weight gain Polycystic ovarian disease Hepatic failure, haemorrhagic pancreatitis, and agranulocytosis	
Carbamazepine	
Ophthalmological: diplopia, blurred vision Gastrointestinal: nausea Neurological: ataxia Dermatological: skin rashes Haematological: leukopenia, thrombocytopenia	Reduce the dose Reduce the dose Reduce the dose Reduce/Stop Carbamazepine Mild leukopenia may resolve on its own, in case of severe leukopenia, stop the medication May require discontinuation of carbamazepine May require addition of levothyroxine Stop Carbamazepine, manage the medical condition
Electrolyte imbalance: Hyponatremia Endocrine: hypothyroidism Serious side effects: agranulocytosis, aplastic anemia, thrombocytopenia, hepatic failure, Stevens-Johnson syndrome, pancreatitis	

Table 18: Signs and symptoms of Toxicity of lithium, valproate and Carbamazepine

Lithium levels 1.5-2.5 meq/litre Neurological: Fine tremors, Apathy, Fatigue, Muscle weakness, Hyperreflexia, Incontinence, Gait disturbances Gastrointestinal: nausea, vomiting, diarrhoea Cardiovascular changes: Bradycardia, T-wave changes, sinoatrial block, AV block
Lithium levels >2.5 meq/litre Neurological: coarse tremors, slurring of speech, dysarthria, ataxia, hypertonia, spasticity, rigidity, myoclonus, seizures, stupor, coma, permanent neurological deficits Gastrointestinal: nausea, vomiting, diarrhoea Cardiovascular changes: bradycardia, T-wave changes, sinoatrial block, AV block, hypotension Renal: Renal failure
Valproate Somnolence, Heart block, Coma

Contd..

Table 18: Contd...

Carbamazepine Dizziness, Ataxia, Sedation, Nystagmus, Ophthalmoplegia, Cerebellar and extrapyramidal signs, Impaired consciousness, Seizures, Respiratory depression, Stupor, Coma, Tachycardia, Arrhythmia, Cardiac conduction disturbances, Hypotension
--

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Merikangas KR, Jin R, He JP et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 2011; 68: 241–251.
- Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry 2011; 72: 156–167.
- Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ,

- & Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *The World Journal of Biological Psychiatry* 2013; 14(3), 154-219.
4. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, Berk M. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar disorders*; 2013;15(1), 1-44.
 5. National Institute for Health and Care Excellence. Bipolar disorder: The assessment and management of bipolar disorders in adults, children and young people in primary and secondary care. Draft for consultation, April 2014. <http://www.nice.org.uk/>
 6. American Psychiatric Association. Guideline Watch: Practice guideline for the treatment of patients with bipolar disorder, 2ndedn. Washington DC: American Psychiatric Association; 2005.
 7. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition- recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2009; 23:346-388.
 8. Cipriani Andrea, et al. "Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis." *The Lancet* 378.9799 (2011): 1306-1315.
 9. Fountoulakis KN, Kontis D, Gonda X, Yatham LN. A systematic review of the evidence on the treatment of rapid cycling bipolar disorder. *Bipolar disorders*; 2013; 15(2), 115-137.
 10. Rao PG. An overview of Indian research in bipolar mood disorder. *Indian Journal of Psychiatry*. 2010;52(Suppl1):S173-S177.
 11. Avasthi A, Grover S, Aggarwal M. Research on mood stabilizers in India. *Indian J Psychiatry* 2010;52, Suppl S3:355-61
 12. Grover S, Avasthi A, Sinha V, Lakdawala B, Bathla M, Sethi S, Mathur D M, Kathuria P, Shah S, Baalalsubramanian D S, Agarwal V, Deka K. Indian Psychiatric Society multicentric study: Prescription patterns of psychotropics in India. *Indian J Psychiatry* 2014;56:253-64
 13. Grover S, Avasthi A. Mood stabilizers in pregnancy and lactation. *Indian J Psychiatry* 2015;57, Suppl S2:308-23
 14. Tighe SK, Mahon PB, Potash JB. Predictors of Lithium Response in Bipolar Disorder. *Therapeutic Advances in Chronic Disease*. 2011; 2(3):209-226.
 15. Cipriani A, Hawton K, Stockton S, & Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. 2013; 346:f3646.
 16. Malhi GS, Tanious M. Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations. *CNS Drugs* 2011; 25(4): 289-98.
 17. Ng F, Hallam K, Lucas N, Berk M. The role of lamotrigine in the management of bipolar disorder. *Neuropsychiatric disease and treatment*; 2007; 3(4), 463.
 18. Bowden, C. L., Asnis, G. M., Ginsberg, L. D., Bentley, B., Leadbetter, R., & White, R. Safety and tolerability of lamotrigine for bipolar disorder. *Drug safety*, 2004; 27(3), 173-184.
 19. Tränkner A, Sander C, Schönknecht P. (2013). A critical review of the recent literature and selected therapy guidelines since 2006 on the use of lamotrigine in bipolar disorder. *Neuropsychiatric disease and treatment*, 2013; 9, 101.
 20. Tohen M, Zhang F, Taylor CC, Burns P, Zarate C, Sanger T, Tollefson, G. A meta-analysis of the use of typical antipsychotic agents in bipolar disorder. *Journal of affective disorders*, 2001; 65(1), 85-93.
 21. Gao K, Gajwani P, Elhaj O, Calabrese JR. Typical and atypical antipsychotics in bipolar depression. *The Journal of clinical psychiatry*, 2005; 66(11), 1376-1385.
 22. Gigante AD, Lafer B, Yatham LN. Long-acting injectable antipsychotics for the maintenance treatment of bipolar disorder. *CNS drugs*, 2012; 26(5), 403-420.
 23. De Berardis D, Marini S, Carano A, Padovan Lang A, Cavuto M, Piersanti M, Di Giannantonio M. Efficacy and safety of long acting injectable atypical antipsychotics: a review. *Current clinical pharmacology*, 2013; 8(3), 256-264.
 24. Chou YH, Chu PC, Wu SW, Lee JC, Lee YH, Sun IW, Yen YC. A Systemic Review and Experts' Consensus for Long-acting Injectable Antipsychotics in Bipolar Disorder. *Clinical Psychopharmacology and Neuroscience*, 2015; 13(2), 121.
 25. Joffe RT, MacQueen GM, Marriott M, Robb J, Begin H, Young LT. Induction of mania and cycle acceleration in bipolar disorder: effect of different classes of antidepressant. *Acta Psychiatrica Scandinavica*, 2002;105(6), 427-430.
 26. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. *Biological psychiatry*, 2000; 48(6), 558-572.
 27. Gijssman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *American Journal of Psychiatry* 2014; 161: 1537-47.
 28. Henry C, Sorbara F, Lacoste J, Gindre C, Leboyer M. Antidepressant-induced mania in bipolar patients: identification of risk factors. *Journal of Clinical Psychiatry*, 2001; 62(4), 249-255.
 29. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Breier A. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of general psychiatry*, 2003; 60(11), 1079-1088.
 30. McElroy SL. Prescribing antidepressants for bipolar depression: what does the evidence say?. *The Journal of clinical psychiatry*, 2014; 75(9), e24-e24.
 31. Silverstone T. Moclobemide vs. imipramine in bipolar depression: a multicentre double-blind clinical trial. *Acta Psychiatrica Scandinavica*, 2001; 104(2), 104-109.
 32. Nivoli AM, Colom F, Murru A, Pacchiarotti I, Castro-Loli P, González-Pinto A, Vieta E. New treatment guidelines for acute bipolar depression: a systematic review. *Journal of affective disorders*, 2011; 129(1), 14-26.
 33. Vázquez GH, Tondo L, Undurraga J, Baldessarini RJ. Overview of antidepressant treatment of bipolar depression. *International Journal of Neuropsychopharmacology*, 2013; 16(7), 1673-1685.
 34. Schöttle D, Huber CG, Bock T, Meyer TD. Psychotherapy for bipolar disorder: a review of the most recent studies. *Current opinion in psychiatry*, 2011; 24(6), 549-555.
 35. Scott JAN, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, Hayhurst H. Cognitive-behavioural therapy for severe and recurrent bipolar disorders. *The British Journal of Psychiatry*, 2006; 188(4), 313-320.
 36. Miklowitz DJ. A review of evidence-based psychosocial interventions for bipolar disorder. *Journal of Clinical Psychiatry*, 2006; 67, 28.
 37. Chanpattana W. Combined ECT and clozapine in treatment-resistant mania. *J ECT* 2000; 16:204-207.
 38. Devanand DP, Polanco P, Cruz R, Shah S, Paykina N, Singh K, and Majors L: The efficacy of ECT in mixed affective states. *J ECT* 2000; 16:32-37.
 39. Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. *Am J Psychiatry* 1994; 151:169-176.
 40. Ismail Shihabuddeen TM, Gopinath PS. Group meetings of caretakers of patients with schizophrenia and bipolar mood disorders. *Indian J Psychiatry* 2005;47:153-6.
 41. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, Laszlovszky I. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *Bipolar Disord*. 2015;17:63-75.
 42. Muneer A. The Treatment of Adult Bipolar Disorder with Aripiprazole: A Systematic Review. *Cureus*. 2016 Apr; 8(4): e562.