INTRODUCTION

Bipolar Affective [Mood] Disorders are a class of psychiatric disorders that are the most distressing either from the point of view of patients [as in depressive phase] or from that of the caregivers [as in manic counterpart]. These disorders have potential remission inbuilt in their defining criteria [American Psychiatric Association, 2000; World Health Association, 2002]. They also are recognized as the psycho-behavioral disorders that are the most well studied ones from the point of view of efficacy of pharmacotherapy. Lithium Carbonate was the first drug that demonstrated its therapeutic and prophylactic potential against recurring Bipolar Affective [Mood] Disorder. Over the years, many new molecules have been examined regarding their thymoleptic properties and a huge literature has gathered. In the other vein, data regarding individual-based and family-based psycho-social interventions have also accumulated. There is a compelling need to review all such data to see where we stand as far as global scientific database is concerned. Simultaneously, we also need to see from the point of view of our country i.e. whether and how our unique circumstances suggest any differences to be considered in management of Bipolar Affective [Mood] Disorders in India. The foregoing introduction summarizes the intention of this review. It should be emphasized that observations and opinions made in this review are only general guidelines and the exact and the best treatment strategies in an individual case have to be based on a number of considerations unique to that case. Further, the data reviewed principally pertain to the pharmacological management and refers to the adult population unless specified otherwise. The abbreviation 'BPAD' has been repeatedly used in this paper to represent the term 'Bipolar Affective Disorders'.

At many places, the format used by the Practice Guidelines of American Psychiatric Association (American Psychiatric Association, 2002), probably the most comprehensive and the most popular treatment guidelines series, has been followed in the present paper on purpose, to retain homogeneity and facilitate comparison. Acknowledgement is also made of other guidelines, wherever referred to (American Psychiatric Association, 1994; Sachs et al, 2000; Steering Committee, 1996; Crismon et al, 2002; Suppes et al, 2001, Maj et al, 2002; Taylor, 2003). These guidelines are in a continuous and periodic review based on new evidence. Hence regular updating is recommended. It may be reiterated that these guidelines can't be quoted as mandatory dictates to be followed especially in countries like India where socio-economic and clinical factors may lead to recourses other than what has been stipulated in this document.

ORGANIZATION OF THIS DOCUMENT: The guidelines encompass a wide range of considerations of different aspects of Bipolar Affective [Mood] Disorders. To facilitate the reader to choose his specific intended area of enquiry, the organization of the entire paper is outlined below:
A. Crossectional treatment of the current episode
   A1. Manic/ Mixed Episode
   A2. Depressive Episode
B. Longitudinal maintenance treatment
C. Course specifiers viz. rapid Cycling & seasonal patterns
D. General guidelines of management

A. CROSSECTIONAL TREATMENT OF THE CURRENT EPISODE

In each of the two categories (A1. Manic/ Mixed Episode, A2. Depressive Episode) included in this heading, the following organization has been followed:

AX.1. Review of literature
AX.2. Summary

A1. MANIC/ MIXED EPISODE

A1.1. Review of Literature

In the management of an acute manic or an acute mixed episode, there are two primary considerations:

a. Safety of the patient and those around him/ her
b. Symptom control

Pharmacological treatment for Acute Manic/ Mixed episode includes the following options:

1. Lithium
2. Antiepileptics (Valproate, Carbamazepine, Other anticonvulsants)
3. Antipsychotics
4. Electroconvulsive Therapy (ECT)
5. Benzodiazepines
6. Combination Treatment

Description of various molecules follows:

1. LITHIUM

Lithium has been used for the treatment of mania for over 50 years now. Lithium was tested for mania in placebo controlled studies (although, with methodological deficiencies) in 1960s-70s. Lithium was found superior to placebo in these four early cross over studies. However, use of cross over designs in these trials contributed to seemingly low response rates on placebo, due to lithium withdrawal induced relapse (Stokes et al, 1971; Schou et al, 1954; Maggs, 1963; Goodwin et al, 1969). Additionally, criteria for patient selection were not clear, and patients were assigned to the two groups non-randomly. The first randomized, parallel group, double blind test of lithium in mania was carried out by Bowden and his colleagues (Schou et al, 1954). Lithium was significantly superior to placebo and overall equivalent to divalproex. The study confirmed the earlier impressions that serum levels of 0.8 mEq/L or greater are associated with significantly better response in BPAD, manic patients.

There have been six controlled trials where lithium has been compared with antipsychotics. None of these trials included a placebo group. Lithium was superior to antipsychotics in reducing manic symptomatology (Platman, 1970; Johnson et al, 1971; Takahashi et al, 1975).

Antipsychotics had a more rapid onset of action and were notably effective in controlling agitation (Keck et al, 1998). Comparison with carbamazepine in two trials showed similar efficacy (Lerer et al,
Open studies (Secunda et al, 1985; Himmelhoch & Garfinkel, 1986; Prien et al, 1988; Kramlinger & Post, 1989) and randomized comparator controlled studies (Freeman et al, 1992; Bowden, 1995; Swann et al, 1997) indicate that lithium is likely to be effective in classical euphoric mania but less so in mixed episodes.

Two studies from India (Desai et al, 1986; Venkoba Rao, 1984) found that addition of Carbamazepine to ongoing Lithium potentiates the effects of Lithium and often converts Lithium non-responders to responders.

ADVERSE EFFECTS:

Majority of the patients treated with lithium experience some side effects. Most of the side effects are minor and are less problematic during acute treatment. Dose related side-effects include polyuria, polydipsia, weight gain, cognitive dulling, tremor, sedation or lethargy, impaired coordination, nausea, vomiting, dyspepsia, diarrhea, hair loss, acne and edema (Peet & Pratt, 1993). These side effects can be managed by dosage adjustment. A 30% reduction in the side effects has been reported in patients treated with average lithium levels of 0.68 mEq/L in comparison to those with levels of 0.85 mEq/L. A sustained release preparation may reduce peak serum levels related side-effects associated with plain preparations of lithium. Gastrointestinal side-effects can be managed by administering lithium with meals. Beta blockers can be used to control tremors. Polyuria usually resolves with time. Persistent polyuria and polydipsia must alert the treating psychiatrist as lithium impairs the concentrating capacity of kidneys by reducing renal response to ADH and the bothersome clinical picture like nephrogenic diabetes insipidus may occur.

Polyuria can be managed by shifting to a once daily bed time dose, ensuring adequate fluid intake, administering diuretics like amiloride or thiazides.

Another fairly common adverse effect which occurs in 5-35% of lithium treated patients is hypothyroidism. One must monitor the patient for symptoms and signs of hypothyroidism which occur more frequently among women and usually appear after 6-16 months of lithium intake (Goodwin & Jamison, 1990; Johnston & Eagles, 1999; Jefferson et al, 1987). Lithium induced hypothyroidism is easily treated with levothyroxine and is not a contraindication to continue lithium (Jefferson et al, 1987; Bauer & Whybrow, 1990).

About 10-20% of patients, after receiving lithium for more than 10 years, display microscopic renal changes in its morphology and it may be associated with impaired water absorption but not with reduction in glomerular filtration rate or development of renal insufficiency (Jefferson et al, 1987; Vestergaard et al, 1982; Schou, 1988; Gitlin, 1993; Bendz et al, 1996).

Lithium may cause benign ECG changes; less commonly, cardiac conduction abnormalities have been reported (Burggraf, 1997).

Indian studies in the area of tolerability of Lithium have given important insights (Trivedi et al, 1996; Prakash et al, 1978; Mohan et al, 1996). Trivedi (1996) demonstrated that Lithium is better tolerated than Carbamazepine. Prakash et al (1978) based on their observation of response to a median dose of 750 mg proposed that it may be a cultural difference and Indian patients might ill tolerate higher doses of Lithium. Mohan et al (1996) concluded based on their retrospective chart review that patients receiving once a day Lithium fared better in terms of Lithium levels as well as effectiveness.

INSTITUTION OF LITHIUM:

Once a decision to start lithium has been taken, patient's general medical history with special attention to systems which might get affected by lithium must be reviewed before beginning lithium. Pregnancy must be ruled out by appropriate tests. Patient and caregivers must be educated about the potential side-effects and precautions about the drug interactions. Patients are generally recommended
Blood Urea Nitrogen and serum creatinine level assessments, a pregnancy test, thyroid function test, and for patients over age 40 years, ECG with a rhythm strip.

Lithium is usually started in low, divided doses and depending upon the tolerability, the dose is titrated upward according to response, side-effects and serum levels (Gelenberg et al, 1989). Steady state levels are reached approximately 5 days after dose adjustment and serum levels should be measured after 5 days of dosage adjustment.

Clinical and laboratory status of the patients receiving lithium must be monitored regularly in view of potentially serious side effects. In general, renal functions should be assessed every 2-3 months during first 6 months of treatment and thyroid function tests should be done once-twice during first 6 months. Subsequently, renal and thyroid function may be checked every 6 months to 1 year or whenever clinically indicated (Jefferson, 1987; Emrich et al, 1981).

2. ANTIEPILEPTICS

VALPROATE

Divalproex and sodium valproate & valproic acid formulations have shown greater efficacy for valproate in four randomized, placebo controlled trials. Response rates ranged from 48% to 59% (Brennan et al, 1984; Pope et al, 1991; Bowden et al, 1994; Schou, 1988). Pope et al (1991) had enrolled only those intolerant to lithium and found over 5-fold greater response among divalproex than placebo treated patients (Bowden et al, 1997). Divalproex was superior to placebo, equivalent to lithium and led to significantly quicker improvement in comparison to lithium. Improvement in sleep, psychosis, elevated mood & elation and grandiosity was more among divalproex than lithium treated patients (Bowden et al, 1997). Divalproex is better tolerated than lithium and this has been demonstrated in many studies (Bowden et al, 2000; Lamberi & Venaud, 1992). Studies suggest that patients with mixed affective symptomatology and those with multiple prior mood episodes were more likely to respond to acute treatment with divalproex than with lithium (Markar & Mander, 1989; Swann et al, 1999; Freeman et al, 1992; Swann et al, 1997).

Valproate was superior to carbamazepine in a randomised double blind study, with early improvement, less use of rescue medications and fewer adverse effects (17% vs. 67%). Greater improvement was noted in valproate treated patients in comparison to carbamazepine treated patients on elevated mood, irritability, rapid speech and thinking disturbance (Vasudev et al, 2000). In a randomised open study of acute psychotic manic patients, divalproex and haloperidol were comparable in reduction of both manic and psychotic symptoms (McElroy et al, 1996). Divalproex was found to have efficacy comparable to olanzapine in reduction of symptoms of mania and psychosis in a randomised controlled trial (Zajecka et al, 2000). In another head-to-head comparison trial, olanzapine was superior to divalproex in the mean reduction of manic symptoms and in the proportion of patients in remission at the end of the study (Tohen et al, 2000). Valproate plus haloperidol were superior in reduction of manic symptoms to the antipsychotic alone in a randomised, double blind study. Additionally the total dose requirements of antipsychotic in the combined regimen was lower in comparison to antipsychotic alone group (Muller-Oerlinghausen et al, 2000).

ADVERSE EFFECTS:

Common side effects are nausea, vomiting, anorexia, dyspepsia, diarrhoea, tremor, sedation which usually resolve with continued treatment or dose adjustment. Other benign side effects include reduced leucocyte & platelets count, and hepatic transaminase elevations. Patients with past or current hepatic disease may be at a greater risk for hepatotoxicity (Sheth et al, 1995; Tannirandorn & Epstein, 2000; Davis et al, 1994). Mild, asymptomatic leucopenia and thrombocytopenia are usually reversible on dose reduction or drug discontinuation. However one should keep a watch as serious cases of thrombocytopenia have been reported (Finsterer, 2001). Other side effects include hair loss (Mercke et al, 2000; Gautam, 1999), increase in appetite and weight gain. Rarely, idiosyncratic events
like hepatic failure, haemorrhagic pancreatitis and agranulocytosis have been reported.

Valproate has a wide therapeutic window. Overdose could result in excessive sedation, heart block, coma and even death. Hemodialysis helps in clearing valproate out of body (Janicak et al, 1993; Gilman et al, 1990).

INSTITUTION:

Before starting valproate, hepatic and hematologic abnormalities must be ruled out by taking a focused history and conducting liver function tests and hemogram. Divalproex can be started at a loading dose of 20-30 mg/kg/day. This may be more rapidly effective in controlling the manic symptoms than a gradual titration from a low dose (Hirschfeld et al, 1999; McElroy et al, 1996; Keck et al, 1993; McElroy et al, 1993; Martinez et al, 1998). Among out-patients and elderly patients a gradual titration is preferred. Usually, it should be started at 250 mg TDS with further graduated hikes to reach a target serum level of 50-125 mg/ml. It is advisable to repeat tests of haematologic and liver function at 6 monthly intervals (McElroy et al, 1993; McElroy et al, 1992; McElroy et al, 1992b).

Extended release preparation of divalproex should be used at a slightly higher dose because the bioavailability is about 15% lower.

CARBAMAZEPINE

Carbamazepine has been studied in several trials in treatment of mania, but methodological weaknesses limit conclusions. One small, placebo controlled crossover study reported that majority had significant improvement in manic symptoms (Ballenger & Post, 1978). Carbamazepine was less effective and associated with more need for adjunctive "rescue medication" than valproate in a randomized blind, parallel - group trial of 30 hospitalized manic patients (Vasudev et al, 2000). Carbamazepine in two randomized comparisons with lithium was found to be inferior to lithium in one and comparable to lithium in the other study (Larer et al, 1987; Small et al, 1991). Two studies found carbamazepine comparable to chlorpromazine (Grossi et al, 1984; Okuma et al, 1979). Carbamazepine appears to be more effective than Lithium for patients with mood incongruent delusions, comorbid conditions, BP II states and mixed states (Greil et al, 1998).

ADVERSE EFFECTS AND DOSAGES -

Carbamazepine is associated with side-effects in majority of patients. Most common dose related side-effects include diplopia, blurred vision, fatigue, nausea, and ataxia. These generally are transient and often improve on dose reduction. Asymptomatic reversible leukopenia, thrombocytopenia and elevated liver enzymes can occur in a minority of patients. Hyponatremia may result from water retention due to antiidiuretic action of carbamazepine (Van Amelsvoort et al, 1994). Weight gain and somnolence are common side effects associated with carbamazepine. Rare, idiosyncratic and potentially fatal reactions like agranulocytosis, aplastic anemia, thrombocytopenia, hepatic failure, exfoliative dermatitis and pancreatitis, usually within 3-6 months of carbamazepine initiation have been reported (Finsterer et al, 2001; Pellock & Willmore, 1991; Seetharam & Pellock, 1991; Schweiger et al, 1988).

Carbamazepine had been used in dose range of 600 to 2600 mg/day in trials of mania, the mean dose around 1000 mg/day. There is no evidence of a threshold serum level significantly associated with response. Since carbamazepine induces cytochrome 3A4 enzyme, a watch must be kept on drug interactions and the requirement for increase in dose of carbamazepine due to autoinduction. The limited evidence of efficacy of carbamazepine, coupled with pharmacokinetic and adverse effect issues have led to lowered usage (Sachs et al, 2000).

OTHER ANTI EPILEPTICS

Ox-carbazepine, a congener of carbamazepine has been shown to have efficacy comparable to lithium and haloperidol ((Muller & Stoll, 1984). The tolerability appears to be better than carbamazepine and the magnitude of induction of Cyt P 3A4 enzyme system is less.
Lamotrigine has been evaluated in three controlled studies for the treatment of mania. The methodological inadequacies limit all the three trials. The two trials failed to show any significant benefit of lamotrigine over gabapentin or placebo in one (Frye et al, 2000) and placebo in other (Pande et al, 2000). In the third study, lamotrigine and lithium treatment groups displayed significant and comparable reductions in manic symptoms.

Gabapentin has been evaluated in two controlled trials. The first failed to show any significant differences in efficacy between gabapentin monotherapy and placebo in reducing manic symptoms. As an add on drug, gabapentin and placebo when added to lithium, valproate or both resulted in similar reduction in manic scores and the decrease in the manic symptom scores was significantly greater in the placebo group (Anand, 1999).

Phenytoin in a small placebo controlled trial resulted in greater improvement in manic symptoms when added to haloperidol treatment (Mishory et al, 2000)

3. ANTIPSYCHOTIC DRUGS

Antipsychotic drugs are one of the most commonly used drugs in the management of a manic or a mixed episode. However, the evidence in the form of controlled trials is limited.

Three atypical antipsychotic drugs have been shown superior to placebo in randomized, placebo controlled studies in mania. Olanzapine was superior to placebo in the treatment of acute bipolar mania in two studies (Tohen et al, 1999; Tohen et al, 2000). Both mania with and without psychotic symptoms responded similarly. The modal dose of olanzapine was 15 mg/ day in the first study and 16mg/ day in the second. In other randomized controlled trials, olanzapine exerted efficacy comparable to lithium (Berk et al, 1999), Divalproex (Zajecka et al, 2000; Zajecka et al, 2000) and haloperidol.

DOISING

Dosing regimens for BPAD have not been very well established. Lower doses are generally used. For Olanzapine, a starting dose of 15mg/day in the hospitalized manic patients may be more rapidly efficacious. For outpatients, lower starting dose of 5-10 mg/d may be indicated (Chou et al, 1999). The mean final dose was about 15 mg/day in the two placebo controlled studies of Olanzapine (Tohen et al, 1999; Tohen et al, 2000). The dosing regimens for other antipsychotics in mania have not been well established.

4. ECT

ECT has been known to improve manic symptoms in a short time. Three prospective studies have assessed efficacy of ECT in acute mania. In all the three studies, ECT was found to be efficacious (Small et al, 1988; Mukherjee et al, 1994; Sikdar et al, 1994). Earlier retrospective comparisons of outcome in mania have also suggested similar results (Black et al, 1987; Thomas et al, 1982). There is evidence to suggest that ECT may be efficacious in treatment of mixed states (Ciapparelli et al, 2001; Devanand et al, 2000; Gruber et al, 2000).

5. BENZODIAZEPINES

Benzodiazepines have been studied in randomized controlled trials for treatment of acute bipolar mania (Chouinard et al, 1993; Meehan et al, 2001; American Psychiatric Association, 2002). Clonazepam and lorazepam have been studied alone and in combination with lithium. Interpretation of many of these studies is limited by small samples, short treatment durations, concomitant antipsychotic use, and difficulties in distinguishing specific antimanic effects from nonspecific sedative effects. Overall, these studies suggest that the sedative effects of benzodiazepines make them effective treatment adjuncts while awaiting the effects of a primary antimanic agent to become obvious. Lorazepam is well absorbed after intramuscular injection and is particularly useful for the management of agitation.

6. COMBINATION TREATMENT

Combination therapy is widely practiced in clinical settings but has not been subjected to rigorous
test in well designed drug trials. However, controlled trials of lithium plus an antipsychotic and of valproate plus an antipsychotic suggest greater efficacy or a more rapid onset of action with these combinations than with any of these agents alone (Scharman et al, 1997; Sachs et al, 2001; Muller-Oerlinghausen et al, 2000).

A1.2. SUMMARY

Goals of treatment include
• Control of symptoms
• Return to normal levels of functioning
• Safety of the patient and others

The clinician has three pharmacological choices
• Mood Stabilizers especially Lithium or Valproate
• Antipsychotics preferably atypical ones especially Olanzapine or Risperidone
• Benzodiazepines e.g. clonazepam or lorazepam

Here, the patients can be divided into two groups
• Those with first episode or where history of response/ non-response to previous treatment is unknown
• Those with 'breakthrough' episodes (vide infra)

Treatment recommended for the first group
• either lithium plus an antipsychotic or valproate plus an antipsychotic like Olanzapine or Risperidone
• Or monotherapy with lithium, valproate, or an antipsychotic
• Alternatives include carbamazepine or oxcarbazepine in lieu of lithium or Valproate and ziprasidone or quetiapine in lieu of another antipsychotic
• Short-term adjunctive treatment with a benzodiazepine
• Antidepressants may precipitate or exacerbate manic or mixed episodes and should be tapered and discontinued unless strongly indicated due to some other reason.

Selection of the initial treatment should be guided by clinical factors like the following
• illness severity
• rapid cycling
• psychosis
• patient preference
• type of affective state e.g. mixed/ dysphoric
• ability/ inability of patient to take oral medication

For patients who, despite having received the aforementioned medications, experience a manic or mixed episode (i.e., a "breakthrough" episode), the following guidelines can be recommended
• Optimize the medication (essentially the mood stabilizer) dose using clinical and laboratory parameters including support of serum drug levels
• Introduction or resumption of an antipsychotic
• Adjunctive benzodiazepine.
These strategies are likely to be effective in majority of patients. However, if these fail, alternative treatment options include

- Carbamazepine or oxcarbazepine in lieu of an additional first-line medication
- Clozapine

ECT, especially in pregnant women, (probably, the treatment of choice).

**A2. DEPRESSIVE EPISODE**

**A2.1. Review of literature**

Medications which have been systematically studied in bipolar depression are lithium, anticonvulsants, antidepressants and ECT. The aims and assessment for the treatment are same as in mania. The important concern while using/choosing a treatment for bipolar depression is its safety in not producing a hypomanic or a manic switch and worsening the course of the disorder.

Somatic treatment for acute depressive episode includes the following options

1. Lithium
2. Antiepileptics i.e. Valproate, Carbamazepine, Lamotrigine, Topiramate
3. Anti depressants
4. Electroconvulsive Therapy
5. Antipsychotics

**1. LITHIUM**

Eight of the nine placebo controlled, cross over designed studies of lithium have suggested a superior efficacy over placebo. A systematic review of these studies utilizing more realistic criteria for response, reported response rates to be 36% (Zornberg & Pope, 1993). It takes about 6-8 weeks for the onset of antidepressant actions of lithium (Zornberg & Pope, 1993).

**2. ANTIEPILEPTICS**

**a) DIVALPROEX AND SODIUM VALPROATE**

No controlled studies have been published. Divalproex yielded an aggregate of 30% response rate in four open studies in depressed patients (McElroy & Keckl 993). Combination of divalproex plus an SSRI is an effective strategy for management of breakthrough depression during maintenance treatment of bipolar I disorder (Bowden et al, 2000).

**b) CARBAMAZEPINE**

Carbamazepine has been studied in bipolar depression in 78 patients in controlled trials though the interpretation of the results is limited by the fact that both unipolar and bipolar depression cases were enrolled. One can conclude that carbamazepine exerts mild to moderate antidepressant effects in bipolar depression (Post et al, 1986; Kramlinger & Post, 1989).

**c) LAMOTRIGINE**

In a well designed Lamotrigine monotherapy double blind study in 195 bipolar depression patients, lamotrigine at doses of 50 mg/d and 200 mg/d showed significantly better results on Montgomery Asberg Depression Rating Scale. Though both doses were effective, the aggregate response was greater with 200 mg/day dose and improvements were noticed earlier in this group (Calabrese et al, 1999).

One double blind, placebo controlled crossover study also found lamotrigine superior to placebo and gabapentin in bipolar depressed patients (Frye, et al, 2000).

An open study of patients with refractory bipolar disorder showed good/marked response in 48%
and moderate response in 20% of 40 patients (Calabrese et al, 1999).

ADVERSE EFFECTS:

Headache is the only side effect consistently more common with lamotrigine than placebo. Other common adverse effects include nausea and xerostomia (Calabrese et al, 2000; Calabrese et al, 1999). Rashes both benign and serious ones like Stevens Johnson Syndrome and toxic epidermal necrolysis can occur in patients on lamotrigine. They are more likely to occur early in the treatment but the risk remains throughout the treatment and one must remain vigilant.

DOsing:

Lamotrigine requires slow dose titration due to risk of serious rash. As a monotherapy it is usually initiated at 25 mg/day for first 2 weeks, then 50 mg/day for next 2 weeks. Further increments of 50 mg can be made per week according to response and tolerability. Maximum recommended dose as a monotherapy is 600 mg/day. Lamotrigine when used in presence of valproate requires a slow titration as pharmacokinetic interactions lead to increase in lamotrigine levels. The dose schedule should be cut to half. Conversely, when administered with carbamazepine, the dose schedule needs to be doubled because of enzyme induction by carbamazepine (Matsuo, 1999; Guberman et al, 1999; Messenheimer et al, 1998; Fitton et al, 1995; Rambeck & Wolf, 1993).

d) TOPIRAMATE

No placebo controlled trials are available, but several trials have suggested efficacy as an add on therapy (McIntyre et al, 2000; Hussein, 1999).

3. ANTIDEPRESSANTS

a) SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Few systematic studies are there in bipolar depression.

Fluoxetine was compared with imipramine and placebo in 89 patients of bipolar depression. The response rates with Fluoxetine were significantly better than imipramine and placebo (Cohn et al, 1989).

Paroxetine has been studied as an add on treatment in three double blind studies. In one study, patients were randomly assigned to receive a combination of lithium and divalproex or the other group where Paroxetine was added to patients maintained earlier on lithium or divalproex. Both treatments were equally effective at week 6 (Young et al 2000). Nemeroff et al (2001) found paroxetine or imipramine plus lithium no different overall from lithium plus placebo. Paroxetine plus lithium and imipramine plus lithium were superior to lithium alone in the subset of patients with serum levels of lithium below 0.8 mEq/L.

Retrospective studies of fluoxetine, venlafaxine and paroxetine suggest response rates above 50% (Amsterdam, 1998; Amsterdam et al, 1998; Baldassano et al, 1995). Citalopram in a 24 week, open label trial as add on treatment was found to improve 64% of 33 patients who completed 8 week acute phase treatment.

b) BUPROPION

Small open studies and one small, placebo controlled study indicate that bupropion is effective in bipolar depression (Haykal, 1990; Mendeth, 1983). Another study found equal efficacy for bupropion and desipramine, but lower rates of manic switching with bupropion (Sachs et al, 1994), a finding which was not replicated in another study (Fogelson et al, 1992).

c) TRICYCLIC ANTIDEPRESSANTS (TCA)

TCAs have equal rates of efficacy in the two forms of depression i.e. Unipolar and Bipolar (Croughan et al, 1988). In aggregate, response rates to TCAs have been about 50 to 70% (Montgomery et al,
2000). One prospective randomized study of TCAs in bipolar disorder indicated higher switch rates than reported with other classes of antidepressants (Wehr et al, 1987).

D) MONO AMINE OXIDASE INHIBITOR (MAOI)

Moclobemide was effective in 60% of BP depressed patients compared with a 49% response rate for various comparator drugs (Angst & Stahl, 1992).

Tranylcypromine was more effective than imipramine in both randomized and a cross over trials (Himmelhoch et al, 1991; Pickar et al).

4. ELECTROCONVULSIVE THERAPY (ECT)

Several controlled studies of ECT in bipolar depressed patients have found ECT to be as or more effective than MAOIs, TCAs or Placebo. ECT should be considered for patients with severe bipolar depression especially when associated with psychotic symptoms.

5. ANTIPSYCHOTICS

Olanzapine monotherapy and olanzapine and fluoxetine combination therapy were both significantly better than placebo in an 8-week double blind study of 830 patients with acute bipolar depression.

A2.2. Summary

Goals of treatment include

- Remission of the symptoms
- Return to normal levels of psycho-social functioning
- To avoid precipitation of a manic or hypomanic episode

Like in Manic/ Mixed episode, the acute management of depressed patients can be divided into two groups

- Those with first episode or where history of response/ non-response to previous treatment is unknown
- Those with 'breakthrough' episodes (vide infra)

The pharmacological treatment for bipolar depression of the first group includes

- Either lithium or lamotrigine.
- For bipolar disorder, standard antidepressants such as SSRIs have been studied as add-ons to mood-stabilizers such as Lithium or Valproate. Antidepressant monotherapy is not recommended in view of the risk of precipitating a switch into mania. For severely ill patients, some clinicians initiate treatment with lithium and an antidepressant simultaneously, although there are limited data to support this approach.
- In patients with life-threatening physical complications, suicidality, or psychosis, ECT also represents a reasonable alternative. In addition, ECT is a potential treatment for severe depression during pregnancy.
- Selection of the initial treatment should be guided by clinical factors such as illness severity, by associated features (e.g., rapid cycling, psychosis), and by patient preference and side effect profiles.
- Small studies have suggested that interpersonal therapy and cognitive behavior therapy may also be useful when added to pharmacotherapy during depressive episodes in patients with bipolar disorder. There have been no definitive studies to date of psychotherapy in lieu of pharmacotherapy for bipolar depression.

For the second group, i.e. patients who, despite having received maintenance medication
treatment, suffer a breakthrough depressive episode, options include

- optimize the dose of the maintenance medication
- add lamotrigine, bupropion, or paroxetine
- add other newer antidepressants (e.g., another SSRI or venlafaxine) or an MAOI.
- ECT should be considered for patients with severe or treatment-resistant depressive episodes or for episodes with catatonic features.
- Patients with psychotic features during a depressive episode usually require adjunctive treatment with an antipsychotic medication. ECT represents a reasonable alternative.
- Tricyclic antidepressants may carry a greater risk of precipitating a switch into hypomania or mania and hence are best avoided.

Existing data suggest that for patients with bipolar II disorder, antidepressant treatment, either alone or in combination with a maintenance medication, is less likely to result in a switch into a hypomanic episode relative to those with bipolar I disorder.

B. LONGITUDINAL MAINTENANCE TREATMENT

The guidelines are presented in the following format:

B1. Review of literature
B2. Summary
B1. Review of literature

Maintenance treatment of patients with bipolar disorder has following goals

- relapse prevention
- reduction of subthreshold symptoms
- reduction of suicide risk
- reduction of cycling frequency and mood instability
- improvement of functioning

Maintenance studies pose two difficulties (not applicable to acute episode studies)

- It is impractical to select a single goal as an adequate index of efficacy
- Few placebo-controlled studies have been conducted, due to ethical reasons (Baldessarini et al., 2000).

Somatic Maintenance treatment comprises the following options

1. Lithium
2. Antiepileptics (Valproate, Lamotrigine, Carbamazepine)
3. Antipsychotic
4. Combinations
5. ECT

1. LITHIUM

Lithium has been claimed to reduce relapse rates in majority of patients (Bastrup et al., 1970; Melia, 1970; Coppen, et al., 1973; Cundall et al., 1972; Prien et al., 1973). These studies raised expectations for lithium therapy unrealistically. A critical look revealed limitations in the design of these studies.

Subsequent large, open, naturalistic studies on the effectiveness of lithium as a maintenance treatment agent in patients with bipolar disorder showed that benefit is there but it is not there in all or
majority of cases and it is not in the form of total symptomatic and functional recovery (Maj et al., 1998; Vestergaard et al., 1998; Markar & Mander, 1989; Harrow et al., 1990; Coryell et al., 1997; Gitlin et al., 1995; Licht et al., 2001). These studies have also reported high dropout rates.

Two recent well designed studies have indicated evidence of efficacy for lithium (Bowden et al., 2000; Calabrese et al., 2001). After initial response, subjects were randomly assigned either to treatment with lithium, placebo, or divalproex (Bowden et al., 2000) or treatment with lithium, placebo, or lamotrigine (Calabrese et al., 2001). The relapse rate into mania was 17% for lithium-treated patients, compared with 41% for placebo-treated patients (Calabrese et al., 2001). However, lithium did not significantly extend time until a new depressive episode in either study and tended to worsen sub-threshold depressive symptoms in the first study (Bowden et al., 2000).

A recent long-term study from India followed up 118 patients for about 11 years and demonstrated that lithium has a definite prophylactic effect on long-term outcome (Kulhara et al., 1999). The authors also observed that psychosocial factors like social support and stress modulate the effectiveness of lithium. Two other studies from India also demonstrated prophylactic efficacy of lithium (Gangadhar et al., 1987; Prakash et al., 1978).

Serum-level guidelines are not well established for maintenance treatment with lithium. In clinical settings, doses and serum levels somewhat lower than those used in treatment of acute mania are generally used (McElroy & Keck, 2000). One randomized study indicated better efficacy for lithium at 0.8-1.0 mEq/liter than at 0.4-0.6 mEq/liter in the prevention of manic episodes although, this did not apply to depressive episodes (Gelenberg et al., 1989). Similarly, an open study reported rates of rehospitalization lower for the patients whose serum levels were consistently above 0.5 mEq/liter compared to those with lower levels (Maj et al., 1998).

2. **ANTIEPILEPTICS**

**DIVALPROEX OR VALPROATE**

In a controlled study (Bowden et al., 2000), there was no significant difference in time until development of any mood episode among patients treated with divalproex, lithium, and placebo. Also two randomized comparisons with lithium are reported (Hirschfeld et al., 1999; Lambert & Venaud, 1992). One randomized, 18-month open study of valproate versus lithium reported a 20% lower rate of new episodes among valproate-treated patients than among lithium-treated patients (Lambert & Venaud, 1992). Divalproex was better on the measures of treatment tolerance. Divalproex and lithium were comparable in a longitudinal 1-year study (Hirschfeld et al., 1999). These findings indicate good efficacy and tolerability of divalproex in maintenance treatment.

There are few data regarding dosing guidelines for maintenance treatment with Valproate.

**LAMOTRIGINE**

Lamotrigine has been studied in an 18-month follow up study of patients who had experienced a manic or hypomanic episode within 60 days of entry into an open treatment (Calabrese et al., 2001). Those improving were randomly assigned to maintenance treatment with lamotrigine, lithium, or placebo. Both lamotrigine and lithium were found superior to placebo for the primary outcome measure i.e. time until additional pharmacotherapy required for treatment of a mood episode. Lamotrigine significantly prolonged the time until a depressive episode (p<0.02), whereas lithium did not (p<0.17) when compared with placebo.

**CARBAMAZEPINE**

Crossover studies have reported carbamazepine to be less effective than lithium in maintenance treatment of bipolar disorder (Denicoff et al., 1997; Stromgren, 1990). A 2.5-year study (Greil et al., 1997) also showed carbamazepine to be inferior to lithium. However, limited data suggests carbamazepine to be nonsignificantly better than lithium among patients with mood-incongruent illnesses.
comorbidity, mixed states, and bipolar II disorder (Greil et al, 1998).

3. ANTIPSYCHOTIC MEDICATIONS

A randomized, open study of clozapine plus usual care compared with usual care alone has indicated benefits of maintenance clozapine treatment over 1 year (Suppes et al, 1999). A placebo-controlled study of prophylactic treatment with flupenthixol plus lithium compared with lithium alone (Esparon et al, 1986) did not show any benefit of adding the antipsychotic.

4. ECT

Many case reports and case series have endorsed its utility (Bush et al, 1996; George et al, 2000; Godemann & Hellweg, 1997; Chanpattana, 2000; Decina et al, 1987; Kramer, 1999; Rhodes, 2000; Gupta et al, 1998; Barnes et al, 1997; Jaffe & Dubin, 1992; Karlner, 1965; Clarke, 1995). A review (Kramer, 1999) reports nine patients with bipolar disorder having received maintenance ECT following successful index treatment: 78% showed at least some improvement, and 33% showed much improved.

Schwarz et al. (Schwarz et al, 1995) used a case-control approach. He compared depressed patients who had responded to ECT and then continued receiving maintenance ECT to patients who received no maintenance ECT. Another comparison group received only pharmacotherapy. In each group, four out of 21 patients had bipolar disorder. Although this number was too small for subgroup analysis, the rate of rehospitalization decreased by 67% for the study group as a whole with inclusion in maintenance ECT group.

Gagne et al. (Gagne et al, 2000) also used a case-control approach to compare patients who received maintenance pharmacotherapy alone with those who received maintenance ECT in combination with maintenance pharmacotherapy in depressed patients who had responded to an acute course of ECT. Out of 58 depressed patients in the study, 12 had bipolar disorder. For the group as a whole, patients receiving maintenance ECT had a less probability of relapse or recurrence at 2 and 5 years than patients receiving only pharmacotherapy. Appropriate statistical analysis did not demonstrate differences between patients with bipolar disorder and those with major depressive disorder.

Thus, the findings suggest that maintenance ECT may be helpful for individual patients with severe bipolar illness who do not tolerate or do not respond to maintenance pharmacotherapy.

Bhaskaran from India (Bhaskaran, 1963) reported of a case whose maintenance phase needed monthly ECT for remission.

B2. Summary

Goals of treatment include

- relapse prevention
- reduction of sub threshold symptoms
- reduction of suicide risk
- reduction of cycling frequency and mood instability
- improvement in overall functioning

Options with the best empirical evidence to support their use as maintenance treatments include.

- lithium or Valproate
- lamotrigine, carbamazepine, oxcarbazepine.
- In general, if one of these medications was used to achieve remission from the most recent depressive or manic episode, it should be continued.
- Maintenance ECT may also be considered for patients whose acute episode responded to ECT.

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• Selection of the initial treatment should be guided by clinical factors such as illness severity, by associated features (e.g., rapid cycling, psychosis), and by patient preference as well as side effect profiles.

• For patients treated with an antipsychotic medication during the preceding acute episode, the need for ongoing antipsychotic treatment should be reassessed upon entering the maintenance phase. Since antipsychotic agents, particularly typical antipsychotics, may cause tardive dyskinesia with long-term use, they should be slowly tapered and discontinued unless they are required to control persistent psychosis or provide prophylaxis against recurrence. While maintenance therapy with atypical antipsychotics may be considered, there is as yet no definitive evidence that their efficacy in maintenance is comparable to that of mood stabilizers such as lithium or valproate.

• Psychosocial intervention may be helpful in adherence, lifestyle changes, and early detection of prodromal symptoms, interpersonal difficulties, and adaptation to a chronic illness, regulation of self-esteem, and management of marital as well as other psychosocial issues.

• For patients who experience either continuing high levels of subthreshold symptoms or a breakthrough episode of illness, the addition of another maintenance medication, an atypical antipsychotic, or an antidepressant may be useful. The existing data is insufficient to support one combination over another. Maintenance ECT may also be considered for patients whose acute episode responded to ECT.

C. COURSE SPECIFIERS VIZ. RCAD & SAD

RAPID CYCLING

Rapid cycling Affective Disorder (RCAD) is more difficult to treat than non RCAD (Avasthi et al, 1999; Cole et al, 1993). The causative agents like antidepressant medications and general medical conditions should be looked for and eliminated if possible or minimized (Dunner & Fieve, 1974; Himmelhoch et al, 1991; Cohn et al, 1989).

It has been suggested that the low efficacy of Lithium in RCAD (Peet, 1994; Cole et al, 1993; Okuma et al, 1981; Denicoff et al, 1997; Bauer et al, 1994) is due to the fact that most of the episodes in this disorder are depressive in nature (Dunner et al, 1976; Shapiro et al, 1989) and both Lithium and Valproate and also probably Carbamazepine are less effective against depressive aspects of RCAD. An open study showed Divalproex to be more effective in those entering the study in manic state than those in depressed state among 107 rapid-cycling patients followed up for a 17 months (Calabrese & Delucchi, 1990; Calabrese et al, 1993).

In a well-designed study of 182 patients with RCAD on maintenance treatment (Calabrese et al, 2000), lamotrigine was superior to placebo especially among patients (Lee, 1998) with bipolar II disorder. Outcome was measured in terms of the median time to discontinuation and the rate of study completion without relapse; such favorable outcome was not seen in those with bipolar I disorder (Mohan et al, 1996).

These data provide support for the use of lamotrigine in rapid-cycling bipolar disorder especially those with BP II type of course.

There is no such data from Indian subcontinent so far regarding effect of Lamotrigine. However, a descriptive study from India (Mathew et al, 1995) proposed based on their findings that RCAD appears to be a severer form of BPAD. Another study from India (Das et al, 2002) did not find differential efficacy of Carbamazepine in non-RCAD vs. RCAD. They proposed based on this observation that kindling hypothesis of RCAD is not supported.

Vanelle et al. (1994) prospectively followed seven individuals with bipolar disorder (four with a rapid-cycling course) with medication-resistance or medication-intolerance for more than 18 months.
of maintenance ECT treatment. The mean number of mood episodes significantly decreased during the maintenance ECT course. None of the patients failed to show a response to maintenance ECT.

SEASONAL AFFECTIVE DISORDER

Seasonal changes in mood and behavior are well recognized and documented (Magnusson, 2000). The degree to which seasonal changes affect parameters of mood, energy, sleep length, appetite, food preference or the wish to socialize with other people is called seasonality (Kasper et al, 1989). Rosenthal et al (1984) introduced the term Seasonal Affective Disorder to describe a condition characterized by recurrent depressive episodes that recur annually at a specific season of the year (Blehar & Levy, 1990). Most seasonal mood disorders are unipolar and majority of winter depressives do not experience manic or hypomanic episodes during summer. Researchers have also described patients with recurrent summer depression at different places (Srivastava & Sharma, 1998; Dam et al, 1998). The concept of seasonality of affective disorders has been incorporated in DSMIV as a course specifier for bipolar disorders.

There is some evidence that the patients of seasonality in affective disorders in Indian conditions may be different (Gupta, 1988; Magroob et al, 1988; Jam et al, 1992 and Srivastava & Sharma, 1998). Reports from the Indian subcontinent have reported consistently reverse patterns of Seasonal Affective Disorder and seasonality of episodes (Gupta, 1988; Srivastava & Sharma, 1998; Avasthi et al, 2001; and Avasthi et al, 2003). Also, reports from India haven’t found atypical vegetative symptoms as reported in other studies. The entire range of treatments for major depressive disorder may be used to treat seasonal depression either alone or in combination with light therapy. In outpatients with winter depression, light therapy alone may be used (Rosenthal et al, 1990). It is recommended that patients with more severe forms of seasonal depression should be treated with psychopharmacologic measures with optional use of light therapy as an adjunct (Baldessarini, 1999).

D. GENERAL GUIDELINES OF MANAGEMENT

D1. FORMULATION OF A TREATMENT PLAN (American Psychiatric Association, 2002)

Initial treatment planning requires a thorough assessment of the patient, with the following goals

- Ensuring safety of the patient and those around him or her
- Attention to possible comorbid psychiatric or medical illnesses
- Understanding longitudinal history of the patient's illness
- Maximizing patient functioning
- Minimizing sub threshold symptoms and adverse effects of treatment

The following subheads describe the different components that should be included in a comprehensive treatment planning for BPAD.

The general guiding principles include, assessment of

- the cross-sectional (i.e., current clinical) status
- longitudinal (i.e., frequency, severity, and consequences of past episodes) history
- potential beneficial and adverse effects of available options
- patient preferences
- ongoing changes as new information becomes available
- insight of the patient and need for the caregivers to take decision about need for treatment

The general goals of treatment of bipolar disorder are

- assess and treat acute exacerbations
• prevent recurrences
• improve inter-episode functioning
• provide assistance, insight, and support to the patient and family

D2. SPECIFIC COMPONENTS OF PSYCHIATRIC MANAGEMENT (American Psychiatric Association, 2002)

D2A. Diagnostic evaluation for associated conditions requiring specific management
D2B. Therapeutic alliance
D2C. Monitor treatment response
D2D. Provide education to the patient and the family
D2E. Enhance treatment compliance
D2F. Promote awareness of stressors and regular patterns of activity and sleep
D2G. Work with the patient and the caregivers to anticipate and address early signs of relapse
D2H. Evaluate and manage functional impairments

D2A. Diagnostic evaluation for associated conditions requiring specific management

[i]. Assessment of Suicide Risk and determination of treatment setting

Suicide rates in patients with bipolar I disorder are very high (Isometsa et al, 1994; Dilsaver et al, 1994; Strakowski et al, 1996; Muller-Oerlinghausen et al, 1996; Baldessarini et al, 1999; Angst & Preisig, 1995); hence, a careful assessment of the patient's risk for suicide and corresponding management is crucial. This includes assessment for

• suicidal ideation
• intention
• planning
• access to means of committing suicide
• lethality of these means
• substance abuse
• other psychiatric co morbidity
• presence of command hallucinations
• prior suicide attempts
• need for hospitalization, even involuntary
• social support

Patients and their caregivers should be educated that during mania, patients may indulge in reckless behavior and free access to cars, credit cards, bank accounts, and telephones or cellular phones, weapons, etc. can be hazardous. Close monitoring and documentation of the therapeutic decision are mandatory.

[ii]. Psychotic features

Antipsychotic medication is frequently prescribed in mania with psychotic features although evidence suggests that mood stabilizers alone are enough (McElroy et al, 1996).

[iii]. Catatonia

Antipsychotic have not shown satisfactory efficacy (Hawkins et al, 1995) in catatonia in manic episodes. Lorazepam has exhibited good promise (Rosebush et al, 1990; Northoff et al, 1995; Bush et
al, 1996; Lee, 1998). In the event of catatonia not responding to lorazepam, ECT may be given (Hawkins et al, 1995).

[iv]. Substance use disorders

Both BPAD and substance related disorder should be treated simultaneously (American Psychiatric Association, 2002). The complications of alcohol and intravenous drug abuse may have pharmacokinetic implications in the pharmacotherapy of BPAD (Hagan & Des, 2000).

[v]. Comorbid psychiatric conditions

As a general principle, BPAD and the comorbid condition (personality disorder, anxiety disorder, etc.) should be treated simultaneously (American Psychiatric Association, 2002).

[vi]. Comorbid Medical-Surgical conditions and concurrent medications

Conditions like thyroid abnormalities and neurological diseases may have important aetiological and therapeutic implications (Strakowski et al, 1994; Peet & Peters, 1995; Cozza & Armstrong, 2001). Drugs like steroids, diuretics, anti-inflammatory agents may have implications for modifications in pharmacotherapy of BPAD.

[vii]. Pregnancy

There are many important considerations:
- Contraception should be practiced while taking drug treatment for BPAD. Further, carbamazepine enhances metabolism of oral contraceptives.
- Pregnancy should be planned in consultation with the treating psychiatrist.
- If the decision to discontinue medication e.g. lithium is made, tapering must be done slowly over extended period of time (Viguera et al, 2000).
- Terratogenic effects of lithium, carbamazepine and valproate are well known (Cohen et al, 1994; Holmes et al, 2001; Arpino et al, 2000).
- Little data are available about the terratogenic effects of newer drugs like bupropion, mirtazapine, venlafaxine, lamotrigine, risperidone, olanzapine, clozapine, quetiapine and ziprasidone (American Psychiatric Association, 2002).
- The traditional drugs like tricyclic antidepressants, high potency antipsychotics i.e. haloperidol and trifluoperazine, SSRIs especially fluoxetine and citalopram and to some extent benzodiazepines like diazepam are considered relatively free of terratogenicity (American Academy of Pediatrics Committee on Drugs, 2000; Wisner et al, 1999). ECT is considered safer than medications for both antimanic as well as antidepressant effects (Shnider & Levinson, 1993).
- When decision is taken to continue lithium during pregnancy, more frequent serum level monitoring has to be done due to marked changes in fluid volume especially during delivery.
- Prophylactic agents like lithium and valproate may prevent postpartum mood episodes (Cohen et al, 1995).
- Breast-feeding is best avoided in mothers on lithium (American Academy of Pediatrics Committee on Drugs, 2000) and lamotrigine (Tomson et al, 1997). Carbamazepine, valproate, antidepressants, antipsychotics and benzodiazepines are generally considered safe (American Psychiatric Association, 2002).

D2B. THERAPEUTIC ALLIANCE

Establishing a supportive relationship is very important for the proper management of an individual patient. An obvious gain from this alliance is that it allows new episodes to be identified earlier. It also
provides a medium to deliver the psycho-education more effectively and eventually achieves co-
operation and compliance on the part of the patient party.

D2C. MONITOR TREATMENT RESPONSE

This variable is especially important in bipolar disorder because of potential for dropping out due
to the fact that the patient may misinterpret improvement from mania to normality or shift to depression
as worsening or as indicative of non-response to ongoing treatment.

D2D. Provide education to the patient and the family

The salient considerations in education of caregivers and the patient include the following (American
Psychiatric Association, 2002).

• Their ability to understand and retain this information varies over time.
• The patients also vary in their ability to accept and adapt to the idea that they have an illness that
  requires long-term treatment.
• Education should therefore be an ongoing process in which the psychiatrist gradually but persistently
  introduces facts about the illness.
• Printed material on cross-sectional and longitudinal aspects of bipolar illness and its treatment
  can be helpful.

D2E. Enhance treatment compliance

Patients with this disorder are frequently ambivalent about treatment. This ambivalence often
takes the form of noncompliance with medication and other treatments, which is a major cause of
relapse.

Medication side effects, cost, and other demands of long-term treatment may be burdensome
and need to be discussed realistically with the patient and family members. Many side effects can be
corrected with careful attention to dosing, scheduling, and preparation. Troublesome side effects that
remain must be discussed in the context of an informed assessment of the risks and benefits of the
current treatment and its potential alternatives.

D2F. Promote awareness of stressors and regular patterns of activity and sleep

The following factors under this head have been observed to be useful

• The patients and their caregivers benefit from an understanding of the role of psychosocial stressors
  and other disruptions; literature suggests their role in all phases of the illness.
• Generation of coping strategies for these stressors
• Recognize distress or dysfunction in the family of a patient with bipolar disorder, since such
  ongoing stress may exacerbate the patient’s illness or interfere with treatment.
• Social rhythm disruption with disrupted sleep/wake cycles may specifically trigger manic (but not
depressive) episodes.

D2G. Work with the patient and the caregivers to anticipate and address early signs of relapse

• Recognize early signs and symptoms of manic or depressive episodes
• Enhance mastery over his or her illness and help ensure that adequate treatment is instituted as
  early as possible in the course of an episode.
• Early markers of episode onset vary from patient to patient but are often usefully predictable
  across episodes for an individual patient.
• The identification of these early prodromal signs or symptoms is facilitated by the presence of a
  consistent relationship between the psychiatrist and the patient as well as a consistent relationship

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• The use of a graphic display of life events and mood symptoms (mood graph) can be very helpful in this process. Such a life chart provides a valuable display of illness course and episode sequence, polarity, severity, frequency, response to treatment, and relationship (if any) to environmental stressors.

D2H. Evaluate and manage functional impairments

• Following mood episodes, the patients may require assistance in addressing the psychosocial consequences of their actions.

• Bipolar disorder is associated with functional impairments even during periods of euthymia, and the presence, type, and severity of dysfunction should be evaluated.

• Impairments can include deficits in cognition, interpersonal relationships, work, living conditions, and other medical or health-related needs.

• Patients should also be encouraged to set realistic, attainable goals for themselves in terms of desirable levels of functioning.

CONCLUSION

The paper has attempted to incorporate the recent research, mainly western, to provide an updated guideline for treatment of various aspects of BPAD. The guidelines for treatment of manic episode are more straightforward and evidence-based while those for depressive episode have some unresolved issues and those are likely to be ironed out by future research. Any such type of document should only be used as broad guide and the specific clinical decisions and recommendations of a given case have to be worked out on individual basis taking into account the unique socio-demographic and clinical characteristics of the case.

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