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Bipolar disorder: a review of current U.S. Food and Drug Administration approved pharmacotherapy

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ABSTRACT

Bipolar disorder (BD) is a chronic disorder which usually has its onset in early adulthood. At one end of the spectrum is depression and at other is mania. Like many psychiatric illnesses, it is not treatable but its symptoms are completely manageable with medications. Commonly used drugs are mood stabilizers and atypical antipsychotics along with adjunctive medications such as anxiolytics and antidepressants. In general, a combination of these drugs is used for treatment. These drugs have significant adverse effects which add to the burden of the disease. Presently, there are 11 US Food and Drug Administration - approved drugs for management of acute mania, 3 for bipolar depression and 7 for bipolar maintenance. This review article details the use of these drugs in BD.

Keywords: Bipolar disorder, U.S. Food and Drug Administration, Mood stabilizers, Atypical antipsychotics, Adverse effects, Bipolar depression

INTRODUCTION

Bipolar disorder (BD), also known as bipolar affective disorder, thymergasia, cyclophrenia (originally called manic-depressive illness), is a psychiatric disorder characterized by alternate periods of elevated mood or "mood swings" and periods of depression. It is a chronic debilitating condition that has a significant impact on social, occupational, and overall quality of life of the patient. This review article focuses on the current US Food and Drug Administration (FDA) approved treatment strategies for BD and adverse effects associated with them (Figure 1).¹

ETIOPATHOLOGY

BD affects men and women equally, and it has its onset in adolescence and early adulthood.²

The etiology of BD is multifactorial. Genetic, neurochemical, and environmental factors interact at many levels to play a role in the onset and progression of this disorder.

BD tends to be familial. About half the people with BD have a family member with a mood disorder. Findings strongly point toward heterogeneity, with different genes being implicated in different families.³ It may involve neurotransmitters like norepinephrine, serotonin, dopamine, glutamate, and gamma-aminobutyric acid.⁴⁻⁶ Recent life events and interpersonal relationship conflicts may contribute to the likelihood of onset or recurrence of bipolar mood episodes in a person with a genetic predisposition. Functional magnetic resonance imaging findings suggest that abnormal modulation between ventral prefrontal and limbic regions, especially the amygdala, likely contribute to poor emotional regulation and mood symptoms.⁷

DIAGNOSIS

The diagnosis of BD is generally based on clinical signs and symptoms of the patient. A detailed history and thorough physical as well as mental status examination is essential for the diagnosis. More often, it is necessary to collect the patient's behavioral history from family members and

friends for a complete assessment. Common rating scales used for mania are Young Mania Rating Scale and Schedule for Affective Disorders and Schizophrenia-Change Manic Syndrome Subscale. The differential diagnosis of BD is quite challenging since the presentation of symptoms is similar to other psychotic disorders, personality disorders, and substance abuse. The classification of BD according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is given in Table 1.⁸

A major depressive episode is essentially characterized by the presence of depressed mood or markedly diminished interest in all activities for most of the day, nearly every day, over a 2 weeks period. The patient may experience significant changes in his weight and sleep patterns which may either increase or decrease. There may be excessive fatigue, psychomotor agitation or retardation, and feelings of worthlessness or guilt. There are recurrent thoughts of death and suicidal ideas which may even culminate in patient attempting suicide. On the other hand, an episode of mania includes a distinct period

during which the person is in an abnormally and persistently elevated or irritable mood, and there is an increased goal-directed activity lasting at least 1 week and present most of the day, nearly every day. There may be distractibility, decreased need for sleep, flight of ideas, feelings of grandiosity, and excessive involvement in pleasurable activities that have a high risk of painful consequences which the patient is not able to appreciate. A hypomanic episode is same as a manic episode, except it is diagnosed when symptoms of mania exist for 4 or <4 days. Between episodes, many people with BD are free of symptoms.

Sometimes, a mood episode may include features of both mania and depression. In DSM-5, this is labeled as “with mixed features.”

In recent years, there has been a continuous effort to develop investigations which may help in early diagnosis of BD. A novel imaging technique of quantitative mapping of T1 relaxation in the rotating frame (T1ρ) showed that T1ρ values were elevated in the cerebral white matter and cerebellum in the BD patients.⁹ A recent study identified sex-specific urinary biomarkers for diagnosing BD. The male-specific biomarkers panel consisted of α-hydroxybutyrate, choline, formate, and N-methylnicotinamide, and the female-specific panel of biomarkers, included α-hydroxybutyrate, oxaloacetate, acetone, and N-methylnicotinamide.¹⁰

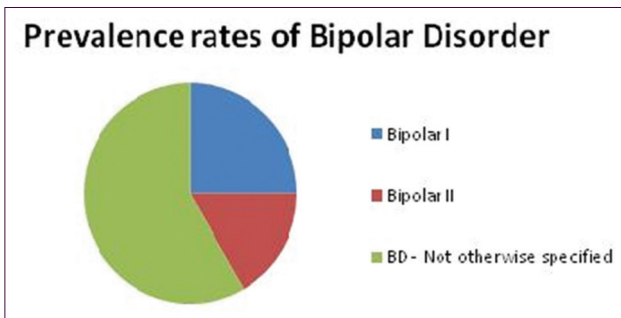


Figure 1: The aggregate lifetime prevalence rates of bipolar disorder according to the 2011 World Health Organization’s World Mental Health survey.

TREATMENT

The treatment for BD is challenging considering the long protracted course of illness, significant adverse drug reactions, cost of prolonged treatment, and consequently patient non-compliance. Figure 2 shows the different

Table 1: DSM-5 classification of BD.

Type	Definition
Bipolar I disorder	At least one manic episode is necessary to make the diagnosis; depressive episodes are common, but are unnecessary for the diagnosis
Bipolar II disorder	No manic episodes, but one or more hypomanic episodes and one or more major depressive episodes
Cyclothymia	A history of hypomanic episodes and periods of depression for at least 2 years that do not meet the criteria for major depressive episode
Secondary mood disorders	Includes: 1. Substance/medication-induced BD (onset either during intoxication or during withdrawal) 2. BD due to another medical condition.
Other specified bipolar and related disorder	Patients experience significant symptoms that do not meet diagnostic criteria of any of the above. It includes: 1. Short-duration hypomanic episodes (2-3 days) and major depressive episodes 2. Hypomanic episodes with insufficient symptoms and major depressive episodes 3. Hypomanic episode without prior major depressive episode 4. Short-duration cyclothymia (<2 years).
Unspecified bipolar and related disorder	Patients experience significant symptoms that do not meet diagnostic criteria of any of the above. It includes presentations in which there is insufficient information to make a more specific diagnosis like in emergency settings

BD: Bipolar disorder, DSM: Diagnostic and Statistical Manual of Mental Disorders

modalities currently available for the treatment of BD. While psychotherapy and lifestyle modifications are important, pharmacotherapy forms the mainstay of treatment. The drug therapy for BD can be divided into three groups: treatment for acute mania, treatment for acute depression, and maintenance therapy.¹¹ Routine baseline investigations are conducted before starting treatment. Tests are also conducted to rule out toxins, substance abuse, contraindications to treatment, and other neurological and medical disorders which may contribute to mood changes such as brain tumor, thyroid conditions, etc. Various drugs currently approved for treatment of BD are given in Table 2.

MOOD STABILIZERS

Lithium

The history of lithium use in psychiatric illnesses goes back to late 19th century when physicians used lithium salts to treat sporadic cases of mania as well as depression. The credit for the modern revival of lithium in the treatment of acute mania goes to Australian psychiatrist, Dr. John Cade, in 1949, after his serendipitous observation that lithium calmed rodents during his experiments.¹² The breakthrough of using lithium in manic-depressive illness came in 1952, when Strömngren and Schou conducted randomized drug trial for the effectiveness of lithium in mania patients.¹³ After gathering evidence from multiple controlled clinical trials, FDA approved lithium for the treatment of mania in 1970 and for maintenance therapy in 1974.

Lithium is considered the first line drug for acute mania and bipolar maintenance therapy. Lithium is an effective treatment for reducing the risk of suicide in people with

mood disorders.¹⁴ But, it is less efficacious in patients with manic episodes with mixed features, rapid cycling disorder, and co-morbid substance abuse. Also, it is less effective in patients with severe psychotic or secondary manias, in adolescents and in patients who have had 3 or more prior episodes. Lithium is found to be superior to anticonvulsant mood stabilizers in the treatment of manic episodes, but it was not effective in treating depressive episodes.¹⁵

The main drawback of lithium is the narrow therapeutic index which necessitates a stringent monitoring of serum levels of the drug. The common side effects associated with lithium use are nausea, vomiting, fine motor tremors, memory deficits, excessive salivation, QTc prolongation, acne, and alopecia. In various comparative studies conducted on the drugs used in BD treatment, weight gain with lithium appears to be more than that with lamotrigine, but less than that with valproate and olanzapine. Lithium is concentrated in thyroid gland, so it may cause direct damage to the gland during treatment. Thyroid abnormalities are significantly higher in women than in men.¹⁶ Studies have concluded that the rate of hypothyroidism in lithium-treated patients is significantly higher than those not treated with lithium. Subclinical hypothyroidism is more prevalent than clinical hypothyroidism.¹⁷ Approximately, 1-2% of lithium-treated patients develop hyperthyroidism.¹⁸ A few trials have also provided evidence that long-term lithium therapy may sometimes lead to hyperparathyroidism and hypercalcaemia.¹⁹ Most patients receiving lithium have polydipsia and polyuria, reflecting mild benign nephrogenic diabetes insipidus. A recent systematic review concluded that lithium should be continued even in the presence of long-term adverse renal effects.²⁰ In severe cases, lithium intoxication can result in irreversible central nervous system, cardiac or renal problems, and even death. There is an increased incidence of cardiovascular malformations, particularly Ebstein’s anomaly in the neonate, if mother was treated with lithium during pregnancy.²¹

Laboratory monitoring includes baseline complete blood count (CBC), renal and thyroid indices, with re-evaluation at 3 and 6 months and then every 6-12 months thereafter. Serum lithium concentrations to be checked as clinically indicated.²²

Valproate

Valproate, an anticonvulsant, is efficacious for acute manic and mixed episodes in adults. It is becoming the leading

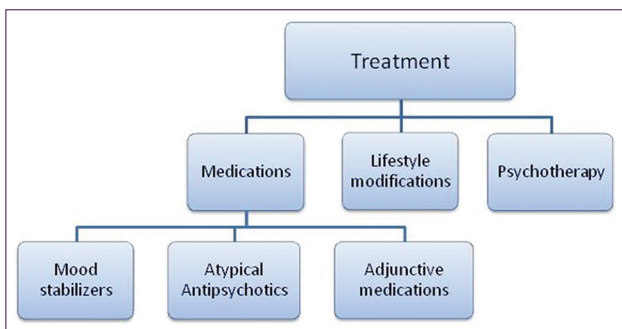


Figure 2: Treatment modalities for bipolar disorder.

Table 2: US FDA-approved drugs for BD.

Acute mania	Maintenance therapy	Bipolar depression
Mood stabilizers – Lithium, valproate, carbamazepine, lamotrigine	Mood stabilizers – Lithium, lamotrigine	OFC
First generation antipsychotic - chlorpromazine		Quetiapine
Atypical antipsychotics – Olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine	Atypical antipsychotics – Olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole	Lurasidone

OFC: Olanzapine-fluoxetine combination, US FDA: US Food and Drug Administration

adjunctive and alternative treatment to lithium in BD. It is considered as a treatment of choice for rapid-cycling BD; or when lithium is ineffective or contraindicated. It is commonly recommended for long-term therapy in patients of BD.²³ In the Bipolar Affective disorder: lithium/Anticonvulsant Evaluation trial, investigators found that the valproate monotherapy was less effective than lithium monotherapy in preventing relapse.²⁴ Though it is routinely used for maintenance therapy, it is not FDA approved for this indication.

The most common dose-related adverse effects with valproate include nausea, vomiting, dyspepsia, diarrhea, hepatic transaminase elevations, tremors, sedation, mild ataxia, and alopecia. It can cause weight gain which is more compared to lithium but less than olanzapine.²⁵ There is also risk of hepatotoxicity (rarely hepatic failure), hyperammonemic encephalopathy, pancreatitis, thrombocytopenia, multiorgan hypersensitivity reactions, and polycystic ovarian syndrome.²⁶⁻²⁹ Exposure during pregnancy may cause increased risk of spina bifida and other neural tube defects, cardiac and limb defects and craniofacial abnormalities in the neonate.²¹

A very important consideration while prescribing valproate is the drug interactions. Since valproate can inhibit hepatic enzymes, it may result in increased levels of other drugs such as phenobarbitone and lamotrigine. Some drugs such as cimetidine and macrolide antibiotics may increase valproate levels. Moreover, anticonvulsants like phenytoin, carbamazepine, etc., induce valproate metabolism and decrease its efficacy.

Laboratory monitoring during valproate therapy commonly includes baseline CBC, differential count, platelet count and hepatic indices, with re-evaluation every 6-12 months.²²

Carbamazepine

It has demonstrated efficacy for acute manic and mixed episodes in adults. Due to the complexity of its use, related to drug interactions and side effects, it is less commonly used now. An extended release preparation is also approved for treatment of acute manic and mixed episodes.³⁰

Side effects such as nausea, vomiting, drowsiness, diplopia, blurred vision, and ataxia are common with carbamazepine. Hematological side effects such as leucopenia, thrombocytopenia, and mild anemia are fairly common whereas agranulocytosis and aplastic anemia, which can be fatal, are quite rare. It may also cause hepatotoxicity and electrolyte disturbances such as hyponatremia. Rash is a common side effect within first 6 months of treatment; it may warrant cessation of drug due to the risk of Stevens–Johnson syndrome (SJS) and other serious dermatological reactions. Carbamazepine can cause a reduction in circulating thyroid hormones and increase in thyroid stimulating hormone,

but frank hypothyroidism is quite rare.³¹ Exposure during pregnancy increases the risk of neural tube defects in the neonate, but it is much lower than with valproate.

A unique feature of carbamazepine is that it induces its own metabolism, thus necessitating an increase in dose in early stages of treatment. Being a potent hepatic inducer, it can decrease serum concentration and efficacy of psychotropics (including valproate, lamotrigine, most second generation antipsychotics [SGA], and anxiolytics) and non-psychotropic medications. Erythromycin, isoniazid, fluoxetine inhibit the metabolism of carbamazepine and cause toxicity.

Laboratory monitoring with carbamazepine includes baseline CBC, hepatic indices, and serum electrolytes with re-evaluation as clinically indicated.²²

Lamotrigine

Lamotrigine is another anticonvulsant which is FDA approved for bipolar maintenance treatment, but not for acute mania, in adults. Clinically, it is also used in the management of bipolar depression. A meta-analysis concluded that lamotrigine has a beneficial effect on depressive symptoms in the depressed phase of BD.³²

Common side effects include headache, dizziness, blurred vision, diplopia, nausea, diarrhea, and pruritus. A benign rash may be seen in 5-10% of patients usually within first 2 months of treatment. There is a risk of serious rashes including SJS, which warrants discontinuation of the drug.³³ It has not been associated with weight gain. Other serious, but rare adverse reactions include blood dyscrasias, acute multiorgan failure, and aseptic meningitis. Two cases of withdrawal seizures have been reported in clinical trials; for this reason, lamotrigine should be gradually tapered over 2 weeks. Data regarding teratogenic potential of lamotrigine is unclear; it may be associated with an increased risk of cleft palate or cleft lip deformity.³⁴

Valproate increases and carbamazepine decreases serum lamotrigine concentrations. Thus, when lamotrigine is added to valproate or carbamazepine, recommended doses are halved or doubled, respectively. Apart from routine investigations, no extra set of investigations are needed, unless clinically indicated (Table 3).

ATYPICAL ANTIPSYCHOTICS

Manic episodes are often accompanied by psychotic symptoms; thus, antipsychotics form an integral part of the treatment of BD. Antipsychotics, also known as neuroleptics, are broadly categorized into two groups: first generation antipsychotics (FGAs) or typical antipsychotics and SGAs or atypical antipsychotics. These drugs, though originally used as a mainstay of treatment in schizophrenia, are now increasingly being used in the treatment of mood disorders.

Table 3: Recommended dosages of mood stabilizers.⁸

Drug	Acute mania	Prophylaxis	Target dose	Serum level
Lithium	Started at 600-1200 mg/day in 2 or 3 divided doses and increased as necessary and tolerated; final dosage not exceeding 1800 mg/day	Started at 300-600 mg/day and increased as necessary and tolerated by 300 mg/day every 4-7 days	900-1800 mg/day	0.6-1.2 mEq/L (0.6-1.2 mM/L)
Valproate	Initiated at 20 mg/kg or even loading with 30 mg/kg/day for 1-2 days followed by 20 mg/kg/day	Initiated at 250-500 mg/day and increased as necessary and tolerated by 250 mg/day every 4-7 days	1200-2500 mg/day	85-125 µg/ml (600-850 mM/L)
Carbamazepine	Initiated at 200-400 mg/day and increased as necessary and tolerated every 2-4 days by 200 mg/day	Started at 100-200 mg/day and increased as necessary and tolerated by 200 mg/day every 4-7 days	600-1200 mg/day	6-12 µg/ml (20-60 mM/L)
Lamotrigine	-	Started at 25 mg/day for 2 weeks, increased to 50 mg/day for next 2 weeks then increased to 100 mg/day for 1 week and finally increased to 200 mg/day in a single daily dose. Maximum dose limit is 200 mg/day		

One of the benefits of antipsychotics is their rapid onset of action compared to mood stabilizers; so, they are often used preferentially or in combination with mood stabilizers till the latter achieve its therapeutic effect.³⁵ Among the two classes of antipsychotics, SGAs are preferred for BD due to lower incidence of extrapyramidal symptoms (EPS), thus increasing patient compliance and achieving better treatment outcomes. In addition to blocking dopamine receptors, particularly D₂ subtype, these drugs act on various other receptors like H₁, 5HT₁, 5HT₂, α₁, α₂, and mACh. Though haloperidol is used in acute mania, the only FDA approved FGA for this indication is chlorpromazine. Among SGAs, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, and asenapine are approved for use in the acute treatment of manic episodes and the maintenance treatment of BD.

Adverse effects

SGAs cause extrapyramidal side effects which include acute dystonic reactions, parkinsonian syndrome, akathisia, and tardive dyskinesia (TD). Acute dystonic reactions, characterized by continuous spasms and muscle contractions, are most disturbing for the patient and are a common cause of non-adherence. Pseudoparkinsonism is manifested by cogwheel rigidity, masked facies, bradykinesia, micrographia, and pill-rolling tremor of hands. Akathisia is inability to sit still and a sense of internal restlessness. TD is characterized by involuntary choreoathetoid movements of extremities, face, or trunk. Often, it occurs after discontinuation of antipsychotic therapy. Risk of TD associated with SGAs may be similar to some FGAs, especially those of low to moderate potency.³⁶ A systematic review suggested that

vitamin E may protect against deterioration of TD, but there is no evidence that it may improve the condition once it is established.³⁷ Dystonias and pseudoparkinsonism respond to amantadine and anticholinergics, whereas akathisia is treated by propranolol.³⁸ Neuroleptic malignant syndrome, a rare adverse effect of SGAs, is characterized by hyperthermia, generalized muscle rigidity (which may sometimes be absent with SGAs), autonomic instability, metabolic acidosis, delirium, elevated creatine kinase, and leukocytosis. Treatment consists of discontinuation of the drug and supportive measures.³⁹

These drugs can cause sedation, postural hypotension, weight gain, mild, and transient elevations in the hepatic enzymes, leucopenia, neutropenia or agranulocytosis, urinary incontinence, dry mouth, blurred vision, QT prolongation, and sudden cardiac death. There is a risk of seizure since these drugs lower the seizure threshold.⁴⁰

Antipsychotics, by blocking the D₂ receptors, cause hyperprolactinemia. Hyperprolactinemia may cause impotence, infertility, sexual dysfunction, galactorrhea, and gynecomastia. In females, it may cause menstrual dysregulation, acne, and hirsutism.⁴¹ It is suggested that sustained hyperprolactinemia may cause a reduction in bone mineral density consequently leading to osteoporosis and an increased risk of fractures.^{42,43} In a case-control study, it was found that higher circulating prolactin is also associated with increased risk of *in situ* breast cancer.⁴⁴

Most antipsychotics are associated with metabolic syndrome.^{45,46} The risk is independent of psychiatric diagnosis or concomitant treatment with a mood stabilizer.⁴⁷ The

metabolic syndrome is defined by five criteria: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein, raised blood pressure, and impaired fasting glucose.⁴⁸ Metabolic syndrome is an independent risk factor for diabetes mellitus and for cardiovascular, cerebrovascular, and peripheral vascular disease.⁴⁹ In general, antipsychotic-induced metabolic changes are proportional to weight gain. Clozapine is associated with the highest risk of weight gain, followed by olanzapine, quetiapine, risperidone, aripiprazole, and ziprasidone.⁵⁰

Till date, no SGAs have been associated with teratogenicity when prescribed during pregnancy.⁵¹

Olanzapine

Olanzapine is the first FDA approved SGA for the treatment of acute mania, as well as the maintenance phase of BD. It is significantly more effective than lithium in preventing manic episode relapse, especially in the early stage of BD.^{52,53} The most common adverse reactions with olanzapine monotherapy include somnolence, dry mouth, and dizziness. Olanzapine causes more weight gain compared to lithium⁵² and valproate.²⁵ Olanzapine can cause weight gain, diabetes mellitus, and hyperlipidemia with the risk being greater than with other SGAs.^{46,54}

Risperidone

A long-acting preparation, risperidone LAI is FDA approved for the bipolar maintenance treatment. The common adverse reactions with risperidone monotherapy include EPS and sedation.⁵⁵ Risk of EPS is significantly greater with risperidone as compared to other SGAs used in BD.³⁶ It can cause weight gain, diabetes mellitus, and hyperlipidemia with intermediate risk – less than with olanzapine, but more than with ziprasidone and aripiprazole.⁴⁶

Quetiapine

Quetiapine is a unique agent for pharmacotherapy of BD since it is approved for management of all the phases of BD, namely manic and mixed episodes, depression, and maintenance treatment, either as a monotherapy or as an adjunctive medication.⁵⁶ An extended release preparation of quetiapine is also approved for once-daily monotherapy in bipolar mania.⁵⁷ The common adverse reactions with quetiapine monotherapy are somnolence and weight gain. It has intermediate risk of causing weight gain, diabetes mellitus, and hyperlipidemia - less than with olanzapine but more than with ziprasidone and aripiprazole.⁴⁶

Ziprasidone

The most common adverse reactions associated with ziprasidone are somnolence and EPS. There are no or minimal changes in weight and lipid profile.⁵⁸ Ziprasidone and aripiprazole cause less sedation and weight gain, but

more akathisia compared to risperidone, olanzapine, and quetiapine. Ziprasidone has maximum incidence of QT prolongation among SGAs.⁵⁹

Aripiprazole

A clinical trial comparing the efficacy of risperidone and aripiprazole in acute mania, found aripiprazole to be more effective than risperidone.⁶⁰ The most common adverse reactions associated with aripiprazole are akathisia, sedation, and gastrointestinal side effects. Risks of obesity, diabetes mellitus, and hyperlipidemia with aripiprazole are similar to those with ziprasidone, and less than with other SGAs.⁵⁸ Aripiprazole, being a partial agonist at dopamine receptors, does not cause hyperprolactinemia. So, it can be used as an adjunctive treatment in patients with antipsychotic-induced hyperprolactinemia. 5-10 mg/day of aripiprazole is effective in reversing antipsychotic-induced hyperprolactinemia and its sequelae.⁶¹

Asenapine

Oral mucosal absorption is unique for this drug. But, the sublingual administration is impractical during a manic episode. Besides, it may cause oral hypoesthesia or a bitter taste.⁶² Most common adverse reactions associated with asenapine are somnolence, dizziness, and weight gain. Effect of asenapine on blood glucose and lipid profile is minimal (Table 4).⁶³

BIPOLAR DEPRESSION

Studies have shown that depressive episodes are much more common than manic episodes in patients with BD. But, they may be misdiagnosed as unipolar depression due to the absence of manic symptoms, leading to wrong treatment, and poor response since traditional antidepressants are not effective in bipolar depression. Mood stabilizers which form the mainstay of treatment for BD are also not effective for depressive episodes. Thus, there is a strong need for the development of management strategies for the treatment of bipolar depression.

Currently, 3 preparations are approved for bipolar depression – olanzapine-fluoxetine combination (OFC), quetiapine and lurasidone.

Olanzapine, in combination with fluoxetine was the first FDA-approved treatment for bipolar depression. OFC is more effective than olanzapine monotherapy, and there is no increased risk of a switch over to mania.⁶⁴

Various randomized controlled trials have proved the effectiveness of quetiapine monotherapy in bipolar depression. EMBOLDEN I study which compared efficacy and tolerability of quetiapine and lithium with placebo in the treatment of bipolar depression concluded that quetiapine, and not lithium, is effective in bipolar depression and is well-tolerated.⁶⁵

Table 4: Recommended dosages of atypical antipsychotics.⁸

Drug	Acute mania	Acute depression	Prophylaxis/adjunctive use
Olanzapine	Initiated at 10-15 mg once a day and titrated at 5 mg increments as necessary and tolerated to final doses as high as 20 mg		Initiated at 10 mg once daily and titrated as necessary and tolerated to final doses as high as 20 mg once daily
OFC		Olanzapine at 5 mg and fluoxetine at 20 mg once daily and titrated as necessary and tolerated to within the ranges of 5-12.5 mg/day of olanzapine and 20-50 mg/day of fluoxetine	
Risperidone	Initiated at 2-3 mg/day and increased by 1 mg/day to final doses as high as 6 mg/day		Started at 0.25-0.5 mg/day and increased as necessary and tolerated every 4-7 days with an initial target dosage of 1-2 mg/day
Quetiapine	Initiated at 100 mg/day on day 1; increased to 200 mg/day on day 2, to 300 mg/day on day 3, and to 400 mg/day on day 4; and further increase by no more than 200 mg/day to final dosages as high as 800 mg/day by day 6	Initiated at 50 mg at bedtime on day 1; increased to 100 mg on day 2, to 200 mg on day 3, and to 300 mg on day 4	Continue the same dose which stabilized the acute phase; generally 400-800 mg/day
Ziprasidone	Initiated at 40 mg twice daily, increased to 60 or 80 mg twice daily on day 2, and titrated as necessary and tolerated to final dosages of 40-80 mg twice daily		Continue the same dose which stabilized the acute phase; generally 40-80 mg twice daily
Aripiprazole	Initiated at 15 mg/day, with a recommended dosage of 15 mg/day and a maximum dosage of 30 mg/day		Initiated at 10-15 mg/day, with a recommended dosage of 15 mg/day and a maximum dosage of 30 mg/day
Asenapine	Initiated at 10 mg sublingually twice daily, which is the maximum dosage, with the recommended dosage being 5-10 mg twice daily		Initiated at 5 mg sublingually twice daily, with a maximum dosage of 10 mg twice daily and the recommended dosage being 5-10 mg twice daily

OFC: Olanzapine-fluoxetine combination

Lurasidone is recently approved as monotherapy as well as an adjunct to mood stabilizers for the treatment of depression in BD.^{66,67} Clinically significant weight gain and metabolic changes and sedation are limitations of OFC and quetiapine, respectively. This does not occur with lurasidone which offers an obvious advantage.⁶⁸

CONCLUSION

Currently, mood stabilizers are the first line of treatment in BD. There is a trend toward increasing use of atypical antipsychotics either as monotherapy or in combination with mood stabilizers. The main limitations with these drugs are their side effect profile and interactions with other drugs which the patient may be taking concurrently. Thus, it calls for a personalized approach to treatment. Also, there

is a substantial need for clinical research to establish new interventions for bipolar depression.

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