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Bipolar Disorder: A Pharmacotherapy Management Overview

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Continuing Education

Bipolar Disorder: A Pharmacotherapy Management Overview

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Goals

This home-study CPE activity has been developed to educate pharmacists on bipolar disorder and its management using non-pharmacologic and pharmacologic therapies.

Objectives

1. Distinguish between Bipolar Disorder I and Bipolar Disorder II and the different mood disorders
2. Compare the differences between a manic and a depressive state
3. Develop a therapeutic plan for a newly diagnosed bipolar patient
4. Compare different pharmacologic agents in terms of efficacy, adverse effects, and monitoring
5. Design treatment recommendations for special population groups

Introduction

Bipolar disorder is a common and debilitating mood disorder, with an estimated lifetime prevalence of bipolar I disorder and bipolar II disorder of 1% and 1.1%, respectively, in the United States.[1] The mean age of onset for bipolar I disorder and bipolar II disorder is 18 and 20 years, respectively, with equal gender prevalence occurring in bipolar I disorder and a higher prevalence in women for bipolar II disorder.[1] The pathophysiology of bipolar disorder is unknown, but the etiology is thought to involve biological, psychological, and social factors. There is a complex genetic component with 80-90% of patients with bipolar disorder having a relative with a mood disorder. The brain structure and function in these patients are also altered, but it is unclear if these changes occurred before or after clinical presentation of the disorder.[1] Environmental influences such as stressful life events, alcohol or substance abuse, and changes in sleep-wake cycle may also affect the course of the disorder by dysregulating neurotransmitters, hormones, endocrine function, neuropeptides, cations, intracellular messengers, and signal transduction pathways. Appropriately diagnosing bipolar disorder is crucial, because there are other psychiatric and neurologic disorders that may present similarly with manic-like or depressive-like symptoms.[1] For example, if an individual with bipolar disorder was misdiagnosed to have attention-deficit/hyperactivity disorder (ADHD), the central nervous system stimulant prescribed can actually worsen symptoms of mania or depression and decrease response to treatment. There are three types of bipolar disorder. Bipolar I Disorder primarily presents with manic, or rapid cycling episodes of mania and depression. Bipolar II Disorder primarily presents with recurrent depression accompanied by hypomanic episodes. Cyclothymic Disorder is a chronic state of cycling between hypomanic and dysthymic episodes that do not reach the diagnostic criteria for bipolar disorder.[1]

Diagnosis

Major Depressive

Depressed mood and/or loss of interest or pleasure for at least 2 weeks and at least 5 of the following:[2]

1. Depressed mood
2. Decreased interest or pleasure in normal activities
3. Unintentional weight loss or gain
4. Insomnia or hypersomnia
5. Agitation or psychomotor retardation
6. Fatigue or decreased energy
7. Feelings of worthlessness or guilt
8. Decreased ability to concentrate or make decisions
9. Suicidal thoughts

Dysthymic Disorder

Depressed mood for more days than not for at least 2 years and at least 2 of the following:[2]

1. Loss of appetite or overeating
2. Insomnia or hypersomnia
3. Fatigue or decreased energy
4. Low self-esteem
5. Decreased ability to concentrate or make decisions
6. Feelings of hopelessness

Manic

Abnormal and persistent elevated mood for at least 1 week and at least 3 of the following:[2]

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep
3. Increased talking
4. Flight of ideas or racing thoughts
5. Distractible
6. Increased activity (socially, at work, or sexually)
7. Increased psychomotor agitation
8. Excessive involvement in pleasurable activities that have high risk for serious consequences

Hypomanic

Abnormal and persistent elevated mood for at least 4 days and at least 3 of the following:[2]

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep
3. Increased talking
4. Increased activity (socially, at work, or sexually)
5. Increased psychomotor agitation
6. Excessive involvement in pleasurable activities that have high risk for serious consequences

Mixed

Criteria for both major depressive and manic episodes that occur almost every day for at least a 1 week period.[2]

Rapid cycling

More than 4 major depressive or manic episodes (manic, hypomanic, or mixed) in 12 months.[2]

Non-Pharmacological Treatments

The goals of treatment for bipolar disorders aim to achieve remission, which is defined as complete return to normal functioning and lack of symptoms, to prevent relapses, to control comorbid conditions including anxiety, panic disorder, obsessive-compulsive disorder (OCD), and ADHD. Three non-pharmacological approaches to the treatment of bipolar disorders encompass health maintenance, mood charting, and a combination of pharmacotherapy plus psychoeducation.[3] Maintaining health through adequate sleep, nutrition, and exercise can improve and prevent signs and symptoms of bipolar episodes. Benzodiazepines, melatonin, enforced darkness, and prolonged bed rest have been shown to help patients sleep. Sleep hygiene is also crucial in obtaining adequate sleep. This includes counseling patients to establish a fixed sleep and wake time, to exercise but not close to bedtime, and to avoid naps. In addition

to getting adequate sleep, nutrition plays an important role in managing bipolar disorders. Patients should be counseled to maintain an adequate intake of essential amino acids, fatty acids, vitamins, and minerals based on the Reference Daily Intake (RDI).[3] Exercise, either strength training or aerobic, can help with sleep and major depressive disorder (MDD) by increasing the synthesis and release of neurotransmitters such as serotonin and norepinephrine.[4] Mood charting is another approach to manage bipolar disorders by assisting patients in detecting signs and symptoms of episodes and assessing their responsiveness and tolerability to the drug regimen. Finally, a combination of pharmacotherapy and psychoeducation can enhance the treatments and prevent relapses of bipolar episodes. Cognitive behavior therapy, reducing psychosocial stressors, mental health organizations, and other support groups, including individual or family therapy, are recommended as adjunct therapies to pharmacologic agents.

Other non-pharmacologic approaches have been shown to be effective in treating patients who have failed pharmacologic agents. These approaches include electroconvulsive therapy (ECT), transcranial magnetic stimulation, and vagus nerve stimulation.

Pharmacological Treatments

Manic Phase (Acute Manic, Hypomanic, Mixed)

The manic phase can be acute manic, hypomanic, or mixed. The treatment plans in the manic phase include remission, assessment of the causes and triggers such as alcohol, drug, or substance abuse. Other contributory factors can be stimulants, caffeine, or antidepressant monotherapy. For severe cases of mania, first line treatments are combinations of lithium plus antipsychotics or valproate plus antipsychotics.[5,6] For less severe cases, lithium, valproate, or antipsychotic monotherapy is sufficient. Alternatives to lithium or valproate can be carbamazepine or oxcarbazepine. Adjunctive therapy with psychosocial approaches can also be beneficial. For mixed or rapid cycling, valproate is preferred over lithium. Whenever psychosis is manifested in the manic phase, antipsychotics need to be considered.[5,6] Second generation antipsychotics (SGAs), also known as atypical antipsychotics are preferred over first generation antipsychotics (FGAs), also known as typical antipsychotics. SGAs have lower risk of extrapyramidal side effects such as tardive dyskinesia, dystonia, and Parkinson's like symptoms and have less effects on prolactin.[5,6] Examples of SGAs are olanzapine, ziprasidone, risperidone, and quetiapine. Examples of FGAs are chlorpromazine, fluphenazine, and haloperidol. For breakthrough manic or mixed episodes, the dose should be optimized to the therapeutic range, add or continue antipsychotics, or consider adding a short-term benzodiazepine. If patients are refractory to the first line treatments, the recommendations are to add another first line agent, carbamazepine or oxcarbazepine, add or switch an antipsychotic, or utilize ECT.[5,6]

Depressive Phase

The treatment plans for the depressive phase aim to achieve remission, avoid antidepressant monotherapy due to precipitation of mania or hypomania, assess causes or triggers of depression such as alcohol, drug or substance abuse, and to taper off antipsychotics, benzodiazepines, and sedative-hypnotics. First line agents for bipolar depression are lithium or lamotrigine. Alternative agents are quetiapine monotherapy or olanzapine plus fluoxetine, valproate, lithium plus antidepressant, or adjunctive psychotherapy.[5,6] In July 2013, lurasidone was approved as monotherapy or adjunctive therapy in the treatment of bipolar depression. For breakthrough bipolar depression, optimize dose of the maintenance drug until it is within therapeutic range.[7] For patients who are refractory to first line treatments, add lamotrigine, bupropion, paroxetine or alternatively add other antidepressants or monoamine oxidase inhibitors (MAOIs). ECT is recommended for severe, refractory depression with psychosis or catatonia.[5,6]

Rapid Cycling

The treatment plans for rapid cycling are to reduce the numbers of episode and assess issues that can contribute to cycling, including hypothyroidism, drug or substance abuse, or alcoholism. First line agents include lithium or valproate, and an alternative would be lamotrigine. Rapid-cycling patients will eventually require combination therapy.[5,6]

Maintenance Treatments

Following an episode, all patients are required to be on maintenance or continuation of therapy for up to six months due to the high risk of relapse. The selection of medications for maintenance agents is the agent that induces remission. Furthermore, psychosocial therapies such as evaluating adherence, support groups, lifestyle, and mood charting are also considered. First line agents for maintenance are lithium or valproate with lamotrigine, carbamazepine, or oxcarbazepine as alternatives. Antipsychotics should be evaluated for risks versus benefits before considering them for long-term use. In bipolar I, the duration of maintenance after one manic episode is 12 months, and lifelong for more than one episode. In bipolar II, the duration of maintenance after one to two hypomanic phases is 12 months, and lifelong if more than two episodes.[5,6]

Drug Therapies

Lithium (Eskalith®, Lithobid®)

Lithium works by affecting the reuptake of serotonin and norepinephrine. In doing so, lithium can be used for the depressive stage of bipolar. However, lithium has a stronger effect on managing mania by suppressing excitatory neurotransmission (e.g. dopamine and glutamate) while increasing inhibitory activity (GABA).[7] Studies have shown that lithium has similar efficacy to valproate, carbamazepine, risperidone, olanzapine, chlorpromazine and other first generation antipsychotics. Its efficacy is enhanced in patients who have fewer prior episodes, family history of responsiveness to lithium, and euthymia between episodes. In mixed or rapid-cycling, the efficacy of lithium is reduced. Lithium is used as a first line agent for mania, hypomania, depression, and maintenance. Combination therapy with carbamazepine, valproate, and antipsychotics can be seen.

Adverse effects are seen in multiple organs and can be dose dependent. Central nervous system (CNS) effects of headache, memory and cognitive impairments, coma, confusion, seizure, sedation, lethargy and stupor are dose related. Other dose related side effects include nausea, vomiting, diarrhea, dyspepsia, weight gain, hair loss, worsening of rash or psoriasis, and tremor. Lithium can decrease response

to antidiuretic hormones (ADH), causing polyuria, polydipsia, and nocturia. Other dose related effects on the kidneys include albuminuria and glycosuria. Lithium can accumulate in the thyroid gland and interfere with synthesis of thyroid hormones, thus causing hypothyroidism. Lithium can also cause cardiac problems such as atrioventricular (AV) block, arrhythmias, hypotension, syncope and ECG changes. Thus, patients with a history of cardiac abnormalities need to have their ECG monitored at baseline and during treatment. Lithium can further lead to leukocytosis and blurred vision. Unlike other pharmacologic treatments for bipolar disorder, the long term use of lithium can reduce risk of suicidal ideation.

Drugs that can increase lithium concentration include ACE inhibitors, NSAIDs, and thiazides while theophylline, caffeine, and loop diuretics can decrease lithium concentration. Dehydration, vomiting, or diarrhea can also raise lithium levels. At the initiation of therapy, serum levels are drawn twice weekly until the level is stabilized. Once stabilized, it is then recommended to draw levels every 2 months. Serum concentrations for acute episodes are 1 – 1.2 mEq/L and 0.6 – 1.2 mEq/L for maintenance. Furthermore, electrolytes, thyroid function tests, hematologic and dermatologic tests should be monitored at baseline and every 6-12 months, with the exception of dermatologic test, which should be done every 3-6 months.

Monitoring serum levels of lithium is important to avoid toxicity, which can be seen when the serum level is greater than 1.5 mEq/L, with signs and symptoms of tremor, nausea, diarrhea, blurred vision, vertigo, and confusion. When the level is greater than 2.5 mEq/L, toxicity is manifested in seizures, dysrryhthmias, and coma. Treatments for lithium toxicity include gastric lavage, induction of emesis, and hemodialysis when serum concentration is above 2.5 mEq/L. For dosing information, refer to Table 1.[8,9]

Valproate (Depakote®)

Formulations of valproate consists of valproate sodium, valproic acid, and divalproex sodium. Valporate increases the availability of gamma-aminobutyric acid (GABA) and enhances or mimics the action of GABA. By increasing GABA activity, valproates can manage the abnormal, persistent, and elevated mood in mania. Studies have shown that valproate has better efficacy than lithium in patients with mixed episodes, many prior mood episodes, and rapid cycling. Similar efficacy is seen with olanzapine and haloperidol. Valproate is used as first line therapy for acute mania, hypomania, mixed, and maintenance. It can also be combined with lithium, carbamazepine, and antipsychotics. After two weeks of initiating therapy, trough levels of acute manic or mixed episodes should be at 50 – 125 mcg/mL.

Adverse effects of valproate target multiple organs and can be dose dependent. The most common adverse effects are dose-related nausea, vomiting, diarrhea, abdominal pain, dyspepsia, and flatulence. Valproate can also cause CNS issues, including headache, somnolence, dizziness, nervousness, and sedation. Caution must be taken in patients with liver disease because valproate can increase liver function test (LFTs) and precipitate hepatic failure. Valproate can further cause tremor, weakness, diplopia, and blurred vision. Rare but serious side effects are hepatic failure, pancreatitis, and agranulocytosis. Valproate is contraindicated in pregnancy, with a black box warning for teratogenicity, pregnancy category X.

When combined with lamotrigine, valproate will inhibit lamotrigine's metabolism and dosing adjustment is therefore required. Valproate is highly protein bound and will displace other drugs readily. Finally, it will inhibit CYP 450 isoenzymes 3A4, 2C9, and 2D6. Hematologic, hepatic, dermatologic and metabolic tests should be monitored at baseline, then every 3-6 months. Serum levels should also be monitored for toxicity, where sign and symptoms include somnolence, heart block, and coma. Treatment of toxicity would be hemodialysis. Behavior changes and suicide ideation should also be assessed periodically. For dosing information, refer to Table 1.[8,9]

Carbamazepine (Tegretol®)

The mechanism of action of carbamazepine is to decrease synaptic transmission, decrease activity in the thalamus, and decrease the transport of sodium across cell membranes, and potentiating GABA receptors. By decreasing synaptic transmission via blockage of sodium across cell membranes, cells are less excitable and an abnormally elevated mood can be better managed. Studies show that the efficacy of carbamazepine is similar to lithium, but less than valproate. Carbamazepine is used as an alternative treatment and be combined with lithium, valproate, or antipsychotics. There is no established goal serum level for carbamazepine in the treatment of bipolar disorder. However, the target serum level of 4 – 12 mcg/mL for seizures is often used for bipolar disorder.

The adverse effects of carbamazepine include multiple organs, with the most common side effects being CNS related: dizziness, drowsiness, headache, ataxia, cognitive and memory impairments, and rare cases of neuroleptic malignant syndrome (NMS). Cardiac issues caused by carbamazepine include hypertension or hypotension, syncope, AV block, arrhythmias, and edema. Gastrointestinal side effects are nausea, vomiting, diarrhea, dry mouth/throat, and anorexia. Impotence and polyuria can occur along with increase in LFTs. Hematologic side effects are agranulocytosis, anemia, and thrombocytopenia. Carbamazepine can induce symptoms of inappropriate ADH (SIADH), abnormal thyroid function test, hypocalcemia, and hyponatremia. Certain populations, such as Asian, Native American, Latin American, African-American, and Indian are at greater risks of developing Stevens-Johnson syndrome (SJS) due to the presence of the HLA-B*1502 allele.

In addition to being a CYP 3A4 inhibitor, carbamazepine also has a unique mechanism of being able to autoinduce its own metabolism. Thus, it is important to adjust the dose based on patient's liver function. Since carbamazepine can decrease the concentration of oral contraceptives (OC), back up methods or an increase in OC dose should be considered. When combined with clozapine, there is an increased risk of bone marrow suppression. And when added to valproate, the concentration of carbamazepine will increase. Monitor serum level for toxicity, which can be manifested in dizziness, sedation, visual changes, respiratory dysfunction, and arrhythmias. Treatments of toxicity include relieving symptoms, gastric lavage, or hemoperfusion. For dosing information, refer to Table 1.[8,9]

Oxcarbazepine (Trileptal®)

The mechanism of action of oxcarbazepine is to decrease synaptic transmission by blocking sodium voltage-gated channels, similar to carbamazepine. Studies have shown that oxcarbazepine has similar efficacy to lithium and haloperidol; however, these studies lack power. Oxcarbazepine is used as an alternative treatment for bipolar either as monotherapy or in combination with other agents, after patients have failed carbamazepine, lithium, and valproate. The advantages of oxcarbazepine over carbamazepine include having fewer adverse effects, fewer drug interactions, and no autoinduction. However, oxcarbazepine causes greater risk of hyponatremia, which can cause nausea, vomiting, confusion, and seizures.

The most common adverse effects are CNS related, including dizziness, drowsiness, headache, ataxia, vertigo, fatigue, sedation. Other side effects are nausea, vomiting, abdominal pain, along with abnormal gait and tremor, diplopia and nystagmus. Cross-sensitivity to oxcarbazepine is seen in approximately 25% -30% of patients who are allergic to carbamazepine. Hypersensitivity reactions include angioedema and SJS. Oxcarbazepine is a CYP 3A4 inducer and CYP 2C19 inhibitor and will decrease concentrations of oral contraceptives and dihydropyridine calcium channel blockers. It is recommended to monitor serum levels of sodium for signs and symptoms of hyponatremia while patients are on oxcarbazepine. For dosing information, refer to Table 1.[8,9]

Lamotrigine (Lamictal®)

Lamotrigine, a mood stabilizer, is commonly used as a first-line treatment for patients with bipolar II disorder. There is a black box warning for serious skin rashes, which may lead to the SJS. The concomitant use with valproate can increase this risk of rash. Signs of rashes should be monitored at baseline and every 3-6 months. Common adverse effects include nausea, vomiting, insomnia, ataxia, dizziness, and headache. Carbamazepine increases the metabolism of lamotrigine which may result in subtherapeutic levels of lamotrigine. There are also drug-drug interactions with oral contraceptives. The estrogen component can decrease the effectiveness of lamotrigine, while lamotrigine can decrease the effectiveness of oral progestin contraceptives. Doses should be decreased in renal and hepatic impairment. LFTs and serum creatinine (SCr) should be monitored regularly during therapy. Anticonvulsants increase the risk of suicidal thoughts and behaviors, so patients should be monitored for emergence or worsening of depression or suicidal ideation. For dosing information, refer to Table 1.[8,9]

Quetiapine (Seroquel®)

Quetiapine, an atypical antipsychotic, is used for the acute treatment of manic episodes associated with bipolar disorder, acute treatment of depressive episodes associated with bipolar I and II, and maintenance treatment of bipolar I disorder. Common adverse effects include increase in diastolic and systolic blood pressure in children, somnolence, headache, agitation, dizziness, metabolic effects, dry mouth, weight gain, and increased appetite. Concomitant use with acetylcholinesterase inhibitors should be avoided since severe extrapyramidal symptoms may be precipitated. CYP3A4 inducers (e.g. progesterone, phenytoin, oxcarbazepine, carbamazepine, and phenobarbital) may decrease the serum level of quetiapine. To maintain therapeutic benefit, quetiapine doses may be increased to up to 5 times when used with CYP3A4 inducers. Fasting lipid profile (FLPs) should be monitored due to metabolic increases in triglyceride and decreased HDL levels. Weight, blood pressure, worsening of depression or suicidal ideation should be monitored regularly. For dosing information, refer to Table 1.[8,9]

Benzodiazepines

The most commonly studied and used benzodiazepines in bipolar disorder are lorazepam (Ativan®) and clonazepam (Klonopin®), which has beneficial effects in the treatment of hypomanic, mild to moderate manic, and mixed episodes.[5] Benzodiazepines are generally used as adjunctive therapy for treating insomnia, agitation, and anxiety in bipolar patients with elevated moods. Common adverse effects include sedation, respiratory depression, hypotension, and changes in appetite, and therefore respiratory and cardiovascular status should be closely monitored. Concomitant use with olanzapine may increase the toxicity of benzodiazepines. Benzodiazepines may also increase the serum level of selective serotonin reuptake inhibitors (SSRIs), which increases the risk of psychomotor impairments. For dosing information, refer to Table 1.[8,9]

Selective Serotonin Reuptake Inhibitors

Examples of SSRIs are citalopram (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®), paroxetine (Paxil®), and sertraline (Zoloft®). SSRIs are generally used as first line antidepressants because of their safety in overdose and improved tolerability. Common adverse effects include nausea, vomiting, diarrhea, headache, insomnia, and sexual dysfunction. Citalopram can also cause dose-related QT prolongation and doses should not exceed 40 mg/day for all patients and should not exceed 20 mg/day for patients over 60 years old, have hepatic impairment, or are concurrently taking a CYP 2C19 Inhibitor (e.g. omeprazole, cimetidine). Abrupt withdrawal can cause flu-like symptoms, light-headedness or dizziness, uneasiness, sleep disturbances, and headache. Therefore, SSRIs should be tapered down when discontinuing treatment with the exception of fluoxetine due to its long half-life. SSRIs are highly bound to plasma protein and co-admission with other highly protein-bound drugs (e.g. valproate, warfarin, digoxin) may cause changes in serum concentrations of either drugs. SSRIs have varying degrees of CYP 2D6 inhibition and may affect drugs that are metabolized by this isoenzyme (e.g. phenothiazine antipsychotics, risperidone). Fluoxetine and paroxetine are strong CYP 2D6 inhibitors while sertraline is a moderate CYP 2D6 inhibitor, and citalopram and escitalopram are weak CYP 2D6 inhibitors. Citalopram and escitalopram are metabolized by CYP 3A4 and CYP 2C19, and concomitant use with a CYP 3A4 inducer (e.g. carbamazepine) may decrease their serum levels. Use of a SSRI with a MAOI is contraindicated due to the increased risk of hypertensive crisis, serotonin syndrome, and delirium. There is a Black Box Warning of increased suicidal ideation with antidepressant use and suicidal thoughts should be assessed and monitored regularly. For dosing information, refer to Table 1.[8,9]

Bupropion (Wellbutrin®)

Bupropion works as an antidepressant

by inhibiting norepinephrine and dopamine reuptake. Common adverse effects include nausea, vomiting, dry mouth, skin reactions, insomnia, and seizures. Bupropion is metabolized by CYP 2B6 and has few drug-drug interactions. However, concomitant use with carbamazepine may lower bupropion levels and dose adjustments may be required. Contraindications with bupropion include concomitant use with a MAOI, seizure disorder, and history of an eating disorder. There is a Black Box Warning of increased suicidal ideation with antidepressant use and suicidal thoughts should be assessed and monitored regularly. For dosing information, refer to Table 1.[8,9]

Venlafaxine (Effexor®)

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) that is generally used as a second-line antidepressant. Common adverse effects include significant nausea, constipation, dry mouth, decreased appetite, headache, somnolence, dizziness, insomnia, dose-related increase in diastolic blood pressure, and sexual dysfunction. Blood pressure should be monitored regularly, and doses should be decreased in patients with renal and/or hepatic impairment. Abrupt withdrawal with SNRIs may be worse than with SSRIs and symptoms may include agitation, confusion, excessive sweating, hallucinations, and hyperreflexia. There are minimal drug-drug interactions but concomitant use with a MAOI is contraindicated. There is a Black Box Warning of increased suicidal ideation with antidepressant use and suicidal thoughts should be assessed and monitored regularly. For dosing information, refer to Table 1.[8,9]

Monoamine Oxidase Inhibitors

MAOIs such as selegiline (Emsam®), phenelzine (Nardil®), and tranylcypromine (Parnate®) work by increasing concentrations of norepinephrine, serotonin, and dopamine. They are rarely used as a first line drug therapy and are indicated for patients with atypical depression or patients unresponsive to other antidepressants. Common adverse effects include orthostatic hypertension, sedation, stimulant, weight gain, and sexual dysfunction. Hypertensive crisis may occur when taken with food containing tyramine and other antidepressants. Overdose can occur and symptoms may include irritability, hyperactivity, anxiety, tachycardia, drowsiness, and hallucinations. There are many drug-drug interactions and contraindications to MAOIs include concomitant use with other antidepressants, pheochromocytoma, congestive heart failure, hepatic impairment, renal impairment, cerebrovascular disorders, cardiovascular disease, hypertension, and history of headache. There is a Black Box Warning of increased suicidal ideation with antidepressant use and suicidal thoughts should be assessed and monitored regularly. For dosing information, refer to Table 1.[8,9]

Olanzapine/ fluoxetine (Symbyax®)

This combination agent contains olanzapine, a SGA that inhibits serotonin, dopamine, histamine, and alpha1-adrenergic reuptake, and the SSRI fluoxetine. Due to the synergistic increase in serotonin, norepinephrine, and dopamine, there is an enhanced antidepressant effect for this drug combination. Olanzapine/fluoxetine is commonly used for depressive episodes associated with bipolar I disorder and treatment-resistant depression, which is defined as being unresponsive to two trials of different antidepressants in the current episode. Common adverse reactions to this combination agent include somnolence, fatigue, hyperprolactinemia, weight gain, increased appetite, and dry mouth. There are many drug-drug interactions associated with olanzapine/ fluoxetine and concomitant use with other SSRIs, antipsychotics, and lithium may lead to serotonin syndrome/toxicity. Concomitant use with a MAOI should be avoided. Doses should be decreased in hepatic impaired and hypotensive patients, and LFTs and blood pressure should be monitored regularly in these patients. For dosing information, refer to Table 1.[8,9]

SPECIAL POPULATIONS

Women and Pregnancy

Due to higher risks of birth malformations associated with medications used to treat bipolar disorder, all female patients of childbearing age are encouraged to practice effective contraceptive methods while on pharmacological therapy.[5] Oral contraceptives should be avoided in patients taking carbamazepine, oxcarbazepine, and topiramate because these medications increase the metabolism of oral contraceptives, thus decreasing their effectiveness. Effective backup contraceptive practices, such as condoms or intrauterine devices, are recommended for birth control in these patients.

When a patient is pregnant, the risks and benefits of continuing versus discontinuing medications for bipolar disorder should be evaluated carefully. Should the decision be made to continue pharmacotherapy, clinicians and pharmacists should choose drugs with fewer known teratogenic effects and when possible, the lowest effective dose should be used. Congenital malformations have been documented with first-trimester exposure to lithium, valproate, and carbamazepine. A common neonatal complication associated with lithium use near labor is the "floppy baby" syndrome, which is characterized by cyanosis and hypotonicity. The use of carbamazepine and valproate sodium during the first trimester has been associated with neural tube defects.[10] Benign risks have been documented with SSRIs use during pregnancy, with fluoxetine and citalopram having the strongest safety data. Similarly, past studies have demonstrated no association between lorazepam and clonazepam with birth defects. However, diazepam remains controversial due to earlier reports of increased risks of oral cleft malformations during the first trimester.[10] Antipsychotic medications may be added to the bipolar regimen to treat psychotic features. High-potency antipsychotic agents are preferred due to their decreased anticholinergic, antihistaminergic, and hypotensive effects.[5] Use of high-potency agents near term, however, has demonstrated short-lived extrapyramidal side effects in neonates. Haloperidol is recommended as the first line therapy because it is not associated with congenital anomalies.[5]

Prenatal monitoring is recommended for all females who choose to remain on lithium, valproate, or carbamazepine during their pregnancy.[12] At the 20th week of gestation, a maternal serum of α-fetoprotein screening for neural tube defects is recommended with amniocentesis. Ultrasound examination at 16-18 weeks gestation is also recommended to detect cardiac abnormalities. Close monitoring of the serum drug levels should be continued

throughout the pregnancy due to changes in hepatic metabolism, renal excretion, and fluid volumes.

Postpartum and Breast-feeding

During the postpartum period, females are more likely to relapse into mania, depression, or psychosis. Women with previous postpartum episodes have the highest risk to have another affective episode after subsequent pregnancies. Therefore, prophylactic medications such as lithium or valproate are recommended in women with bipolar disorder to prevent postpartum mood episodes.[5] Pharmacists should also counsel women on the importance of maintaining a normal sleep pattern to avoid precipitating episodes of mania.

Although all medications used in the treatment of bipolar disorder are secreted in breast milk at different degrees, the risks of breastfeeding must be weighed against the benefits in this patient population. Lithium is not recommended during lactation, because it is secreted in breast milk at 40% of maternal serum concentration.[5] Lamotrigine level is secreted at 25% of maternal level, but no recommendations are made concerning its use in breastfeeding.[5] Other antipsychotics, antidepressants, and benzodiazepines are found in measurable levels in breast milk and have the potential to affect the infant's central nervous system.

Pharmacist Role/Conclusion

Bipolar disorder can be effectively managed with the help of pharmacists, physicians, and psychiatrists. As clinical pharmacists, obtaining an accurate and complete medication history is critical to identifying potential medication-related causes of mood episodes. Pharmacists can also help to assess the number of manic and depressive episodes throughout the course of therapy to optimize the patient's medication therapy. Patient education is an important component to successful therapy management. By educating the patient about the disease state and the drug therapy, patients are empowered to take charge of their own health and are therefore more likely to maintain medication adherence. In addition, performing long-term monitoring as part of medication therapy management can increase patient adherence and reduce future hospitalizations.

It is crucial that the patients and their family members understand the importance of medication adherence for safety and efficacy purposes. For instance, patients may not be aware that abrupt discontinuation of an SSRI may lead to withdrawal syndromes or that non-adherence can worsen their mood episodes. It is especially essential to educate special patient populations, such as patients with pregnancy and lactation concerns due to the high teratogenic risk. It is also important to educate the patients and their family members to identify behavioral changes and early signs of suicidal ideation as serious side effects of the medication. Overall, pharmacists can have a significant role in the management and well-being of their bipolar patients by helping them to monitor and provide education about their disease state.

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Table 1

Drug	Initial Dose (mg/day)	Usual Dose (mg/day)
Lithium	900 in 3-4 divided doses	0.5-1.2 mEq/L (serum level)
Valproate	750 in 3 divided doses	60 mg/kg
Carbamazepine	400 in 2 divided doses	800-1000
Oxcarbazepine	600	1200
Lamotrigine	25-50	100-400
Olanzapine/Fluoxetine	6/25	6-12(O)/25-50(F)
Quetiapine	50	300-800
Citalopram	20	20-40
Escitalopram	10	10-20
Fluoxetine	20	20-60
Paroxetine	20	20-60
Sertraline	50	50-200
Buproprion	150	150-300
Venlafaxine	37.5-75	75-375
Selegiline	6	6-12
Phenelzine	45 in 3 divided doses	45-90
Tranylcypromine	10	30-60