2014

Bipolar Disorder: A Pharmacotherapy Management Overview

Huong Le  
*Midwestern University*

Tina Pham  
*Midwestern University*

Laura Tsu  
*Chapman University*, ltsu@chapman.edu

Follow this and additional works at: [http://digitalcommons.chapman.edu/pharmacy_articles](http://digitalcommons.chapman.edu/pharmacy_articles)

臊 Part of the Medical Education Commons, Mental and Social Health Commons, Other Pharmacy and Pharmaceutical Sciences Commons, and the Science and Mathematics Education Commons

Recommended Citation


This Article is brought to you for free and open access by the School of Pharmacy at Chapman University Digital Commons. It has been accepted for inclusion in Pharmacy Faculty Articles and Research by an authorized administrator of Chapman University Digital Commons. For more information, please contact laughtin@chapman.edu.
Continuing Education

Bipolar Disorder: A Pharmacotherapy Management Overview
by Huong Le, Pharm.D. Candidate 2014, Julie Nguyen, Pharm.D. Candidate 2014, Tina Pham, Pharm.D. Candidate 2014, Laura Tsu, Pharm.D., BCPS, Midwestern University College of Pharmacy – Glendale

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. 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. 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. 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.

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.

Diagnosis

Major Depressive
Depressed mood and/or loss of interest or pleasure for at least 2 weeks and at least 5 of the following:
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:
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:
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:
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.

Rapid cycling
More than 4 major depressive or manic episodes (manic, hypomanic, or mixed) in 12 months.

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. 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). 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. 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. 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. 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 disease. 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 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). 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. 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. 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. 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 disease. 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, dysrythmias, 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 divalprox sodium. Valproate 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

Benzodiazepines

The most commonly studied and used benzo diazepines 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.3 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, un easiness, 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 SSRIs 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

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.
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.

References

ACPE UAN#0100-0000-14-018-H01-P

Table 1

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