Bipolar disorder (BD), also referred to as manic-depression, presents with dramatic swings in a person's mood and energy level, which affects their ability to perform daily tasks. Bipolar Disorder affects approximately 2.6% (some estimate as high as 6%) of the U.S. adult population with the average age of onset occurring at 25 years old. An estimated 82.9% of cases are classified as 'severe.' Approximately 48.8% of those with the disorder are receiving treatment, but of those, an estimated 38.8% are receiving minimally adequate treatment.

Although the diagnosis and treatment of BD is complex, effective treatment can lead to positive outcomes for many patients. Primary care providers are in a key position to provide an early diagnosis and treatment.

The U.S. treatment guidelines were last updated by the Veterans health Administration and the Department of Defense (VA/DoD) in 2010 (http://www.healthquality.va.gov/bipolar/bd_306_sum.pdf). In 2013 the Canadian Network for Mood and Anxiety Treatments (CANMAT/ISBD) and International Society for Bipolar Disorders released updated guidelines (http://canmat.org/resources/CANMAT%20Bipolar%20Disorder%20Guidelines%202013%20Update.pdf).

**Types of Bipolar Disorder**

In the U.S. there are 4 types of BD, per the DSM-IV-TR.

- **Bipolar I Disorder**—defined by manic or mixed episodes that last at least seven days, or by manic symptoms that are so severe that the person needs immediate hospital care. Usually, depressive episodes occur as well, typically lasting at least 2 weeks.

- **Bipolar II Disorder**—defined by a pattern of depressive episodes and hypomanic episodes, but no full-blown manic or mixed episodes.
  - Bipolar 2 is less common than BD1 and affects women more than men.
  - There are fewer studies assessing treatment of BP2 but neuroimaging suggests both Bd1 and BD2 should respond to therapy similarly.
  - Canadian guidelines address therapy of BD2 separately.

- **Bipolar Disorder Not Otherwise Specified (BP-NOS)**—diagnosed when symptoms of the illness exist but do not meet diagnostic criteria for either bipolar I or II. However, the symptoms are clearly out of the person’s normal range of behavior.

- **Cyclothymic Disorder, or Cyclothymia**—a mild form of bipolar disorder. People with cyclothymia have episodes of hypomania as well as mild depression for at least 2 years. However, the symptoms do not meet the diagnostic requirements for any other type of bipolar disorder.

**Diagnosis and Assessment of Bipolar Disorder**

At least half of patients with BP1 and most patients with BP2 will initially present during a major depressive episode. It is important to obtain a thorough history for past manic or hypomanic symptoms to ensure an accurate diagnosis. The Mood Disorders Questionnaire (http://www.dbsalliance.org/pdfs/MDQ.pdf) is a valid and useful tool to assist in differentiating between major depression and bipolar depression. Ensuring a correct diagnosis is important due to the risk of antidepressants precipitating a manic episode.
In addition to assessment of mood history, evaluation of secondary causes of mania and depression must be performed such as screening of thyroid function, tests for infectious disease, urine drug screen, B12 level, and neurologic contributors. vi

**Treatment of Bipolar Disorder**

Mood Stabilizers (e.g., lithium, valproate, lamotrigine) are the base of therapy for bipolar disorder. Antipsychotics, alone or in combination with mood stabilizers are commonly used. Therapy compliance is poor in bipolar disorder and counseling patients that the full efficacy of therapy may take weeks may help improve initial compliance.

Many patients with BD will not respond to the first medication(s) they receive. If there is not an adequate response than switching from monotherapy to another medication or beginning combination therapy should be considered.

Use of antidepressants, especially as monotherapy, in treating BD should be done with caution do to the risk of switching (an abrupt change from depression to mania). The risk of switching is more common in those with BD1, especially in juveniles and young adults.

**Treatment of Mania/Hypomania or Mixed Bipolar Episodes**

- **Severe manic or severe mixed episode** combination therapy with an antipsychotic plus lithium or valproate is recommended as first line therapy. Data on treatment of mixed episodes is very limited.
  - **First Line Antipsychotics** – select Abilify (aripiprazole), Saphris (asenapine), Zyprexa (olanzapine), Invega (Paliperidone), Seroquel (quetiapine), Risperdal (risperidone) or Geodon (ziprasidone). For Mixed episodes one may also consider Haldol (haloperidol) as a first line agent.
    - Clozapine may be combined with valproate or lithium based on past therapeutic history or failure of other antipsychotics.
  - **For acute agitation** – Abilify, Zyprexa or intramuscular benzodiazepine plus haloperidol.
- For **hypomania or non-severe mania** monotherapy with an antipsychotic (see above), lithium, carbamazepine, or valproate are first line treatment options.
  - Second line therapy - Oxcarbazepine
- For **Bipolar 2 hypomania** first line therapy is quetiapine.
  - Second line therapies - Lithium, lamotrigine, or valproate, or lithium + valproate
  - Third line therapies – quetiapine + lamotrigine.
  - The use of an antidepressant alone should be reserved for those with infrequent hypomania
- For **non-severe mixed episode**, monotherapy with carbamazepine, valproate, Abilify (aripiprazole), Saphris (asenapine), Zyprexa (olanzapine), Risperdal (risperidone) or Geodon (ziprasidone).
  - Oxcarbazepine is a second line therapy.
  - Lithium is not a drug of choice for mixed episodes.

Patients should be assessed every one to two weeks for the first six weeks. If no response within two to four weeks, a dose adjustment should be considered. Full remission is defined as at least two months with no significant mania or depression for mixed episodes.
Treatment of Bipolar Depression
Those with bipolar 1 disorder may spend up to three weeks depressed for every one week they are manic. On the other hand, BD2 patients may spend up to 37 weeks depressed for every one week they are hypomanic. There is an elevated risk of suicide during the depressive phase and continued monitoring is necessary. The goal of therapy is to achieve remission of the depression without precipitating mania or hypomania.

- **First line therapy:**
  - Monotherapy – lithium, lamotrigine, quetiapine and Lurasidone (Latuda).
    - Data shows efficacy of lamotrigine and quetiapine
  - Combination therapy (when monotherapy fails) - valproate or lithium + lamotrigine

- **Second line therapy:**
  - Monotherapy – valproate or olanzapine
  - Combination therapy – Lamotrigine + lithium, olanzapine + fluoxetine (use cautiously due to metabolic effects of olanzapine and risk of fluoxetine causing a switch to mania)

Antidepressants in BD1 should not be used as monotherapy but may offer benefit in combination with a mood stabilizer. The full effect of antidepressant therapy can take eight to 12 weeks and antidepressants should be discontinued if hypomania, mania or agitation occurs.

- Antidepressants should be avoided if there are ≥ 2 core manic symptoms with agitation or rapid cycling; during episodes with mixed features; history of rapid cycling.
  - Combination therapy - Lithium or valproate + an SSRI, Lithium or valproate + bupropion, quetiapine + an SSRI
    - Paroxetine seems to have poor efficacy.
    - Avoid SNRIs (e.g., Effexor, Cymbalta) and tricyclics due to higher risk of switching.

Patients should be assessed every one to two weeks. The patient is considered in remission when there are no signs or symptoms of depression for at least two months.

Maintenance of Bipolar Depression
Therapy should continue for at least six months after remission has been achieved.

- For those patients that have had more than one manic episode, one manic and one depressive episode or ≥ 3 depressive episodes life-long preventive treatment is necessary.
- If therapy is to be discontinued it should be slowly tapered over 2 to 4 weeks (with a reduction of 20-25% weekly).
- In patients with BD2 the focus of treatment is on prevention of depression

- **First line therapy for BD1:**
  - Monotherapy – lithium (best for prevention of mania or hypomania), lamotrigine (superior to lithium to prevent depression), or the use of an antipsychotic such as olanzapine, quetiapine, or aripiprazole to prevent mania.
    - Use of antipsychotics for maintenance therapy is tempting due to their efficacy in acute mania but data shows they are not as effective as lithium.
  - Combination Therapy should only be used as maintenance in those patients with recent or severe mania. Lamotrigine + lithium, olanzapine or aripiprazole; lithium or valproate + olanzapine, quetiapine, aripiprazole, ziprasidone
  - Risperidone IM can be used as monotherapy or an adjunct for those with frequent manic episodes.

- **First line therapy for BD2:**
  - Monotherapy – lithium, lamotrigine or quetiapine
• **Second line therapy for BD1:**
  - Monotherapy – Carbamazepine or Invega
  - Combination Therapy – lithium + olanzapine, valproate, carbamazepine, lamotrigine or risperidone; olanzapine + fluoxetine (reserve antidepressants for patients who relapse into depression on an attempted antidepressant discontinuation)

• **Second line therapy for BD2:**
  - Monotherapy – Valproate
  - Combination therapy – 2 mood stabilizers (lamotrigine, valproate, or lithium); atypical antipsychotic + lithium, valproate or lamotrigine; antidepressant + lithium, valproate or an atypical antipsychotic.

• **Third line therapy for BD2:**
  - Monotherapy – carbamazepine, oxcarbazepine or an atypical antipsychotic

**Complimentary therapy:** Fish oil as an adjunct seems to improve symptoms of depression (not mania) and prolong remission.

**Mood Stabilizers**

**Lithium**

- **DOSE:** *Immediate release:* Initiate at low dose (e.g., 300 mg 3 times daily or less); increase gradually based on response and tolerability; usual dosage: 900 to 1,800 mg daily in 3 to 4 divided doses. *Extended release:* Initiate at low dose (e.g., 450 mg 2 times daily or less); increase gradually based on response and tolerability; usual dosage: 900 to 1,800 mg daily in 2 divided doses
  - Dosing: Renal Impairment: CrCl 10 to 50 mL/minute: Administer 50% to 75% of normal dose. CrCl <10 mL/minute: Administer 25% to 50% of normal dose. End stage renal disease (ESRD) with hemodialysis: Dose after dialysis
  - COMMON SIDE EFFECTS: mild hand tremor, weakness, lack of coordination, dry mouth, altered taste perception, weight gain, increased thirst, increased frequency of urination, mild nausea or vomiting, loss of appetite, stomach pain or upset, impotence, decreased libido, diarrhea, thinning or drying of the hair, itching skin, and kidney abnormalities
  - MONITORING: Renal function including BUN and SrCr (baseline, every 2 to 3 months during the first 6 months of treatment, then once a year in stable patients or as clinically indicated); serum electrolytes (baseline, then periodically), serum calcium (baseline, 2 to 6 weeks after initiation, then every 6 to 12 months; repeat as clinically indicated) (Broome, 2011); thyroid (baseline, 1 to 2 times with in the first 6 months of treatment, then once a year in stable patients or as clinically indicated); beta-hCG pregnancy test for all females not known to be sterile (baseline); ECG with rhythm strip (baseline for all patients over 40 years, repeat as clinical indicated), CBC with differential (baseline, repeat as clinically indicated); serum lithium levels (twice weekly until both patient’s clinical status and levels are stable, then repeat levels every 1 to 3 months or as clinically indicated); weight (baseline, then periodically)
  - Trough lithium concentrations 0.8-1.2 mEq/L

**Depakote (divalproex)**

- **DOSE:** Initial: 750 mg/day in divided doses; dose should be adjusted as rapidly as possible to desired clinical effect; maximum recommended dosage: 60 mg/kg/day. Depakote ER: Initial: 25 mg/kg/day given once daily; dose should be adjusted as rapidly as possible to desired clinical effect; maximum recommended dose: 60 mg/kg/day.
  - COMMON SIDE EFFECTS: drowsiness, weakness, nausea, vomiting, stomach upset, diarrhea, constipation, mood swings, changes in menstrual periods, enlarged breasts, weight changes, agitation, tremor (shaking), vision changes, unusual or unpleasant taste in your mouth, and hair loss.
MONITORING: Liver enzymes (at baseline and frequently during therapy especially during the first 6 months), CBC with platelets (baseline and periodic intervals), PT/PTT (especially prior to surgery), serum ammonia (with symptoms of lethargy, mental status change), serum valproate levels; suicidality (eg, suicidal thoughts, depression, behavioral changes); motor and cognitive function (for signs or symptoms of brain atrophy)
  - Trough valproate concentration 50-125 mcg/mL. Test yearly

Lamictal (lamotrigine) -

DOSE: Immediate release formulation:
  - Regimens not containing carbamazepine, phenytoin, phenobarbital, primidone, rifampin, lopinavir/ritonavir, or valproic acid: Initial: Weeks 1 and 2: 25 mg once daily; Weeks 3 and 4: 50 mg once daily; Week 5: 100 mg once daily; Week 6 and maintenance: 200 mg once daily
  - Regimens containing valproic acid: Initial: Weeks 1 and 2: 25 mg every other day; Weeks 3 and 4: 25 mg once daily; Week 5: 50 mg once daily; Week 6 and maintenance: 100 mg once daily
  - Regimens containing carbamazepine, phenytoin, phenobarbital, primidone, rifampin, or lopinavir/ritonavir, and without valproic acid: Initial: Weeks 1 and 2: 50 mg once daily; Weeks 3 and 4: 100 mg daily in divided doses; Week 5: 200 mg daily in divided doses; Week 6: 300 mg daily in divided doses; Maintenance: Up to 400 mg daily in divided doses

DISCONTINUING THERAPY: Decrease dose by ~50% per week, over at least 2 weeks unless safety concerns require a more rapid withdrawal.

COMMON SIDE EFFECTS: tremor, blurred vision, skin rash, nausea, ataxia, vomiting, diplopia, insomnia, rhinitis, dizziness, headache, drowsiness, abdominal pain, and fever. Other side effects include dyspepsia, dysmenorrhea, vaginitis, pain, constipation, pruritus, bronchitis, weakness, abnormal gait, and emotional lability

DRUG INTERACTIONS: Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, rifampin, lopinavir/ritonavir, or atazanavir/ritonavir should prolong the half-life of lamotrigine; discontinuing valproic acid should shorten the half-life of lamotrigine
  - MONITORING: LFTs, renal function, hypersensitivity reactions (especially rash); seizure, frequency and duration; suicidality (eg, suicidal thoughts, depression, behavioral changes); signs/symptoms of aseptic meningitis.

Tegretol (carbamazepine) -

DOSE: Initial: 400 mg/day in 2 divided doses (tablets, extended release tablets, or extended release capsules) or 4 divided doses (oral suspension), may adjust by 200 mg/day increments; maximum dose: 1600 mg/day.

COMMON SIDE EFFECTS: Nausea, vomiting, dizziness, drowsiness, constipation, dry mouth, dizziness

MONITORING: CBC with platelet count and differential, reticulocytes, serum iron, lipid panel, liver function tests, urinalysis, BUN, serum carbamazepine levels, thyroid function tests, serum sodium; pregnancy test; ophthalmic exams (intraocular pressure, pupillary reflexes); observe patient for excessive sedation, especially when instituting or increasing therapy; signs of rash; HLA-B*1502 genotype screening prior to therapy initiation in patients of Asian
  - Trough concentration 4-12 mcg/mL. Check level every 2 weeks for 3 months then yearly.
## Mood Stabilizers*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Generic</th>
<th>Dosage Forms</th>
<th>Recommended Dose</th>
<th>Cost for #30 Tabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Tegretol</td>
<td>Yes</td>
<td>Oral</td>
<td>400 mg – 1600 mg/day divided</td>
<td>200 mg tablet</td>
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<tr>
<td></td>
<td>Tegretol ER</td>
<td>Yes</td>
<td>Oral</td>
<td>400 mg – 1600 mg/day divided</td>
<td>200 mg ER Tablet</td>
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<tr>
<td>Lithium</td>
<td>Lithobid IR</td>
<td>Yes</td>
<td>Oral</td>
<td>900-1800 mg/day</td>
<td>300mg capsule</td>
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<tr>
<td></td>
<td>Lithobid ER</td>
<td>Yes</td>
<td>Oral</td>
<td>900-1800 mg/d</td>
<td>300mg ER capsule</td>
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<tr>
<td>Lamotrigine</td>
<td>Lamictal</td>
<td>Yes</td>
<td>Oral</td>
<td>100mg – 400 mg daily</td>
<td>500 mg tablet</td>
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<tr>
<td>Divalproex**</td>
<td>Depakote</td>
<td>Yes</td>
<td>Oral</td>
<td>750 mg/day – 60 mg/kg/day divided</td>
<td>500 mg tablet</td>
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<tr>
<td></td>
<td>Depakote ER</td>
<td>Yes</td>
<td>Oral</td>
<td>25 mg/kg/day – 60 mg/kg/day</td>
<td>500 mg ER tablet</td>
</tr>
</tbody>
</table>

*Use of gabapentin or topiramate as mood stabilizers is not recommended.

**Strengths of divalproex sodium and valproate sodium products are expressed in terms of valproic acid

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3 ibid

For detailed information about antipsychotic medications please refer to 2015 3rd quarter P&T report or contact Kimberly Griego at KGriego@contractpharmacy.com.