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Three medication pathways for bipolar disorder

By Tim Blake, MS, RN

NO MATTER WHERE you work, you're likely to care for patients with bipolar disorder, which affects about 2.6% of people age 18 and older per year.¹ Prevalence declines by age, with a lifetime prevalence of 3.9%.² To care for these patients safely, you must understand the medications prescribed to treat bipolar disorder, which include lithium, antiepileptic drugs, and atypical antipsychotics.

The information in this article applies to adults, not children. Consult a pharmacist or the package insert for information about each drug's safety during pregnancy and breastfeeding. Consult a pharmacist, the package insert, or a comprehensive

drug reference for more details on precautions, drug interactions, and adverse reactions for the drugs discussed in this article.

Understanding bipolar disorder

According to the *Diagnostic and Statistical Manual of Mental Disorders IV-TR*, bipolar disorder, also known as manic-depressive illness, causes extreme mood swings with episodes of mania and depression, or a mixture of both.³

People with depression may feel sad or have difficulty with activities of daily living. The vegetative signs of depression—a set of the classic

signs of depression—include the following:

- alterations of sleep (difficulty falling or staying asleep, or sleeping too much)
- *anhedonia*, or little or no interest in any activity formerly found to be pleasurable, including sex
- alterations in appetite (loss of appetite or eating too much).³

Other symptoms may include the following:

- a low threshold for becoming irritated
- fatigue, loss of energy, or sluggishness
- feelings of worthlessness or guilt
- difficulty concentrating and making decisions

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- recurring thoughts of death or suicide.³

A patient in the manic phase may demonstrate a period of abnormally elevated or irritable mood for at least 4 days (for hypomania) to 7 days (for mania) and display these symptoms:

- rapid, pressured speech; more talkative
- inflated ego or even grandiosity
- flight of ideas or complaints of racing thoughts
- decreased need for sleep (such as 2 to 3 hours of sleep)
- distraction that occurs easily
- psychomotor agitation or increase in goal-directed activity (for instance, social or occupational activity)
- hypersexuality
- overindulgence in pleasurable activities (sexual indiscretions, buying sprees, unwise business decisions).³

A “mixed” episode is characterized by a period of a week or more in which the symptoms of both a major depressive episode and a manic episode are present daily. These episodes may last from a week to a few months. The patient may experience mixed episodes, manic, and/or depressed episodes over the course of the illness. A mixed episode may evolve from a manic or a major depressive episode, or it may emerge on its own. Besides extreme mood swings, patients with bipolar disorder can experience anger, panic attacks, agitation, anxiety, restlessness, suicidal thoughts, persecutory delusions, hallucinations, and confusion.³

Subtypes of bipolar disorder include the following.

- **Bipolar I disorder.** At least one episode of mania alternates with major depression. Mania may also include symptoms of psychosis.
- **Bipolar II disorder.** Episodes of hypomania alternate with major depression. This form of bipolar disorder, which isn't as severe as bipolar I disorder, often increases the patient's functioning when in the hypomanic state.⁴ Hypomania is a milder form



Bipolar disorder may be caused by overexcitement of neurons in the brain; lithium interacts with sodium and potassium at the cell membrane to stabilize electrical activity.

of mania that lasts for at least 4 days at a time but tends not to interfere with the patient's daily activities.⁵ The patient with hypomania tends to be euphoric, but suicidal tendencies are a particular risk for patients experiencing major depression.³

- **Cyclothymia.** Patients alternate between hypomania and minor depression for a period of at least 2 years.³
- **Bipolar disorder not otherwise specified.** Patients experience episodes of hypomania without major depression.³

Treatment of bipolar disorder is very patient-specific. Healthcare providers must use their expertise, time, and patience to find the correct combination of medications to attain satisfactory results.

The role of psychotherapy

After a patient is no longer in a state of mania, a practitioner may use psychotherapy to help the patient cope

more adaptively to stressors and decrease the possibility of relapse.¹ Pharmacology and psychotherapy are considered crucial during the continuation and maintenance phases of bipolar disorder.¹

Interpersonal and social rhythm therapy is another formalized therapy that's been tested in combination with pharmacologic interventions in randomized clinical trials as treatment for patients who are in the maintenance phase of bipolar disorder. This therapy focuses on factors that are related to recurrence of symptoms, including nonadherence, stress reduction, and support systems.⁶

Sizing up lithium

Lithium is a psychotropic agent with an established record of efficacy for treating acute manic episodes of bipolar I disorder as well as recurrent manic and depressive episodes. It inhibits 80% of acute manic and hypomanic episodes within 10 to 21 days of beginning treatment.⁷ Lithium isn't as effective for symptoms of mixed mania or for rapid cycling.^{1,8}

Lithium's mechanism of action isn't completely understood. Chemically similar to sodium and potassium, lithium is a positively charged ion that seems to affect electrical conductivity in neurons. According to one theory, bipolar disorder is caused by an overexcitement of neurons in certain parts of the brain; lithium interacts with sodium and potassium at the cell membrane to stabilize electrical activity.^{1,9}

Lithium improves mood in patients with bipolar disorder who are depressed, and augments antidepressant therapy when antidepressants alone fail to improve mood in patients who are depressed. Lithium is also effective as prophylaxis against recurrent depression in patients with bipolar disorders.¹

Because lithium must reach a therapeutic blood level, it can take

Watch out for interactions with lithium

Drugs and substances that interact with lithium	Effect when used with lithium	Nursing considerations
Acetazolamide, alcohol, alkalinizing agents such as sodium bicarbonate, caffeine, urea, xanthine preparations	Decrease lithium levels by increasing lithium excretion	Closely monitor serum lithium levels when administering drugs concurrently. Warn patient about effect of alcohol and caffeine.
Angiotensin-converting enzyme (ACE) inhibitors, diuretics	Increase lithium levels by increasing sodium excretion, increasing the risk of lithium toxicity	Avoid using together. When they must be used together, exercise extreme caution.
Calcium channel blocking agents	May increase risk of neurotoxicity	Monitor patient closely for ataxia, tremors, nausea, vomiting, diarrhea, and tinnitus.
Carbamazepine	Increases risk of neurotoxic adverse reactions	Monitor serum lithium levels.
Fluoxetine	May increase or decrease lithium levels	Monitor patient closely.
Iodide preparations, especially potassium iodide	Extended use may cause hypothyroidism	Monitor thyroid function studies; assess patient for decreased thyroid function.
Metronidazole	May cause lithium toxicity due to reduced renal clearance	Monitor patient closely.
Neuromuscular blocking agents	Prolong the paralyzing effect of some agents	Use together cautiously.
Nonsteroidal anti-inflammatory drugs	Increase lithium levels by reducing renal elimination	Closely monitor serum lithium levels.

Source: Noven Therapeutics. Lithobid (lithium carbonate) Prescribing Information. Miami, FL: Noven Therapeutics; 2011.

up to 3 weeks to control symptoms in patients with mania. Generally, the target serum level for acute treatment in adults is between 0.8 and 1.4 mEq/L.¹⁰ Slightly lower levels (0.6 to 1.2 mEq/L) are suggested for older adults due to decreased renal clearance.¹¹

Adverse reactions

Fine hand tremors, polyuria, and mild thirst are common adverse reactions during initial treatment. The patient may also experience transient mild nausea and general discomfort during the first few days of lithium administration.

These adverse reactions should subside shortly after initiation of treatment, but if they persist, a reduced dosage or cessation of therapy is indicated.¹² Tell patients using lithium at home to discuss any

troublesome adverse reactions with their healthcare provider, and warn them not to stop taking the drug or alter the dosage on their own.

Some drugs and substances interact with lithium. See *Watch out for interactions with lithium*.

Toxicity concerns

Err on the side of caution when you administer lithium to a patient. Make note of any complaints the patient has about possible adverse reactions. Lithium has a very narrow therapeutic window, so always be concerned about possible toxicity.

Because of the risk for toxicity, serum lithium levels must be obtained regularly throughout treatment. Serum lithium levels greater than 1.5 mEq/L carry a greater risk of toxicity than lower levels. When signs and symptoms of toxicity appear,

notify the healthcare provider, withhold the medication, and obtain a lithium level as prescribed. The healthcare provider can then reevaluate the dosage.¹⁰ Teach patients the signs and symptoms of lithium toxicity, and tell them to contact the healthcare provider immediately if they experience them.

Early signs and symptoms of toxicity include nausea, vomiting, diarrhea, thirst, polyuria, lethargy or drowsiness, slurred speech, muscle weakness, incoordination, and fine hand tremor.¹²

With serum levels between 1.5 and 2.0 mEq/L (advanced toxicity), patients begin experiencing coarse hand tremors, persistent gastrointestinal (GI) upset, mental confusion, muscle hyperirritability, electroencephalographic changes, incoordination, and sedation.¹⁰

When serum lithium levels are 2.0 to 2.5 mEq/L (severe toxicity), the patient may display ataxia, giddiness, serious electroencephalographic changes, tinnitus, and blurred vision. Other signs include clonic movements, large output of dilute urine, seizures, stupor, severe hypotension, and coma.¹² Severe toxicity may be fatal; death is usually secondary to pulmonary complications.¹⁰

Nursing implications

- Monitor lithium levels closely, especially during initiation of therapy. (In most acute care settings, levels are determined twice weekly. Once patients are stabilized, levels may be obtained monthly and then quarterly.)
- Notify the healthcare provider and hold the patient's lithium if the serum level is 1.5 mEq/L or greater.¹³

Teaching patients about lithium

- Bipolar disorder requires long-term treatment. Don't change the dose or stop taking lithium, even when you feel better. Only your healthcare provider can determine the dosage and length of lithium treatment that's right for you. Missing doses of lithium may increase your risk for a relapse in your mood symptoms.
- Lithium may make you drowsy. Don't drive or operate machinery until you know how this medication affects you.
- You shouldn't drink alcohol or use recreational drugs while taking lithium.
- Lithium may be prescribed by itself or along with other medications to manage your mood symptoms.
- The amount of lithium in the blood can be measured. In the beginning of treatment, your healthcare provider may check your blood once or twice a week. Once your symptoms are well controlled, blood samples will be drawn less frequently. High blood levels can result in more adverse reactions, and low blood levels may not treat symptoms.
- Tell your healthcare provider if you take medications for pain or high blood pressure, as some of these types of medication may interact with lithium.
- The loss of too much water or salt from your body can lead to serious adverse reactions from this medication. Make sure you drink enough water in hot weather, during activities that cause you to sweat (exercise, saunas, hot baths), or when you're ill and are experiencing vomiting and/or diarrhea.
- Lithium tablets or capsules are usually taken two or three times daily; however, lithium may be taken once daily as long as you tolerate the possible stomach upset. Your healthcare provider will determine the dose that's right for you based upon blood level and your response.
- If you're taking a slow-release formulation, be sure to swallow the tablets whole. Don't crush or chew the tablets.
- If you're taking the liquid formulation, ask your pharmacist for a measuring device (spoon or oral syringe) to make sure you get the right amount of medication. Lithium liquid may be mixed with juice, but it shouldn't be mixed with coffee, tea, or cola.
- Taking lithium with food can help decrease or avoid stomach upset.
- Don't start a low-salt diet without talking with your healthcare provider because low sodium blood levels can increase the risk of lithium toxicity.
- Use a pillbox or calendar to help you remember to take your medication.
- If you miss a dose of lithium, take it as soon as you remember if it's not too close to when your next dose is due—discuss this with your healthcare provider. If it's close to your next dose, wait until then to take the medication and skip the missed dose. Don't double your next dose or take more than what you've been told to take.

Source: NAMI: National Alliance on Mental Illness. Medications: lithium. http://www.nami.org/Template.cfm?Section=About_Medications&Template=/TaggedPage/TaggedPageDisplay.cfm&TPLID=51&ContentID=20820. Copyright 2012, NAMI, the National Alliance on Mental Illness, www.nami.org. This information was last updated in 2010.

- Prior to lithium administration, patients should have thyroid and renal function tests and/or urinalysis, an ECG if they're older than 40, a pregnancy test if appropriate, complete blood cell (CBC) count, and general chemistry screening.¹
- Monitor patients for drugs and substances that could interact with lithium.
- In some patients, concomitant administration of lithium and haloperidol has resulted in irreversible central nervous system toxicity.¹⁴ Encephalopathic syndrome is characterized by lethargy, weakness, tremulousness, fever, and confusion. Extrapyramidal symptoms, leukocytosis, and increased blood urea nitrogen, followed by irreversible brain damage, have occurred in a few patients treated with lithium plus haloperidol, although a causal relationship hasn't been established. Monitor patients who are receiving a combination of lithium and haloperidol closely; notify the healthcare provider right away if the patient shows signs of toxicity.¹⁵
- Lithium isn't typically given to women who are pregnant due to the potential for harm to the fetus. Lithium is categorized as a category D drug because of evidence of human fetal risk, but it may be used in the event of a life-threatening risk to the mother or threat of serious illness.¹⁶
- Lithium is also contraindicated in women who are breastfeeding.¹

For details about patient education, see *Teaching patients about lithium*.

Eye on AEDs

Although classified as antiseizure medications, antiepileptic drugs (AEDs) are also used to treat many other health problems, including bipolar disorder.¹⁴ Under certain circumstances, AEDs including valproate and carbamazepine are now

being used as mood stabilizers. See *Adverse reactions to AEDs* for more information.

Valproate

Valproate products FDA-approved to treat manic or mixed episodes associated with bipolar disorder include valproate sodium, valproic acid, and divalproex sodium. Divalproex is a formulation of valproate that can minimize GI distress.^{17,18}

Valproate is believed to decrease the firing rate of very-high-frequency neurons in the brain. This membrane-stabilizing effect may account for its ability to decrease mood swings in patients with bipolar disorder.¹ Valproate may also increase levels of gamma-aminobutyric acid, an inhibitory neurotransmitter in the brain.¹²

Serum valproate levels are usually collected in the morning before the first dose of the day and about 12 hours after the last drug dose (trough level).¹⁸ Target serum valproate levels are based on clinical response with trough levels between 50 and 125 mcg/mL.¹⁸ As with lithium, initiating valproate therapy requires closely evaluating the patient's clinical response and regularly monitoring blood levels.

Valproate products are available in several formulations including

Adverse reactions to AEDs

AED	Common adverse reactions	Uncommon serious adverse reactions
Divalproex, valproate sodium, and valproic acid	<ul style="list-style-type: none"> • somnolence • GI upset • dizziness • tremors • weight gain • transient hair loss 	<ul style="list-style-type: none"> • thrombocytopenia (dose related) • pancreatitis (rare) • hepatotoxicity (rare)
Carbamazepine	<ul style="list-style-type: none"> • nausea • vomiting • anorexia • sedation • poor coordination • skin reactions • hyponatremia 	<ul style="list-style-type: none"> • thrombocytopenia • leukopenia • anemia • agranulocytosis • Stevens-Johnson syndrome (sometimes fatal) • toxic epidermal necrolysis (sometimes fatal)
Lamotrigine	<ul style="list-style-type: none"> • sedation • tremor • weight gain • increased appetite • GI upset • hypotension • ataxia 	<ul style="list-style-type: none"> • boxed warning for serious skin rashes including Stevens-Johnson syndrome

Source: Spratto GR, Woods AL. *Nurse's Drug Handbook*. Clifton Park, NY: Delmar; 2011.

delayed-release tablets, extended-release tablets (which shouldn't be crushed), sprinkle capsules, a suspension, and an I.V. formulation.¹⁸

Carbamazepine

Carbamazepine, another AED, is an effective alternative to both lithium

and valproate for treating bipolar disorder in some patients. Carbamazepine's exact mechanism of action isn't known.

Carbamazepine may cause life-threatening dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). (See *Beware of dangerous reactions to carbamazepine*.) These reactions may cause severe damage to the skin and internal organs. The risk of SJS or TEN is highest in people of Asian ancestry who have a genetic risk factor.⁵ Patients should be instructed to call their healthcare provider immediately if they develop a rash, blisters, or a fever during their treatment with carbamazepine.⁵

SJS or TEN usually occurs during the first few months of treatment with carbamazepine. If patients have already been taking carbamazepine for several months or longer, they probably won't need to be tested for

Beware of dangerous reactions to carbamazepine



Stevens-Johnson syndrome (left) can cause bullae and crusts on the lips and targetoid lesions on the hand. Toxic epidermal necrolysis (right), causes distinct blisters and a characteristic Nikolski sign (arrow) of normal-looking skin between the bullae.

genetic risk factors, even if they're of Asian descent.⁵

Nursing implications

- Because these AEDs, especially carbamazepine, can cause blood dyscrasias, nurses working with inpatients should monitor CBC results closely.^{18,19} Leukopenia increases the risk of infection, so assess the patient for signs and symptoms of infection, as well as signs and symptoms of bleeding resulting from thrombocytopenia. Notify the healthcare provider immediately of adverse reactions.
- Provide symptomatic relief of nausea and vomiting.
- Initiate fall precautions as indicated if the patient is experiencing sedation or lack of coordination.
- After performing medication reconciliation, notify the healthcare provider of any potentially dangerous drug interactions.
- Because carbamazepine induces liver enzymes, it often causes lower

What are extrapyramidal side effects?

EPS often occur after a patient begins therapy with psychotropic medications. Three of these adverse reactions, which are reversible by either reducing the dosage or changing to another medication, include the following:

- *acute dystonic reaction*: spasmodic contractions of skeletal muscle throughout the body, including laryngeal spasms
- *akathisia*: inability to stop moving
- *pseudoparkinsonism*: symptoms similar to those of Parkinson disease, such as tremors and shuffling gait.

The fourth type of EPS, seen more often in patients taking phenothiazines and related drug, is irreversible:

- *Tardive dyskinesia*: involuntary muscle spasms of the fingers, toes, tongue, neck, trunk, and pelvis.

Source: Varcarolis EM, Halter MJ. *Foundations of Psychiatric Mental Health Nursing: A Clinical Approach*. 6th ed. St. Louis, MO: Saunders/Elsevier; 2010.



Your patients with bipolar disorder can be effectively managed over the long term with careful monitoring, support, and patient education.

serum concentrations of other drugs given with it.

- Because carbamazepine interferes with hormonal contraceptives, advise female patients who want to avoid conception to use other forms of contraception.¹⁹

Tapping atypical antipsychotics

In the past few years, atypical antipsychotics, also known as second-generation antipsychotics, have been used as part of a regimen for treating bipolar disorder. Some examples of these drugs include olanzapine, quetiapine, risperidone, and ziprasidone.

Adverse reactions

- Atypical antipsychotics have a boxed warning against their use in older patients with dementia due to an increased risk of death compared with placebo.^{20,21}
- Neuroleptic malignant syndrome (NMS) is a potentially life-threatening situation that can develop after a patient begins treatment with tradi-

tional or atypical antipsychotics. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and signs of autonomic instability including diaphoresis, cardiac dysrhythmias, and BP changes. Other signs may include myalgia, increased serum creatine kinase, myoglobinuria, and acute kidney injury.²¹ Teach patients to report these signs and symptoms to the healthcare provider right away. The antipsychotic should be immediately discontinued. Monitor the patient, who will need symptomatic treatment.²¹

- Tardive dyskinesia (TD) is a serious, and sometimes permanent, adverse reaction. Patients with TD experience involuntary movements of the face, tongue, and other parts of the body. The risk for developing TD and the chance that it will become permanent are thought to increase the longer a person takes the medication and the more medication a person takes over time. TD can develop after a person has been taking the medication for a short time at low doses, although this is much less common. Teach the patient to report these signs and symptoms to the healthcare provider right away.¹⁸

• Patients taking atypical antipsychotics, especially olanzapine, quetiapine, and risperidone, are at risk for metabolic problems including weight gain, diabetes mellitus, glucose intolerance, and dyslipidemia. Monitor patients' weight, waist circumference, BP, and serum glucose and lipid levels.¹⁸

- Monitor patients, especially those taking aripiprazole, risperidone, or ziprasidone, for the development of extrapyramidal side effects (EPS). (See *What are extrapyramidal side effects?*)

Balancing act

Although bipolar disorder has no cure, it can be effectively managed

over the long-term with your careful monitoring, support, and patient education. ■

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