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Identification and management of bipolar disorder

Abstract: Bipolar disorder is a complex and chronic mental illness. Individuals with this disorder usually have medical comorbidities needing management in primary care. This article focuses on bipolar disorder identification and medication management concerns for primary care nurse practitioners.

By Debra A. Scrandis, PhD, CRNP, PMHNP-F

About 3% to 21.6% of patients diagnosed with depression in primary care actually have bipolar disorder (BPD).[1] Individuals with hypomanic symptoms do not seek care, since they see this behavior as normal, and usually present during their depressive symptoms.[2] It can be difficult to diagnose on initial assessment when patients are depressed if they actually have BPD. The identification of BPD by primary care nurse practitioners (NPs) can assist patients with this disorder to receive appropriate treatment for their illness.

Accurate diagnosis and management of BPD is critical and can impact patient longevity. It is a chronic, severe mental illness with progressive, cognitive, and social functioning impairments, comorbid medical problems, and premature death.[3] A cohort study found women and men with BPD died earlier than the general population (9.0 years and 8.5 years, respectively).[3] Both genders had an 8- to 10-fold increased risk of suicide and increased mortality from cardiovascular disease, diabetes mellitus (DM), chronic obstructive pulmonary disease, influenza, pneumonia, and unintentional injuries.[3]

Primary care NPs treat depression and manage patients with chronic diseases, some of whom may have BPD. Early identification of BPD and adequate management of diagnosed patients is in the realm of primary care NPs. It is important for primary care NPs to have knowledge of symptoms, long-term maintenance treatment options, potential drug-to-drug interactions (DDIs), and lab monitoring criteria for patients with BPD. This article will focus on adults only, since children have other diagnostic and treatment considerations.

DSM-5 BPD diagnostic criteria

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) lists two types of BPD: bipolar I and bipolar II.[4] Both types include these two symptoms: abnormally and persistently elevated, expansive, or irritable mood and increased goal-directed activity or energy. Other symptoms include inflated self-esteem, decreased need for sleep and feeling rested, racing thoughts, ease of distractibility, more talkative or rapid speech, and more interest in sex or risk-taking/impulsive behaviors, such as spending large sums of money. These behaviors tend to be unusual for the person. If these symptoms last at least 1 week, the individual meets criteria for a manic episode. If they last at least 4 consecutive days, it would be a hypomanic episode and consistent with bipolar II. If an individual ever had a manic episode, they are diagnosed with bipolar I. Patients can have more manic symptoms, more depressive symptoms, psychotic symptoms,

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anxious distress, or mixed features (manic and depressive symptoms at same time) in the course of their illness.

Assessment

Patients who are in a manic episode usually do not present in primary care. If they do, they need to be immediately referred to psychiatric providers and possibly be admitted to a psychiatric unit. This section will discuss the necessary screening for mania, substance use, and suicide in patients with depression, since patients with undiagnosed BPD usually present with depressive symptoms.

Medical/psychiatric history

It has been suggested that major depressive disorder is a diagnosis of exclusion, and BPD needs to be excluded when patients present with depressive symptoms.[5] It is important to screen all patients who present with depressive symptoms for past manic or hypomanic episodes. Patients are likely to convert to mania when treated with antidepressants alone if they have a past history of mania. Hirschfield et al. recommend using the Mood Disorder Questionnaire (MDQ) for screening mania in clinical practice.[5,6] This tool has 13 questions in a yes/no format and can easily be completed by patients. Sasdell et al. found the MDQ had higher sensitivity (0.91) and specificity (0.67) and was more feasible than the Hypomania Checklist, a 32-item yes/no format, for primary care settings.[7] NPs need to have patients with depression complete the MDQ prior to prescribing antidepressant medications.

A history of medical and psychiatric symptoms is important for differentiating medical causes of symptoms from psychiatric symptoms alone. Medical conditions and substances need to be ruled out before assigning a psychiatric diagnosis. There are numerous medical conditions and medications that mimic manic and depressive symptoms. The most common conditions for manic symptoms are head injuries, multiple sclerosis, central nervous system (CNS) tumors, and HIV/syphilis infections. Depressive symptoms may be related to an underlying hypothyroidism or anemia. Positive review of systems in cardiovascular (palpitations), endocrine (cold intolerance), neurologic (head trauma, mental status changes), and abnormal physical examinations (abnormal cranial nerves, decreased deep tendon reflexes) can alert NPs to consider potential medical conditions. NPs need to rule out medication-induced manic and depressive symptoms. Common substances that may induce manic symptoms include stimulants, corticosteroids, sympathomimetics, decongestants, caffeine, and antidepressant medications. Substances that may lead to depressed mood include CNS depressants, such as alcohol and benzodiazepines. NPs need to conduct the CAGE screen to identify high-risk drinking behavior that may be masking underlying BPD.

When assessing psychiatric symptoms, it is important to pay attention to risk factors for BPD–particularly family history–since it has a high genetic component.[8] Patients with BPD usually have onset of symptoms in late adolescence or young adulthood with a distinct change in their behavior.[8] NPs need to keep in mind that bipolar II can peak later in life (45 to 54 years) after many depressive episodes.[9]

Suicide. Patients with BPD are at high risk for suicide. NPs can ask directly "Do you feel like killing yourself?" to assess suicidality. The question "Do you feel like hurting yourself?" may assess for self-mutilating behaviors, not suicide risk. If the patient admits to suicidal thoughts, the NP needs to assess for active plan, substance use, access to lethal means, and determine the patient's contract for safety and possibly send the patient for emergency evaluation. The Ask Suicide-Screening Questions (ASQ) assesses suicidal thoughts.[10] The ASQ consists of four questions that assess thoughts regarding vague death wishes, suicide plans, and suicide within the last few weeks with a yes or no response format. It also asks about past suicide attempts and their means and timing. This instrument is available on the National Institute of Mental Health's website for free distribution.[10] Patients who exhibit an acute suicide ideation with plan need to be sent for emergency psychiatric evaluation.

Psychiatric referral. If patients with depression do not improve after two adequate trials of antidepressants or describe excessive energy and low need for sleep, these symptoms may indicate a switch to mania. All patients with strong indication toward BPD need a referral for psychiatric evaluation for treatment initiation. Primary care NPs can assist these patients to navigate entry into mental health services. It is critical to discuss the importance of managing symptoms with patients and working collaboratively with mental health providers.

Psychotherapy referral. It is prudent for primary care NPs to refer patients for ongoing psychotherapy to decrease affective symptoms, improve engagement in pharmacologic treatment, and assist in adapting to this chronic disorder. A review of psychological treatments did not find any one type to be more effective, yet success of a treatment may depend more on the illness stage and how the therapy is personalized for the patient.[11] In a 5-year follow-up evaluation of a psychoeducation and cognitive behavioral therapy combination with pharmacologic treatment intervention, only 20% of patients in the intervention group had affective symptoms compared with 88.9% of the pharmacologic treatment group.[12] The mean duration of illness was 13.7 years (range 5 to 25 years), suggesting psychotherapy with pharmacology is superior to pharmacologic treatment alone even in long-term patients. Primary care NPs can support patients with BPD

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to continue psychotherapy to improve and/or maintain their overall functioning.

Maintenance medication treatment of BPD

Patients with BPD need to be on maintenance medication treatment throughout their lives to prevent manic and hypomanic symptoms, reduce depressive symptoms, and suicide risk.[7,13]

These patients may still have relapses in the course of their illness. Patients with BPD can have other psychiatric disorders complicating their treatment. One study (n = 784) found 69.3% of individuals with BPD had previous diagnoses, including affective disorders, attention deficit hyperactivity disorder, and substance use disorder.[14] The lifetime prevalence of alcohol misuse in bipolar I disorder patients is 34.1%: One out of five women and two out of five men.[15] Individuals with BPD frequently self-medicate their depressive symptoms with substances and stop medication treatment due to adverse reactions or their perceptions of feeling well.[16] Inconsistent medication adherence, psychiatric care, and medical care follow up can lead to poor management of the illness, inpatient psychiatric hospitalizations, deteriorating social and occupational functioning, and complex medical problems.

Medical effects from pharmacologic treatment. There are many medical conditions resulting from medication treatment of BPD. There is a high likelihood of polypharmacy. One study found patients with BPD take an average of 3.31 psychotropic medications.[17] These medications can contribute to metabolic syndrome and metabolic abnormalities. Vancampfort et al. found in their meta-analysis (n = 81 studies) that these patients are twice as likely to have metabolic syndrome than the general population.[18] Out of all patients with BPD, they found metabolic syndrome was more prevalent in patients treated with antipsychotics than patients without antipsychotic treatment.

Medication management

NPs in primary care need to know the psychotropic medications used for bipolar maintenance before prescribing any medications for medical problems in patients with this disorder. Primary care NPs also need to monitor and address medical complications resulting from patients' treatment for BPD. The three classes of medications used for BPD treatment include mood stabilizers, second-generation antipsychotics (SGAs), and antidepressants. Only FDA-approved medications for BPD will be described in this section (see *FDA-approved maintenance medications for BPD*). NPs need to check for up-to-date DDIs before prescribing any medications for patients on these psychotropic medications (see *Monitoring for BPD maintenance medications*).

FDA-approved maintenance medications for BPD[22]

Medication	Common adverse reactions	Common drug-to-drug interactions	Pregnancy category
Lithium	Tremor Polyuria Polydipsia GI distress Weight gain Sedation	NSAIDs Diuretics ACEIs Metronidazole CCBs	D
Valproate	Sedation Tremor Dizziness GI distress Weight gain	Phenytoin Erythromycin Fluoxetine Aspirin	D
Lamotrigine	Benign rash	Valproate Phenytoin Oral contraceptives	C
Quetiapine	Sedation Weight gain Dizziness	Antihypertensives	C
Lurasidone	Weight gain Sedation	Rifampin Ketoconazole Fluoxetine Antihypertensives	B
Aripiprazole	Dizziness Akathisia Insomnia GI distress	Ketoconazole Paroxetine Antihypertensives Fluoxetine Duloxetine	C
Olanzapine and fluoxetine	Increased appetite Dry mouth Tremor	Antihypertensives NSAIDs Monoamine oxidase inhibitors	C

See the manufacturer's prescribing information for dosages and complete product information.

NSAIDS=non-steroidal anti-inflammatory drugs
ACEI=angiotensin-converting enzyme inhibitor
CCB=Calcium channel blockers
GI=gastrointestinal

Mood stabilizers

The mainstay treatment for BPD is mood stabilizers to decrease the likelihood of manic and hypomanic symptoms. All women of childbearing age need consistent contraception due to increased risks of congenital abnormalities with these medications. Primary care NPs can discuss the importance of contraception and advise them to talk with their psychiatric providers about the risks and benefits of treatment during pregnancy before trying to

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conceive. Both lithium and valproate contribute to weight gain. Primary care NPs can focus their education on healthy dietary portions and physical activity to decrease risks of medical comorbidities. Primary care NPs should not prescribe mood stabilizers. These patients need psychiatric providers with expertise in mood stabilization.

Lithium. Lithium is FDA approved for acute manic episodes and preventive maintenance. The evidence on its effectiveness for mania treatment and suicide prevention is high.[19] It has a slow onset of action, usually taking 1 to 3 weeks for adequate effect and is rapidly absorbed orally with peak serum concentrations in 1 to 1.5 hours. It is not metabolized or protein-bound and is excreted by the kidneys. It has a half-life of 18 to 30 hours, where the higher range is found after use for 1 year.[20] Obesity increases the rate of drug clearance, so dosing usually needs to be higher in this population.

Lithium toxicity is a serious concern. Symptoms of toxicity include delirium, mental status changes, severe tremor, ataxia, diarrhea, vomiting, and high sedation. These patients need to be referred for emergency care. Lithium levels need to be performed periodically due to their narrow therapeutic index. Patients need continued education on maintaining hydration to decrease the risk of toxicity.

Common medications that can increase lithium plasma blood levels include nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, and diuretics (especially thiazides). Lithium decreases sodium reabsorption by the renal tubules and could lead to sodium depletion.[21] Caffeine and high dietary sodium intake decrease lithium levels.[22] Patients on lithium also need to avoid low sodium dietary regimens and situations where excessive sodium depletion can occur, such as heavy exercise with excessive sweating that can contribute to increased lithium concentrations and lithium toxicity. The NP needs to reinforce the importance of patients maintaining an adequate sodium intake and fluid intake (2,500 to 3,000 ml/day).[21,23]

Other medication classes that increase toxicity without affecting lithium levels include serotonin selective reuptake inhibitors (SSRIs), calcium channel blockers, phenytoin, and methyldopa.[22] NPs need to use these medications with caution in patients on lithium for maintenance.

Patients with excessive fluid loss from vomiting, diarrhea, or ongoing infections with fevers are at risk for lithium toxicity. Their lithium dosage will need to be temporarily reduced or discontinued.[21] Primary care NPs need to consult with or refer to psychiatric providers for lithium adjustments.

Monitoring for BPD maintenance medications[22]

Medication	Recommended lab/test monitoring	Frequency	Concerns
Lithium	• Lithium level • Electrolytes, urea, creatinine • Calcium • Thyroid-stimulating hormone • ECG • Last menstrual period (LMP) • Weight	Every 3-6 months Every 6 months initialy, then annually	• Subtherapeutic or toxic level • Renal insufficiency • Nephrogenic diabetes insipidus • T-wave flattening or inversion • Leukocytosis • Hypothyroidism • Pregnancy • Weight gain
Valproate	• Valproate level • Complete blood cell count • LMP • Liver function tests • Weight	As clinically indicated Every 3 months x 1 year, then annually	• Subtherapeutic/toxic level • Weight gain • Dysmenorrhea • Liver failure • Thrombocytopenia • Pregnancy
Lamotrigine	• Monitor for rash • No recommended testing	N/A	• Stevens-Johnson syndrome
SGAs	• Weight • BP • Fasting blood glucose • Lipid profile • Monitor for abnormal movements • ECG • Prolactin as clinically indicated	Monthly x 3 months, then every 3 months x 1 year then annually	• Weight gain • Metabolic syndrome • Acute dystonia • Drug-induced parkinsonism • Tardive dyskinesia • QTc prolongation • Dysrhythmias • Hyperprolactinemia

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Valproate. Valproate is indicated for acute mania and mania prevention. It is rapidly absorbed with peak plasma concentrations in 4 to 5 hours (half-life of 10 to 16 hours). It is highly protein-bound. Individuals can take valproate with food and consolidate their dosages to bedtime. Dosages can be divided if they have tremors. Any CNS depressant, such as alcohol, will have additive CNS depression. Phenobarbital, primidone, lamotrigine, zidovudine, and lorazepam levels will increase with valproate. Valproate inhibits platelet aggregation, so the use of warfarin needs to be monitored carefully. Aspirin and other salicylates displace valproate from protein-binding sites, increasing the potential for toxicity. Low-dose aspirin (81 mg) daily is acceptable. Antacids increase stomach pH and dissolve the enteric coating, leading to more gastrointestinal (GI) distress; therefore, it is important to educate patients to avoid antacid use before taking valproate enteric coated.

Valproate has an FDA boxed warning for hepatic failure since it has occurred, resulting in fatalities in some patients usually within the first 6 months of therapy.[24] The drug is contraindicated in patients known to have mitochondrial disorders caused by a mutation of the polymerase gamma gene (for example, Alpers-Huttenlocher syndrome) due to high risk of acute liver failure and liver-related death. Patients who exhibit nonspecific symptoms (malaise, weakness, lethargy, anorexia, facial edema, and vomiting) early in treatment may have serious or fatal hepatoxicity and need a referral for emergency care. There have also been cases of life-threatening pancreatitis, so primary care NPs need to refer patients on valproate who present with abdominal pain, nausea, vomiting, and/or anorexia presenting as possible pancreatitis.

Lamotrigine. Lamotrigine is FDA approved for maintenance treatment of bipolar I. It is completely absorbed, 98% bioavailable, and has a 25-hour half-life. Food has no effect on its absorption, and 55% is protein-bound. Lamotrigine doses need to be lower when coadministered with valproate due to increased plasma levels and a higher incidence of rash. Lamotrigine has an FDA black box warning for severe and potentially life-threatening skin rashes requiring hospitalization (mostly occurring in the first 8 weeks of treatment). However, isolated cases may occur after prolonged treatment. Rare cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema have been reported. The primary care NP needs to pay close attention to patients on lamotrigine who present with new-onset rash. Lamotrigine will need to be discontinued, and the NP will need to consult with psychiatric providers about alternative mood stabilization for these patients.

Women on oral contraceptives may need a higher dose of lamotrigine, since they lower plasma levels. Pregnancy registry data support some increased risk of isolated cleft palate/lip deformity with exposure to lamotrigine in the first trimester.

Second-generation antipsychotics. All SGA medications (also known as atypical antipsychotics) are FDA indicated for acute mania, and some agents (aripiprazole, lurasidone, olanzapine, quetiapine) are for BPD maintenance either as monotherapy or adjunct therapy. These medications are serotonin-dopamine antagonists. SGAs are more specific to the mesolimbic than striatal dopamine system, so they have lower incidence of extrapyramidal symptoms (EPS) than first generation antipsychotics (for example, haloperidol). One study found patients who had aripiprazole or quetiapine adjunct with lithium had 20% to 30% lower all-cause mortality than patients who only used lithium, so SGAs have a place in bipolar treatment.[3] SGAs have been associated with the development of hyperglycemia, and in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death.[25] Some of these drugs have a strong risk for weight gain, DM, and metabolic syndrome. Olanzapine has the highest weight gain risk and risk for hyperglycemia, while ziprasidone and aripiprazole have little weight gain.[5,22] Quetiapine has moderate weight gain concerns.[5] All SGAs need to be used with caution in patients who have diabetes or other disorders of glucose regulation. The FDA states patients with risk factors for diabetes need a baseline fasting blood glucose and ongoing assessment of glucose levels.[25] The primary care NP needs to watch for symptoms and signs of hyperglycemia in patients on SGA. Long-term management of all individuals on SGAs includes assessment of body mass index, waist circumference, BP, fasting blood glucose, and lipid profile.

Aripiprazole. Aripiprazole is indicated for acute mania and bipolar maintenance. It has a long half-life (75 hours) and is 99% protein-bound. It is a good choice for individuals with DM, coronary artery disease, or dyslipidemia due to its low risk for weight gain. It also has a low risk of sedation. Aripiprazole carries a FDA boxed warning of increased risk of suicidal thinking and behavior in young adults in short-term studies of major depressive disorder and other psychiatric disorders.[26] This medication is used as an adjunct for major depressive disorder. The considered use of aripiprazole in young adults must balance this risk with clinical need. The primary care NP needs to consistently assess for suicidality in younger patients on aripiprazole for BPD.

Lurasidone. Lurasidone is FDA approved for bipolar depression. It needs to be taken with food for best absorption. Lurasidone reaches peak serum concentration in 1 to 3 hours (half-life 18 hours). Cigarette smoking does not have an effect on the metabolism of lurasidone. It is contraindicated for patients with liver disease, heart disease, hyperlipidemia, or myocardial infarction history. Patients

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need monitoring for postural hypotension. Lurasidone has moderate weight gain risk. Lurasidone carries the same boxed warning for suicidality, so the primary care NP needs to continue assessment for suicidal thoughts or behaviors.

Olanzapine. Olanzapine is FDA approved for monotherapy in acute mania, mixed, and maintenance. It is approved in combination with fluoxetine for bipolar depression. It is 85% absorbed in the gut with a 31-hour half-life. Alcohol increases its absorption, thereby increasing sedation. Olanzapine has more frequent weight gain than other SGAs. Weight gain peaks by 9 months of use and continues slowly afterward. Fluoxetine does not contribute to weight gain or sedation, so adverse reactions may be decreased in combination with olanzapine.

Quetiapine. Quetiapine is used first line for acute bipolar depression and maintenance. It is rapidly absorbed in the GI tract with peak plasma concentration in 1 to 2 hours (half-life 7 hours). It is not associated with EPS or an increase in prolactin levels. It does have moderate risk for weight gain and carries a boxed warning for suicidality. There is an extended release formulation for once at bedtime dosing.

Ziprasidone. Ziprasidone is FDA indicated for adjunct to lithium or valproate for maintenance treatment. Peak plasma concentration is reached in 2 to 6 hours (half-life 2 to 5 hours) and may have some antidepressant potential.[27] It is best absorbed with food. Ziprasidone can contribute to corrected QT interval (QTc) prolongation, so any medication with the potential to prolong QTc interval is contraindicated. It should not be used in patients with a history of cardiac dysrhythmias.

Antidepressants. Antidepressant medication use has not demonstrated favorable outcomes for treating bipolar depression. The International Society for Bipolar Disorder consensus statement on antidepressant use was unable to endorse a broad statement for their use, but they acknowledge that some individuals may benefit from their effects.[28] If individuals had previous response to antidepressants, they may be beneficial for acute bipolar I or II depressive episodes as adjunct with mood stabilizers. Tricyclic and tetracyclic antidepressants and serotonin norepinephrine reuptake inhibitors should be considered only after trials of other antidepressants, such as SSRIs or bupropion, since they have a higher risk to cause mania switch.[23] The World Federation of Societies of Biological Psychiatry guidelines also found antidepressant use controversial. Efficacy of their use is not supported, but they did find high evidence for preventing suicide.[19] The risk of manic switch is higher in bipolar I versus bipolar II, stressing the importance of only using antidepressants as an adjunct to mood stabilizers.[5] The only antidepressant combination, olanzapine-fluoxetine, is supported by evidence for its efficacy and is FDA approved for bipolar I depression.[19,28,29]

Patient education

It is important for primary care NPs to monitor and educate patients with BPD about early triggers for mood switches. Sleep disturbance is a common trigger. NPs can assess sleep in these patients by asking "How long do you sleep" and "When do you sleep?"[30] Sleep hygiene, which includes dim lights at night, no stimulating activities before bed, and sleeping in a cool room, is critical for helping patients establish a routine. The National Sleep Foundation has resources on sleep hygiene for professionals and patients (sleepfoundation.org). Weight management, medication adherence, substance use, and medical comorbidities all need to be addressed in these patients.

A collaborative approach

Primary care NPs have several roles in caring for patients with BPD. When treating depression, NPs need to monitor for manic symptoms and identify patients at high risk for BPD. The early identification of heart disease and diabetes may reduce mortality for BPD patients.[3] Primary care NPs can review the patients' psychotropic medications, screen for comorbidities, conduct frequent weight monitoring, and order appropriate lab tests for patients with BPD. Communication with mental health providers is critical for effective treatment of patients with BPD. This collaborative approach may result in well-coordinated health education for weight management, medication regimen changes to best address adverse reactions, and improved functioning for these patients. NP

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