is it bipolar depression?

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Funding: This manuscript was supported by funding from Allergan (before its acquisition by AbbVie). The authors had full control of the content and approved the final version.

Competing interests: D. Rolin has no pharmaceutical relationships to disclose. J. Whelan has relationships with Otsuka, Neurocrine, Avanir, and Genomind, and is a speaker for Allergan (now AbbVie). C. B. Montano has received research funding from Acadia, Allergan (now AbbVie), Arbor, Avanir, Axsome, Biohaven, Sage Therapeutics, Sanofi, Sunovion, and Tonix. Additionally, he has received consultant and speaker honoraria from Alkermes, Allergan (now AbbVie), Arbor, Eisai, Neos, Rhodes, Shire, Sunovion, and Takeda.

Authors' contributions: All authors participated in the writing, editing, and critical revision for intellectual content, and approval of the final version of this manuscript. All authors met ICMJE authorship criteria and agree to be accountable for all aspects of the work. Neither honoraria nor payments were made for authorship.

Journal of the American Association of Nurse Practitioners 32(10):p 703-713, October 2020. | DOI: 10.1097/JXX.0000000000000499

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Abstract

This review is intended to guide primary care providers in differentiating patients with bipolar depression from those with unipolar depression and inform patient management. Up to 64% of clinical encounters for depression occur in primary care, with misdiagnosis of bipolar depression common in both primary care and psychiatry. Although bipolar disorder is characterized by manic, hypomanic, and depressive episodes, the most common and debilitating symptomatic presentation is depression. Misdiagnosis as unipolar depression is common, often resulting in mistreatment with an unopposed monoamine antidepressant. Antidepressants are often ineffective for treating bipolar depression and may cause detrimental consequences such as treatment-emergent hypomania/mania, rapid cycling, or increased suicidality. Factors that are suggestive of bipolar disorder versus unipolar depression include early-onset depression, frequent depressive episodes,

family history of serious mental illness, hypomania/mania symptoms within the depressive episode, and nonresponse to antidepressants. Comorbid medical (e.g., cardiovascular disease, hypertension, obesity) and psychiatric (e.g., attention-deficit/hyperactivity disorder, anxiety disorder, personality disorders, and substance use disorder) conditions are common and contribute to premature mortality for patients with bipolar disorder compared with the general public. Cariprazine, fluoxetine/olanzapine, lurasidone, and quetiapine are approved to treat bipolar depression; only cariprazine and quetiapine are approved to treat both bipolar mania and depression. Primary care providers who can differentiate presenting symptoms of bipolar depression from unipolar depression and offer appropriate treatment options will optimize patient care in clinical practice. Relevant information for this review was identified through a multistep literature search of PubMed using the terms bipolar depression/bipolar disorder plus other relevant terms.

Introduction

Is it unipolar depression or bipolar disorder?

Approximately half of all mental illness is treated in primary care (Lewis et al., 2004), putting nurse practitioners (NPs), physician assistants (PAs), and primary care physicians on the front line of mental health treatment. Given the changing health care landscape, access to psychiatric services is limited for many people for reasons as varied as a shortage of psychiatrists and psychiatric advanced practice registered nurses, distance to a provider, long wait times for appointments, and cost (including lack of insurance coverage) (Butryn et al., 2017; Frye et al., 2005). These barriers make the mental health services provided by primary care providers and NPs crucial, with services for depression care a case in point. Up to 10% of all primary care visits are depression related and as many as 64% of all clinical encounters for depression occur in the primary care rather than in a specialty care setting (Unutzer & Park, 2012). Although clinically significant depressive symptoms may at first glance suggest a diagnosis of unipolar depression, major depressive episode, or major depressive disorder (MDD), a premature diagnostic conclusion could unintentionally conceal a more ominous and complicated mental illness: bipolar disorder.

Bipolar disorder is a chronic and complex disorder that is associated with reduced quality of life, functional and cognitive impairment, and premature death (Grande et al., 2016). Previously conceptualized as an episodic disorder with distinct periods of mania or depression alternating with periods of mood stability, bipolar disorder is now more accurately defined as a progressive disorder consisting of manic, hypomanic, mixed, and depressive episodes; significant subsyndromal symptoms are often present between clinically distinct major mood episodes (Grande et al., 2016; Leboyer & Kupfer, 2010). The complexity of bipolar disorder is exacerbated by the presence of numerous medical (i.e., hypertension, diabetes, obesity) and psychiatric (i.e., anxiety disorders, substance use disorders) comorbidities in most patients (Krishnan, 2005).

At least 50% of patients with bipolar disorder initially present with a depressive episode (Mitchell et al., 2008) and up to almost 40% of patients with bipolar disorder receive treatment exclusively in primary care (Kilbourne et al., 2012). Regardless of the specialty or type of provider that is consulted, misdiagnosis of bipolar depression as MDD occurs in 60% of patients and only 20% of patients with bipolar disorder are correctly identified within the first year of seeking treatment (Hirschfeld et al., 2003a). Misdiagnosis as unipolar depression can result in inappropriate treatment of bipolar depression with antidepressants, which may worsen the disorder, delay the initiation of correct treatment, and potentially lead to harmful outcomes, including antidepressant-emergent mania and suicidality (Fornaro et al., 2018; Goldberg et al., 2001; McElroy et al., 2006). Given the abundance of patients with depressive illnesses who present for treatment in primary care, it is certain that all

primary care providers will be responsible for recognizing, diagnosing, and treating illnesses that are defined by depressive symptoms, including bipolar disorder.

The role of nurse practitioners and primary care providers

Nurse practitioners have extensive academic postgraduate education and are board certified to assess, diagnose, educate, and prescribe pharmacologic and nonpharmacologic treatment to manage illness. These qualifications make both family practice and psychiatric specialist NPs ideal practitioners to provide safe and effective evidence-based treatment services for patients with mental health conditions. In their fundamental capacity as licensed health care providers, various types of NPs, including family NPs, adult NPs, and those with specialized psychiatric training like psychiatric mental health NPs (PMHNPs), manage patients with depressive symptoms. The philosophies of nursing are well matched to the goals of bipolar disorder management, which include establishing a therapeutic alliance; monitoring quality of life, psychiatric, functional, and social status; providing education; enhancing treatment adherence; encouraging regular patterns of activity and sleep; and helping patients cope with stressors to effectively treat and minimize the risk of relapse (Miller, 2006). To reduce morbidity and mortality among patients, the requisite integration of mental health care into primary care may require that certain NP specialties receive more education on diagnosis, management, and effective screening of bipolar disorder (Kriebel-Gasparro, 2016). As well-informed clinicians, PMHNPs may in turn provide guidance and education to their primary care peers, helping to inform and integrate the health care team (i.e., registered nurses, primary care physicians, social workers, emergency personnel) to enhance patient care. This article was designed to provide a brief overview of bipolar disorder to help NPs and other primary care providers learn to differentiate bipolar depression from unipolar depression to improve diagnosis and treatment strategies.

Methods

The PubMed database was searched in May 2019 for English-language review articles published in the past 5 years using the terms “bipolar disorder” AND “primary care” (239 results) and “bipolar disorder” AND “nurse practitioner” (13 results). Additional search terms including bipolar depression, burden, caregiver burden, costs, economic, prevalence, quality of life, and suicide were also individually searched in conjunction with “bipolar disorder.” The search results were reviewed and studies relevant to our article were manually selected for inclusion. Additional references were obtained by reviewing the reference lists of the articles found through our electronic search; English language articles published at any time were included if relevant; articles that contained outdated information were excluded.

Genetics and neuropathology of bipolar disorder

Genetic factors are known to play an important role in the development of bipolar disorder as shown by evidence from twin studies that suggests concordance for monozygotic twins is between 40% and 70% and lifetime risk in first-degree relatives is between 5% and 10%, which is about seven times higher than the risk in the general population (Craddock & Jones, 1999). However, no single established causative gene or genetic risk factor has been identified (Kato, 2007), and the majority of genetic risk in bipolar disorder is associated with multiple polymorphisms and very small contributions from copy number variants and other rare variants (Craddock & Sklar, 2013; Muhleisen et al., 2014; Shinozaki & Potash, 2014). Although studies of bipolar disorder pathophysiology have produced several hypotheses, the neurobiological mechanisms that underpin bipolar disorder remain largely unknown. Early investigations related to monoamine disturbances have given way to more recent inquiries into glutamatergic influences, glial dysfunctions, and neuroinflammation, but

findings are largely inconclusive and no definitive disease theory or candidate gene has emerged (Berk et al., 2007a,2011; Gigante et al., 2012; Maletic & Raison, 2014; Reus et al., 2015).

Prevalence and time spent unwell with depression

Lifetime and 12-month prevalence estimates for bipolar I disorder are 2.1% and 1.5%, respectively, based on criteria from the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association, 2013). However, across the bipolar spectrum, which includes bipolar I, bipolar II, and mixed or subthreshold symptoms, lifetime (4.4%) and 12-month (2.8%) prevalence is considerably higher (Merikangas et al., 2007). Depressed mood accounts for the majority of time patients with bipolar disorder spend unwell (Figure 1) (Forte et al., 2015).

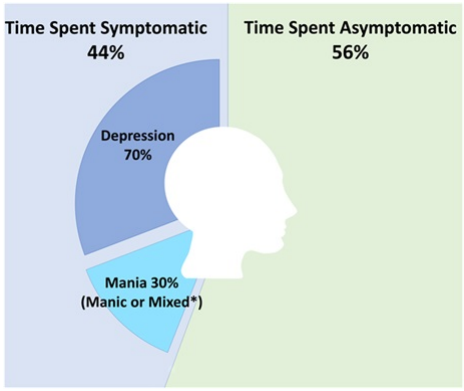

Figure 1.:
Proportion of time spent in mood states with bipolar disorder. *Mixed features of bipolar disorder include mania with depression, mania with subsyndromal depression, or hypomania with depression.

Bipolar depression is the leading cause of morbidity in patients with bipolar disorder (Baldessarini et al., 2010), with depressive episodes having greater morbidity and mortality, as well as higher risks of suicide, interepisode panic attacks, and psychosis than manic episodes (Post, 2005).

Diagnostic classification

The diagnosis of bipolar I disorder requires the occurrence of at least one lifetime manic episode; however, depressive episodes are far more common (American Psychiatric Association, 2013). Because many individuals experience bipolar-like symptoms but do not meet the full criteria for bipolar I disorder, other relevant diagnoses in the bipolar spectrum must also be considered (American Psychiatric Association, 2013). Bipolar disorder with mixed features is a complex presentation in which a manic or depressive mood episode is complicated by the presence of subsyndromal but clinically significant symptoms from the opposite pole. The diagnosis of bipolar II disorder requires the occurrence of at least one hypomanic episode and one major depressive episode. Bipolar II disorder is no longer considered a milder form of bipolar disorder because it is associated with extensive depression time, functional impairment, anxiety, and the potential to escalate into a severe outcome, such as suicide (American Psychiatric Association, 2013). These softer, less obvious, symptomatic expressions of bipolar disorders are the presentations that are more commonly seen in primary care.

Clinicians should be mindful that DSM-5 criteria for a depressive episode are identical for unipolar and bipolar depression (American Psychiatric Association, 2013). As such, depressive symptoms should always arouse a suspicion of bipolar disorder and trigger appropriate assessment and screening in the clinic for both conditions. When a patient presents with clinically significant depressive symptoms, bipolar depression should always be ruled out before a diagnosis of unipolar depression

is made. Approaching MDD as a diagnosis of exclusion will help clinicians avoid incorrect diagnoses and potential mismanagement and mistreatment.

Consequences of bipolar disorder

Burden of illness

Ranked among the leading causes of worldwide disability (Whiteford et al., 2015), the individual and societal burdens associated with bipolar disorder are immense. Individually, the burdens of bipolar disorder include premature mortality from medical comorbidities and suicide, long-term dysfunction and disability, psychosocial impairment, lost work productivity, cognitive impairment, and diminished quality of life (Miller et al., 2014).

The total economic burden of bipolar I disorder in the United States (2015) was estimated at $202 billion, with indirect costs (e.g., caregiving, unemployment, lost productivity, premature mortality, suicide) far exceeding direct costs (e.g., pharmacy, inpatient services, outpatient services, emergency department costs) (Cloutier et al., 2018). When compared with US general population, the excess cost of bipolar I disorder ($119.8 billion) is comparable with the excess cost of schizophrenia (Cloutier et al., 2016) and only somewhat lower than diabetes, a disease that is almost 10 times more prevalent than bipolar I disorder (Menke et al., 2015).

The burden of bipolar disorder in the workplace is also substantial, with approximately 50% of individuals with bipolar disorder underemployed, working below their qualifications, working part-time, working in a limited or restricted capacity, or otherwise unable to work (Suppes et al., 2001). Bipolar depression contributes to more workplace impairment than either bipolar mania or MDD as measured by absenteeism and presenteeism (Kessler et al., 2006). The burden of illness also extends to the families and caregivers of patients with bipolar disorder, with caretakers experiencing increased financial responsibility, depressive symptoms, poorer general health, and chronic medical conditions (Perlick et al., 2008). High levels of caregiver distress have been reported in relation to patient behaviors (89%), adverse effects on the household (61%), and patient role dysfunction (52%) (Perlick et al., 2007). Practitioners may consider consulting case management or social workers to help patients and their families access more services to assist with their health care needs.

Functional and cognitive impairment

Impairments in psychosocial and cognitive functioning further impinge on a patient's ability to perform daily tasks and have meaningful relationships. Patients with bipolar depression or mania are reported to have greater functional impairment than patients in remission, and patients with depressive symptoms have greater disability than patients with manic symptoms (Rosa et al., 2010; Simon et al., 2007). Depressive symptoms, even when subsyndromal, are associated with functional role impairment across multiple domains including work or school, home, and interpersonal relationships (Altshuler et al., 2006). When asymptomatic, patients with bipolar disorder have relatively good psychosocial functioning, although premorbid functional levels are seldom attained (Grande et al., 2016).

Cognitive impairment, which is associated with social deficits, worse course of illness, functional disability, and diminished global functioning, is also an issue for patients with bipolar disorder (Kapczinski et al., 2016). Some evidence suggests that cognitive impairment can persist in states of remission, indicating that improving cognition should be a treatment target for bipolar disorder so functional recovery and quality of life can be enhanced (Miskowiak et al., 2018).

Suicide

Suicide is the most dangerous threat for premature mortality in patients with bipolar disorder, with prevalence estimated to be 20–30 times greater than in the general population (Pompili et al., 2013). The risk for suicide in bipolar disorder is most pronounced during the depressive or mixed phases of the illness (Miller et al., 2014). Although reported rates of suicide attempts and suicide vary greatly across studies and populations, people with bipolar disorder are estimated to account for 3.4%–14% of all suicide deaths (Schaffer et al., 2015). A positive lifetime history for suicide attempt is noted for 25%–50% of patients with bipolar disorder, with suicide rates estimated at 8%–19% (Herrera, 2018; Latalova et al,, 2014; Marangell et al., 2006). Risk factors for suicidal behavior in patients with bipolar disorder include family history of suicide, early onset of illness, depressive symptoms, high severity of illness, mixed affective states, rapid cycling, comorbid psychiatric disorders, and alcohol or drug abuse (Isometsa, 2014). In the clinic, patient safety should be addressed by assessing suicide status and risk factors and taking appropriate actions if suicidality is suspected (Figure 2).


Figure 2.:
Suicidality in the clinic. Suicide safety plans should not include a “no harm” or “no suicide” contract because evidence to support their effectiveness is lacking.

Psychiatric and medical comorbidities

Comorbid physical and psychiatric illnesses are common and they contribute to premature mortality in patients with bipolar disorder compared with the general public (Merikangas et al., 2007; Osby et al., 2001) (Figure 3). Because of high rates of simultaneous comingling symptoms from interrelated conditions, such as anxiety disorders, substance use disorders, or attention-deficit/hyperactivity disorder (ADHD), it can be difficult to distinguish bipolar disorder from an overlapping psychiatric illness or comorbid disorder. For example, ADHD and bipolar disorder are common comorbidities that are bidirectionally related, with ADHD occurring in 10%–21% of people with bipolar disorder and bipolar disorder found in 5%–47% of people with ADHD (Pallanti & Salerno, 2020). Further, psychiatric comorbidities complicate the diagnosis and treatment of bipolar disorder, suggesting that patients with comorbidities may be better served by collaborative care from primary care practitioners and psychiatric specialists. Suspected comorbid borderline personality disorder and bipolar disorder is a case in point; because differentiating these conditions is challenging due to mutual symptoms of mood dysregulation, depression, and negative cognitions, and appropriate treatment for each disorder varies greatly, psychiatric consultation is advised to promote best practices for patients like these (Bassett et al., 2017; Gunderson et al., 2006). Disentangling comorbidities so that bipolar disorder can be the first condition that is treated may help to avoid unintentional mistreatment and the failure of antidepressant monotherapy, or the potential destabilization of patients into bipolar mania or hypomania; comorbid substance use or abuse should be treated in parallel with bipolar disorder.


Figure 3.:
Common medical and psychiatric comorbidities associated with bipolar disorder. OCD = obsessive–compulsive disorder.

In all cases, patients with bipolar disorder should be thoroughly screened for all medical comorbidities, including overlapping endocrine, rheumatological, or inflammatory illnesses, because they should be considered part of the illness presentation and treated in concert. Of note, because the American Heart Association recognizes bipolar disorder in adolescents as an independent risk factor for early onset cardiovascular disease (Goldstein et al., 2015), clinicians should

be alert for signs and risk factors of cardiovascular disease in patients with bipolar disorder, regardless of their age.

Diagnosis

Differentiating bipolar depression from MDD is a significant challenge for all practitioners who treat patients with clinically significant depressive symptoms. Although a manic or hypomanic history or incident must be identified to establish a diagnosis of bipolar I or II, establishing a history of mania/hypomania can be especially difficult. Many patients do not consider manic or hypomanic symptoms to be a part of their illness and may even find an elevated mood episode to be enjoyable. In a study where patients were screened for bipolar disorder, only 18% of those who screened positive reported receiving a previous clinical diagnosis of bipolar disorder; 42% received diagnosis of something other than bipolar disorder and 41% received no diagnosis. Psychiatric clinicians missed the correct bipolar disorder diagnosis in 53% of patients and primary care clinicians missed the diagnosis in 78% of patients ([Frye et al., 2005]).

The mean delay between symptom onset and diagnosis of bipolar disorder is 10 years ([Berk et al., 2007b; Hirschfeld et al., 2003a]), which puts patients at risk of harm given the progressive course of the illness and its association with cognitive, functional, and medical repercussions ([Grande et al., 2016]). Misdiagnosis as unipolar depression is more likely to occur if a patient is evaluated early in the course of illness because the first mood episodes in bipolar disorder are likely to be depressive. With patient consent, having family members or friends present during a clinical interview can be helpful in describing prior mood episodes and corroborating patient information. Ongoing assessment in patients who initially seem to have unipolar depression is also important for detecting manic or hypomanic symptoms that may emerge ([Bowden, 2001; Perlis, 2005]).

Although no single symptom constellation distinguishes unipolar from bipolar depression, some clinical characteristics are more likely to be associated with each diagnosis. As such, providers should be vigilant for symptoms that have a high probability of being associated with bipolar depression ([Mitchell et al., 2008]) (Figure 4).


Figure 4.:
Key differentiating characteristics for bipolar depression.

Of additional concern, mixed features (subsyndromal mania symptoms), such as distractibility, racing thoughts, irritation, and agitation, occur as part of a unipolar or bipolar depressive episode in 25%–35% of patients ([McIntyre et al., 2015]). Mixed features are associated with greater illness complexity, reduced treatment response, lack of response to antidepressants, worse outcomes, and increased risk of suicide ([Sole et al., 2017]). Unfortunately, the recommendations for managing mixed features are limited and there are currently no approved treatments. Mixed symptoms in either bipolar or unipolar depression are complex and may require an individualized treatment approach using a dopamine antagonist/partial agonist (DAPA) or other mood stabilizers.

All patients with depressive symptoms should be screened for bipolar disorder ([Manning, 2005]), which should be ruled out before a unipolar depression diagnosis is considered. Although nothing can replace thorough clinical assessment and physical examination, initial screening with a validated tool for bipolar disorder, such as the Mood Disorder Questionnaire ([Hirschfeld et al., 2003b]) or Bipolar Spectrum Diagnostic Scale ([Ghaemi et al., 2005]), can improve the time to diagnosis and diagnostic accuracy ([Das et al., 2005; Kriebel-Gasparro, 2016]). Because patients with bipolar depression often lack insight into or recall of their manic symptoms, they may underestimate or inaccurately report them to the clinician; as such, having caregivers or family members answer the same screening tool as the patient can be very informative in regard to a history of mania or hypomania.

Suspicion of bipolar disorder should be increased in patients who present with anxiety disorders, history of substance use disorders, postpartum mood symptoms in women, obesity/eating disorders, seasonal affective disorder, ADHD, and borderline personality disorder ([Krishnan, 2005]). Additionally, cyclothymic temperament, characterized by intense and rapid hypomanic and depressive mood changes and the tendency to overreact to external stimuli, is associated with frequent depressive or mixed depressive recurrences and may reflect a predisposition toward bipolar disorder ([Perugi et al., 2017]). Barriers that must be overcome to effectively screen patients for bipolar disorder in primary care include forgetting to do so, lack of knowledge, patient reluctance, and shortage of time ([Kriebel-Gasparro, 2016]).

Treatment

Evidence suggests that earlier pharmacologic and psychosocial treatments produce better outcomes in bipolar disorder ([Joyce et al., 2016]). First-line acute treatment options for a manic episode include DAPAs, which have a class effect for mania, and other types of mood stabilizing drugs (e.g., lithium, valproate) ([Ostacher et al., 2016; Yatham et al., 2018]) (Table 1). Fewer treatment options are available for bipolar depression than for mania, with cariprazine, fluoxetine/olanzapine combination, lurasidone, and quetiapine (immediate- and extended-release) the only Food and Drug Administration (FDA)-approved treatments; further, cariprazine and quetiapine are the only agents approved to treat symptoms of both mania and depression associated with bipolar I disorder. The evidence base for the treatment of bipolar II is not well established ([Yatham et al., 2018]), and there are no approved treatments for mixed bipolar states ([McIntyre et al., 2018]).

Table 1. - Pharmacological options for bipolar disorder

FDA Approved for: Bipolar I Disorder		Pharmacological Agent	Advantages	Disadvantages
Mania	Depression			
✓	✓	Cariprazine	Treats both manic and depressive symptoms; good cardiometabolic profile; low drug–drug interaction	AEs such as nausea, akathisia, and restlessness
✓	✓	Quetiapine; immediate and extended-release	Treats both manic and depressive symptoms	AEs such as weight gain and somnolence
	✓	Fluoxetine–olanzapine combination (SSRI—atypical antipsychotic)	Antidepressant combination, not monotherapy	AEs such as weight gain and sedation
✓		Lurasidone	Good cardiometabolic profile	AEs such as akathisia, extrapyramidal symptoms, and somnolence; needs to be taken with food
✓		Other medications for borderline personality disorder (aripiprazole, asenapine, olanzapine, risperidone, ziprasidone)	Efficacy in mania	AEs vary by agent (e.g., extrapyramidal symptoms, cardiometabolic issues, akathisia, sedation, nausea)
✓		Lithium	Approved for maintenance therapy;	Requires laboratory monitoring of renal function, serum levels,

FDA Approved for: BipolarI I Disorder Mania	Depression	Pharmacological Agent	Advantages	Disadvantages
			evidence for reduced risk of suicide/attempts	TSH, and ECG; potential for weight gain, hypothyroidism, cognitive impairment, nausea/vomiting, acne, changes in renal function, fetal harm in pregnancy, drug–drug interactions
✓		Carbamazepine	Good efficacy for acute manic episodes	Many drug interactions, including with other bipolar treatments; risk of serious AEs including aplastic anemia, agranulocytosis, Stevens–Johnson syndrome; teratogenic
✓		Valproate	Good efficacy for acute manic episodes; doses can be consolidated to bedtime	Requires laboratory monitoring for hepatotoxicity, serum levels (recommended); teratogenic, including spina bifida; not well-tolerated with AEs including weight gain, hair loss, nausea, and sedation; potential drug–drug interactions
		Lamotrigine	Approved for maintenance in bipolar I disorder; good for prevention of depressive episodes; fairly well-tolerated	Not approved for acute mood episodes; not effective for manic episodes; 6-wk titration period to therapeutic goal dose; risk for Stevens–Johnson syndrome; AEs including nausea, insomnia, somnolence, back pain, fatigue; potential drug–drug interactions
		Antidepressants		Commonly used (incorrectly) for bipolar depression; not effective in bipolar depression; concerns about safety related to mood switching

Note: AE = adverse event; ECG = electrocardiogram; FDA = Food and Drug Administration; SSRI = selective serotonin reuptake inhibitor; TSH = thyroid-stimulating hormone.

Although antidepressants have been shown to be ineffective in treating either depressive episodes or mixed features of bipolar depression (Goldberg et al., 2007), they remain the most commonly prescribed medication for bipolar disorder (47%); other currently prescribed medications for bipolar disorder include DAPAs (22%) and mood stabilizers (31%) (IQVIA, 2018). Prescribing antidepressant monotherapy for patients with bipolar disorder is not recommended and may be associated with several potential adverse effects including worsening symptoms of depression, agitation, irritability, a switch into mania, or suicidal ideation (Pacchiarotti et al., 2013). This is important information for NPs, primary care physicians, and PAs, although many are also currently prescribing medications such as DAPAs for mental illness according to a large pharmacy database (Figure 5) (IQVIA, 2018).


Figure 5.:
Prescribers of dopamine antagonists/partial-agonists (2018). Independent study conducted by Allergan using IQVIA LAAD; June 2015 to May 2018; extracted October 2018.

Until recently, only D_2 receptor antagonists with additional activity at other receptors (e.g., serotonergic) and one antidepressant/dopamine antagonist combination were approved to treat bipolar depression. In May 2019, cariprazine, a dopamine D_3-preferring D_3/D_2 receptor partial agonist, became the first partial agonist to gain FDA approval to treat bipolar depression. Partial agonists may have lower intrinsic activity at receptors than full agonists and they may act either as a functional agonist or as a functional antagonist, depending on the surrounding level of naturally occurring dopamine neurotransmitter (Lieberman, 2004). As such, cariprazine, which exhibits much higher in vitro affinity for the D_3 receptor than the D_2 receptor, may offer benefits in treating bipolar depression because D_3 receptors are associated with regulation of mood and cognition, increased motivation, and reward regulation (Kiss et al., 2010; Stahl, 2017).

Given their different receptor affinities, individual DAPAs are associated with different propensities for causing specific adverse events such as weight gain, extrapyramidal symptoms, sedation, and metabolic dysfunction (Yatham et al., 2018). As such, it is important that clinicians consider medications in the context of the overall patient health when prescribing. For example, an agent with higher metabolic risk, despite being indicated for bipolar depression, may not be an appropriate choice for a patient with increased risk of diabetes, obesity, or insulin resistance. Further, a patient with a history of hyperprolactinemia would not generally be a candidate for a full dopamine blocking receptor agent, whereas a patient with gait difficulties or psychomotor retardation may not wish to be on a medication with sedating cholinergic or histaminergic side effects.

Mood stabilizers are also commonly used to treat bipolar disorder. Lithium has been recognized for decades as an effective treatment for acute and long-term mania, although its antimanic action is relatively slow and there has been little testing in bipolar depression. Of interest, a consistent association between long-term lithium treatment and reduced rates of suicide and suicide attempts has been noted (Baldessarini et al., 2019). Anticonvulsants (e.g., carbamazepine, valproate) are also often used as mood stabilizers to treat mania in patients with bipolar disorder, although antimanic activity is not a class effect and evidence for treating bipolar depression is lacking (Baldessarini et al., 2019). Potential adverse effects associated with mood stabilizers include weight gain, gastrointestinal symptoms, renal toxicity, cardiovascular effects, tremor, sedation, Stevens–Johnson syndrome, and hypothyroidism; patients receiving lithium, divalproex, and carbamazepine need laboratory testing to monitor for toxicity (Yatham et al., 2018).

Because bipolar disorder is a long-term chronic disorder that generally needs to be treated across the span of the illness, psychosocial interventions (e.g., cognitive behavioral therapy) and psychoeducation should be offered in conjunction with pharmacological treatment. Although no psychosocial intervention is considered first line for bipolar depression, several strategies may help provide a social support network that can promote medication adherence, reduce residual symptoms, help identify early signs of relapse, and support functional recovery (Yatham et al., 2018). In addition, referral to psychiatric specialty care should be considered if there are diagnostic uncertainties, treatment-refractory symptoms, suicidality, a need for intensive outpatient therapy or inpatient treatment, or in the case of clinician or patient preference.

Conclusions

Primary care physicians and NPs who work in family care and PMHNPs who work in psychiatric settings play a key role in screening, identifying, and treating patients with bipolar disorder. Bipolar disorder is a progressive illness with high burdens and complicated sequelae, with depressive symptoms far more common than manic symptoms and responsible for the majority of time that patients are symptomatic with their illness. Because misdiagnosis is common, differentiating bipolar depression from unipolar depression is the key diagnostic priority. Major depressive disorder should only be diagnosed when bipolar disorder has been ruled out by historical and contemporary screening because misdiagnosis often results in inappropriate antidepressant monotherapy treatment and delays the initiation of effective treatment. Given the intermingling of mood symptoms and episodes in bipolar disorder, treatment with an FDA-approved medication that has efficacy at both the manic and the depressive poles of the bipolar spectrum may be an advantage for patients.

Although bipolar disorder is a complex and serious psychiatric illness, it is frequently encountered by primary care providers. As such, it is imperative that NPs stay abreast of current trends in psychiatric treatment because they play a key role in all aspects of patient care. Because referral to specialty psychiatric care (i.e., psychiatrist, PMHNP) is advised in cases of serious mental illness, when comorbid psychiatric conditions are present, or when patients or clinicians prefer, close collaboration between primary care and psychiatric providers will benefit patients and providers alike. Given their central position in the health care network and their prominent role in diagnosing and treating patients, NPs have an opportunity to improve mental health services in family practice by becoming better informed and sharing their expertise with primary care colleagues for the purpose of optimizing the treatment of all patients with bipolar disorder.

Acknowledgements: *Writing and editorial assistance was provided by Carol Brown, MS, ELS, at Prescott Medical Communications Group (Chicago, IL), a contractor of AbbVie.*

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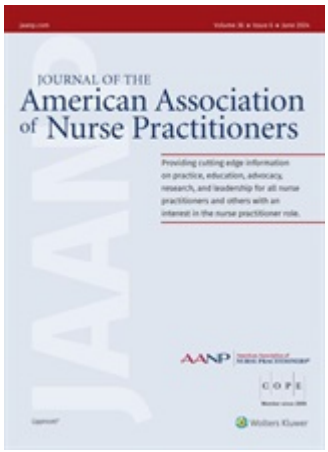

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