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REVIEW ARTICLE

Bipolar depression: the clinical characteristics and unmet needs of a complex disorder

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ABSTRACT

Objective: We reviewed important clinical aspects of bipolar depression, a progressive psychiatric condition that is commonly treated in primary care. Bipolar depression is associated with considerable burden of illness, high suicide risk, and greater morbidity and mortality than bipolar mania.

Methods: We identified articles relevant to our narrative review using a multistep search of the literature and applying terms that were relevant to bipolar depression or bipolar disorder.

Results: Bipolar depression accounts for the majority of time spent unwell for patients with bipolar disorder; high rates of morbidity and mortality arise from full symptomatic episodes and interepisode subsyndromal symptoms. Bipolar depression is an important contributor to long-term dysfunction for patients with bipolar disorder due to psychosocial impairment, loss of work productivity and high rates of substance abuse. Missed and delayed diagnosis is prevalent due to overlapping symptoms with unipolar depression and other diagnoses. Medical comorbidities (i.e. cardiovascular disease, hypertension, obesity, metabolic syndrome) and psychiatric comorbidities (i.e. anxiety disorder, personality disorder, eating disorder, attention-deficit/hyperactivity disorder) are common. Currently, only three treatments are FDA-approved for bipolar depression; monotherapy antidepressants are not a recommended treatment option.

Conclusions: Bipolar disorder is common among primary care patients presenting with depression; it is often treated exclusively in primary care. Clinicians should be alert for symptoms of bipolar disorder in undiagnosed patients, know what symptoms probabilistically suggest bipolar versus unipolar depression, have expertise in providing ongoing treatment to diagnosed patients, and be knowledgeable about managing common medication-related side effects and comorbidities. Prompt and accurate diagnosis is critical.

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Overview of bipolar disorder

Bipolar disorder is a chronic and complex mood disorder that is characterized by an admixture of manic (bipolar mania), hypomanic and depressive (bipolar depression) episodes, with significant subsyndromal symptoms that commonly present between major mood episodes[1]. Ranked among the leading causes of worldwide disability[2], bipolar I disorder has been consistently associated with significant medical and psychiatric comorbidity, premature mortality, high levels of functional disability and reduced quality of life[3]. The essential feature of bipolar I disorder requires the occurrence of at least one fully syndromal lifetime manic episode, although depressive episodes are common[4]. Bipolar II disorder requires the occurrence of at least one hypomanic episode and one major depressive episode; it is no longer considered a milder form of bipolar disorder as it is associated with considerable time spent depressed and with functional impairment that accompanies mood instability[4]. Bipolar disorder with mixed features is a complex presentation in which a mood episode from either the manic or depressive pole is complicated by the presence of subsyndromal but clinically significant symptoms from the opposite pole. Patients with bipolar depression have greater morbidity and mortality than patients with bipolar mania, with depressed patients having a higher risk of suicide, interepisode panic attack and psychosis[5].

On the bipolar spectrum, bipolar depression is the leading cause of morbidity in patients with bipolar disorder[6]; at least 50% of patients initially present with a depressive episode[7]. Even with treatment, bipolar depression accounts for the majority of time spent unwell with the disorder and it is an important contributor to long-term dysfunction, psychosocial impairment and loss of work productivity. In light of reports that up to 10% of all visits to primary care are depression-related and as many as 64% of all clinical encounters for depression occur in this setting rather than in specialty care[8], it is especially important for clinicians to be vigilant for symptoms of bipolar disorder in their patients. In settings other than primary care, clinicians treating patients with substance use disorders, women with mood symptoms during the

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pregnancy postpartum period, forensic populations, patients presenting for bariatric surgery/obesity treatment and patients being treated at attention-deficit/hyperactivity disorder (ADHD) centers should also be attentive for the presence of bipolar depression since these conditions commonly present comorbidly. Understanding the challenges associated with bipolar depression requires understanding bipolar disorder in its entirety since fluctuating symptoms intermingle across the phases of illness to create a complex whole.

Methods

To identify articles that would be relevant to our review of bipolar depression, we conducted a multistep search of the literature cited in PubMed using the term "bipolar depression" and limiting the results to review articles; this search retrieved 687 entries. To ensure that entries specific to our interests were not missed, we additionally searched "bipolar depression" in conjunction with individual terms including prevalence, assessment, comorbidities, diagnosis, differential diagnosis and treatment. Reference lists from the articles we retrieved were manually searched for additional articles of relevance. English language articles that were published in peer-reviewed journals, with no date limitation, were included as sources for our review.

Prevalence

Lifetime and 12 month prevalence for bipolar I disorder have been estimated at 2.1% and 1.5%, respectively, based on criteria from the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)[4]; rates for men and women are similar[3]. The prevalence of bipolar disorder decreases with increasing age and education level, while its prevalence is higher in unemployed/disabled individuals than in employed individuals; prevalence does not appear to be consistently related to race/ethnicity or income[9]. Depressive and subsyndromal depressive symptoms are very common in bipolar disorder and it is noteworthy that patients spend considerably more time ill with depression (34% of the time) than with elevated/mixed symptoms (12% of the time)[10].

Among patients who see primary care physicians for depression, the correct diagnosis for many may be bipolar disorder, with over 25% of patients from a family practice clinic who presented with anxiety or depression actually having a bipolar spectrum illness as diagnosed on a semistructured diagnostic interview[11]. Another primary-care-based study reported that of 72% of patients who screened positive for bipolar disorder on the Mood Disorder Questionnaire (MDQ)[12] only 8% received the supporting diagnosis[13]. In light of evidence suggesting that 10% to 38% of patients with bipolar disorder are treated exclusively in primary care[14], primary care providers should be alert for historical and emerging symptoms of bipolar disorder in undiagnosed patients, have expertise in providing ongoing treatment to diagnosed patients, and be knowledgeable about managing common medication-related side effects and disorder comorbidities.

Lifetime and 12 month prevalence of bipolar II disorder, a common bipolar phenotype that is related to chronic depression[15], have been estimated at 1.1% and 0.8%, respectively, with briefer and less severe hypomanic episodes thought to be experienced by up to 4–6% of the population[16]. More than 90% of individuals who have a manic episode proceed to develop recurrent mood episodes and about 60% of manic episodes occur immediately before a major depressive episode[4].

Burden of illness

The significant burdens of bipolar disorder for individual patients, caregivers and society are the result of the interaction of social factors with both economic factors (socioeconomic) and factors related to individual thoughts and behaviors (psychosocial). In the US in 2015, the total estimated direct (e.g. treatment-related costs, inpatient and outpatient services) and indirect (e.g. lost productivity for patients and caregivers, unemployment) cost of bipolar I disorder was $202.1 billion dollars, with indirect costs far exceeding direct costs[17]. Due to the pervasiveness of depressive symptoms over time and higher indirect costs, a greater proportion of the overall costs of bipolar disorder are attributed to depressive symptoms than to manic or mixed symptoms; manic and mixed symptoms account for higher direct costs because of higher inpatient treatment expenses[10].

The burden of bipolar depression in the workplace is consequential. Patients with bipolar disorder and at least one past-year depressive episode had greater levels of absenteeism, presenteeism and total lost work days than patients with only manic/hypomanic episodes during the past year[18]. Further, unemployed individuals with bipolar disorder compared with those who are employed had significantly greater severity of depressive, but not manic, symptoms and employed individuals with at least one major depressive episode missed an additional 4 days of work per months than those without depressive symptoms[19]. Beyond the workplace, depressive symptoms related to bipolar disorder are associated with considerable impairment in domains of individual functioning (e.g. social, household, interpersonal relationships) and quality of life[9,20,21]. Subsyndromal depression, which is almost ubiquitous between major mood episodes, has also been associated with poorer outcomes among patients with bipolar disorder[22].

Course of bipolar illness and clinical characteristics

Classically characterized as a cyclical disorder with full manic or depressive episodes separated by periods of euthymia, bipolar disorder is more accurately described as having a chronic and subtle course of mood disturbances with residual symptoms, emotional dysregulation, circadian rhythm sleep disturbances, cognitive impairment, and greater risk of psychiatric and medical comorbidity between mood episodes[23] (Figure 1). The progressive course of bipolar

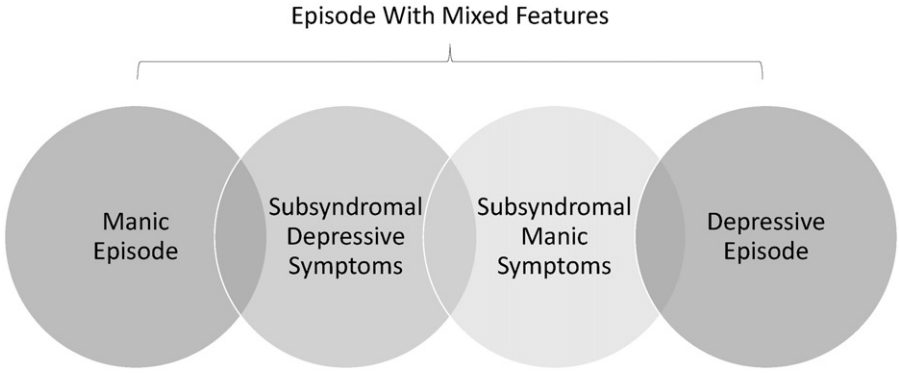

Figure 1. Bipolar disorder: a dimensional approach.

disorder, in conjunction with its cognitive, functional and medical repercussions, has been acknowledged for almost a century, with a more recent focus on the effects of neuroprogression (pathological central nervous system reorganization) on psychosocial functioning and perhaps even premature aging[1,24].

A life-chart database evaluation of 1130 patients with bipolar disorder found that the average depressive episode was 5.2 months and 50% longer than the average manic episode, which lasted 3.5 months[25]. The first episode of bipolar disorder usually occurs before the age of 30 years. In a study of more than 1000 patients, over 60% of patients experienced onset before the age of 18 years, with early onset associated with greater rates of comorbid anxiety disorders and substance abuse, more recurrences, shorter periods of euthymia, and greater likelihood of suicide attempts[26]. In at least 50% of patients, bipolar disorder initially presents with a depressive episode[7], which commonly results in a misdiagnosis of unipolar depression and the potential for mistreatment with antidepressant monotherapy[27].

For bipolar I and II disorders, the proportion of time spent ill (e.g. major or minor depression, mania or hypomania, anxiety or mixed bipolar states) was found to be similarly high (44% and 43%, respectively), with major or minor depression the predominant morbidity in both disorders (70% and 81%, respectively)[28]. Naturalistic data strongly support the concept that the longitudinal course of bipolar disorder is expressed as a dimensional spectrum involving the complete range of depressive and manic symptom severity, greater depressive than manic morbidity, and frequent subsyndromal symptoms from both affective poles[29,30]. Subsyndromal, minor depressive and hypomanic symptoms combined (29.9%) are found to be nearly three times more frequent in bipolar disorder than syndromal-level major depressive and manic symptoms (11.2%); longer initial episodes, episodes with depression only and cycling polarity predicted greater chronicity during long-term follow-up, as did comorbid drug-use disorder[30].

Suicidality

Among patients with bipolar disorder, the annual rate of attempted and completed suicide is 3.9% and 1.4%, respectively, which is considerably higher than corresponding rates in the general population (0.5% and 0.02%, respectively)[31]. Further, the risk of suicide is higher for bipolar patients experiencing a depressive episode or mixed state than for patients with pure mania[10,32]. For bipolar patients, depression-related risk factors for suicide attempt include multiple hospitalizations for depression and having suicidal thoughts while depressed; conversely, a past suicide attempt has also been shown to be predictive of an increased amount of time spent depressed, more severe depression and suicidal ideation[33].

Psychosocial disability and cognitive impairment

Patients with bipolar depression experience psychosocial disability that fluctuates in parallel with the severity of symptoms[34]. As noted earlier, depressive episodes and symptoms are more common, and equally or more disabling than corresponding levels of manic or hypomanic symptoms; subsyndromal depressive symptoms are also common and associated with significant impairment. When asymptomatic, patients with bipolar disorder have relatively good psychosocial functioning, although premorbid functional levels are seldom reached[1].

Along with depressed mood, anhedonia, which is the inability to experience pleasure, is a cardinal symptom of a major depressive episode in either MDD or bipolar depression[4]. In one clinical study, over half of patients experiencing bipolar depression had self-reported anhedonia[35], suggesting that this is a clinically relevant symptom for clinicians to be aware of. Importantly, patients with anhedonia and depression have a worse prognosis than patients who have depression without anhedonia[36,37]. Anhedonia can be divided into consummatory (subjective pleasure) and motivational components (anticipation of and drive towards rewarding stimuli), with each component possibly having a distinct biological basis[38]. Research suggests that patients with MDD or bipolar depression who are currently depressed may have substantial deficits in motivational anhedonia, but not in consummatory anhedonia[39,40]. Despite its occurrence across several psychiatric disorders, there is no approved treatment for anhedonia[41].

Cognitive impairment, which is consistently observed in patients with bipolar disorder, is associated with social impairment, worse course of illness, functional disability and diminished global functioning[42]. Dysfunction in several

cognitive areas has been noted in acutely ill bipolar patients, with some evidence showing that cognitive dysfunctions may persist in states of remission[43]. A study of cognitive impairment found that manic/hypomanic, depressed or euthymic patients with bipolar disorder all performed worse than healthy comparison subjects on new learning tasks and recall, suggesting that verbal learning and memory could be impaired in bipolar disorder independently of the clinical state[44]. Results further suggested that complex memory processes seemed to be impaired in remitted patients, with clinical implications including chronicity of cognitive deficits, treatment noncompliance and poor social functioning.

Several studies have also confirmed the association between reduced quality of life, a subjective measure of a patient's well-being, and depressive symptoms in bipolar disorder[10,45,46]. Collectively, findings suggest that patient functioning, anhedonia, cognitive impairment and quality of life should be actively monitored in the clinic and interventions, including pharmacologic and psychosocial treatments, should be implemented to improve patient outcomes.

Comorbid conditions

Bipolar disorder is associated with high levels of medical and psychiatric comorbidities that contribute to premature mortality for patients with bipolar disorder compared with the general public[9,47].

Medical comorbidities

Cardiovascular disease, hypertension, obesity, metabolic syndrome and diabetes are highly prevalent in patients with bipolar disorder[10,48], with an almost two-fold risk of cardiovascular disease mortality reported compared with general population estimates[49]. In the National Comorbidity Survey Replication, 94.6% of patients with bipolar disorder reported having at least one comorbid medical condition[50], which is an important consideration for clinicians since patients with comorbid conditions have a more severe bipolar illness course, worse functioning, more complex psychiatric treatment, treatment resistance, recurrence and higher utilization of medical services[51]. Although medical comorbidities in bipolar disorder have been extensively covered elsewhere[51–53], some conditions that appear to be strongly associated with bipolar depression are highlighted here.

The link between obesity and bipolar depression, long established in patients with bipolar disorder[54], is possibly underpinned by aberrations in the reward–motivation neural network[55]. In a large, nationally representative sample, a nearly two-fold age-, race- and sex-adjusted increased risk of obesity was found among adults with bipolar disorder versus controls[56]. Obese individuals with bipolar disorder had less improvement in global illness severity, more comorbid anxiety disorders, longer depressive episodes, more medical conditions, and poorer physical and mental health functioning than individuals with bipolar disorder who were not obese[56,57]. Similarly, the rate of metabolic syndrome in individuals with bipolar disorder is increased relative to the general population, and this comorbidity was associated with more complex illness presentation, less favorable response to treatment, and adverse course and outcome[48]. Although some studies link obesity and its sequelae to medications used to treat bipolar disorder, a significant number of medication-naïve patients with bipolar disorder also have obesity and features of metabolic syndrome, suggesting a more complex association[58–60]. Of additional importance is the question of whether obesity is changing the phenotype of bipolar disorder from primarily euphoric toward mixed presentations[61]. Given the greater disease burden for obese individuals with bipolar disease, monitoring for weight gain, and clinical interventions in diet, exercise and nutrition are important components of a complete treatment plan.

Adding to the clinical challenge, patients with bipolar depression appear to be particularly sensitive to variations in thyroid function and hypothyroidism. Accumulating evidence suggests that hypothalamo-pituitary-thyroid (HPT) axis dysfunction may be relevant to the pathophysiology and clinical course of bipolar affective disorder[62]. Overt or subclinical hypothyroidism is a frequent abnormality in patients with bipolar disorder, with depression and cognitive dysfunction the most commonly related psychiatric symptoms. Additionally, lower pretreatment thyroid function has been associated with slow response to treatment in patients with bipolar depression[63]. A suboptimal thyroid state may be a modifiable risk factor that can be treated in the clinic for patients with bipolar depression.

Psychiatric comorbidities

Multiple psychiatric comorbidities, including ADHD, anxiety, personality disorders, eating disorder and substance use disorders interfere with the diagnosis and treatment of bipolar depression, and likely contribute to increased disease morbidity and mortality, including increased suicide risk[64,65]. Psychiatric comorbidity is reported in 90% of patients with bipolar I or II disorder[9], with anxiety, impulse control and substance use disorders found to be two to three times more prevalent than in the general population[9,66]. Comorbid anxiety and bipolar disorder is specifically associated with earlier age of the first depressive episode, greater number of depressive episodes, fewer days well, longer time to recovery from a depressive episode, shorter time to relapse, poor role functioning and reduced quality of life[67,68].

At least 50% of adults with bipolar disorder experience substance use disorders at some point in their lives[69], making this both an important comorbidity and a potential differential diagnosis criterion. Similar to comorbid obesity, substance use disorder is thought to be associated with an aberrant reward–motivation neural network[55]. The prognosis for substance use disorder is mainly predicted by the number and severity of comorbid episodes of bipolar depression. People with alcohol use disorder are at four times greater risk of having bipolar disorder than are people without alcohol use disorder; illicit drug users have a five times greater risk of having bipolar disorder than nonusers[70]. Patients with these comorbid disorders have a much greater burden of

illness than other patients, with sequelae including delayed recovery from mood episodes, increased suicidality, functional impairment, decreased medication adherence and decreased quality of life[70].

It is of additional concern that a comorbid syndrome of bipolar disorder and ADHD appears to be common, although more studies are needed to clarify its diagnostic validity and treatment approach. Comorbid ADHD and bipolar disorder, which is present in up to 47% of adult ADHD populations and 21% of bipolar disorder populations, has a more severe course of illness compared with that of bipolar disorder alone, and high rates of comorbidity with other psychiatric disorders[71].

Comorbid eating disorders, which are particularly associated with the depressive phases of bipolar disorder[72], have a much higher prevalence for patients with bipolar disorder (range, 6–27%) than for individuals in the general population (4–10%)[73,74]. Binge eating behavior is an important consideration for clinicians since it may serve as an early predictor of eating disorders in patients with bipolar spectrum disorder[75].

Diagnosis

Given the high number of comorbid conditions and differential diagnoses associated with bipolar disorder, correct diagnosis is a challenge for healthcare professionals. In a survey of bipolar patients involved with National Depressive and Manic–Depressive Association support groups, 69% reported that they were initially misdiagnosed by psychiatrists, with a mean of 3.5 other diagnoses received and 4 psychiatrists consulted before an accurate diagnosis was received[76]. For 60% of patients, the misdiagnosis was MDD, with women more likely than men to receive an MDD diagnosis (68% vs. 43%). Only 20% of patients with bipolar disorder and a depressive episode are diagnosed with bipolar disorder within the first year of seeking treatment[77]; the mean delay between the onset of illness and diagnosis is 5 to 10 years[78]. Primary care physicians treat approximately half of all patients with mental illness[79], and among patients who screened positive for bipolar disorder, the diagnosis was missed by primary care physicians 78% of the time[80]. Given the progressive nature of bipolar disorder, timely and accurate diagnosis is extremely important and clinicians should be especially attentive to symptoms that are suggestive of the disorder.

Diagnostic criteria require that patients with bipolar depression have a history of at least one manic episode and present with either a depressed mood most of the day, nearly every day, or loss of interest and pleasure in all activities (anhedonia); additional symptoms may include weight loss, insomnia, psychomotor agitation or retardation, feelings of worthlessness or guilt, decreased ability to concentrate, and recurrent thoughts of death or suicidal ideation[4]. Depressive symptoms must be severe enough to cause clinically significant distress and impairment in social or occupational functioning. Diagnosis can be complicated because the criteria for a bipolar depressive episode are the same as those for a unipolar depressive episode, making an accurate history of mania or hypomania the crucial differentiating factor. In addition, while patients are typically troubled by depressive symptoms, they may not recognize that manic or hypomanic symptoms are also part of the illness so an incomplete symptomatic profile may be reported to the clinician, further clouding the diagnostic picture.

The DSM-5 also provides a mixed features specifier that can be applied to manic or hypomanic episodes that have depressive features and, conversely, to depressive episodes that have manic features. Patients must meet the full criteria for a manic/hypomanic episode or depressive episode and concurrently have at least three symptoms emanating from the opposite pole. Approximately 25–35% of patients have been identified as having mixed features as part of a depressive mood episode in either bipolar disorder or unipolar depression[81]. Accurate diagnosis is important since mixed features in either illness are associated with greater illness complexity, reduced treatment response, lack of response to antidepressants, worse outcomes and increased risk of suicide[82]. In bipolar disorder, even mood episodes that appear to be purely depressive have at least subtle manic-like symptoms, such as distractibility, racing thoughts, irritation and agitation, that are present in up to two thirds of patients[83]. Specific recommendations for managing mixed features are limited and there are currently no approved treatments[82].

Differential diagnosis

The diagnosis of bipolar disorder can be challenging because the first episode of mood disturbance in bipolar disorder is usually depression, not mania, and most patients seek treatment for depressive symptoms[84–86]. Initial misdiagnosis of patients with bipolar disorder results in delay of appropriate treatment and the potential for mistreatment with antidepressant monotherapy, which may subsequently increase the risk of recurrence and chronicity in this progressive disorder[27,84]. The primary differential diagnoses are major depression, anxiety disorders, ADHD, personality disorder, drug and alcohol misuse, schizophrenia, in addition to consequences of trauma/brain injury.

Although nothing can replace careful clinical assessment, screening tools may help to identify bipolar disorder or rule out an incorrect diagnosis in primary care and clinical practice. For example, the MDQ is an easy-to-use self-report instrument consisting of 13 questions that assess clustering of symptoms and functional impairment in bipolar disorder[12,16,87]. When used with follow-up questioning and evaluation, the MDQ has been shown to have good sensitivity (~70%) and specificity (~90%) for diagnosing bipolar disorder[12,87]. Advanced practice registered nurses reported that screening depressed patients with validated screening tools could reduce the time to correct diagnosis and treatment of bipolar depression[88], suggesting that screening tools may improve diagnostic accuracy in primary care.

Unipolar depression

Misdiagnosis of unipolar depression in patients with bipolar depression is a common and challenging problem. Of

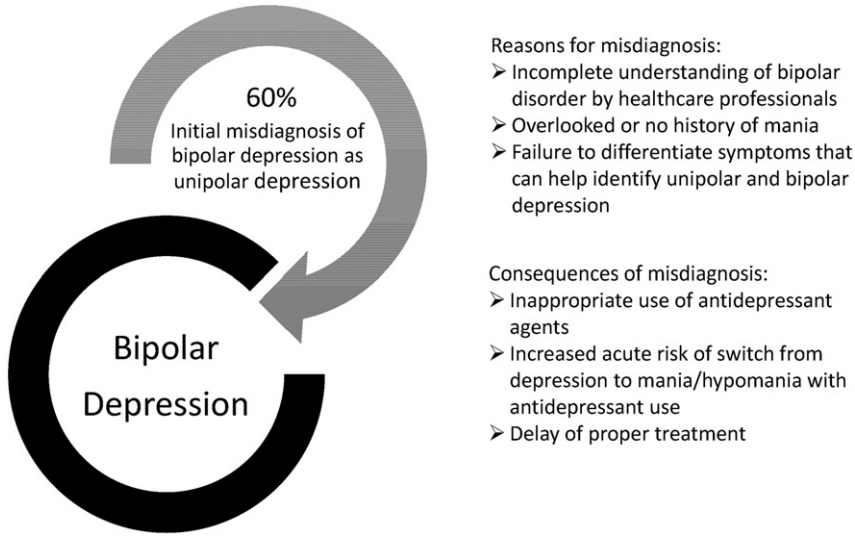

Figure 2. Unipolar or bipolar depression?

patients with bipolar disorder, a majority are initially misdiagnosed with MDD, leading to the possibility of incorrect treatment and poor outcomes (Figure 2)[76].

Since the diagnostic criteria for a major depressive episode are the same in bipolar depression and MDD, with no single constellation of symptoms diagnostic for either disorder, clinicians should be aware that specific symptoms have a higher probability of being associated with each diagnosis (Figure 3)[7].

In patients from academic centers followed up for at least 1 year in the National Institute of Mental Health Collaborative Depression Study, approximately 25% of patients initially diagnosed with MDD subsequently experienced a manic or hypomanic episode, resulting in a revised diagnosis of bipolar I or II disorder[89]. The presence of subthreshold hypomania predicted progression from unipolar depression to bipolar depression. Misdiagnosis as unipolar depression is more likely when patients present to clinicians during a depressive episode since unipolar depression is more common and it is difficult to retrospectively establish a manic/hypomanic history[90]. Misdiagnosis as unipolar depression is also more likely if the patient is evaluated early in the course of illness, since the first bipolar mood episodes are likely to be depressive, or if there is no validating information from family/caregivers or friends[91,92]. Patients with greater number of failed antidepressant trials are more likely to have bipolar disorder[7], which is a clinical concern since the use of monotherapy antidepressants in bipolar depression is not backed by a strong evidence base, although it is an exceedingly common practice. Concerns pertaining to the use of antidepressant treatment without mood stabilizing treatment include the possibility of increased acute risk of switch from depression to mania/hypomania[7,93], as well as a delay in receiving approved bipolar depression treatment.

Attention deficit hyperactivity disorder

Differentiating ADHD and bipolar disorder is complicated by similarities between the disorders including early age of onset, reciprocal comorbidity, similar psychiatric comorbidities, chronic course and persistence into adulthood; both disorders are also associated with impaired educational, occupational and interpersonal functioning, and increased morbidity and mortality in adulthood[94]. Clinical differentiation is most challenging when ADHD is comorbid with conduct disorder and/or oppositional defiant disorder, since the presenting symptoms (e.g. temper tantrum, aggressive behavior) can overlap with symptoms of a manic or mixed state. In uncomplicated cases, the appearance of prominent mood dysregulation, sleep irregularities and aggressive behaviors are more likely to predict a diagnosis of bipolar disorder than ADHD, especially if there is impulsive behavior associated with spending money, sex, or tobacco, alcohol or drug use[94]. Conversely, fidgeting, restlessness, and inefficient and disorganized behaviors arising from inattentiveness, distractibility and forgetfulness, often suggest ADHD.

Substance abuse

Clinicians treating patients for substance abuse should be aware that approximately 60% of patients with bipolar I disorder have a lifetime diagnosis of substance use disorder[95]. Comparatively, just one third of patients with MDD have a comorbid substance use disorder, making this a diagnostically important symptom[96]. Substance abuse and bipolar disorder are both associated with mood symptoms, anxiety symptoms, family history of mood/anxiety problems, disruptive behaviors and relationship problems[97]. Patients with bipolar disorder and comorbid substance abuse are likely to have developed substance abuse disorder before age 13; comorbid occurrence is also associated with cocaine and amphetamine use, episodic substance use, mood problems that persist without substance use, manic symptoms and a family history of bipolar disorder[97]. Differentially, substance abuse that occurs independently of bipolar disorder is more likely to have onset after age 13, and to be associated with multiple substances, continuous substance use, no manic/

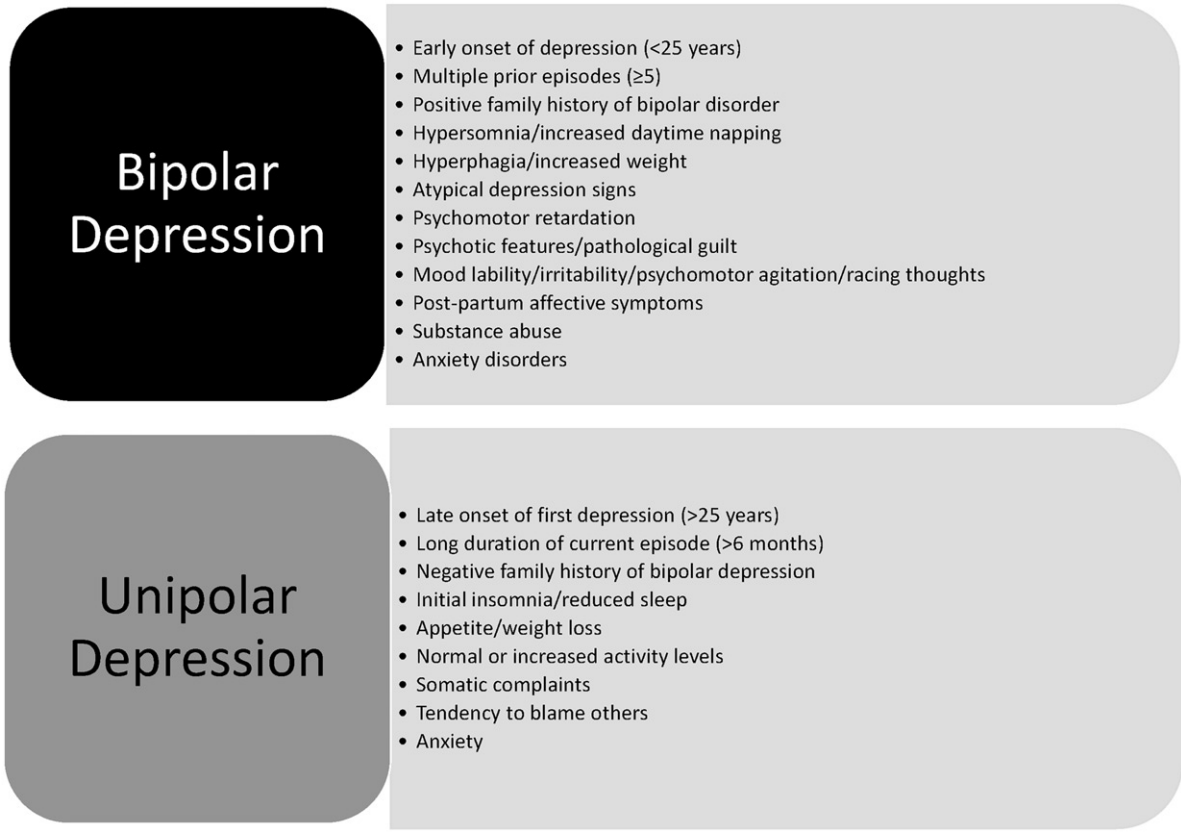

Figure 3. Symptoms with potential diagnostic utility in bipolar and unipolar depression[1,7].

hypomanic symptoms and family history of anxiety disorders[97].

Borderline personality disorder

Since emotional dysregulation and depression accompanied by negative cognitions are ubiquitous features of both borderline personality disorder and bipolar disorder[98], mistaken diagnosis of these two conditions is predictable. The lifetime co-occurrence of borderline personality disorder and bipolar disorder is 27.6%[99], with evidence that 15% of patients with bipolar disorder have comorbid borderline personality disorder. Having either disorder may increase the risk that the other disorder will be misdiagnosed[100]. To differentiate the disorders, clinicians should look for emotional shifts between depression and rage for borderline personality disorder and between depression and mania for bipolar disorder; depression and rage in borderline personality disorder can mimic a mixed bipolar episode[98]. In borderline personality disorder, mood shifts tend to be rapid, with changes lasting hours to days and closely linked to interpersonal events, whereas bipolar mood shifts tend to be more enduring (except in cases of rapid cycling or mixed features). Additionally, patients with borderline personality disorder tend to have more intense and severe disruptions in interpersonal relationships than do patients with bipolar disorder. A longitudinal approach to diagnosis may be best practice for a clinician since typically the onset of borderline personality is around puberty, while bipolar disorder usually appears in late adolescence or early adulthood[98]. Borderline personality symptoms are also likely to become less striking as the patient ages, while bipolar disorder persists and depressive symptoms may possibly become more severe and disabling with aging. To date, borderline personality disorder has not demonstrated response to pharmacological therapy, with psychological and psychosocial therapies the current mainstays of management.

Treatment

The first step in treatment for bipolar disorder is confirming the diagnosis, including a history of a manic or hypomanic episode, and determining the nature of the presenting episode. Timely diagnosis is extremely important since bipolar disorder is a highly progressive illness[1]. In acute management, the primary goal of treatment is to stabilize presenting symptoms with minimal adverse events and ensure the patient's safety. Although there are many first-line acute treatment options for a manic episode, including most antipsychotic agents that are approved for bipolar I disorder and mood stabilizing drugs (e.g. lithium, lamotrigine)[93,101], only a few treatment options are available to treat bipolar depression. Immediate- and extended-release quetiapine, fluoxetine/olanzapine combination, cariprazine and lurasidone are the only medications currently approved by the FDA to treat bipolar depression; cariprazine and quetiapine are the only

agents that are approved to treat symptoms of both mania and depression associated with bipolar I disorder. According to current treatment guidelines, antidepressants should not be used as monotherapy in patients with bipolar depression since available evidence does not support their efficacy and there are concerns about safety related to mood switching[93,102,103]. The limited number of approved treatments for bipolar depression is a clinical concern since not all patients respond to available treatment options and response may decrease over time. A comprehensive literature review found consistent evidence suggesting that pharmacological and psychosocial treatment in the earlier stage of illness resulted in better outcomes for response, relapse rate, time to recurrence, symptomatic recovery, remission, psychosocial functioning and employment[104].

Possibly due to the long-standing, but discredited, view that bipolar II is a less severe form of bipolar disorder, its treatment has been understudied relative to bipolar I and the evidence base for treatment is not well established[93]. Additionally, there are currently no approved treatments for mixed bipolar states and treatment guidelines for this symptom profile are limited[82]; antidepressants have been shown to be an ineffective treatment for mixed bipolar depression[105].

Although antipsychotics and mood stabilizers are the foundation of treatment in bipolar disorder, it is estimated that between 40% and 50% of patients are nonadherent or only partially adherent to their treatment[106]. Several studies have reported that specific demographic and illness characteristics, including younger age, male sex, being unmarried, minority ethnicity, comorbid substance abuse, illness severity, inadequate social support and poor insight, may be associated with nonadherence[106]. Negative patient attitudes are of further importance since fear of adverse events, denial of illness severity and the need for treatment, perceived medication ineffectiveness, fears of medication dependence, and the stigma of being on medication are cited as additional contributing factors. The consequences of nonadherence can be serious and patients may experience poor outcomes, worse quality of life, functional impairment, and increased risks of relapse, rehospitalization and suicidality[106]. Although manic symptoms have been particularly noted in association with treatment nonadherence in bipolar disorder, bipolar depression may contribute to social isolation or a lack of engagement in self-care that may precipitate or worsen nonadherence[107].

All effective treatments for bipolar disorder have potential side effects that need to be acceptable to patients to maximize treatment adherence and favorable outcomes; monitoring for common adverse effects should be common practice for clinicians. Although individual antipsychotic agents are associated with different propensities for causing specific adverse events, common effects associated with atypical antipsychotics include weight gain, extrapyramidal symptoms, sedation and metabolic dysfunction[93]. Similarly, mood stabilizers used to treat bipolar disorder, including lithium, divalproex, carbamazepine and lamotrigine, have a variety of adverse effects including weight gain, gastrointestinal symptoms, renal toxicity, cardiovascular effects, tremor, sedation and hypothyroidism[93]. Patients on lithium, divalproex or carbamazepine need to have their serum medication levels monitored regularly to ensure that that they are in a therapeutic range to avoid toxicity.

The potential for drug–drug interactions is a particular concern for patients with bipolar disorder, who tend to have complex and varied treatment regimens[108]. Given the long-term, chronic, progressive nature of bipolar disorder and the level of associated impairment, a strategy that combines pharmacological treatment, psychosocial intervention and lifestyle approaches is recommended beginning at the first episode. Psychosocial interventions that have shown efficacy include cognitive behavioral therapy, psychoeducation, interpersonal and family psychotherapy, and functional remediation[1]. Awareness of the increased risk of cardiovascular disease and metabolic abnormalities in patients with bipolar depression should also prompt clinicians to perform physical examinations to assess risk factors. Additionally, healthy behaviors, such as smoking cessation, exercise and weight control, should be encouraged and patients should be monitored for treatment-related issues and suicidality.

Unmet needs

Given the large amount of time spent unwell as a result of mood episodes and subsyndromal symptoms, as well as considerable levels of associated impairment and disability, it is not surprising that there are significant unmet needs in bipolar disorder and bipolar depression. Studies of treated patients with bipolar I disorder have found residual morbidity in 40% of patients during the follow-up period, with approximately three quarters of it related to depressive or dysthymic symptoms[30,109,110]. Unresolved depressive morbidity is likely an important contributor to substance abuse, functional disability and excess mortality in bipolar disorder[111].

Unmet needs in bipolar disorder may differ considerably when comparing the viewpoints of the patient, provider and caregivers; current research suggests that patient-centric outcomes should be recognized as important factors in the assessment and treatment of bipolar depression[112]. From the patient perspective, unmet needs are generally associated with treatment satisfaction, quality of life, level of functioning and general health (Figure 4)[102,113].

Medication side effects and concerns about the return of symptoms were reported by patients with bipolar depression to be the leading factors related to decisions about changing a treatment or trying a new one[114]. Intolerable adverse events are a frequent cause of treatment nonadherence, although events that are often thought of as mild and/or transient by clinicians (e.g. gastrointestinal issues, dry mouth) were reported as the reason for treatment discontinuation for 20–30% of patients who were surveyed by the Depression and Bipolar Support Alliance[115]. Weight gain was reported as the treatment-emergent event most commonly related to medication discontinuation in real-world treatment; lethargy, anxiety, shaking/trembling and suicidal thoughts were also highly associated with treatment discontinuation. Circadian rhythm disturbance, as shown by sleep alterations during and between episodes of bipolar

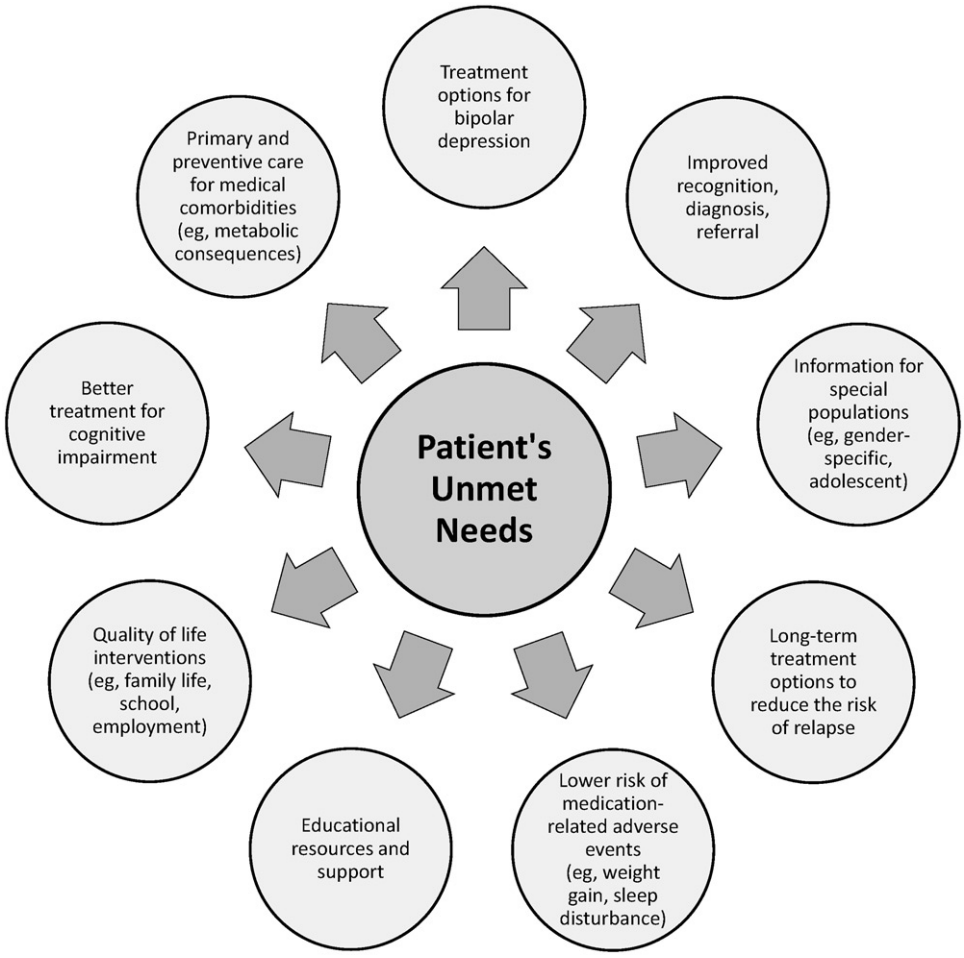

Figure 4. Unmet patient needs in bipolar disorder.

depression, is another unmet patient need that may represent a risk factor for relapse/recurrence and comorbidity, making it a frequent target of treatment[116].

From a clinician's perspective, better patient education and support, referral to specialist care as necessary, improved treatment effectiveness, and better medication adherence have been identified as pressing clinical needs[102]. Since bipolar illness is increasingly recognized as an illness that is treated in primary care, complex factors such as diagnosis, psychiatric comorbidities, greater suicide risk and confusion about appropriate treatment may become impediments to treatment success[117]. Knowing the specific symptoms that differentiate bipolar and unipolar depression, using screening tools to aid diagnosis and using evidence-based treatment guidelines, which recommend ongoing symptom/side-effect monitoring, psychosocial interventions, medication monitoring, and dose adjustment or switching to a different oral antipsychotic, may help improve treatment adherence for patients in clinical practice and ease some burdens for primary care providers[117,118].

Caregivers also experience considerable burdens (e.g. depression, work disruption) that adversely affect patient recovery and the home environment[102], highlighting the need for a strong alliance among the patient, the family and the mental health provider[113]. To meet patient and caregiver needs, clinicians should rely on evidence-based practices in the clinic and seek out education pertaining to accurate diagnosis and appropriate treatment[102].

Conclusions

The preponderance of patients with mental illness and depression are seen by primary care clinicians. Since bipolar depression is commonly misdiagnosed as unipolar depression, special vigilance for symptoms that probabilistically suggest bipolar versus unipolar depression is called for. Critically evaluating presenting symptoms can improve diagnostic accuracy and avoid inappropriate treatment with monotherapy antidepressants. Medical and psychiatric comorbidities, which increase the complexity of bipolar disorder treatment, must be managed to improve patient outcomes. Compared with bipolar mania, bipolar depression is associated with a higher burden of illness related to the amount of time spent unwell, the higher level of functional impairment and the limited number of approved treatment options. Prompt diagnosis and appropriate treatment of bipolar depression is vitally important given the progressive nature of the illness and its considerable unmet needs. Clinical care of patients with bipolar disorder should be a

collaborative effort between the patient, the clinician and the patient's family/caregivers.

Transparency

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Author contributions

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