Unipolar vs bipolar depression:

A clinician's perspective

A careful assessment of select criteria can help make the distinction

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Mrs. W, age 36, who is married, has a history of military service, and is currently employed as a paralegal, is referred to our practice by her family physician. She complains of severe depression that impairs her ability to function at work. She had seen several other psychiatrists in both military and civilian settings, and had been treated with multiple antidepressants, including fluoxetine, sertraline, bupropion, and paroxetine.

At the time of her initial psychiatric evaluation, she is taking duloxetine, 90 mg/d, but still is experiencing depressive symptoms. She is tearful, sad, lacks energy, spends too much time in bed, and is experiencing thoughts of hopelessness, despair, and escape, verging on thoughts of suicide. As a result, she needs to scale back her work schedule to part-time. When asked about how long she had been suffering from depression, she responds "I've been depressed all my life." She had been briefly hospitalized at age 16, when she made a suicide attempt by overdose. There had been no subsequent suicide attempts or psychiatric hospitalizations, although she acknowledges having intermittent suicidal thoughts.

Mrs. W's clinical presentation is similar to that of many patients entering our practice—patients who have recurrent depression that began in early life and a history of failure to respond to multiple antidepressants. She and other patients with similar presentations are not suffering from treatment-resistant depression and in need of a trial of electroconvulsive therapy, transcranial magnetic stimulation, direct current stimulation, vagus nerve stimulation, or intranasal esketamine. She has bipolar disorder, and had been repeatedly misdiagnosed and treated inappropriately with antidepressant monotherapy.

In a previous article[1] ("Controversies in bipolar disorder: Trust evidence or experience?," CURRENT PSYCHIATRY, February 2009, p. 27-28,31-33,39), we endorsed the concept of a bipolar spectrum. We also argued that subthreshold hypomania is the rule and not the exception in bipolar

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Clinical Point

Eliciting a history of brief periods of improved mood is the key to differentiating between unipolar and bipolar depression

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II disorder, that antidepressant monotherapy rarely causes manic switches but is more likely to worsen depression, and that although antidepressant monotherapy usually destabilizes bipolar illness, antidepressants can be helpful when combined with mood stabilizers. We observed that bipolar disorder occurs frequently in children and adolescents and that psychosis is a common occurrence in patients with bipolar disorder. We also outlined what we consider to be the major clinical features of bipolar depression and noted the role of thyroid hormones in managing mood disorders.

In this article, based on our more than 25 years of experience in diagnosing and treating psychiatric disorders in patients of all ages, we expand on those observations.

Misdiagnosis is common

Bipolar depression is frequently misdiagnosed as unipolar depression in outpatient[2-8] and inpatient[9] settings, and in children and adolescents.[10] Mrs. W is typical of patients who have what we consider a bipolar spectrum disorder and receive an inaccurate diagnosis and treatment that is ineffective or may worsen the course of their illness.

Reliance on DSM-5[11] and its predecessor, DSM-IV, is a part of the problem of misdiagnosis because the diagnostic criteria for bipolar disorder fail to capture the clinical features of many patients with "softer" (less obvious manic and hypomanic) variants of the disorder.[12,13] For example, DSM-5 criteria for a hypomanic episode (the mild high experienced by patients with a soft bipolar disorder) require that the episode lasts "at least 4 consecutive days" and is "present most of the day, nearly every day." In our experience, the majority of hypomanic episodes are shorter—ranging from a half-day to 2 days, averaging perhaps 1.5 days.

DSM-5 also requires severity criteria for hypomania that patients with unequivocal hypomanic episodes often do not meet. For example, they may fail to experience flight of ideas or racing thoughts, or engage in activities such as "unrestrained buying sprees, sexual indiscretions, or foolish business investments." These patients usually describe these mild highs as feeling normal and report a happier mood, more smiles and laughter, increased energy, less sleepiness, increased talkativeness, increased socialization, and improved motivation to complete tasks left undone and projects left unfinished because of the previous depressive episode. These softer (subthreshold) hypomanic episodes are authentic and, if clinicians do not identify them, may lead to misdiagnosis and inappropriate treatment.

Patients who present with depression often fail to report these brief, subthreshold hypomanic episodes or consider them to be irrelevant to their diagnosis and treatment.[12,13] Probing questions can often elicit these unreported highs. For example, a patient with depression should be asked, "Have you had a single good day during the last month?" and "Where were you and what did you do during that day?" Eliciting a history of brief periods of improved mood is the key to differentiating between unipolar and bipolar depression. Screening instruments such as the Mood Disorders Questionnaire[14] and the Bipolar Spectrum Diagnostic Scale[15] may be helpful in distinguishing between unipolar and bipolar depression. However, we offer our thoughts on making that crucial distinction.

Distinguishing between these 2 types of depression

Although it may be difficult to distinguish between unipolar and bipolar depression, especially in the absence of a history of distinct manic or hypomanic episodes, we find the following criteria to be useful in making that determination.

Age of onset. Bipolar spectrum disorders typically begin earlier in life than unipolar depression.[10,16-19] A typical presentation of bipolar disorder in children and adolescents is depression or agitated mixed states with features of both mania and depression, often accompanied by rapid mood cycling.[20,21] Unipolar depression usually begins later in life, and patients do not have a history of significant depressive episodes or mood swings in childhood or adolescence. An important question to ask a patient with a chief complaint of depression is, "How old were you

when you first experienced an episode of depression?"

Gender differences. Bipolar spectrum disorders with more subtle (softer) presentations, such as subthreshold highs, occur more often in women than men.[22] However, overall rates of bipolar disorder may be slightly higher in men than in women.[23] Unipolar melancholic depression occurs at approximately the same frequency in men and women.[24]

Rapidity of onset. Bipolar depressive episodes develop more rapidly than unipolar episodes. It is common for a patient with a bipolar spectrum disorder to transition from normal to very depressed virtually overnight, whereas in our clinical experience, unipolar episodes progress more slowly, often over several months.

Deliberate self-harm. Adolescents and young adults with a bipolar spectrum disorder frequently engage in self-injurious behavior, usually cutting with a knife, razor, or even sharp fingernails.[25] Although these patients may also have thoughts of suicide and make suicide attempts, the individual usually perceives cutting as a means of gaining relief from tension and distress. These behaviors are often associated with a diagnosis of a personality disorder; in our opinion, however, they are hallmarks of a bipolar spectrum disorder.

ADHD. Bipolar disorder frequently co-occurs with attention-deficit/hyperactivity disorder (ADHD).[26,27] Adults with bipolar disorder often have ADHD symptoms, which can complicate their treatment and cause functional impairment even after their mood disorder has been stabilized.[28]

Substance use disorders. Excessive use of alcohol and drugs is common among people with a wide range of psychiatric disorders, but patients with bipolar disorder have an unusually high rate of co-occurring substance use disorders—40% to 50%.[29,30]

Appetite and weight differences. Patients with unipolar depression usually experience loss of appetite and weight loss, whereas in our clinical experience, patients with bipolar depression often overeat, crave carbohydrates, and gain weight.

Sleep problems. Patients with bipolar depression have an increased need for sleep (the opposite of what they experience during highs), are sleepy during the day regardless of how many hours they sleep, and have difficulty getting up in the morning. Patients with unipolar depression also have a sleep disturbance: they may fall asleep easily, sleep for a few hours, and then awaken but are unable to fall back to sleep.[31] Yet these patients usually do not complain of sleepiness during the day.

Diurnal variation of mood. Patients with unipolar depression often report that their depressive symptoms fluctuate in a circadian manner. For example, they may report that their depression is worse in the morning but improves toward evening.[31] This regular alteration of circadian rhythm usually is not evident in patients with bipolar depression, whose mood may vary unpredictably or in response to stressors. Some patients with bipolar disorder, however, exhibit ultradian (ultra-rapid) mood cycling, which may be confused with the diurnal mood variation seen in patients with unipolar depression.

Tendency to recur. Although both unipolar and bipolar depressive episodes recur, a pattern of multiple recurring episodes beginning in early life is characteristic of bipolar spectrum disorders.

Behavioral history. Patients with bipolar depression are more likely than patients with unipolar depression to have a history of multiple marriages, multiple romantic relationships, episodes of promiscuity, legal problems, or financial extravagance.

Response to antidepressants. Patients with bipolar depression exhibit atypical responses to antidepressant monotherapy, such as worsening of depressive symptoms, initial improvement of mood with subsequent loss of effectiveness, premature response to an antidepressant (eg, improvement of mood

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Clinical Point

It's important to ask patients, 'How old were you when you first experienced an episode of depression?'

Unipolar vs bipolar depression

Clinical Point

We believe that a history of multiple failed antidepressant trials is evidence of misdiagnosis of bipolar disorder as unipolar depression

Box 1

The role of thyroid hormones

Conventional laboratory reference ranges often indicate that thyroid-stimulating hormone (TSH) levels as high as 4.0, 4.5, or 5.0 mU/L are normal. A recent meta-analysis determined that treatment of subclinical hypothyroidism (elevated TSH with normal free thyroxine) does not benefit patients' quality of life.[38] Patients with mood disorders, however, often fail to respond to mood stabilizers and other psychiatric medications unless their TSH is <3.0 or even <2.5 mU/L.[39,40] We typically augment with liothyronine because, unlike levothyroxine, it works quickly, does not require deiodination to be activated, and, contrary to some reports, its elimination and biologic half-life are sufficient for single daily dosing.[41]

within 1 to 2 days of beginning the antidepressant), fluctuation of depressive symptoms (mood cycling), or precipitation of a hypomanic or manic episode. We believe that a history of multiple failed antidepressant trials is compelling evidence of misdiagnosis of a bipolar spectrum disorder as unipolar depression.

Genetics. Bipolar disorder is one of the most heritable of illnesses.[32] Family history is important, but affected relatives may have been misdiagnosed with unipolar depression or schizophrenia, or said to have experienced "nervous breakdowns."

Consequences of misdiagnosis

Misdiagnosis of patients with bipolar disorder is not benign. We see patients who have suffered needlessly for years with severe depression and mood instability. After trying antidepressant after antidepressant without benefit, they begin to feel hopeless, believing they have tried everything and that nothing works for them. Often, these patients have dropped out of high school or college, or lost jobs, friends, and spouses due to their disabling but misdiagnosed psychiatric disorder. Patients with misdiagnosed bipolar disorder have an increased risk of suicide attempts and psychiatric hospitalization.[5,8]

Misdiagnosis of patients with bipolar disorder is not limited to nonpsychiatric physicians. The majority of patients with bipolar spectrum disorders are misdiagnosed by outpatient psychiatrists as having unipolar depression.[2-7] At least 45% of patients hospitalized for depression have bipolar disorder—and most of these patients are treated inappropriately with antidepressants.[9] The STAR*D study,[33,34] a large randomized clinical trial of antidepressants, concluded that more than one-third of patients had not remitted from their depression after treatment with 3 different antidepressants. In our opinion, many of the nonresponding patients may have undiagnosed bipolar depression, which predictably leads to a failure to respond adequately to antidepressants. We believe that the customary inclusion and exclusion criteria used to select participants for these research studies miss subtle (subthreshold) hypomanic episodes that fall short of meeting DSM criteria for duration and severity. This phenomenon may account for the results of studies that conclude that antidepressants are, at best, minimally more effective than placebo.[35]

When a patient with a bipolar spectrum disorder is misdiagnosed and treated with an antidepressant, the usual result is mood destabilization. Reports of mood swings, increased crying, and suicidal thoughts and suicidal gestures in children, adolescents, and young adults treated with antidepressants led the FDA to issue a "black-box" warning.[36] Because bipolar depression typically begins in youth,[10,18,19] the behaviors cited in the warning may reflect misdiagnosis of bipolar depression as unipolar depression, and consequent mood destabilization as a result of treatment with an antidepressant in the absence of a mood stabilizer.

Depression and life stressors

Since many patients who are depressed present with a history of significant stressors, clinicians often face the problem of distinguishing between clinical depression and stress-induced depression. We believe that one typical symptom of depression—increased sensitivity to stressors—may help in making that distinction. A patient who is depressed will often attribute depression to stressors such as marital conflict, divorce,

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Box 2

Bipolar disorder in DSM-5: 2 issues

Based on our clinical experience treating thousands of patients over 25 years, we have 2 issues with DSM-5 regarding bipolar disorder:

1. The DSM-5 criteria for hypomania fail to reflect the features of clinical presentations commonly seen in our practice. The majority of patients with authentic bipolar syndromes do not have hypomanias that last for at least 4 days or reach the level of severity required for a DSM-5 diagnosis of hypomania. This results in misdiagnosis of patients with bipolar depression as suffering from unipolar depression, which leads to inappropriate treatment with antidepressant monotherapy.

2. Bipolar disorder frequently makes its first appearance in childhood and adolescence,[10,18,19] and increasing numbers of young patients have been receiving this diagnosis.[42] In our opinion, this increase reflects clinicians' improved diagnostic skills. Perhaps alarmed by the increase in young people receiving a diagnosis of bipolar disorder, the authors of DSM-5 created a new diagnosis for children: disruptive mood dysregulation disorder. This diagnostic addition is based on the finding that children with these mood symptoms may not subsequently exhibit classic DSM-5 manic or hypomanic episodes. But the lack of such episodes does not preclude a diagnosis of bipolar disorder, because many adults with unequivocal bipolar spectrum disorders have subthreshold hypomanias and thus fail to exhibit classic manic or hypomanic episodes.[12,13]

A rose by any other name would smell as sweet. Children who exhibit symptoms of disruptive mood dysregulation disorder—chronic irritability and protracted temper outbursts—usually suffer from depression and mood instability. In our opinion, it is irrational and confusing to clinicians to separate out with a new diagnosis an arbitrarily defined group of children who exhibit substantially the same symptoms as those who receive a diagnosis of bipolar disorder.

Clinical Point

When a patient with bipolar disorder is misdiagnosed and treated with an antidepressant, the usual result is mood destabilization

problems with a teenage child, work pressures, financial pressures, or the illness or death of a family member or pet. If clinical depression (unipolar or bipolar) is present, the symptoms are persistent, sometimes antedate the stressor by days or weeks, often outlast the stressor, increase in severity over time, and are disproportional to the stressor. Clinical depression can also cause the patient to become obsessed with traumatic events or losses that occurred many years earlier.

Our approach to treatment

Patients with mood disorders often benefit from a combination of pharmacologic management and psychotherapy. Psychotherapy is particularly important in addressing the functional impairment, diminished self-worth, and interpersonal conflicts that often accompany clinical depression. Several styles or systems of psychotherapy have been developed to benefit patients with mood disorders. Their effectiveness may depend on the patient's ability to gain insight,[37] but in our opinion, the most important attribute of helpful psychotherapy is the rapport established between the patient and the therapist, and the therapist's ability to empathize with the patient and instill in the patient a sense of optimism and hope. We often recommend that patients attend meetings of the Depression and Bipolar Support Alliance (DBSA), a national support group with chapters throughout the country. Patients often find that attending these meetings is both educational and emotionally rewarding.

The foundational pharmacologic treatment for bipolar disorder is a mood stabilizer. The medications we consider to be effective mood stabilizers (some with an FDA indication for bipolar maintenance, some without) are lithium carbonate, divalproex sodium, carbamazepine, oxcarbazepine, and lamotrigine.

Each of these mood stabilizers has its advantages, disadvantages, risks, and adverse effects. For example, although divalproex is a reliable mood stabilizer, it has a significant risk of causing birth defects if taken during pregnancy and can cause increased appetite and weight gain. Carbamazepine has significant drug interactions and the potential to cause neurologic adverse effects, while oxcarbazepine, a derivative of carbamazepine, has fewer drug interactions but is more likely to cause hyponatremia. Lamotrigine must be titrated very slowly to reduce the risk of a potentially fatal skin

rash (ie, Stevens-Johnson syndrome or toxic epidermal necrolysis). Lithium is effective but has a significant adverse-effect burden: impairment of renal function with long-term use, nephrogenic diabetes insipidus, hypothyroidism, hyperparathyroidism, acne, and weight gain. Lithium also has potential interactions with multiple commonly prescribed medications, including antihypertensives and diuretics, as well as over-the-counter pain relievers such as ibuprofen and naproxen.

Second-generation antipsychotics (SGAs) have mood stabilizing, antidepressant, and anti-manic properties and are often useful in managing bipolar disorder. In our experience, for patients with bipolar disorder, SGAs are best used in combination with a mood stabilizer. Although virtually all SGAs have demonstrated effectiveness in the treatment of psychosis and some phases of bipolar disorder, the newer agents (aripiprazole, brexpiprazole, lurasidone, and cariprazine) are relatively free of metabolic adverse effects such as weight gain, abnormal cholesterol levels, increased prolactin levels, insulin resistance, and increased risk of diabetes.

Antidepressants may be effective in treating unipolar depression, but when treating bipolar depression, they should be used cautiously and only in combination with a mood stabilizer.

As we observed in our previous article,[1] thyroid laboratory monitoring and supplementation are critical components of managing mood disorders (***Box 1,***[38-41] ***page 14***).

Moving towards better diagnoses

The emergence of a criteria-based psychiatric system in 1980 with the publication of DSM-III, and its subsequent revisions and updates, constituted a major advance in psychiatric diagnosis. As we learn more about the pathophysiology, genetics, and epigenetics of psychiatric symptoms and syndromes, future diagnostic systems will improve problems of validity that have yet to be resolved. While we believe that, for the most part, DSM-5 was an advance over the previous diagnostic iteration, we have 2 issues with DSM-5 in terms of the diagnosis of bipolar disorder (***Box 2,***[10,12,13,18,19,42] ***page 16***).

Patients with a chief complaint of depression are often given a diagnosis of "major depression, rule out bipolar disorder." We believe that this formula should be turned on its head. In our opinion, based on our clinical experience, we think that most patients who present to a clinician's office or psychiatric hospital with depression have bipolar depression, not unipolar depression. We hope that our experience and observations derived from treating thousands of patients over more than 25 years may be helpful to clinicians who sometimes struggle to bring relief to their patients with mood disorders.

continued

Related Resources

- Nasrallah HA. Misdiagnosing bipolar depression as major depressive disorder. Current Psychiatry. 2013;12(10):20-21,A.
- Ghaemi SN. Bipolar spectrum: a review of the concept and a vision for the future. Psychiatry Investig. 2013;10(3):218-224.

Drug Brand Names

Aripiprazole • Abilify
Brexpiprazole • Rexulti
Bupropion • Wellbutrin
Carbamazepine • Tegretol, Equetro
Cariprazine • Vraylar
Divalproex • Depakote
Duloxetine • Cymbalta
Esketamine • Spravato
Fluoxetine • Prozac
Lamotrigine • Lamictal
Levothyroxine • Synthroid, Levoxyl
Liothyronine • Cytomel
Lithium • Eskalith, Lithobid
Lurasidone • Latuda
Oxcarbazepine • Oxtellar XR, Trileptal
Paroxetine • Paxil
Sertraline • Zoloft

Bottom Line

Patients with bipolar depression are often misdiagnosed with unipolar depression and treated inappropriately with antidepressant monotherapy, which often results in mood destabilization. Based on our clinical experience, a careful assessment of select criteria, including age of onset, rapidity of onset, comorbidities, diurnal mood variations, and more, can be useful for distinguishing between unipolar and bipolar depression.

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Clinical Point

The DSM-5 criteria for hypomania fail to reflect the features of clinical presentations commonly seen in our practice

Clinical Point

When treating bipolar depression, antidepressants should be used cautiously and in combination with a mood stabilizer

CASE CONTINUED

Return to work

Mrs. W is now doing well. She is taking a lower dosage of duloxetine, 60 mg/d, in combination with the mood stabilizer lamotrigine, 200 mg/d. She returns to work full-time as a paralegal and no longer is experiencing depressive episodes.

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