Differential Diagnosis of Major Depressive Disorder Versus Bipolar Disorder: Current Status and Best Clinical Practices

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This evidence-based ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* was derived from survey and focus group data, faculty presentations, and discussions between experts captured during the roundtable meeting "Differential Diagnosis of Major Depressive Disorder Versus Bipolar Disorder: Current Status and Best Clinical Practices," which was held October 26, 2018, in Orlando, Florida. The purpose of this article is to provide psychiatrists and other health care professionals who treat patients with major depressive disorder and bipolar disorder a set of best practices, tools, and other methods to improve their ability to make a more accurate diagnosis between major depressive disorder and bipolar disorder and to reach this diagnosis sooner, given a particular set of patient-related circumstances and comorbidities.

The live roundtable discussion was chaired by **Roger S. McIntyre, MD, FRCPC**, Department of Psychiatry & Pharmacology, University of Toronto; Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada. The faculty were **Mark Zimmerman, MD**, Rhode Island Hospital, Providence, Rhode Island; **Joseph F. Goldberg, MD**, Icahn School of Medicine at Mount Sinai, New York, New York; and **Michael B. First, MD**, Department of Psychiatry, Columbia University, New York, New York.

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Given the similarity in clinical presentation between major depressive disorder (MDD) and the depressive episodes of bipolar disorder (BP), it is inevitable that diagnostic errors will occur. Both overdiagnosis and underdiagnosis of BP are all too common, and it may take a decade or longer to reach a correct diagnosis.[1] While diagnostic errors may never completely be eliminated, it is important to lessen their likelihood by better understanding the diagnostic criteria for MDD and both bipolar I (BP I) and bipolar II (BP II) disorders as well as the many psychiatric disorders and medical conditions that may have overlapping symptoms. In reaching an accurate diagnosis sooner, the significant psychosocial morbidity and excess mortality of BP may be lowered, along with the higher costs of care incurred by a delayed diagnosis.

The purpose of this article is to provide psychiatrists and primary care clinicians with a set of best practices to improve their ability to make an accurate differential diagnosis between MDD and BP while recognizing complexities related to not only psychiatric and medical comorbidities but also the evolving presentation of symptoms as the disorders progress.

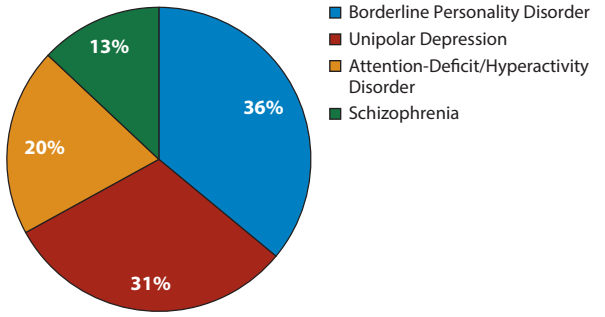
WHERE DO WE STAND TODAY? ONLINE POLL DATA, FOCUS GROUPS, AND FACULTY DISCUSSION

To set the stage for this evidence-based exploration of the differential diagnosis of MDD versus BP, 3 online surveys were deployed at Psychiatrist.com, and 2 focus group teleconferences were facilitated by Dr. McIntyre in order to gain an understanding of how clinicians are currently conducting a differential diagnosis. The questions also explored which rating scales were being used, psychiatric and medical comorbidities that may be hindering their efforts, the greatest predictors of an accurate diagnosis, and the risk factors that they believe predispose a patient to BP as opposed to unipolar depression. The online polls received 473 responses, and 20 clinicians participated in the focus groups. The majority of the participants who responded to the surveys as well as those in the focus groups were psychiatrists. This section will provide a summary of highlights from the polls, focus group discussions, and excerpts taken from the roundtable meeting.

Of the Following Disorders, Which Do You Have the Greatest Difficulty Differentiating From Bipolar I Disorder? (Figure 1)

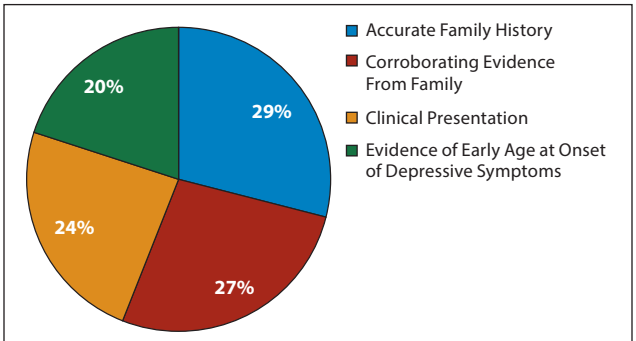
The poll respondents chose borderline personality disorder as the most difficult to differentiate from BP I, followed by unipolar depression and attention-deficit/hyperactivity disorder (ADHD).

Figure 1. Current Status: Disorders Most Difficult to Differentiate from Bipolar I Disorder[a] (N = 154)



[a]Data from an online poll of registered users at Psychiatrist.com from 8/15/18–8/24/18.

Figure 2. Current Status: Best Predictor of Achieving Accurate Diagnosis of Unipolar vs Bipolar Disorder in New Patients Presenting With a Depressive Episode[a] (N = 168)



[a]Data from an online poll of registered users at Psychiatrist.com from 8/31/18–9/10/18.

The focus group participants concurred with the poll results and also mentioned substance abuse, undiagnosed traumatic brain injury among combat veterans, and posttraumatic stress disorder (PTSD) as challenges. Mood swings were mentioned frequently during the focus group discussion, and the expert panel made a special effort to stress that mood instability is not among the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), symptoms of BP but is more of a defining element. It was suggested that clinicians should regard abrupt changes in mood as less likely to be a symptom of BP than of other disorders, such as borderline personality disorder or ADHD.

To set the stage for the focus groups, the following scenario was presented to the focus group to discuss: *The patient presents with depressive symptoms. You are not familiar with their personal history and don't know if the patient has ever had a manic episode. What steps do you take to establish your diagnosis for the patient?* Common themes from the discussion included the following:

- Establish the patient's level of depression
- Determine when the depressive episodes began
- Gather present and previous history, including episodes of hypomania, mania, and mood swings, as opposed to a surge of energy after prolonged depression
- Employ a screening tool, such as the Mood Disorders Questionnaire (MDQ), the Patient Health Questionnaire-9, and the Adult ADHD Self-Report Scale
- Gain insight from family members about the patient's history
- Obtain a family psychiatric history, including episodes of BP, psychosis, and substance abuse

When a New Patient Presents With a Depressive Episode, What Factor Is the Best Predictor of Achieving an Accurate Diagnosis of Unipolar Versus Bipolar Disorder? (Figure 2)

The online poll response to this question was fairly evenly distributed, with an accurate family history leading the way, followed by corroborating evidence from family, clinical presentation, and finally, evidence of early age at onset of depressive symptoms.

According to the focus groups, the best predictors of achieving an accurate diagnosis of unipolar or bipolar disorder included clinical presentation, number of episodes and the age at which they occurred, illness severity, sleep history and habits, and grandiosity. Other comments suggested that the doctors did not consider patients and their families to be reliable informants since they used terms to describe a host of behaviors that they associated with "bipolar" rather than those defined in medical literature. Several also noted that family histories were often vague.

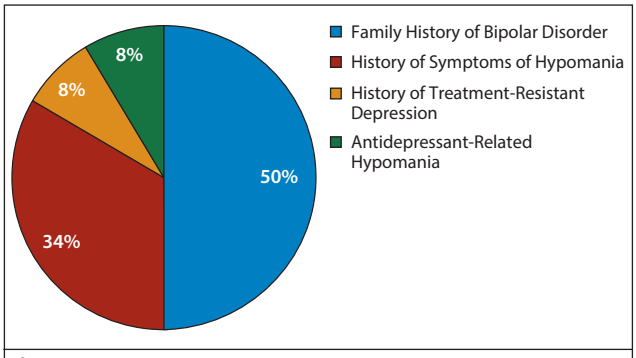
The role of psychosis in differential diagnosis of MDD and BP arose several times in the focus group discussions as one of the factors that could be used in predicting subsequent BP and as a term that family members sometimes used to describe the patient's behavior, a potential red flag for a diagnosis of BP. The experts, though, stressed that symptoms of psychosis in themselves cannot differentiate BP from MDD, since it can occur in both. However, it may be a gateway signal of a more complex mood disorder.

The expert panel agreed that both the vocabulary used to describe psychiatric disorders and the reliability of the medical history of family members should be regarded with skepticism although not discounted. They also urged caution when comments from the focus groups suggested an overreliance on screening tools serving as a diagnostic proxy to a more in-depth clinical assessment.

After the panel reviewed the results of the focus groups, Dr Goldberg noted a factor not mentioned: that experienced clinicians have often acquired the clinical acumen, or "chops," to discern nonverbal cues from patients, such as cadence or motor function, that may aid in diagnosis.

The experts were also surprised that clinical presentation was not the most important factor identified in the poll, falling behind an accurate family history and corroborating evidence from family members. Dr First stressed that the clinical presentation cannot be relegated to among the least important factors. It should be the most important,

Figure 3. Current Status: Greatest Risk Factor for a Subsequent Bipolar I Diagnosis When a Patient[a] Presents With Current Depressive Symptoms[b] (N = 151)



[a]Patient's complete family history is known.
[b]Data from an online poll of registered users at Psychiatrist.com from 8/24/18–8/31/18.

with other aspects of the diagnostic process corroborating what is learned through the clinical presentation. However, the group noted the relatively small difference in percentages for each choice, which seemed to indicate that the respondents considered all 4 factors essential for an accurate diagnosis.

In a Patient That Currently Presents With Depressive Symptoms, in Your Experience What Is the Greatest Risk Factor for a Subsequent BP I Diagnosis (Assuming You Have a Complete Patient History)? (Figure 3)

Half of the respondents to this poll question cited a family history of BP as the greatest risk factor, while a third chose a history of symptoms of hypomania. Conversely, the focus group participants identified symptoms of hypomania as well as the possibility of antidepressant-induced hypomania, although not all agreed that antidepressant mobilization of hypomania could be used to diagnose BP.

Dr Goldberg asserted the importance of a systematic assessment of symptoms as a basis for diagnosis and the need to fit together a constellation of signs and symptoms. This can be achieved only with persistence, the willingness to continue probing even with reluctant patients, and going beyond the responses on screening questionnaires.

In both the focus groups and the polls, some respondents emphasized treatment-resistant depression (TRD) as a primary risk factor in development of BP. While it is among the risk factors, the expert clinicians suggested it was being given more weight than was appropriate, perhaps due to misleading messages about the effectiveness of antidepressants.

In Your Clinical Experience, What Percentage of Patients Originally Diagnosed With Unipolar Depression Were Later Found to Have BP I (Based on Confirmation of a Present or Prior Manic Episode)? How Long After the Original Diagnosis Does This Occur? (Focus Group Responses)

The modal answer to the first question was 10%–30%, the choice of 54% of the respondents and a figure the expert panelists deemed reasonable for this scenario. The focus groups also agreed, though several participants believed the percentage to be much lower, around 5%.

The final discussion point asked the groups how long would it be that patients after a diagnosis of unipolar depression might develop symptoms of BP. Answers varied, with some suggesting 6 months to a year and others either up to a year or within a couple of years. The suggestion of shorter time frames seemed to puzzle the panel, although they pointed out the difficulty of retrospectively calculating progression.

Themes Uncovered by Expert Panel That Could Lead to Diagnostic Missteps

- Ruling out of BP initially by labeling all depressed patients as potentially having BP
- Assumption that TRD is probably misdiagnosed BP without consideration of the many other possible factors that can account for TRD
- Lack of clarity about hallmark symptoms as outlined in *DSM-5,* which leads to uncertainty in differential diagnosis, due to overlapping symptoms and comorbidity
- Lack of clarity about best predictors of achieving an accurate diagnosis of MDD vs BP and also risk factors that predispose a patient to a bipolar diagnosis
- Overreliance on screening tools to serve as a proxy for diagnosis in lieu of complete clinical assessment and data gathering to fit together the constellation of signs and symptoms
- Discounting of the family history too quickly by inappropriately dismissing it or, conversely, giving it too much weight
- Misinterpretation of the words used by the patient to describe a family member's psychiatric history

DIAGNOSTIC CLARIFICATION BETWEEN MDD AND BP

In making a differential diagnosis between MDD and BP, certainty is a rare commodity. Diagnosis is based on symptoms, but there is a degree of arbitrariness in the minimum number of features and the minimum duration necessary for a definitive diagnosis. Even the most thorough clinician, having conducted a comprehensive clinical evaluation, consulted family members, elicited details about the patient's history of mania and hypomania, used standard screening questionnaires, and taken other essential steps, may still have difficulty in arriving at diagnostic certainty.

In this section, the expert panel will cover common challenges that clinicians face when making a differential diagnosis, the consequences associated with a misdiagnosis, the appropriate use of screening instruments, and coupling these tools with a thorough clinical interview and evaluation.

BP is both underdiagnosed (false negatives) and overdiagnosed (false positives). Using the *DSM-5*, clinicians

will inevitably encounter patients who seem to meet the criteria for BP but who do not in fact have the condition, while longitudinal follow-up will show that some patients undeniably have BP despite not meeting all of the diagnostic criteria.

Both over- and underdiagnosis have negative impacts, which reinforces the importance of becoming more skilled at making and reasoning through a differential diagnosis. When the disorder is missed, consequences include underprescribing of mood-stabilizing medications, greater risk of rapid cycling, and higher costs of care.[2] The problems associated with overdiagnosis include improper psychoeducation and treatment with unneeded medications, potentially causing serious side effects and associated medical risks.[1] And if BP is mistakenly diagnosed, the clinician may overlook the actual cause of the patient's symptoms and fail to initiate appropriate treatment.

BP can go unrecognized for several reasons. One is that diagnosis tends to be based on retrospective reports rather than prospective assessments. In addition, patients who seek treatment for BP are more often experiencing symptoms of depression and anxiety than of mania or hypomania.[2]

To help reach an accurate diagnosis, Dr Zimmerman reinforced that persistent and rigorous inquiries about episodes of mania or hypomania should be a routine part of the evaluation. These should result in a more complete picture of the patient's status. The use of screening questionnaires has also been recommended,[2] although they should be considered the first stage of an evaluation, to be followed by a diagnostic interview, rather than sufficient in themselves for reaching a diagnosis.

> *"I spend a great deal of time trying to piece together as much information as I can gather. It is a time-intensive but worthwhile process to get collateral history, to clarify what the patient is saying—for instance, when patients say they had a bad reaction to an antidepressant, do they mean they had a side effect, a discontinuation effect, a worsening of their underlying condition that's unrelated to medication, an unmasking effect that persisted after the antidepressant was stopped, or an artifact of substance misuse or an unrecognized medical condition? So there are often a lot of things to clarify and if you don't know the patient well or if they have been to many other providers, it can be challenging to gather an accurate history. But the clinicians have to be very rigorous. You can't just take one piece of the puzzle out of its broader context and know what to call it."* —Dr Goldberg

The prevailing view that underdiagnosis was more prevalent than overdiagnosis has changed over the last 10 to 15 years, with overdiagnosis now regarded by some as an equally significant concern, perhaps an even greater problem.[1] For example, in 3 clinical studies[1,3,4] exploring this issue, only 33%–43% of patients who had previously been diagnosed with BP after being administered the Structured Clinical Interview for *DSM-IV* met the diagnostic criteria following further evaluation.

Common reasons for overdiagnosis of BP include failure to meet a sufficient number of *DSM-IV*–associated B criteria symptoms for mania or hypomania, insufficient duration, and inability to identify abstinent periods in patients with substance abuse disorders.[4] Clinicians in busy practice settings also may not approach diagnosis the way investigators do, by evaluating individual symptom criteria and establishing whether their number and duration are sufficient to establish the presence of a *DSM*-defined syndrome.

In another follow-up study[5] of patients who had been previously diagnosed with BP, investigators found, as expected, that this population was more frequently diagnosed with borderline personality disorder. One-quarter of these patients met *DSM-IV* criteria for borderline personality disorder due to the overlap of symptoms such as brief episodes of sudden anger or irritability. Other disorders independently associated with overdiagnosis of BP in a logistic regression analysis were current PTSD, lifetime MDD, lifetime eating disorder, lifetime impulse-control disorder, and antisocial personality disorder.[5]

The Role of Screening Instruments

The frequency of misdiagnosis and the challenge of differentiating MDD and BP (or distinguishing either from the multitude of psychiatric conditions with overlapping symptoms) highlight not only the importance of accurate differential diagnosis but also the need for and appropriate use of reliable diagnostic tools. The MDQ is one of several self-administered instruments developed to improve detection of BP.[2] It was intended to be used as a screening instrument, not as the diagnostic measure.[2] Unfortunately, some clinicians regard a positive screen result in the MDQ as a presumptive diagnosis.[6]

> *"There has been a desire to get an easy-to-use bipolar screening tool in the hands of busy clinicians that can quickly and easily be almost a proxy for making a formal diagnosis. But screens are just that—screens; they are not proxies for actual diagnoses. Screens are meant to cast a wide net to not miss true cases; they are less focused on excluding false positive cases. When we used the MDQ as a structured interview with patients to clarify their self-reported responses, we found very high positive and negative predictive value of a true bipolar diagnosis. The questions within the MDQ provide an excellent basis for a semi-structured interview with the patient that allows an experienced clinician to clarify and contextualize patients' responses."* —Dr Goldberg

> *"Yes, you have to do a clinical interview after you administer the MDQ, or any other screening tool, because of the modest positive predictive value [on their own]."* —Dr Zimmerman

> *"That is a profound nugget in all of this—if you do a screen, you now have to evaluate it. This is opening a door, and I don't think people necessarily realize that screening is a starting point rather than an endpoint."* —Dr Goldberg

High sensitivity is important in a screening scale to help identify those patients in most need of additional evaluation.[7] However, an analysis of 20 studies on the MDQ's performance found that sensitivity was a relatively modest 61.3%; specificity, 87.5%; positive predictive value, 58.0%; and negative predictive value, 88.9%.[2] Therefore, if clinicians follow screening by further evaluating only patients with positive scores, they would miss a diagnosis of BP in approximately one-third of patients.

The screening tool may suggest a preliminary diagnosis, but either a negative screen or a false positive may also point the clinician to a different pathway, particularly in the latter situation. While the patient may not meet the criteria for BP, the information gleaned from the initial screening may warrant additional assessment for conditions that share some of its characteristics, such as PTSD, borderline personality disorder, or substance use disorder (SUD).

Another risk of overreliance on the MDQ, or other screening instruments for diagnosis, is that it can be difficult to undo a diagnostic error. It may be easier to remedy a false negative diagnosis if, for example, a patient subsequently experiences a manic or hypomanic episode. However, a false negative diagnosis of BP should not automatically be the end of the clinical evaluation. If the symptoms suggest MDD rather than BP, surveillance and treatment should be ongoing, especially given the risk of suicide with either MDD or BP.[8]

False positives have consequences as well, as it is harder to undo than to add a diagnosis. If a patient has been mistakenly diagnosed with BP and prescribed a mood stabilizer, then the absence of any further manic or hypomanic episodes would be interpreted as "success" (disregarding any side effects or other consequences the patient may have experienced from the unnecessary medication). The false positive may also have closed the door, so to speak, to recognizing other diagnoses that may explain the patient's symptoms. They may also trap clinicians in an inappropriate mindset to avoid antidepressants or other interventions that might be relevant for TRD.

Summary of Key Concepts

An initial evaluation may require multiple visits, and utilizing a reliable diagnostic instrument is an invaluable initial step in differential diagnosis. Screening questionnaires are a step in the process, not a substitute for a thorough diagnostic evaluation, but can serve as a structured interview guide to explore patient responses and their correlation to diagnostic criteria. Ongoing surveillance, follow-up, and vigilance are extremely important.

Case Practice Question

George is a 32-year-old single, white man presenting for the treatment of depression. This is his fourth episode; the first occurred in his teens. He meets full criteria for an episode of major depression. He had also been diagnosed with generalized anxiety disorder and social anxiety disorder. During the next year, he developed a hypomanic episode, and upon careful questioning he described 2 prior hypomanic episodes, the first occurring when he was a teenager. He screened negatively on the Mood Disorders Questionnaire. The negative result on the MDQ is indicative of a problem with the scale's _____.

a. Sensitivity
b. Specificity
c. Positive predictive value
d. Negative predictive value

Preferred response: a. Sensitivity refers to a screening measure's ability to detect individuals with the disorder. False negatives (ie, instances in which a patient with the index disorder are not detected by the screening test) indicate problems with a scale's sensitivity. Because screening scales for BP have modest sensitivity of around 65%, clinicians risk missing the diagnosis of BP in one-third of patients if they inquire about BP only in patients who screen positive. It is therefore recommended that clinicians inquire about BP in all depressed patients regardless of the results of the screening scale.

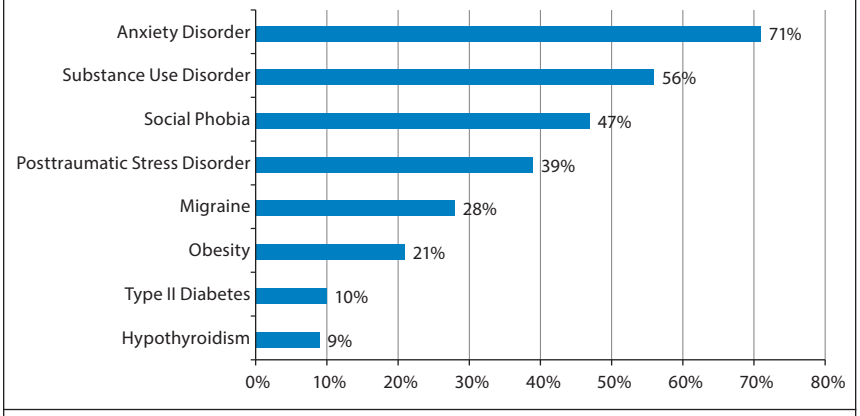
HOW DO PSYCHIATRIC COMORBIDITIES CLOUD AND COMPLICATE DIAGNOSTIC ACCURACY?

Psychiatric and medical comorbidities with overlapping symptoms occur frequently in patients living with MDD and BP, which clouds the picture for clinicians and increases the complexity of reaching a definitive diagnosis. Psychiatric comorbidities, in particular, are common in both disorders. In a recent survey of more than 36,000 adults, the lifetime prevalence of any comorbid SUD among patients with MDD was 57.9%, and the rates for any anxiety disorder and any personality disorder were 37.3% and 31.9%, respectively. Within those categories, the comorbid conditions with the highest lifetime prevalence were alcohol use disorder (40.8%), generalized anxiety disorder (20.5%), and borderline personality disorder (26.6%).[9]

The estimated rate of lifetime psychiatric comorbidity in BP I ranges from 50% to 70%.[10] Comorbid conditions are so common, in fact, that they are the rule rather than the exception, and the term encompasses both cross-sectional comorbidity (ie, symptoms occurring at the same time) and those occurring at different times during the course of the disorders.[10]

Making diagnosis and treatment even more complicated is that many patients with MDD and BP have more than 1 comorbidity. While the high rates of comorbidity between MDD and another psychiatric illness are well established, one author has suggested that in "real world clinical care," a sizable majority of individuals with MDD may have more than 1 comorbid psychiatric disorder.[11] Further, one study found that 65% of bipolar patients had symptoms that also met criteria for at least one additional Axis I disorder; 42%, two or more; and 24%, 3 or more.[10] This psychiatric comorbidity was

Figure 4. Comorbidity of Bipolar Disorder With Other Psychiatric and Medical Disorders[a]



[a]Based on data from Krishnan.[10]

Figure 5. Overlapping Symptoms of Bipolar and Other Disorders

Mania/Hypomania[a]	Substance-Related Disorder With Overlapping Symptoms
Elevated/euphoric mood	Cannabis intoxication Inhalant intoxication Opioid intoxication Stimulant intoxication
Irritable mood	Caffeine withdrawal Cannabis withdrawal Tobacco withdrawal
Decrease in need for sleep	Caffeine intoxication
Distractibility	Opioid intoxication
Increase in activity/ psychomotor agitation	Alcohol withdrawal Caffeine intoxication Cannabis withdrawal PCP intoxication Opioid intoxication Sedative withdrawal Stimulant intoxication Stimulant withdrawal Tobacco withdrawal
Involvement in activities with high potential for painful consequences	Substance use disorders Alcohol intoxication

[a]Based on *DSM-5* criteria for manic episode.

correlated with factors such as poorer overall outcome, high rates of suicidality, and less favorable response to treatment (especially lithium). Comorbidity was also associated with more mixed features and treatment noncompliance.[10] To be diagnosed with the new mixed features specifier in the case of major depression, the new *DSM-5* specifier will require the presence of at least 3 manic/hypomanic symptoms that do not overlap with symptoms of major depression. In the case of mania or hypomania, the specifier will require the presence of at least 3 symptoms of depression in concert with the episode of mania/hypomania.[12]

There are several types of comorbidity: 2 independent disorders co-occurring by chance, 2 disorders with shared underlying causal factors or genetic predisposition (eg, MDD and generalized anxiety disorder), or 1 disorder that causes another (eg, alcohol use disorder causing secondary dementia). The list of comorbidities that may occur with BP is long and includes both psychiatric and medical conditions (Figure 4).[10]

Although many studies of comorbidities with BP fail to distinguish between BP I and BP II, including the Stanley Foundation Bipolar Treatment Outcome Network study,[10] a few differences have been found. For example, comorbid migraine may be up to 5 times as frequent in patients with BP II.[10] However, other studies have reported higher rates of substance abuse or dependence in BP I subjects, with the limitation that these studies included relatively few individuals with BP II.[10]

A literature review of comorbidities of BP reported a 36% rate of comorbidity between BP and personality disorder,[10] much of which was presumed to be borderline personality disorder. Studies of comorbidity between BP and borderline personality disorder have found that about 10% of patients with borderline personality disorder had BP I and an equal percentage were diagnosed with BP II. Also, 20% of patients with BP II were diagnosed with borderline personality disorder compared to only 10% of patients with BP I.[13]

Given the strong possibility of a multitude of comorbid conditions, both psychiatric and medical, frequent and infrequent, how should a clinician approach the differential diagnosis of MDD and BP? Since the differentiating factor between these two is the presence of a manic or hypomanic episode or mixed symptoms, in their absence the more likely diagnosis would be MDD.

Comorbidity With SUD

The comorbidity of alcohol and SUDs with BP presents diagnostic challenges. To start, there is a bidirectional causal relationship between them, and substance misuse may precede or follow the BP. Substance intoxication may mimic mania or hypomania, obscuring the diagnosis.[10] However, there are occasions when substances such as stimulants can trigger a full-blown manic episode, which would then justify a diagnosis of BP.

Numerous substance-related disorders have symptoms when the patient is either intoxicated or in withdrawal that overlap with those of the manic and hypomanic episodes of BP (Figure 5). In particular, an increase in activity or psychomotor agitation is associated with many of the withdrawal and intoxication syndromes. If a patient is depressed and using or abusing a substance—alcohol, cannabis, opioids, even caffeine or tobacco—the psychomotor agitation occurring as part of an intoxication or withdrawal syndrome may mimic mania, potentially contributing to misdiagnosis of BP.

In a clinical setting, the scenario might look something like this: a patient with MDD and opioid use disorder describes symptoms including euphoric mood, distractibility, psychomotor agitation, and impaired judgment, which are consistent with a BP diagnosis. Knowing the patient's history of MDD, it would be understandable to interpret the new symptoms as a manic or hypomanic episode and change the diagnosis to BP. Even though some studies[14] have found that half or more of bipolar patients have comorbid SUD, caution is in order. Keep an open mind, consider multiple potential diagnoses, and if possible, evaluate the patient at a time when he or she is not taking the substance. In the immediate aftermath of active substance misuse, *DSM-5* identifies manic, hypomanic, or depressive episodes as occurring secondary to the substance misuse; a period of at least 1 month is generally necessary to distinguish mood disorders as independent phenomena from the aftereffects of psychoactive substances.

Comorbidity of Other Disorders

The same principles should be applied when symptoms or information gathered from the patient evaluation and history raise the suspicion that their comorbidity involves other disorders, not substance use. The overlap of bipolar symptoms with conditions such as PTSD, ADHD, generalized anxiety disorder (GAD), disruptive mood dysregulation disorder (DMDD), oppositional defiant disorder (ODD), premenstrual dysphoric disorder (PMDD), borderline personality disorder, antisocial personality disorder (ASPD), or narcissistic personality disorder also needs to be factored into consideration. Confusion over the implication of the symptoms may lead to either underdiagnosis or overdiagnosis of bipolar disorder.

Bipolar symptoms that can cause the most difficulty in determining their origin include irritable mood, which shares characteristics with at least 6 other nonsubstance disorders (DMDD, PMDD, GAD, PTSD, ODD, and ASPD). Irritable mood is also highly common in people with MDD. ADHD has more overlapping symptoms than the other disorders likely to be confused with BP: talkativeness, distractibility, and increase in activity or psychomotor agitation. Finally, involvement in activities with high potential for painful consequences, which is included in the criteria for a manic episode, is also included in the diagnostic criteria for borderline personality disorder.

> *"Keep an open mind, consider multiple potential diagnoses, and if possible, evaluate the patient at a time when he or she is not taking the substance."* —Dr First

Treatment Challenges

Making the correct differential diagnosis is a task of first sorting out the diagnosis and then selecting a treatment approach. The basis of the therapeutic challenge is the risk that pharmacologic treatment of the comorbid disorder could sometimes worsen the course of the BP.[10] In particular, treatment with antidepressants, often prescribed for an array of potential comorbid disorders—particularly anxiety disorders—could exacerbate the core mood disturbance. Similarly, use of psychostimulants for suspected ADD/ADHD could potentially exacerbate psychotic, manic, or hypomanic symptoms. Judging which medication to prescribe for these comorbid conditions is hindered by the lack of evidentiary support from clinical trials focusing on comorbidly ill populations. Given that subjects with comorbidities are typically excluded from trials evaluating medications for psychiatric disorders, the efficacy and safety of standard treatment in the significant proportion of patients with comorbid conditions are often unknown. Use of a mood stabilizer along with any other pharmacologic treatments being considered may reduce the risk of treatment-induced mania.[10]

In a patient with a psychiatric comorbidity, both the BP and any additional disorders must be treated, which is likely to require a more complex or integrated management strategy than when only 1 disorder is present.

Summary of Key Concepts

Comorbidity of MDD and BP with other psychiatric disorders is common; thus, a comprehensive evaluation is necessary to identify any comorbid conditions. Comorbidity complicates the differential diagnosis due to overlapping symptoms that may mistakenly be attributed to mania or hypomania. The core differentiating factor between MDD and BP is the presence of a manic or hypomanic episode; in their absence, the likely diagnosis is MDD.

Case Practice Question

Martha, a 20-year-old female college student who has suffered from persistent mild depression since she started high school, reports having "borrowed" her roommate's supply of methylphenidate tablets to help her finish several papers and cram for exams during the 10-day "reading period" prior to finals. She took the medication 3 times a day to improve her concentration and to help her pull "all-nighters." As the week wore on, she became euphoric and increasingly social and then more irritable and agitated. She has been brought into the student health facility by her concerned roommate for an evaluation. What should the doctor's initial course of action be?

a. Stop the methylphenidate and immediately start risperidone to control her presumed manic episode
b. Stop the methylphenidate and observe her for several days to see if her mood changes resolve
c. Continue the methylphenidate for a few more days to help her finish studying during the reading period
d. Stop the methylphenidate and immediately start lithium to control her presumed manic episode

Preferred response: b. At this time, it is not clear whether her agitation and euphoria represent the beginnings of a manic episode or methylphenidate intoxication. The best course of action is to observe her after discontinuing the methylphenidate. If her symptoms persist or worsen without the methylphenidate, assessment and treatment for a manic episode could then be initiated.

USE OF STAGING MODELS OF PROGRESSION TO AID IN DIFFERENTIAL DIAGNOSIS OF MDD AND BP

Despite the constraints imposed on clinicians by our current health care system, it is to the benefit of everyone—patients, families, the community, and medical professionals as well—to spend an adequate amount of time reaching a diagnosis. Rushing to a decision without sufficient evidence risks misdiagnosis and multiple repercussions, and it also bypasses the importance of understanding progression or staging of BP and MDD, which can aid with differential diagnosis.

On the basis of his clinical experience, Dr Goldberg noted that it is advantageous to cast a wider net of diagnostic possibilities first and then narrow down the list as more data are collected. Clinicians must consider several factors, such as logical time frames, risk windows in youth, and the evolution of symptoms (eg, frequency, severity, comorbidity, cognitive) that may surface before affective symptoms begin. If a diagnosis is particularly challenging, it is critical to see the patient more often and to remain in contact with the family to gain consistent feedback and insight. Communicating with the patient's family about signs and symptoms to look for in their loved one (eg, substance use or dysregulated sleep-wake cycle) can aid with differential diagnosis, thus forestalling multiple episodes and psychosocial sequelae and possibly avoiding neuroprogression.

Staging Models for BP and TRD

Time can be your ally or your worst enemy when making a differential diagnosis. To aid in the process, the use of staging models is growing in the field of psychiatry.[15] The premise of staging models for BP is that early intervention is more effective and often less complex than later-stage intervention.[15] However, individuals with BP will not always fall neatly into the linear, stepwise progression of a model and may have less or more severe symptoms at different phases.[15] With these caveats, the staging model for BP proposed by Berk et al[15] sets out 4 stages: stage 0, asymptomatic; stage 1, prodrome; stage 2, first episode; stage 3, recurrence, persistence, first threshold relapse, and multiple relapses; stage 4, treatment resistance. The model also suggests treatment approaches for each stage.

A host of methodological issues makes the process of accurately and systematically assessing TRD a challenge for clinicians. As a result, 5 staging models have been developed[16]: the Antidepressant Treatment History Form, Thase and Rush Model, European Staging Model, Massachusetts General Hospital (MGH) staging method, and the Maudsley Staging Model. While all utilize clinical staging algorithms to characterize the type of treatment resistance, from mild to complex, the MGH model is the only one thus far that has been used to predict nonremission.[17]

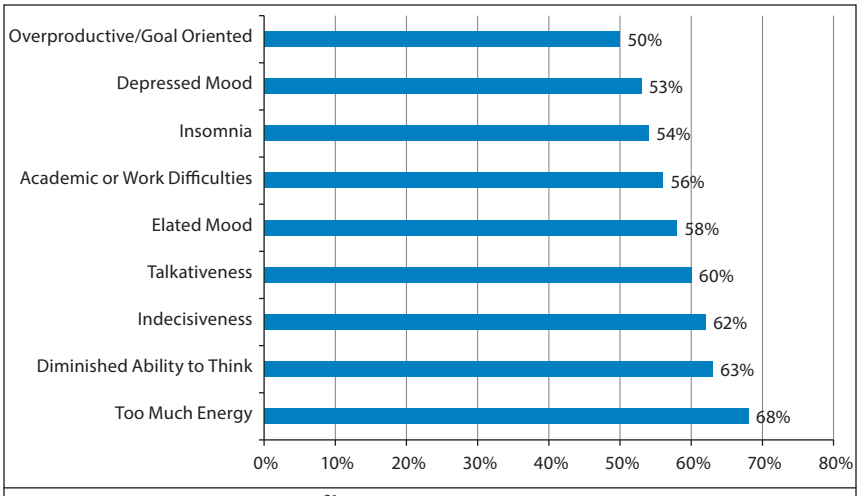
Prodromal Phases

Unipolar depression and BP are lifelong conditions. For bipolar, if it can be identified early and management initiated, the effects on physical, emotional, and social function may be less damaging.[18] Most people who develop BP do so in their late teens or early adult years.[19] Research is lacking in the area of prodromal symptoms of unipolar depression; however, in a substantial portion of patients with MDD, a prodromal phase can be identified.[20]

Nevertheless, some prodromal symptoms have been identified that may precede an initial mood episode and thereby aid in the differential diagnosis of BP (Figure 6). These symptoms may be particularly helpful when treating young people at risk of developing this condition.[21] However, in a meta-analysis[21] of symptom prevalence prior to mood episodes, only 1 symptom occurred in more than half of the participants before a recurrent mood episode: too much energy, reported in 51%. Besides the 10 most frequent symptoms, the meta-analysis[21] found 30 others that occurred less often, suggesting that the characteristics in the prodromal phase are heterogeneous, and as of now there is neither a single symptom nor small cluster of symptoms that conclusively points toward a diagnosis of BP. But given the evidence that most people experience more than 1 prodromal symptom,[21] it eventually may be possible to identify symptom clusters that serve as more specific indicators of risk.

This study[21] also found that the onset of BP tended to be insidious rather than sudden. The average duration of

Figure 6. Most Prevalent Bipolar Prodromal Symptoms (≥ 50% of patients)[a]



[a]Based on data from Van Meter et al.[21]

the initial prodrome was 27.1 ± 23.1 months, which could allow clinicians to complete serial patient evaluations, gathering data over time to support a most-likely diagnostic impression, and begin treatment at an early stage.[21] It is important to remember that psychiatric differential diagnoses often cannot be made cross-sectionally and require monitoring of the course over time to lend credence to one suspected diagnosis versus another. Provisional or working diagnoses can be made when there is uncertainty about the chances that an ambiguous mood disorder in youth will ultimately develop into major depression or BP or an entirely different condition (such as schizophrenia or borderline personality disorder)—but it is therefore especially important for clinicians not to reach premature closure in their thinking about a psychiatric disorder that has not yet fully developed.

Several studies have examined prodromal symptoms in patients with unipolar depression. One[20] revealed that 4 symptom patterns emerged: (1) sudden-onset depressions, (2) gradual-onset depressions, (3) neurotic-onset depressions, and (4) "fluctuating-onset" depressions. About 30% of patients suffering from "depressive psychosis" showed a prodromal phase characterized by tension and vague feelings of anxiety.[20] Other prodromal symptoms included indecision and impaired concentration. In this study by Fava and Tossani,[20] each of the patients investigated reported having at least 1 prodromal symptom before the onset of a depressed mood. Generalized anxiety was present in 87% of the patients and irritability in 6%. Other common symptoms were impaired work initiative, fatigue, and initial and delayed insomnia.

First-Episode Versus Multiple-Episode Factors

First-episode and multiple-episode patients can differ in their phenomenology, prognosis, and treatment response. Because most bipolar patients have a depressive episode before ever having mania or hypomania, it is important to consider risk factors for eventual polarity conversion in first-episode major depression patients, particularly in youth. Although not universally applicable, a number of phenomenological and clinical changes across episodes have been identified that may be helpful in differentiation and earlier recognition of BP.

Psychosis and environmental stressors are typically more common in first-episode mania than in multiepisode disease. In a study[22] of the baseline and prodromal characteristics of first- vs multiepisode patients with BP, the univariate analysis showed that first-episode patients scored higher on measures of psychosis and euphoria on the Manic State Rating Scale. First-episode patients also had fewer mixed episodes than did the multiepisode patients, although the difference was not significant. However, the multiepisode patients had a higher baseline level of depressive symptom severity.[22] In a separate observational study[23] conducted in France comparing baseline characteristics and outcomes in first- and multiepisode patients, a higher percentage of mixed-episode patients had experienced a mixed episode before entry. Also in this study,[23] conducted in 13 European countries, past or current substance misuse was more common in patients experiencing their first manic episode.

Dr Goldberg related that you may do better with a particular treatment early on than later on, when more illness complications may accrue over time. Lithium, for example, has been shown to work better before multiple episodes have elapsed. Multiepisode patients sometimes experience a decline in their psychosocial functioning, potential multiple job loss, loss of social supports, and disability. Early recognition and intervention could improve the long-term outcomes for people living with these mood disorders. Clinicians want to prevent illness complexity and treatment resistance. Over time, persistent psychosocial problems can snowball into a worsening prognosis, and the goals of achieving and sustaining remission become all the more difficult and sometimes not possible.

Effect of MDD and BP Progression on Cognitive Function

While it is often believed that if progression happens, cognition should also decline in BP, there is no clear evidence that proves it.[24] Cognitive deficits occur throughout all stages of BP, although not all patients are equally affected.[25] Studies now suggest that cognitive decline is not inevitable, and, in fact, some patients may experience selective improvements in cognition after resolution of a first manic episode.[26] Findings from a meta-analysis[25] of longitudinal studies of cognitive deficits in BP show no evidence of significant decline in global cognitive function, phonemic fluency, backward digit span, or Stroop interference over a nearly 5-year period; these results add to the data contradicting the hypothesis that cognitive deficits are unavoidably progressive. Cognitive dysfunction may improve with treatment or resolution of depressive symptoms; however, cognitive deficits can still be detected in periods of symptom remission.[27]

Effect of MDD and BP Progression on Suicide Risk

Increased risk of suicide occurs with all mental disorders.[8] Evidence suggests it is particularly high in patients with BP, with the risk being at its highest in the early stages, and it has been estimated that half of all individuals who complete suicide meet criteria for MDD.[28] The analysis of an observational study[22] from France suggested a correlation between suicide attempts and the first episode of mania, occurring in the first year (odds ratio = 2.49 [95% CI, 1.45–4.28]). In a study[8] of the absolute risk of suicide in 176,000 individuals in Denmark who had already experienced their first psychiatric contact, the highest risk of suicide among men was in those diagnosed with BP (7.77%), while among women, the incidence of suicide was 4.7%. The risk increased steeply during the first few years, and, despite some leveling off, did not remain consistently stable until some 25 years after initial contact with health services.[8]

This ongoing risk necessitates steps to lessen suicidal ideation in patients with BP during the first few years of treatment and follow-up as well as ongoing vigilance, given that the risk remains for many years and is much higher than among people with no history of mental illness (cumulative incidence of 0.72%).[8] With MDD patients as well, earlier recognition and more effective acute and long-term treatment of depressive disorders are key elements in reducing suicide risk.[29]

Summary of Key Concepts

Start with a wide range of plausible diagnostic possibilities and narrow the list as you collect data. See patients more frequently at first, gather collateral information simultaneously from family members, and monitor suicidal intent or behavior. Keep a watchful eye on the evolution of symptoms over time, especially frequency and severity, comorbidity, and cognitive, particularly those that may precede affective symptoms. The longitudinal course tends to be more favorable for unipolar depression than BP.

Case Practice Question

Janice is a 36-year-old woman with a full confluence of depressive symptoms who has neither ideation of harm nor psychotic features. She mentions intermittent use of recreational cannabis. She also reports anxiety, distractibility, and significant anhedonia. Janice recollects the onset of her mood disorder as age 18 years. She has had 3 prior episodes of depression and has seasonal worsening of mood. Hyperphagia and hypersomnia are problematic because of significant associated weight gain and interference with day-to-day functioning. Which of the following features would suggest that Janice's depression is more likely to be bipolar disorder than major depressive disorder?

a. Onset in youth
b. Atypical depressive symptomatology
c. Higher episode frequency
d. All of the above

Preferred response: d. Persons with depression who have onset in youth, atypical depressive symptoms, and greater episode frequency are more likely to be experiencing BP than MDD.

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Clinical Recommendations

- Screen all patients for BP at first visit and subsequent visits if there are insufficient treatment outcomes
- Recognize the demographic factors and high-risk time periods (specifically look at age at onset and, more particularly, declaration of mood disorder associated with reproductive life event)
  - MDD is more common in women than men
  - BP is comparable across sexes
  - Onset in youth may be more likely in BP than MDD
- Family history may point more to a unipolar or a bipolar diathesis (family history provides suggestive evidence separating the diagnosis)
- Screening tools do not diagnose or make a differential diagnosis, but are a part of the initial interview
- A clinical evaluation is needed regardless of the results of a screening tool
- Ruling out secondary causes (medical and medication) is fundamental
- Lack of treatment response, especially to antidepressants, suggests potential BP
- When judging a nonresponse to a medication, or an observed worsening after a medication is begun, take into consideration factors such as inadequate dosing, poor adherence, or spontaneous worsening due to the natural course of illness
- Course of illness over time is the "great validator" of a suspected diagnosis
- Clinicians who remain alert to recognizable symptom constellations, relapse risk factors, psychosocial correlates, common comorbidities, and longitudinal course consistencies are in the strongest position to make a non-arbitrary, evidence-based differential diagnosis