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Review

Differential diagnosis of bipolar disorder and major depressive disorder

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ABSTRACT

Background: Patients with bipolar disorder spend approximately half of their lives symptomatic and the majority of that time suffering from symptoms of depression, which complicates the accurate diagnosis of bipolar disorder.
Methods: Challenges in the differential diagnosis of bipolar disorder and major depressive disorder are reviewed, and the clinical utility of several screening instruments is evaluated.
Results: The estimated lifetime prevalence of major depressive disorder (i.e., unipolar depression) is over 3 and one-half times that of bipolar spectrum disorders. The clinical presentation of a major depressive episode in a bipolar disorder patient does not differ substantially from that of a patient with major depressive disorder (unipolar depression). Therefore, it is not surprising that without proper screening and comprehensive evaluation many patients with bipolar disorder may be misdiagnosed with major depressive disorder (unipolar depression). In general, antidepressants have demonstrated little or no efficacy for depressive episodes associated with bipolar disorder, and treatment guidelines recommend using antidepressants only as an adjunct to mood stabilizers for patients with bipolar disorder. Thus, correct identification of bipolar disorder among patients who present with depression is critical for providing appropriate treatment and improving patient outcomes.
Limitations: Clinical characteristics indicative of bipolar disorder versus major depressive disorder identified in this review are based on group differences and may not apply to each individual patient.
Conclusion: The overview of demographic and clinical characteristics provided by this review may help medical professionals distinguish between major depressive disorder and bipolar disorder. Several validated, easily administered screening instruments are available and can greatly improve the recognition of bipolar disorder in patients with depression.

Contents

1. Introduction

Although mania and hypomania are the signature and most recognizable characteristics of bipolar disorder, depression is its most frequent clinical presentation. This is dramatically demonstrated in a long-term follow-up of 146 patients with bipolar I disorder, which found that nearly half of the time over 13 years patients were symptomatic in some fashion, overwhelmingly with depressive symptoms (Judd et al., 2002). Thus, nearly 40% of the time over 13 years, individuals with bipolar disorder were depressed. In contrast, patients were manic or hypomanic less than 10% of the time and without symptoms about half the time (Judd et al., 2002). The predominance of depressive compared with mood elevation symptoms was even greater when considering patients with bipolar II disorder (Judd et al., 2003).

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Bipolar patients are much more likely to present to clinicians, especially in outpatient settings, when they are depressed (Hirschfeld et al., 2005). However, unipolar depression is more prevalent than bipolar disorder: the lifetime prevalence of unipolar major depressive disorder is 16.2%, whereas the lifetime prevalence of bipolar spectrum disorders is 4.5% (Table 1) (Kessler et al., 2003; Merikangas et al., 2007). The clinical presentation of a patient with bipolar disorder when depressed may not differ from that of a non-bipolar depressed patient. In light of the higher prevalence of unipolar depression compared with bipolar disorder and the similarities in clinical presentation of a depressive episode in both unipolar and bipolar depression, without appropriate screening, bipolar patients may be misdiagnosed.

Several studies have addressed the prevalence of bipolar disorder in patients with depressive symptoms. In a general population sample of 85,358 US adults aged 18 or older, nearly 4% screened positive for bipolar disorder using the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2003a). Most of those who screened positive for bipolar disorder had never received a diagnosis of bipolar disorder, and nearly a third reported having been diagnosed with unipolar depression (Hirschfeld et al., 2003a). In a primary care clinic, 21% of patients being treated for depression screened positive for bipolar disorder, and nearly two-thirds of those patients reported they had never received a diagnosis of bipolar disorder before (Hirschfeld et al., 2005). The figures are somewhat higher for psychiatric samples, where estimates suggest that up to more than 49% of depressed patients may have bipolar disorder (Benazzi, 1997). This finding strongly confirms that there are many people suffering from bipolar disorder in depressed samples, most of whom are not recognized as being bipolar, suggesting that the true prevalence, as discussed above, may not be accurate.

2. Consequences of misdiagnosis

There are significant potential consequences of misdiagnosing a bipolar disorder patient experiencing a depressive episode as having unipolar depression and treating the patient as though he or she is suffering from a unipolar depression. In general, standard antidepressant therapy has not been shown to be effective in the treatment of depression episodes in patients with bipolar disorder, and treatment guidelines recommend using antidepressants only as adjunct therapy to mood stabilizers for bipolar depression (Goodwin, 2009; Yatham et al., 2013).

Several antidepressants, including paroxetine, imipramine, sertraline, fluoxetine and bupropion, have been studied as treatments for depression in bipolar disorder patients adjunctive with mood stabilizers. In general, with the important exception of fluoxetine in combination with olanzapine (Tohen et al., 2003), adjunctive use of these antidepressants has shown modest efficacy at best (Nemeroff et al., 2001; Post et al., 2001; Sachs et al., 2007). In the Systematic Treatment Enhancement Program for Bipolar Disorder trial, neither adjunctive (added to mood stabilizer or antipsychotic) paroxetine nor adjunctive bupropion was found to be more effective than adjunctive placebo in yielding sustained or transient recovery (Sachs et al., 2007). In a placebo-controlled study that evaluated monotherapy with paroxetine or quetiapine for the treatment of bipolar depression, paroxetine 20 mg/day was not found to be more efficacious than placebo, whereas quetiapine 300 mg/day and 600 mg/day was more efficacious than placebo (McElroy et al., 2010). Although antidepressants are widely used in the treatment of such patients (Baldessarini et al., 2008; Baldessarini et al., 2007; Ghaemi et al., 1999), these research studies do not support the efficacy of antidepressants alone or as adjunctive to mood stabilizers in the treatment of bipolar depression.

Table 1
Lifetime prevalence of bipolar disorders and major depressive disorder.

Disorder	Prevalence (%)
Bipolar disorder I	1.0
Bipolar disorder II	1.1
Subthreshold bipolar disorder	2.4
All bipolar disorders	4.5
Major depressive disorder	16.2

Data from Kessler, R.C. et al., 2003, JAMA 289 (23), 3095-3105; and Merikangas, K.R., et al., 2007, Arch. Gen. Psychiatry 64 (5), 543-552.

Whether the prescription of antidepressants for bipolar patients causes harm is a subject of considerable debate. Earlier studies indicated that antidepressants could cause an acceleration of mood cycles and an overall destabilization of patients with bipolar disorder in addition to precipitating a manic or hypomanic episode (Altshuler et al., 1995; Boerlin et al., 1998; Peet, 1994; Wehr et al., 1988). These studies involved the earlier antidepressants, particularly tricyclic antidepressants. More recent studies of the selective serotonin reuptake inhibitors (SSRIs) do not, in general, support destabilization or switch into mania (Sidor and MacQueen, 2011), at least with shorter-term treatment.

The overall conclusion from this research and the use of SSRI antidepressants in patients with bipolar disorder is that they in general are not particularly effective in terms of treating depression, but they may not be as dangerous as originally believed.

3. Identifying bipolar patients in depressed samples

The key clinical question at this point is how to identify patients with bipolar disorder among the patients presenting with symptoms of depression, to ensure that these patients receive proper treatment. There are several demographic and clinical characteristics that are more commonly observed in bipolar disorder compared with unipolar depression (Table 2) (Goodwin and Jamison, 2007).

Patients with bipolar disorder are much more likely to have a family history of bipolar disorder (Goodwin and Jamison, 2007). With regard to clinical course, patients with bipolar disorder typically have an earlier age of onset than those with unipolar depression. People with bipolar disorder have a mean age of onset of 22 years, whereas those with unipolar depression have an average age of onset of 26 years (Goodwin and Jamison, 2007; Zisook et al., 2007). Symptoms of bipolar disorder may occur even earlier in many patients: in one survey, nearly two-thirds of respondents said that they had significant symptoms of the disorder prior to age 19 (Hirschfeld et al., 2003b).

Those with bipolar disorder also are much more likely to have had a greater number of prior affective episodes and perhaps psychiatric hospitalizations than unipolar depressed patients (Goldberg and Harrow, 2004; Goodwin and Jamison, 2007). They are more likely to have a history of treatment-resistant depression. They may have had difficulties with antidepressant treatment, such as becoming more depressed or irritable or experiencing mood elevation symptoms during antidepressant treatment. In fact, they may have even shifted into mania or hypomania on antidepressants. Patients with bipolar disorder may display marked seasonality, most often experiencing depression during winter months. They may also have had more prior suicide attempts than patients with unipolar depression (Goodwin and Jamison, 2007; Rihmer and Kiss, 2002).

With regard to clinical presentation, individuals with bipolar disorder are more likely to display mood reactivity rather than simply sad mood (Goodwin and Jamison, 2007). There may be

Table 2
Possible indicators of bipolar disorder in depressed patients.

Family history of bipolar disorder
Earlier onset of illness (early 20's)
Seasonality
Numerous past episodes
History of psychiatric hospitalization
Mixed states
Mood reactivity
History of treatment-resistant depression
Switching on antidepressants
History of suicide attempt

Data from Goodwin, F.K., Jamison, K.R., 2007. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. 2nd ed. Oxford University Press, New York, NY.

symptoms associated with mania or hypomania during depressive episodes in this population, particularly increased motor activity, rapid or pressured speech, and grandiose or other delusions. Patients with bipolar disorder, when depressed, are more likely to experience "inverse" neuro-vegetative symptoms, particularly hypersomnia, weight gain, and increased appetite. They also are more likely to be psychotic (Goodwin and Jamison, 2007) and have cognitive impairment (Borkowska and Rybakowski, 2001; Wolfe et al., 1987). Conversely, patients with unipolar depression are more likely to experience typical depressive symptoms including insomnia, sad mood, and somatic depressive and anxiety symptoms (Goodwin and Jamison, 2007).

4. Screening for bipolar disorder and measures of depression

Recognition of bipolar disorder in patients with depression may be improved by using screening instruments (Table 3). The most widely used screening instrument for bipolar disorder is the MDQ, a validated self-rated questionnaire that screens patients for bipolar disorder; however, it is not a diagnostic instrument (Hirschfeld et al., 2000).

The MDQ consists of 15 questions and takes approximately 5 minutes to complete (Hirschfeld et al., 2000). The first 13 questions are designed to identify manic or hypomanic symptoms the patient may have experienced in the past. The last 2 questions assess symptom clusters and functional impairment. Patients who answer yes to at least 7 of the first 13 questions and the symptom cluster question, as well as "moderate problem" or "serious problem" on the functional impairment question, are considered to be a positive screen for bipolar disorder. The MDQ had a sensitivity of 0.73 and a specificity of 0.90 in a validation study of 198 psychiatric outpatients, indicating that the MDQ can correctly identify almost three-quarters of patients with bipolar disorder and will screen out bipolar disorder in 9 of 10 patients without the condition (Hirschfeld et al., 2000). It has been widely used throughout the world, having been translated into 19 languages and cited in more than 600 publications.

The Hypomania/Mania Symptom Checklist (HCL-32), another validated self-report screening tool for bipolar disorder (Angst et al., 2005), has 2 introductory questions, the first on the subject's current emotional state, and the second on the subject's usual level of activity, energy, and mood. Following this are 32 questions, most of which address specific symptoms of mania and hypomania. Other HCL-32 questions are more general, including questions on whether patients get into more quarrels, drink more coffee or alcohol, or smoke more cigarettes when they are in a manic state. A score is calculated by summing the number of positive responses to the 32 questions in the third section. A score of 14 or greater is considered positive for bipolar disorder. The HCL-32 has a sensitivity of 0.8 and a specificity of 0.51 (Angst et al., 2005).

Both the MDQ and the HCL-32 are validated, useful screening instruments for bipolar disorder. The MDQ was introduced earlier and has been more widely used than the HCL-32, and may be preferred because it is shorter and can be completed more quickly.

Another widely used self-report instrument that can be completed very quickly is the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a multi-purpose instrument used for screening, diagnosing, monitoring, and measuring the severity of depression (Spitzer et al., 1999). It has 9 questions, some of which incorporate Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnostic criteria, along with others describing other symptoms of major depressive disorder (such as decreased interest or pleasure, loss of appetite, and poor energy). Each question is graded from zero to 3, depending on the frequency of a symptom. A total score is calculated by adding the responses to each of the 9 questions, indicating a categorization of no depression to severe depression (Spitzer et al., 1999).

The most important differences between the PHQ-9 and both the MDQ and HCL-32 are the symptoms assessed and when these symptoms occurred. The MDQ and HCL-32 focus on assessing lifelong symptoms of mania and hypomania, while the PHQ-9 assesses current depressive symptoms (Angst et al., 2005; Hirschfeld et al., 2000; Spitzer et al., 1999). The PHQ-9 has a sensitivity of 88% and a specificity of 88% for major depressive episodes (Kroenke and Spitzer, 2002; Kroenke et al., 2001), but does not address the challenge of distinguishing bipolar disorder from major depressive disorder.

There are several other instruments available to assess the occurrence and severity of depressive symptoms. The Beck Depression Inventory (BDI), developed by Aaron Beck, was originally published in 1961 (Beck et al., 1961) and revised in 1996 to align with DSM-IV diagnostic criteria for major depressive disorder (Beck et al., 1996a). The main version consists of 21 questions reflecting the symptoms of depression, with responses ranging from zero to 3 on degree of severity. Examples of questions include: "I am sad all the time," "I am disappointed in myself," and "I am too tired or fatigued to do most of the things I used to do" (Beck et al., 1996b). These responses are summed to create a total score, which then will translate into diagnosis of minimal to severe depression (Beck et al., 1961). The original BDI and other variations of it have also been used very widely in clinical and research settings.

The Inventory of Depressive Symptomology (IDS-SR) was developed by John Rush and colleagues to provide a more sensitive measure for assessing depression in outpatients than the Hamilton Depression Rating Scale (HAM-D) (Rush et al., 1996). Originally 28 items (Rush et al., 1986), the current version is a 30-item self-report scale that includes 2 additional questions assessing the atypical features included in DSM-IV and was validated in 1996 (Rush et al., 1996). Details on a 16-item Quick Inventory of Depressive Symptomology (QIDS), also developed by Rush and colleagues, were first published in 2003 (Rush et al., 2003). Similar to the other self-report inventories, the IDS and the QIDS include items that assess symptoms of depression such as waking up too early, energy level, and thoughts of death or suicide (Rush et al., 1996; Rush et al., 2003). The IDS and the QIDS were developed to provide equivalent weightings for each symptom item (other scales have variable weights), clear anchors for symptom frequency and severity, inclusion of all symptoms in the DSM-IV major depressive episode criteria, and to provide parallel clinician-rated and patient-rated scales (Rush et al., 1996; Rush et al., 2003).

The PHQ-9 is probably the best choice for general patient screening for depression because of its brevity and widespread use. The BDI is more sensitive to change in clinical state and,

Table 3
An overview of screening tools for bipolar disorder and depression.

	Type of Scale	Number of Questions	Duration	Scoring Algorithm
Bipolar Scales				
Mood Disorder Questionnaire (Hirschfeld et al., 2000)	Self-report	15	<10 minutes	Yes >7 of the first 13 questions and the symptom cluster question, as well as "moderate problem" or "serious problem" on the functional impairment question, = positive screen for bipolar disorder
Hypomania/Mania Symptom Checklist (Angst et al., 2005)	Self-report	32 (plus 2 unscored introductory items)	<15 minutes	Total score ≥14 = potentially bipolar
Depression Scales				
Patient Health Questionnaire (Spitzer et al., 1999)	Self-report	9	<5 minutes	Total score 5–9 = minimal symptoms Total score 10–14 = mild depression Total score 15–19 = moderately severe depression Total score >20 = severe depression
Beck Depression Inventory-II (Beck et al., 1996b)	Self-report	21	<10 minutes	Total score 0–9 = minimal depression Total score 10–18 = mild depression Total score 19–29 = moderate depression Total score 30–63 = severe depression
Inventory of Depressive Symptomology (IDS) and Quick Inventory of Depressive Symptomology (QIDS) (Rush et al., 1996; Rush et al., 2003)	Self-report or clinician-rated	30 (IDS) 16 (QIDS)	<15 minutes (IDS) <7 minutes (QIDS)	Total scores 0–13 (IDS)/0–5 (QIDS) = none 14–25 (IDS)/6–10 (QIDS) = mild 26–38 (IDS)/11–15 (QIDS) = moderate 39–48 (IDS)/16–20 (QIDS) = severe 49–84 (IDS)/21–27 (QIDS) = very severe
Hamilton Depression Rating Scale (Hamilton, 1960)	Clinician-rated	21 (score 1st 17 only)	<20 minutes	Total score 0–7 = normal Total score 8–13 = mild depression Total score 14–18 = moderate depression Total score 19–22 = severe depression Total score ≥23 = very severe depression
Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979; Snaith et al., 1986)	Clinician-rated	10	<15 minutes	Total score 0–6 = absence of symptoms Total score 7–19 = mild depression Total score 20–34 = moderate depression Total score 35–60 = severe depression

therefore, may be more useful for monitoring these clinical states in depressed patients. Although the IDS is much less well-known than the BDI, it is more balanced in terms of symptom contributions and may be more sensitive than the BDI to changes in clinical status.

There are 2 clinician-administered rating scales for depression that are used in both clinical and research settings: the HAM-D and the Montgomery-Åsberg Depression Rating Scale (MADRS). The HAM-D was developed by Max Hamilton in England more than 50 years ago (Hamilton, 1960). It requires a clinically experienced rater to provide numerical ratings on 21 depressive symptoms. Examples include depressed mood, feelings of guilt, and agitation (Hamilton, 1960). There are several different versions of the HAM-D with different numbers of items. It is the most widely used assessment instrument for clinician-rated depression in the world and has been used in many clinical trials.

The MADRS was developed by Montgomery and Åsberg nearly 40 years ago to be more sensitive to changes in depressed clinical state than the HAM-D, particularly for use in trials to test the efficacy of antidepressant medication (Montgomery and Åsberg, 1979). It consists of 10 clinician-administered items, each of which may be rated from zero to 6. Items include apparent sadness, reported sadness, lassitude, and suicidal thoughts (Montgomery and Åsberg, 1979). The MADRS also has been used very widely in research studies.

It is important to keep in mind that the PHQ-9, BDI, HAM-D, and MADRS do not address the bipolar versus unipolar diagnostic challenge.

5. Conclusion

Bipolar disorder is highly prevalent in samples of depressed patients and can easily be missed, which can have negative consequences. Careful clinical assessment, including screening for bipolar disorder by investigating whether there is a history of manic or hypomanic episodes (by using a scale like the MDQ), can help substantially with correctly identifying patients with bipolar disorder. Although there are multiple validated instruments to diagnose major depressive episodes, most do not address the bipolar versus unipolar diagnostic challenge.

Conflict of interest

For the period 10/1/2010 through 9/31/2013, Dr. Hirschfeld has received royalties from Jones & Bartlett. He also has been a consultant for Grey Healthcare Group, bioStrategies Group, Merck Manual Editorial Board, and Equinox Group. Additionally, he has received honoraria from Physicians Postgraduate Press, Inc, Health and Wellness Partners, Merck Manual Editorial Board, CME Outfitters, Letters & Sciences, Nevada Psychiatric Association, and CMEology.

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