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# Differentiating Bipolar Disorders from Major Depressive Disorders: Treatment Implications

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***Background.*** *Bipolar disorder is a highly prevalent mood disorder, frequently misdiagnosed as unipolar major depressive disorder.*
***Methods.*** *In order to summarize the historical and clinical features that may distinguish bipolar disorder and major depressive disorder, a MedLine search was conducted of all English-language articles published between 1996 and 2006 using the key search terms bipolar disorder and manic-depression cross-referenced with major depressive disorder.*
***Results.*** *Better methods for arriving at the correct diagnosis of bipolar disorder include a clinical history that evaluates symptoms beyond narrow DSM-IV criteria and the use of self-reported screening tools. Twenty-six separate features were identified that are believed to aid in the differentiation of bipolar disorder from unipolar major depressive disorder.*
***Conclusions.*** *It is estimated that as many as 1 in 5 depressed outpatients may have undeclared bipolar disorder. Recognition of bipolar disorder can be improved by increasing the clinical acumen of diagnosticians and through the use of screening tools.*

**Keywords** Bipolar disorder, Major depressive disorder, Treatment, Antidepressants

## *INTRODUCTION*

Bipolar disorder (BD) affects approximately 2.6% of the population according to the National Comorbidity Survey-Replication, a recently completed large-scale epidemiologic study of psychiatric disorders in the United States (1). When the full spectrum of BD is considered, the prevalence may be approximately 6% (2). During the past decade, it has been increasingly recognized that depressive symptoms and episodes dominate the longitudinal course of BD, and when compared to mania are associated with greater loss of work productivity and more severe impairments in social and family relationships (3). Despite the upward revision of the estimated lifetime prevalence of BD in epidemiological and clinical settings, under-recognition and failure to diagnose BD remain modifiable deficiencies (4–6).

There is no pathognomonic feature or biomarker to reliably differentiate bipolar depression from other psychiatric disorders, particularly unipolar major depressive disorder (MDD; 7, 8). Consequently, several investigations have reported on sociodemographic and clinical features that can aid clinicians in the diagnostic process (9– 12). Diagnostic clarification is of more than subsidiary importance as the treatment for MDD differs from the treatment for BD. Moreover, extant data indicate that antidepressant monotherapy may worsen the course of BD by promoting rapid-cycling or an increased rate of switching into mania or hypomania (13, 14).

In contrast to Kraepelin's unification hypothesis which conceptualized depression and manic-depression as a single,

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disorder (15), several factors have provided the impetus for disaggregating and categorizing mood disorders as separate and distinct entities. For example, results from descriptive phenomenological studies by Angst (16), Perris (17), Leonhard (18) and others have indicated that the clinical presentation, course, natural history, and response to somatic therapies differ between "unipolar" and "bipolar" disorder. Moreover, the introduction of rule-based classification schemas (e.g., Diagnostic and Statistical Manual (DSM)) as well as the development of novel pharmacological treatments has provided further basis for the accurate classification of BD as a distinct clinical entity.

The primary aim of this review is to summarize clinical features that may distinguish BD and MDD. In addition, we review operating characteristics of available screening tools for BD and briefly discuss treatment implications in the management of depressive syndromes.

## *METHODS*

A MedLine search of all English-language articles published between 1996 and 2006 was conducted using the key search terms bipolar disorder and manic-depression cross-referenced with major depressive disorder. The search was supplemented with a manual review of relevant article reference lists. Articles selected for review were determined by author consensus based on the adequacy of sample size, the use of standardized diagnostic instruments, validated assessment measures, and overall manuscript quality.

## *RESULTS*

### *Underdiagnosis of Bipolar Disorder*

Depression is the index presentation of BD in the majority of individuals affected (19). In keeping with this view, timely and accurate diagnosis of BD and differentiation from MDD and other psychiatric disorders is warranted. Depressive symptoms and episodes tend to dominate the longitudinal illness course regardless of the bipolar subtype (type I or II) (20). Patients with BD are also more likely to utilize health care services for the evaluation and treatment of depressive symptoms as compared with manic symptoms, necessitating reliance upon the elucidation of historical mania or hypomania to make a correct diagnosis (21). Such histories are often difficult to establish, especially the occurrence of past hypomanic episodes, which may not be recognized by the patient as abnormal. Several surveys have reported protracted delays between the onset of symptoms, the seeking of treatment, and the establishment of an accurate diagnosis of BD.

For example, approximately 70% of individuals responding to the National Depressive and Manic Depressive Association constituent survey reported incorrect earlier diagnoses (most often MDD). In approximately one-third of patients with BD, it took nearly a decade or longer to arrive at the correct diagnosis (22,23). This 10-year gap prior to BD diagnosis has also been reported in an Australian study (24). Early detection of BD provides an opportunity to reduce the hazardous effects of the illness on personal, social and occupational function.

Results from studies evaluating patients in primary care as well as outpatient psychiatric settings indicate that approximately 20% of outpatients diagnosed and/or treated for MDD screened positively for BD (25,26). Anecdotally, many practitioners have encountered depressed patients for whom the diagnosis of BD was later determined after in-depth probing for subtle clues of past hypomanic episodes, collection of collateral information from family members, or the passage of months or years of caring for the patient before diagnostic clarity emerged. It is therefore imperative that better methods for arriving at the correct diagnosis be advanced in order to potentially decrease the added morbidity and mortality associated with delays in its recognition and diagnosis.

### *Screening for Bipolar Disorder*

The use of screening procedures has been demonstrated to enhance awareness and possibly detection of BD (27). Although screening for a psychiatric disorder should not supplant a thorough history obtained by an experienced clinician, screening instruments can be used as a tool to aid in confirming or disconfirming the diagnosis in question. Screening tools require careful interpretation as well as recognition of their operating characteristics (e.g., sensitivity, specificity). Although the operating characteristics of a validated structured diagnostic interview (e.g., Structured Clinical Interview for DSM, Mini-International Neuropsychiatric Interview) are superior to a screening instrument, they are too lengthy and cumbersome for real world application.

The Mood Disorder Questionnaire (MDQ) is a validated screening instrument for BD that presents a checklist of manic/hypomanic symptoms derived from DSM-IV and clinical experience (6,27). Respondents are asked to either endorse or deny experiencing the symptoms at any point during their lifetime. Those endorsing sufficient numbers of experienced symptoms must also endorse having symptoms occur or cluster together in time, as well as cause significant dysfunction to be considered a positive screen. Recently, the MDQ has been validated as a screening instrument in an adolescent population through parent report of their adolescent's symptoms (28). The sensitivity of the MDQ improves from 0.28 in the community adult population to 0.73 in the adult outpatient psychiatry setting, while the specificity remains $\geq 0.90$ across both settings (6, 27). The MDQ is available at no cost and versions have been published in both English and Spanish.

An alternate screening tool, the Bipolar Spectrum Diagnostic Scale (BSDS) (29) is a simple-to-use, one-page story depicting typical mood swings experienced by patients and instructs them to place a check-mark at the end of each

sentence which comports with his or her own experience. Validation of the BSDS was accomplished in an adult outpatient psychiatric population where the sensitivity and specificity was 0.73 and 0.90, respectively (29).

The sensitivity of the MDQ is lower for the detection of bipolar II as compared with bipolar I disorder (30). In an attempt to improve recognition of bipolar II disorder, a self-report questionnaire known as the Hypomania Checklist-32 (HCL-32) has also been developed (31). A preliminary study documented the sensitivity and specificity for differentiating BD from MDD to be 0.80 and 0.50, respectively. Yet, the instrument could still not reliably discriminate between bipolar subtypes. Administration to larger and more diverse samples is necessary to determine whether the HCL-32 provides added utility over existing screening tools.

As mentioned previously, the clinical utility of screening tools must be approached judiciously. Screening tools do not supplant a thorough and comprehensive patient evaluation. The positive predictive value of each of these scales is less than 100%, underscoring the need for ongoing surveillance for clinical presentations commensurate with BD. Indeed, the MDQ has been reported to be less useful in patients with impaired insight and milder bipolar spectrum disorders (30).

Several investigators have recently addressed the issue of predictive value of screening tests in BD, examining both the MDQ and BSDS (30). When clinicians administer a screening tool to patients, a positive screen is much more likely to represent a "true positive." In such circumstances, the screening instrument will carry a higher positive predictive value (PPV) than when administered at random, such as when every patient in a clinician's waiting room is asked to complete a screen. In this latter scenario, more false positives will be present and will serve to lower the PPV of the test. Similarly, a negative screen would much more likely be truly negative and hence "rule out" BD when clinicians employ the instrument in the context of a larger diagnostic process. Investigators therefore noted that "any improvement in clinicians' ability to form an accurate 'hunch' will improve the performance of these tests" and advocate for efforts to improve recognition and interpretation of clinical clues for the presence of BD.

## *CLINICAL CLUES TO BIPOLAR DISORDER*

Based on DSM criteria, the diagnosis of BD requires a distinct period of mania or hypomania. When patients present in states of mania or hypomania, the diagnosis of BD is often apparent. However, in the context of a major depressive episode, DSM criteria do not reliably differentiate BD from MDD (unless the patient is experiencing a mixed episode). Given the predominance of depressive symptoms in BD, the initial and foremost feature suggesting BD is the presence of a depressive episode.

Attempts to differentiate bipolar from unipolar depression based on clinical, biological, genetic, or treatment variables, have proven insufficient with respect to accurately parsing out the patient with BD from those with MDD. Awareness of those factors that have been associated with, or tend to be observed in BD, serves as an important initial step in affirming and or refuting a diagnosis of BD. Table 1 lists clinical and familial features indicative of BD.

The historical course of the mood disorder may itself be a diagnostic clue. The age at onset of BD is earlier relative to MDD. The age of onset for MDD is typically in the mid to late 20s (mean age 25.6 years), while the index episode of BD appears in the late teens to mid 20s (mean age 18.1 years) (32). Patients with BD also evince more frequent episodes as well as a briefer well-interval between episodes.

A family history of BD is more likely documented in patients with BD relative to those with MDD. It is reported that the presence of any mood disorder in three or more first-degree relatives is indicative of family loading and should heighten the suspicion for BD (33). Complex polygenetic factors are hypothesized to contribute to the vulnerability of BD. Preliminary evidence indicates that BD subtypes are inherited within families.

For example, bipolar I is more common than bipolar II in relatives of subjects diagnosed with bipolar I disorder; whereas the converse is true for probands with bipolar II disorder (34,35). Although an increased rate of BD is reported among family members of bipolar probands, the most commonly inherited mood disorder is MDD (34,35). The presence of an extensive family history of BD in a patient with criteria for major depression, even in the absence of a prior mania or hypomania, should alert the clinician to the higher risk of bipolarity emerging in this particular patient. Opportunistic screening for BD is warranted in any depressed patient particularly in those with positive family history.

In individuals presenting with depression, a past history of chaotic psychosocial events and developments, multiple jobs, multiple marriages, multiple geographic relocations, bankruptcies, and overall unpredictability of behaviors might be more indicative of BD than MDD. Taken together, many of these anamnestic events represent the chaos and unpredictability of BD.

The presence of medical comorbidities in the depressed patient may provide further evidence suggestive of BD. Results from the recent Canadian Community Health Survey (N=36,984) indicated that among the 2.4% of individuals with a lifetime history of a manic episode, the rates of chronic fatigue syndrome, asthma, chronic bronchitis, hypertension, gastric ulcer, multiple chemical sensitivities, and migraine headache were significantly higher than those without a past episode of mania (36). Bipolar individuals with medical comorbidities were much more likely to experience psychosocial distress or dysfunction and to utilize healthcare services. The greater medical burden in patients with BD may account for an observed mortality rate that is approximately twice as high as individuals in the general population (37).

**Table 1** Clues in the Differential Diagnosis of BD from MDD

| Characteristic | Bipolar | MDD (unipolar) |
|---|---|---|
| Family history of BD (34,35) | High | Low |
| Family history of unipolar MDD (34,35) | High | High |
| Age of onset (32) | Teens and 20's | Over 30 years |
| Sex Ratio (32) | Equal | Women > Men |
| Substance abuse (38) | High | Moderate |
| Seasonality (61) | Common | Occasional |
| Postpartum episodes (4,62) | More common | Less common |
| Episode onset (4) | Often abrupt | More subtle |
| Episode frequency (4) | High | Low |
| Recurrent major depressive episodes (> 3) (4) | Typical | Unusual |
| Atypical features when depressed (42) | More common | Less common |
| Rapid on/off pattern (4) | Typical | Unusual |
| Brief major depressive episodes (< 3 months) (4) | More common | Less common |
| Psychotic features under age 35 (4,63) | More common | Less common |
| Psychomotor activity (4) | Retardation > agitation | Agitation > retardation |
| Sleep (46) | Hypersomnia > insomnia | Insomnia > hypersomnia |
| Treatment-refractory depression (4) | More common | Less common |
| Short-lived antidepressant efficacy (4) | More common | Less common |
| Risk for antidepressant-induced mania or hypomania (4) | High | Low |
| Mixed features (hypomanic symptoms while depressed) (43,46) | Predictive | Rare |
| Comorbid anxiety (26) | Very common | Common |
| Recent depression diagnosis (26) | Possibly predictive | Common |
| History of legal problems (26) | More common | Less common |
| Feelings of people being unfriendly (26) | More common | Less common |
| Irritability and anger (43,45) | More common | Less common |
| Medical comorbidities (migraine, asthma, chronic fatigue, chronic bronchitis, hypertension, gastric ulcer) (64) | More common | Less common |

Compared with MDD, individuals with BD are much more likely to report a history of alcohol or substance use disorders (38). Bipolar disorder, relative to other psychiatric disorders, is associated with the highest lifetime rate of substance abuse or dependence, affecting approximately 60% of patients (38). Although the complexities of differentiating substance-induced mood disorders from primary mood disorders can be challenging, the clinician should make every effort to delineate a chronological history of mood and substance use. Since the majority of patients with BD have a current or past alcohol and/or substance abuse problems, some admixture of primary mood and substance-induced or substance-aggravated mood symptoms should be expected as the rule, rather than the exception.

Response to conventional antidepressants may provide further ancillary information salient to differentiating bipolar from unipolar depression. Patients with BD may be more likely to experience highly variable responses to antidepressants including inefficacy, transient response, poor tolerability and possible mobilization of manic symptomatology (39).

Failure to respond to an antidepressant, regardless of number of prior failures, should draw attention to the possibility of a covert bipolar presentation. For example, the results of a recent, 60-site study including 602 individuals treated for MDD by their outpatient psychiatrist documented that the rate of MDQ-positive screening was unaffected by the number of failed antidepressant trials or regimens (26). Nearly 20% of these depressed patients were found to be at risk for BD based on a positive MDQ. The PPV of the MDQ in this depression cohort was enhanced by the clinical suspicion of BD. In this study, the average number of failed antidepressants was three, but the rate of positive screens did not significantly change based on the number of antidepressant failures.

The results of this study underscore the dictum that any depressed patient manifesting insufficient response to antidepressant therapy and/or incapable of tolerating treatment should be carefully screened. The risk of prescribing antidepressants to individuals who have undiagnosed BD is the possibility of precipitating manic switches and continued delay in the establishment of the appropriate diagnosis and initiation of mood stabilizer therapy. Practitioners should have a higher index of suspicion for the presence of BD in depressed patients who have failed conventional antidepressant(s) and have recent onset of problems with depression (within 5 years), comorbid anxiety, a family history of BD, a history of legal problems, and feelings of people being unfriendly towards them. This latter risk factor may represent a learned cognition arising from impaired and/or tempestuous prior relationships.

A further tactic to differentiate BD and MDD is to characterize longitudinal course of illness in addition to cross-sectional phenomenology. Individuals with BD are differentially affected by atypical depressive symptoms (40,41). Consistent

with this finding, Perugi and colleagues reported that 72% of patients with atypical depression had a bipolar spectrum disorder (42). Mixed depressive episodes (e.g., depressive mixed states) have also been reported to differentially affect bipolar versus unipolar depression (43). Although not a formal diagnosis in DSM-IV, mixed depression is a frequently encountered phenotype that has recently been empirically validated (44). A depressive mixed state is postulated to exist when intradepressive non-euphoric manic or hypomanic symptoms intrude into an episode of major depression (43,44). A threshold of at least three manic symptoms has been frequently operationalized as a minimum definition for mixed states. Often reported symptoms include irritability, mental overactivity, and behavioral activation (43,45).

In addition to atypical and mixed depressive episodes, the greater instability of the clinical portrait of bipolar depression may suggest a diagnosis of BD. Bipolar depression tends to be more intense, more unstable, more clinically complex, and less predictable in course than its unipolar counterpart. This "tempestuous" nature may be a signature for bipolar depression, particularly in bipolar II disorder where despite hypersomnia patients may remain excessively psychomotor activated (46). Enhanced clinical acumen, not simply use of screening tools, is needed in order to minimize missing the diagnosis of BD in depression.

### *Diagnostic-Treatment Implications*

A review of existing treatments of BD is beyond the scope of this article (interested readers are encouraged to review recently published guidelines) (47,48). Evidence-based guidelines that address treatment options and algorithms have been published extensively and continue to receive updates as emerging data changes directions of treatment. The use of guidelines in the selection and sequencing of treatments improves the consistency, appropriateness, quality, and cost-effectiveness of treatment. Over the past decade approximately 12 evidence- and consensus-based guidelines have been published. Table 2 contains links to 4 of the most recent and well-known practice guidelines (47,49– 51).

The majority of guidelines published to date as well as expert consensus caution against the use of traditional antidepressant medications as monotherapy for acute bipolar depression. At issue is the possibility that antidepressants may cause manic switching or acceleration of cycling in patients with BD. To date, there has been no clear and convincing evidence that antidepressants are both safe and effective for acute bipolar depression. A recently conducted trial as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) initiative has recently been completed (52). In the STEP-BD trial, subjects with bipolar depression taking a mood stabilizer were randomized to either an antidepressant (paroxetine or bupropion) or placebo and followed for up to 26 weeks. The results of this trial indicate that adjunctive conventional antidepressants were not more effective than placebo and did not mobilize hypo/manic switches at a higher rate than placebo.

As of May 2007, only quetiapine (53,54) and the combination of olanzapine/fluoxetine (55) have been US-FDA approved for the treatment of bipolar depression. Lithium, lamotrigine, other atypical antipsychotics and a few select anticonvulsants (carbamazepine, valproate) used alone or in combination with conventional antidepressants are also recommended by many guidelines although their evidence is less robust.

Diagnostic implications can be found in the patterns of response or non-response to traditional antidepressant treatment. Conventional wisdom suggests that patients being treated with antidepressant medication(s) who manifest manic symptoms have BD. Antidepressants do carry a risk of switching patients into mania or hypomania. However, the evidence for which particular antidepressants may be more hazardous remains limited. Noradrenergic antidepressants may be associated with a higher switch risk liability, as both desipramine and venlafaxine have been shown to induce mood switch to a greater frequency than other antidepressants (14,56–58). During the acute and continuation management of bipolar depression with adjunctive antidepressants, venlafaxine was shown to have a three-fold higher ratio of threshold switches to subthreshold hypomania in comparison to treatment with bupropion (58). It has been estimated that between one-quarter to one-third of patients with BD may be susceptible to hypo/manic switching while receiving antidepressants, with elevated risk particularly in those with a prior history of antidepressant-induced switching, a family history of BD, and exposure to multiple antidepressant trials (59). Bipolar II patients are less likely to switch than bipolar I patients (60).

Some patients with undiagnosed BD may exhibit an adequate response to an antidepressant medication and in this case no notable difference from MDD can be detected at this chronological point. However, as with the spectrum of diagnostic

**Table 2** Evidence Based Guidelines for Bipolar Depression

| Guidelines | URL |
|---|---|
| Texas Implementation of Medication Algorithms (TIMA) | http://www.dshs.state.tx.us/mhprograms/TIMABDalgos2005.pdf<br>http://www.dshs.state.tx.us/mhprograms/TIMA.shtm |
| Canadian Network for Mood and Anxiety Treatments (CANMAT) | http://www.canmat.org/resources/PDF/Bipolar_Guidelines.pdf |
| American Psychiatric Association Practice Guidelines | http://www.psych.org/psych_pract/pract_mgmt/apapractguidecme.cfm |
| British Association for Psychopharmacology Consensus Group | http://www.bap.org.uk/consensus/FinalBipolarGuidelines.pdf |

issues, so too can be the responses seen to antidepressants in BD ranging from adequate response to rapid mobilization of mania.

Patients with BD in the depressed phase may be more likely than their counterparts with MDD to experience either treatment-refractory depression or more commonly short-lived or partial responses to antidepressant agents (39). The depressed patient who has an immediate but non-sustained improvement in neurovegetative symptoms while receiving an antidepressant may be at elevated risk for BD. Clinicians should be particularly alerted by depressed patients with a pattern of such transient or incomplete responses to antidepressants. Although there are reports in the literature of rather dramatic manic reactions and/or induction of rapid cycling in association with antidepressant usage in misdiagnosed patients with BD, clinical experience would suggest that more commonly these patients simply do not respond to the treatment.

If untoward activation occurs when antidepressants are prescribed, irritability, agitation, and anxiety are frequently reported. Rarely is the feeling induced a comfortable or pleasant one, for the patient and for those in contact with the patient. Previously docile and negativistic, these antidepressant-induced "stirrings" produce changes in energy, sleep, thought, and mood that can be mistaken for agitation, irritability, or psychosis. Although the addition of pharmacotherapies such as antipsychotics or benzodiazepines may commonly be used by clinicians not suspecting bipolarity, removal of the antidepressant alone may quickly ameliorate the unwanted "stirrings." Unfortunately, in many cases, these individuals are often treated with dose-optimization and/or combination treatment strategies on the basis that they are poorly responsive to treatment. This course of action may aggravate the clinical presentation, producing more severe manic reactions and increases the risk for suicidality.

## *CONCLUSION*

Bipolar disorder is popularly discussed and commonly misdiagnosed as MDD, despite increasing attention to the topic and much debate over the issue. Although not conclusive, based on recent studies it can be estimated that as many as 1 in 5 depressed outpatients may have BD (25,26). Recognition of BD can be improved by the systematic use of simple screening tools as well as a thorough clinical evaluation at index visit with ongoing vigilance for clinical presentations suggestive of BD. Increasing recognition of "less than manic" presentations as well as a variable expression of bipolar spectrum disorders provides an opportunity for timely diagnosis in the initiation of guideline-concordant care.

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