# "Cade's Disease" and Beyond: Misdiagnosis, Antidepressant Use, and a Proposed Definition for Bipolar Spectrum Disorder

**S Nassir Ghaemi, MD[1], James Y Ko, AB[2], Frederick K Goodwin, MD[3]**

The diagnosis and treatment of bipolar disorder (BD) has been inconsistent and frequently misunderstood in recent years. To identify the causes of this problem and suggest possible solutions, we undertook a critical review of studies concerning the nosology of BD and the effects of antidepressant agents.

Both the underdiagnosis of BD and its frequent misdiagnosis as unipolar major depressive disorder (MDD) appear to be problems in patients with BD. Underdiagnosis results from clinicians' inadequate understanding of manic symptoms, from patients' impaired insight into mania, and especially from failure to involve family members or third parties in the diagnostic process.

Some, but by no means all, of the underdiagnosis problem may also result from lack of agreement about the breadth of the bipolar spectrum, beyond classic type I manic-depressive illness (what Ketter has termed "Cade's Disease"). To alleviate confusion about the less classic varieties of bipolar illness, we propose a heuristic definition, "bipolar spectrum disorder." This diagnosis would give greater weight to family history and antidepressant-induced manic symptoms and would apply to non-type I or II bipolar illness, in which depressive symptom, course, and treatment response characteristics are more typical of bipolar than unipolar illness.

The role of antidepressants is also controversial. Our review of the evidence leads us to conclude that there should be less emphasis on using antidepressants to treat persons with this illness.

(Can J Psychiatry 2002;47:125–134)

***Key Words:*** *bipolar disorder, manic-depressive illness, antidepressants, diagnosis, treatment, nosology, mood stabilizers*

Misdiagnosis and consequent mistreatment of bipolar disorder (BD) are potentially life-threatening issues for patients, yet in contemporary practice there exist several potential inadequacies in the diagnosis of BD. A synergy of cultural and clinical factors results in its common misdiagnosis. Baldessarini has noted that the culture of modern medical practice appears to be guided by a "pharmacocentric view of the world" (1). This is to say that the rate of diagnosis of an illness, as well as scientific interest in a particular disease, is often increased following the introduction of new medications for it (2). Thus, the sheer number of antidepressants available may influence the diagnosis of unipolar major depression, often to the detriment of BD diagnosis. This may be exacerbated by the fact that virtually all patients with BD experience long periods of depression (3), which usually causes more subjective distress than does mania. As such, patients are more likely to seek help for depression than for mania. Given a growing awareness of the need to diagnose and treat depression, increases in depression research, and a rise in public interest, the underdiagnosis of BD is an understandable result. Further, limitations of the DSM-IV nosology may impede the diagnosis of BD, because the DSM-IV has rather broad criteria for MDD and narrow criteria for BD. Pharmacocentric logic may have helped to perpetuate the underdiagnosis problem, but it could also steer the mental health community in a new direction, with the emergence of a new generation of

mood-stabilizing agents derived from novel anticonvulsants and atypical neuroleptic agents.

## Underdiagnosis and Misdiagnosis of Classic Type I BD ("Cade's Disease")

*Empirical Evidence*

Even standard mania, bipolar I disorder, is prone to underdiagnosis, as reviewed below. Ketter has suggested using the term "Cade's disease" in honour of John Cade, the discoverer of lithium, to refer to classic, lithium-responsive, type I manic-depressive illness (Terence Ketter, 2002, personal communication). The Epidemiologic Catchment Area (ECA) study, upon which much of the conventional wisdom regarding the prevalence of BD is based, reported that mania and hypomania occur in 1.2% of the general population over a lifetime (4). This prevalence is about one-fourth that of major depression and somewhat higher than the prevalence of schizophrenia.

The 4 to 1 ratio of unipolar to bipolar disorder has been doubted by researchers specializing in BD. In a comprehensive review of the epidemiological literature, Goodwin and Jamison (3) estimated a 2 to 1 ratio of unipolar to bipolar disorder; in an epidemiologic study among the Amish, the observed ratio was 1 to 1 (5).

Follow-up studies on the diagnostic validity of the ECA study cast further doubt upon its findings. Anthony and associates found quite poor interrater agreement (kappa values) for Axis I psychiatric diagnoses in 1 of 5 cities in the ECA study (the Baltimore site). They used a gold standard of clinical reappraisal based on DSM-III criteria to reassess diagnoses made by the lay researchers using the Diagnostic Interview Schedule (DIS; a research diagnostic interview designed for use in the ECA [4,6]). In the ECA study, no kappa value exceeded 0.35, although conventionally acceptable kappas for epidemiological studies are generally above 0.70. Further, the kappa for mania was an abysmal 0.05. As such, in only 5% of cases in this sample were the data used in the ECA study confirmed by clinicians experienced in diagnosing mania. Helzer and colleagues reported similar findings at the St Louis ECA site (7). These problems with the ECA data were further highlighted by Dohrenwend (8). Robins, the developer of the DIS, also expressed concern about those findings (9). It is quite possible that the ECA data have contributed to the neglect of research on BD.

The Iowa 500 project (10) reported that consulting hospital charts resulted in increased diagnosis of mania in relatives of psychiatric probands. Surprisingly, even the most rigorous research-based clinical interview (mean duration, 102 minutes) underestimated the incidence of mania in relatives by almost one-third (morbidity risk 1.9 [SD 1.07] excluding hospital charts, compared with 5.3 [SD 1.73] including hospital charts). It is clear that many patients forget or deny past hospitalization for mania in the course of clinical interviews. In the absence of external sources of information (as was the case in the ECA study), the diagnosis of BD is probably underestimated. The frequency of BD misdiagnosis has been assessed in a few recent empirical studies. In 1 survey, 48% of the members of the National Depressive and Manic Depressive Association (NDMDA) reported that they had seen 3 or more mental health professionals before receiving a diagnosis of BD (11); 57% of the members received another major psychiatric diagnosis during that time most commonly unipolar major depressive disorder (MDD) (44%), followed by schizophrenia (34%). On average, it took 8 years of clinical treatment before the diagnosis of BD was correctly made. However, the results should be interpreted with some caution, because it is possible that people with poor treatment experiences are more likely to gravitate toward the NDMDA. Also, because the data are based on a self-report survey rather than a clinical interview, they may not be generalizable.

A second study examined the charts of all inpatients prospectively diagnosed with bipolar ($n$ = 44) or schizoaffective disorder ($n$ = 4) by a psychiatrist with expertise in affective disorders (12). These patients were diagnosed over 1 year, using DSM-IV criteria. Patient interviews and chart reviews were used to obtain referral diagnoses before hospitalization. Patients who had not previously sought psychiatric treatment, or were currently experiencing their first manic episode, were excluded. Nineteen (40%) were identified as having BD previously misdiagnosed as unipolar depression. Time to bipolar diagnosis after a patient's first contact with a mental health professional was 7.5 years (SD 9.8) in the total sample (vs 0.9 years [SD 2.2] in 25 patients who had already been diagnosed with BD). Mood stabilizers were underused and antidepressants overused in this patient population; on admission, only 38% of the total sample were taking mood stabilizers, and, notably, a similar number (33%) were taking antidepressants. Thus, systematic application of DSM-IV criteria identified previously undiagnosed BD in 40% of a referred population of patients with mood disorders; all these patients had previously been misdiagnosed with unipolar MDD. Because the sample consisted only of BD I, the underdiagnosis of BD could not be attributed to difficulty diagnosing hypomania.

A confirmation study was conducted, with a more detailed assessment of natural history and the effects of antidepressants on illness course (13). This outpatient study included patients with BD I as well as BD II and BD not otherwise specified (NOS) (according to Akiskal's criteria of either hypomania or mania occurring only with antidepressant use or a diagnosis of unipolar disorder and a first-degree relative with BD I [14]). The study assessed 54 patients with BD (BD I, $n$ = 27; BD II, $n$

= 11; BD NOS, *n* = 16) and found that about 7 years elapsed between the first visit to a mental health professional and the diagnosis of BD I. For BD II or BD NOS patients, about 12 years elapsed between first visit and diagnosis. In the total sample, major depressive episodes (MDEs) occurred about 5 years earlier than manic episodes and were more frequent than manic episodes. Patients spent about 50% of their lives with depression, compared with 11% of their lives experiencing manic or hypomanic symptoms. Of the sample, 57% had been diagnosed with unipolar MDD before being diagnosed with BD. When the authors controlled for patients who had received unipolar diagnoses due to MDEs occuring before the first manic episodes, 37% of patients were still misdiagnosed with unipolar MDD after the onset of their first manic or hypomanic episode. This appears to be the first true misdiagnosis rate established in a study of BD that took into account a simultaneous assessment of natural history factors.

*Clinician Failure to Recognize BD*

As suggested by these previous studies, disparities in clinician awareness of mania vs depression contribute to misdiagnosis. Sprock conducted a study of 20 clinicians (mostly psychiatrists) at an academic institution (15). To assess their diagnostic skill in distinguishing schizoaffective disorder from other mood disorders, she asked the clinicians to write all the symptoms of mania and depression that they could recall in the 3 minutes allotted for each. The clinicians displayed relatively greater knowledge of symptoms that are DSM criteria for major depression: 18 clinicians described sleep disturbance, 17 decreased appetite, 15 suicidal ideation, 11 anhedonia, and 10 decreased weight and libido. Conversely, for manic symptoms only 7 clinicians reported euphoria and grandiosity, symptoms that can be straightforwardly inferred as DSM criteria; 13 described sleep disturbance and 12, decreased sleep, neither of which reflects the exact criterion of decreased need for sleep. Twelve described depressed mood (which is not required for mania), and 8 each described "energy disturbance," cycling, and spending sprees. Energy is not always elevated in mania, cycling is a course criterion, and spending sprees are a subtype of 1 criterion. Thus, fewer than one-half of the clinicians described only 2 of the 7 cardinal DSM-IV manic criteria (euphoria and grandiosity), compared with the fact that most clinicians recalled most of the major depressive criteria. These results suggest that clinicians' inefficient assessment of manic symptoms results in misdiagnosis of patients.

*Lack of Insight Into Manic Symptoms Among Patients*

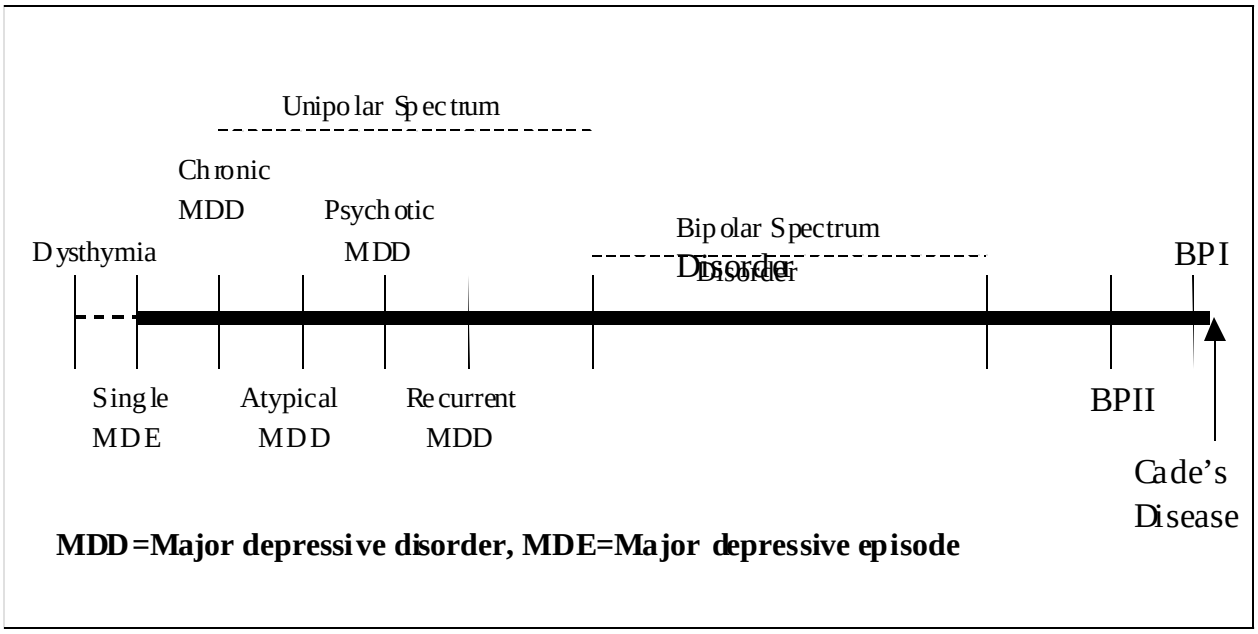
Apart from the shortcomings of clinicians' diagnostic skills, patients' lack of insight into mania also contributes to underdiagnosis of BD. Empirical studies published specifically on insight in BD were rare before 1994. Since then, however, 2 groups have noted that lack of insight is almost as prominent in mania as in schizophrenia, and it is less impaired in depression (16,17). Using different methods, the DSM-IV field trials also demonstrated that lack of insight is a major clinical finding in BD, one that is similar in severity to that in patients with schizophrenia, and more severe than in patients with psychotic depression (18). Because insight is more impaired in mania than in depression, reliance on patient self-report probably contributes to underdiagnosis of mania (as was alluded to in the discussion of the Iowa 500 project) and relative overdiagnosis of unipolar depression. Involving patients' families and caregivers in the diagnosis process and extending the collection of data beyond the patient to third parties is a possible solution to this dilemma. For example, in a study of prodromal symptoms of mania and depression, families reported behavioural symptoms of mania more than twice as frequently as patients (47% vs 22%) (19). This finding did not hold for depression, where families and patients reported similar symptom rates. Hence, the obfuscating effects of patients' impaired insight can be counteracted by obtaining family or third-party data (for example, from therapists, nurses, social workers, and residential staff). In our experience, most patients can identify at least 1 close family member or friend to whom they are willing to allow access for vital history taking. Lacking this, even the best psychiatric evaluations can be confounded by a patient's impaired insight. Concerns about confidentiality may be raised, but it is important to set up an expectation from the very beginning that the patient is entering a medical relationship, in which access to third parties for information is vital to proper treatment. This contrasts with a purely psychotherapy relationship, in which outside contact is commonly avoided.

## Is There a Bipolar Spectrum Beyond Type I Illness?

We have just reviewed evidence regarding underdiagnosis or misdiagnosis, mostly of BD I. We wish to emphasize that the problem of the misdiagnosis of BD occurs even with classic manic-depressive illness, what Ketter has termed "Cade's disease." In addition, however, there are possibly many less classic forms of bipolar illness, in which spontaneous mania or hypomania do not occur.

For over 2 decades, "soft signs" of bipolarity have been studied and discussed by Akiskal and others (14,20,21). A recent review of 6 studies done since 1978 suggests that broadening the BD diagnostic criteria to include other aspects of the bipolar spectrum (hypomania and cyclothymia) yields a higher prevalence range (3.0% to 8.8%) than is commonly believed (22). On the other hand, Baldessarini has pointed out the potential research pitfalls of such a broadening of the diagnostic spectrum (23). Baldessarini suggests that a broadening of bipolar diagnosis beyond conventional BD I disease may retard

**Figure 1.** The affective spectrum. Adapted from FK Goodwin, SN Ghaemi. *New Oxford Textbook of Psychiatry, 2000*(56). Cade's disease = classic manic-depressive illness, characterized by pure manic episodes and pure major depressive episodes, with extensive euthymic intervals and an excellent response to lithium (personal communication, Terence Ketter, MD, 2002)




our understanding of the illness and that biological and genetic studies may best proceed within more narrow diagnostic parameters. A consensus has yet to be reached on the approach to (and definition of) the bipolar spectrum.

Examining the underdiagnosis of BD naturally leads to a discussion of how broad the spectrum of bipolar diagnosis should be. Clinical and genetic data suggest that nonclassic parts of the bipolar spectrum (that is, BD II, NOS, and cyclothymia) may be more common than classic type I manic-depressive illness (21). In fact, as Grof has suggested, classic type I manic depressive illness may differ in many respects from less typical forms of bipolar illness, especially in being more lithium-responsive. It is this classic syndrome that Ketter has called "Cade's disease." Figure 1 suggests a possible conceptualization of these conditions on the affective spectrum. Bipolar spectrum conditions exhibit less severe mania, but they are not less severe in terms of depressive symptoms. Apart from the major morbidity and substantial suicide risk that these depressive symptoms present (3), varieties of BD produce unstable lives, failed careers, high divorce rates, and stormy biographies. Hence, we believe that the entire bipolar spectrum needs to be aggressively diagnosed and treated.

The problem of BD underdiagnosis is partly (although not entirely) related to failure to recognize bipolar spectrum states such as hypomania, assuming a version of the spectrum beyond full mania is accepted. Because hypomania is the only major DSM-IV diagnosis in which the essential criterion of social and occupational dysfunction is not required (and in fact, one must rule out significant social and occupation dysfunction), many clinicians find hypomania to be a difficult condition to diagnose. Thus, hypomania is mainly distinguished from mania based on function, rather than symptoms. Because the term "significant" is deliberately vague, psychiatrist identification of hypomania is not reliable (24). Given this situation, hypomania may be underdiagnosed as "normality," and mania may be underdiagnosed as hypomania.

Also, the complete focus on polarity found in the diagnostic schema of DSM-III/IV obscures the relation between bipolar and highly recurrent forms of unipolar depression. BD is diagnosed when mood elevation is present, and its place in the diagnostic schema implies a totally separate illness. However, phenomenologic studies dating back to Kraepelin put primary emphasis on illness course and considered cycling to be as important as polarity. Cases of recurrent depression may be more likely to have genetic characteristics and treatment responses similar to those encountered in BD (3). Patients presenting with mainly depressive symptoms may exhibit other clues to possible bipolarity, and these are outlined in Table 1.

Given the debate and confusion surrounding the bipolar spectrum, we propose here a heuristic definition based on these

**Table 1. Bipolarity: clues in the history**

1. Recurrent major depressive episodes (> 3)
2. Early age of onset of major depressive episode (< age 25)
3. Family history of bipolar disorder in first-degree relative
4. Hyperthymic personality (at baseline, nondepressed state)
5. Atypical depressive symptoms (DSM-IV criteria)
6. Brief major depressive episodes (on average, < 3 months)
7. Psychotic major depressive episodes
8. Postpartum depression
9. Antidepressant-induced mania or hypomania
10. Antidepressant "wear-off" (acute but not prophylactic response)
11. Lack of response to ≥ 3 adequate antidepressant treatment trials

Reprinted with permission. SN Ghaemi, JY Ko, FK Goodwin (57)

**Table 2. A proposed definition of bipolar spectrum disorder**

A. At least one major depressive episode

B. No spontaneous hypomanic or manic episodes

C. Either of the following, plus at least 2 items from criterion D, or both of the following plus 1 item from criterion D:
   1. A family history of bipolar disorder in a first-degree relative
   2. Antidepressant-induced mania or hypomania

D. If no items from criterion C are present, 6 of the following 9 criteria are needed:
   1. Hyperthymic personality (at baseline, nondepressed state)
   2. Recurrent major depressive episodes (> 3)
   3. Brief major depressive episodes (on average, < 3 months)
   4. Atypical depressive symptoms (DSM-IV criteria)
   5. Psychotic major depressive episodes
   6. Early age of onset of major depressive episode (< age 25)
   7. Postpartum depression
   8. Antidepressant "wear-off" (acute but not prophylactic response)
   9. Lack of response to ≥ 3 antidepressant treatment trials

Reprinted with permission. SN Ghaemi, JY Ko, FK Goodwin (57)

clues (Tables 1 and 2). We propose placing all versions of bipolar illness apart from BD I or II in a single category, labelled "bipolar spectrum disorder (BSD)." This is in contrast to others who have suggested types of bipolar illness (III-VI) beyond BD I and II (21,25). We envision that this BSD diagnosis might replace the current nonspecific DSM-IV diagnosis of BD NOS. We heuristically define BSD as a diagnostic category that possesses several of the potential signs of bipolarity listed in Table 1, with greater weight given to family history and antidepressant-induced manic symptoms (26). Even in patients that have not spontaneously experienced a manic or hypomanic episode, we suggest that BSD can be diagnosed if they have MDEs with several signs of bipolarity (Table 2).

The relation of these clues to bipolarity is well documented in the literature (26 28). Several studies have advocated including patients with antidepressant-induced mania or hypomania in the bipolar spectrum (29 31). Akiskal has also noted that, when followed prospectively, many adult patients with antidepressant-associated hypomania are found to progress to bipolar states with spontaneous mania or hypomania months or years later (26). In that study, in fact, treatment-induced hypomania was 100% specific for the eventual end point of BD, closely followed by a family history of BD, which was 98% specific. Consequently, we give greater weight to these 2 factors as predictive of a bipolar illness.

Over a prospective observation period of 11 years, 48/559 patients in a 1995 National Institutes of Mental Health (NIMH) collaborative depression study converted to BD II (32). At study entry, both early onset-age (that is, < age 25 years) of the first MDE, as well as recurrent depression, seemed to characterize those who switch from unipolar to BD II depression. A French multicentre study (33) also showed that early onset-age significantly differentiated BD II from unipolar patients. Atypical depressive symptoms also predicted bipolarity in the NIMH sample, a finding corroborated by a recent study showing that patients with atypical depression have

higher rates of BD II than do patients without atypical depression (34). A recent bipolar depression study conducted in New Zealand compared 39 BD I patients who were age- and sex-matched with 39 unipolar patients. The patients were also matched by DSM-IV melancholic subtype, and it was found that patients with BD were more likely to demonstrate atypical depression and were also more likely to have a history of psychotic depression (35). Other studies also support an increased association between psychotic depression and BD, as opposed to unipolar illness (27). Family history of BD also appears elevated in persons with hyperthymic personality (36), although not all studies agree on this point (37).

According to natural history studies, untreated bipolar depressive episodes are more brief (mean, 3 to 6 months) than unipolar depressive episodes (mean, 6 to 12 months) (3). Recent data also link a higher likelihood of lithium response for depression to very brief, recent depressive episodes (38). The experience of acute but not prophylactic response to antidepressants (a phenomenon we refer to as "wear off") has been linked to BD (39), as have postpartum depressive episodes, which are more frequent in bipolar than in unipolar individuals (3). Lastly, lack of response to 3 or more adequate antidepressant treatment trials has long been considered a reason to reassess for the unipolar diagnosis (3). We recently confirmed these associations in a clinical study that is currently in progress (to be presented at the Annual Meeting of the American Psychiatric Association, May 2002, in Philadelphia).

## The Antidepressant Controversy

One major reason to carefully distinguish between BD (whether BD I, BD II, or BSD) and unipolar depression has to do with the different profile of antidepressant effects in BD. While often alluded to, this profile is not simply a question of risk of acute mania or hypomania. More importantly, there is no evidence of efficacy with antidepressants in the long-term maintenance treatment of BD. Conversely, there is significant evidence of iatrogenic worsening of the bipolar illness course with antidepressant treatment. We review this evidence below.

*Lack of Prophylaxis*

Antidepressants have not been proven to prevent depression in the treatment of BD. In other words, while they may have acute efficacy in treating current depression, they have not been effective in prophylaxis of depressive episodes in bipolar disease, in sharp contrast to unipolar depression. We identified all 7 published controlled long-term double-blind studies of antidepressant use in BD (mostly BD I) 5 with tricyclic antidepressants (TCAs), 1 with bupropion, and 1 with fluoxetine (see Table 3).

In the studies with lithium comparison arms (all of which involved TCAs) no antidepressant proved to be more effective than, or in some cases even as effective as, lithium alone (40–44). In 1 study, increased manic episodes over time indicated that antidepressants (alone or even combined with

**Table 3. Blind controlled trials of long-term antidepressant treatment in bipolar disorders**

| Study | Diagnoses (*n*) | Treatment | Duration (months) | Outcome | Results |
|---|---|---|---|---|---|
| (40) | BP-I (44) | Li vs IMI vs PBO | up to 24 | Hospitalized or new treatment | Efficacy: Li > IMI = PBO in BP |
| (41) | BP-I (5) | Li vs Li + DMI | 27 (mean) | Nurse ratings | Efficacy: Li + DMI > Li<br>Switch and cycling rate: Li + DMI > Li |
| (42) | BP-I (75) | Li vs Li + IMI | 19 (mean) | RDC episodes | Efficacy: Li = IMI<br>Mania: IMI > Li (women) |
| (43) | BP-II (27), UP (22) | Li vs IMI vs Li + IMI vs PBO | 11 (mean) | RDC episodes | Efficacy: Li > PBO; IMI = PBO |
| (44) | BP-I (117), UP (150) | Li vs Li + IMI vs IMI | up to 24 | RDC episodes | Efficacy: Li = Li + IMI; IMI more mania |
| (45) | BP-II (80), matched UP (79), unmatched UP control subjects (661) | FLX vs PBO | up to 14 | DSM-III-R episodes | Efficacy: FLX similar in BPII and UP; switch rate: BP > UP |
| (46) | BP-I (15) (19 treatment trials) | BUP vs DMI | up to 12 | DSM-III-R episodes | Efficacy: Li + BUP = Li + DMI; Mania: DMI > BUP |

BP = bipolar disorder (type I or II); BUP = bupropion; DMI = desipramine-HCl; FLX = fluoxetine; IMI = imipramine-HCl; Li = lithium carbonate; PBO = placebo; RDC = Research Diagnostic Criteria (58); UP = unipolar major depressive disorder. Efficacy results related to bipolar depressive symptoms unless stated otherwise.

Adapted from SN Ghaemi, MS Lenox, RJ Baldessarini (59).

lithium) seemed to actually worsen long-term outcome (42). Amsterdam and associates reported on a post hoc analysis of unipolar clinical trials and noted that the acute mania switch rate with fluoxetine was higher in BD II (about 5%) than in unipolar depression (about 0.5%, $P < 0.05$) (45). At 1-year follow-up, however, no difference in switch rates was found between the group with BD II and the group with unipolar depression. The authors interpreted this as evidence of the relative safety of the selective serotonin reuptake inhibitor (SSRI). This result is inconclusive, however, since this study did not possess a mood-stabilizer control arm, nor did it systematically assess manic symptoms with rating scales. Further, because of the planned discontinuation at earlier time points of the various studies underlying this pooled analysis, the initial sample of 80 subjects was reduced to 10 subjects at 1-year follow-up. Thus, the high risk of BD II statistical error makes this finding of no difference in 10 patients at 1 year essentially uninterpretable. The clearest finding of this study was that the acute manic switch rate was higher with fluoxetine in BD II than in unipolar depression. In the study of bupropion by Sachs and colleagues, only 5 patients were followed up to 1 year, allowing even less room for interpretation (46).

*Risk of Iatrogenic Worsening of the Long-Term Course of Bipolar Illness*

Antidepressants have not been proven to effectively prevent depression in BD over the long term, and it is possible that they may actually cause more and more mood episodes over time.

This possibility is supported by 3 randomized studies. The first study (42) reported almost 2.5 times more frequent manic episodes with double-blind treatment using lithium plus imipramine (24%), compared with lithium alone (10%), over a mean of 1.6-year follow-up in 75 patients with BD I (statistically significant in the female subgroup). Depressive relapse rates were no worse for lithium alone (10%), compared with lithium plus imipramine (8%). The second study (41) was a small ($n = 5$) double-blind placebo-controlled on-off-on study that demonstrated repeated increased cycling with TCAs. The third study (47) found that double-blind randomized replacement of TCAs with placebo led to remission of rapid cycling in 17/51 (33%) patients with BD. In that study, 10 patients (a subset of the total sample of 51) also received double-blind on-off-on comparisons of TCA and placebo use, again supporting an association between TCA use and rapid cycling. In 1 case, rapid cycling became irreversible after 2 separate TCA trials, despite later discontinuation. There are no randomized data refuting these observations.

There is also a naturalistic literature suggesting a relation between antidepressant use and worsened long-term outcome. In the first large naturalistic report, Kukopulos and associates reported that antidepressant use was associated with rapid continuous cycling without intervals of normal mood in 59/115 (51%) subjects (48). This early report continues to be confirmed in this group's experience 20 years later (49), in which practically all cases of observed rapid cycling ($n = 120$) were associated with antidepressant use. The long-term experience of this highly respected group raises the question of whether rapid cycling may not be almost entirely iatrogenic, secondary to antidepressant use. It is worth noting that the psychiatric literature before 1960 rarely observes the existence of rapid cycling, despite the careful descriptive work of Kraepelin, Bleuler, and others. Yet, since the introduction of antidepressants, rapid cycling has been consistently reported to occur in about 20% of patients with BD. Kukopulos' group identified a few apparently spontaneous rapid cyclers (32/118, 27%); compared with antidepressant-induced rapid cyclers (86/118, 73%), the major clinical difference noted between the groups involvement temperament (cyclothymic temperament was more prevalent in the spontaneous rapid-cycling group, and hyperthymic temperament was more prevalent in the antidepressant-induced rapid-cycling group) (50). The recent experience of Kukopulos' group provides some relative good news: 79% of the rapid-cycling cases followed for 10 years ($n = 50$) resolved after antidepressants were discontinued and mood stabilizer treatment was instituted. Conversely, however, antidepressant-related rapid-cycling may be permanent in about 20% of persons, even after they discontinue antidepressants (49).

The experience of this Italian group was later confirmed by Post's NIMH group (29), with antidepressant-associated rapid cycling identified in 26% of 51 patients. However, all of these reports involved primarily TCAs. The hope has grown that new-generation antidepressants will not have these risks. We have examined this topic in 2 studies, the first published and the second soon to be fully presented publicly.

In the first study (13), based on data obtained in 1997 from patients who had mostly received new antidepressants such as SSRIs, we reconfirmed the naturalistic association between antidepressant use and rapid cycling in 24% of 54 patients with BD. This rate is similar to those reported by the Italian and NIMH studies involving TCAs. In our most recent dataset, collected in 2001, we again confirmed a similar rate of antidepressant-induced rapid cycling (35% of 40 patients with BD), and we demonstrated that it did not occur at all in a sample of 38 patients with unipolar depression (to be presented at the Annual Meeting of the American Psychiatric Association, May, 2002, in Philadelphia). Again, most of these patients received new-generation antidepressants, rather than TCAs.

Not all studies agree with these findings. In the NIMH psychobiology of depression study, for example,

antidepressant use was associated with poor outcome secondarily due to an underlying association between depression and rapid cycling (52). When the researchers controlled for depression (which is itself a poor prognostic factor), antidepressant use did not appear to be a sufficient mechanism to produce rapid cycling or a poor outcome. However, this finding is based on a statistical manipulation of naturalistic treatment and is therefore not as rigorous as a finding based on randomized data. Further, the subjects were followed for a limited part of their illness during the study (10 years), and the sample comprised rather ill patients with many previous episodes of illness. Since some patients might have reached a maximal state of rapid cycling related to antidepressant use before study enrollment, even more worsening could have been difficult to detect.

If antidepressants are associated with rapid cycling and a long-term worsening of BD, it would seem logical to avoid these agents in long-term maintenance treatment. Hence, recent expert recommendations have suggested that, if antidepressants are used for acute MDEs in BD, they should be tapered off after euthymic recovery, in the maintenance phase (2 to 6 months later) (52). This recommendation, with which we agree, has been criticized by some investigators who, in a recent study of 41 patients with BD, reported a statistical association between stopping antidepressants and relapse into depression (53). Even if accepted at face value, that study does not result in clear evidence for utility of antidepressants in most patients with BD. In another dataset from the Stanley group, antidepressants were still associated with acute mania or treatment nonresponse in about 75% of patients (54). These reports, however, also have a major methodological problem: they are nonrandomized naturalistic studies, and there is a potentially important bias in the composition of the 2 groups in each study. In the published study, antidepressants were discontinued in one group ($n$ = 25) and continued in the other ($n$ = 19). Based on current guidelines and the literature described above, we suspect that clinicians would have been more likely to discontinue antidepressants in patients with rapid-cycling vs non-rapid-cycling BD. However, the very definition of rapid-cycling BD is that episodes occur more frequently than in non-rapid-cycling BD. Hence, one would expect to find, by natural history, that relapse into a mood episode would occur earlier in the rapid-cycling group. In a nonrandomized assignment of antidepressant continuation to patients with non-rapid-cycling BD and discontinuation of antidepressants in rapid-cycling BD, such a finding would have nothing to do with the antidepressants themselves. Only a randomized study can answer this question, and indeed such a study exists (44). In that study, 150 patients with BD I received lithium plus imipramine openly for 2 months. They were then double-blind randomized to continuation of lithium plus imipramine, or to discontinuation of imipramine (lithium plus placebo), or to imipramine alone (plus placebo). In up to 2-year follow-up, there was no increased rate of depressive relapse upon discontinuation of imipramine (29% in the lithium-alone group, vs 22% in the lithium-plus-imipramine group, vs 28% in the imipramine-alone group). At the very least, one can say that this randomized study failed to find evidence of increased relapse into depression after withdrawl of antidepressant treatment in BD.

We recently conducted a naturalistic study, in which we compared patients with bipolar and unipolar depression. We found that relapse into depression after antidepressant discontinuation was infrequent in 40 patients with BD (about 20%) and much less common than in 38 patients with unipolar depression (over 50%) (unpublished data to be presented at the Annual Meeting of the American Psychiatric Association, May 2002, in Philadelphia). This finding agrees with our previously published experience, in which we used antidepressants in only 19% of 38 patients with BD treated for 1.7 years, with excellent results for treatment of depressive symptoms with mood stabilizers (55). If the problem of depression after antidepressant discontinuation occurs in BD, it appears to be infrequent.

In summary, randomized and naturalistic data support an association between antidepressant use and rapid cycling. Such an association argues for caution in using antidepressants to treat BD, limiting them to severe acute depression and generally stopping them in long-term maintenance treatment. Withdrawal relapse into depression may occur but appears infrequent. In our experience, antidepressants are needed only in about 20% of patients with BD, whether for acute or for maintenance treatment. Most patients with BD appear to do best with mood-stabilizing treatments, in the absence of antidepressant use.

## Conclusions

The underdiagnosis of BD partly indicates a lack of agreement on a definition of the bipolar spectrum. We propose a heuristic definition of bipolar spectrum disorder. Yet even mania and BD I (classic "Cade's disease") are prone to underdiagnosis. This may be due to clinicians' failure to recognize manic symptoms and patients' lack of insight. Since antidepressant use can be problematic in many patients with BD, the accurate differential diagnosis of bipolar vs unipolar depression is

essential. If diagnostic practice improves, new mood-stabilizing treatments may provide new hope for clinicians and patients.

## References


1. Baldessarini RJ. American biological psychiatry and psychopharmacology, 1944-1994. In: Menninger RW, Nemiah JC, editors. American psychiatry after World War II (1944-1994). Washington (DC): American Psychiatric Press; 2000. p 371–412.
2. Stoll AL, Tohen M, Baldessarini RJ, Goodwin DC, Stein S, Katz S, and others Shifts in diagnostic frequencies of schizophrenia and major affective disorders at six North American psychiatric hospitals, 1972-1988. Am J Psychiatry 1993;150:1668–73.
3. Goodwin FK, Jamison KR. Manic Depressive Illness. New York: Oxford University Press; 1990.
4. Regier DA, Kaelber CT. The epidemiologic catchment area (ECA) program: studying the prevalence and incidence of psychopathology. In: Tsuang MT, Tohen M, Zahner GEP, editors. Textbook in psychiatric epidemiology. New York: John Wiley; 1995. p. 133–57.
5. Weissman MM, Leaf PJ, Tischler GL, Blazer DG, Karno M, Bruce ML, and others Affective disorders in 5 US communities [published errata appears in Psychol Med 1988;18:following 792]. Psychol Med 1988;18:141–53.
6. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health diagnostic interview. Arch Gen Psychiatry 1981;38:381–9.
7. Helzer JE, Robins LN, McEnvoy LT, Spitznagel EL, Stoltzman RK, Farmer A, and others A comparison of clinical and diagnostic interview schedule diagnoses: Physician reexamination of lay-interviewed cases in the general population. Arch Gen Psychiatry 1985;42:657–66.
8. Dohrenwend B. "The problem of validity in field studies of psychological disorders" revisited. In: Tsuang M, Tohen M, Zahner G, editors. Textbook in psychiatric epidemiology. New York: Wiley-Liss; 1995. p 3–22.
9. Robins LN, Locke BZ, Regier DA. An overview of psychiatric disorders in America. In: Robins LN, Regier DA, editors. Psychiatric disorders in America. New York: Free Press; 1991. p 328–66.
10. Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression, and surgical conditions. Br J Psychiatry 1980;137:497504.
11. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RMA. The National Depressive and Manic-depressive Association (NDMDA) survey of bipolar members. J Affect Disord 1994;31:281–94.
12. Ghaemi SN, Hebben N, Stoll AL, Pope HG. Neuropsychological aspects of lack of insight in bipolar disorder: a preliminary report. Psychiatry Res 1996;65:113–20.
13. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. J Clin Psychiatry 2000;61:804–8.
14. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996;16(Suppl 1):4S–14S.
15. Sprock J. Classification of schizoaffective disorder. Compr Psychiatry 1988;29(1):55–71.
16. Michalakeas A, Skoutas C, Charalambous A, Peristeris A, Marinos V, Keramari E, and others Insight in schizophrenia and mood disorders and its relation to psychopathology. Acta Psychiatr Scand 1994;90(1):46–9.
17. Ghaemi SN, Stoll AL, Pope HG. Lack of insight in bipolar disorder: The acute manic episode. J Nerv Ment Dis 1995;183:464–7.
18. Amador XA, Flaum M, Andreasen NC, Strauss DH, Yale SA, Clark SC, and others Awareness of illness in schizophrenia and schizoaffective and mood disorders. Arch Gen Psychiatry 1994;51:826–36.
19. Keitner GI, Solomon DA, Ryan CE, Miller IW, Mallinger A, Kupfer DJ, and others Prodromal and residual symptoms in bipolar I disorder. Compr Psychiatry 1996;37:362–7.
20. Akiskal HS, Djenderedjian AH, Rosenthal RH, Khani MK. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am J Psychiatry 1977;134:1227–33.
21. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22:517–34.
22. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–51.
23. Baldessarini RJ. A plea for the integrity of the bipolar concept. Bipolar Disorders 2000;2(1):3–7.
24. Gershon ES, Guroff JJ. Information from relatives. Diagnosis of affective disorders. Arch Gen Psychiatry 1984;41:173–80.
25. Klerman GL. The spectrum of mania. Compr Psychiatry 1981;22(1):11–20.
26. Akiskal HS, Walker P, Puzantian VR, King D, Rosenthal TL, Dranon M. Bipolar outcome in the course of depressive illness. J Affect Disord 1983;5:115–28.
27. Mitchell P, Parker G, Jamieson K, Wilhelm K, Hickie I, Brodaty H, and others Are there any differences between bipolar and unipolar melancholia? J Affect Disord 1992;25:97–106.
28. Bourgeois ML. The bipolar spectrum of depressions. In: Vieta E, editor. Bipolar disorders: clinical and therapeutic progress. Madrid: Panamericana; 2001. p 113–26.
29. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130–8.
30. Benazzi F. Antidepressant-associated hypomania in outpatient depression: a 203-case study in private practice. J Affect Disord 1997;46(1):73–7.
31. Post R, Denicoff K, Leverich G, Frye M. Drug-induced switching in bipolar disorder. CNS Drugs 1997;8:352–5.
32. Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, and others Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 1995;52:114–23.
33. Hantouche EG, Akiskal HS, Lancrenon S, Allilaire J-F, Sechter D, Azorin J-M, and others Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study. J Affect Disord 1998;50:163–73.
34. Agosti V, Stewart JW. Atypical and non-atypical subtypes of depression: comparison of social functioning, symptoms, course of illness, co-morbidity, and demographic features. J Affect Disord 2001;65(1):75–9.
35. Mitchell PB, Wilhelm K, Parker G, Austin M, Rutgers P, Malhi GS. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. J Clin Psychiatry 2001;62:212–6.
36. Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H-J, Hirschfeld RMA. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. J Affect Disord 2000;59(Suppl):S5–S30.
37. Cassano GB, Dell'Osso L, Frank E, Miniati M, Fagiolini A, Shear K, and others The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment method ology. J Affect Disord 1999;54:319–28.
38. Bschor T, Canata B, Muller-Oerlinghausen B, Bauer M. Predictors of response to lithium augmentation in TCA-resistant depression. J Affect Disord 2001;64:261–5.
39. Sharma V. Loss of response to antidepressants and subsequent refractoriness: diagnostic issues in a retrospective case series. J Affect Disord 2001;64(1):99–106.
40. Prien RF, Klett CJ, Caffey EM. Lithium carbonate and imipramine in prevention of affective episodes. Arch Gen Psychiatry 1973;29:420–5.
41. Wehr TA, Goodwin FK. Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 1979;36:555–9.
42. Quitkin FM, Kane JM, Rifkin A, Ramos-Lorenzi JR, Nayak DV. Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. Arch Gen Psychiatry 1981;38:902–7.
43. Kane JM, Quitkin FM, Rifkin A, Ramos-Lorenzi JR, Nayak DD, Howard A. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. Arch Gen Psychiatry 1982;39:1065–9.
44. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, and others Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: A report of the NIMH collaborative study group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 1984;41:1096–1104.
45. Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JR, and others Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. J Clin Psychopharmacol 1998;18:435–40.
46. Sachs GS, Lafer B, Stoll AL, Banov M, Thibault AB, Tohen M, and others A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391–3.
47. Wehr TA, Sack DA, Rosenthal NE, Cowdry RW. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. Am J Psychiatry 1988;145:179–84.
48. Kukopulos A, Reginaldi P, Laddomada G, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatments. Pharmakopsychiatrie 1980;13:156–67.
49. Kukopulos A. The role of antidepressant treatments in rapid-cycling (abstract). In: Proceedings of the symposium at the second International Conference on Bipolar Disorder; 1997 June 19–21; Pittsburgh, PA.
50. Kukopulos A, Caliari B, Tundo A, Minnai G, Floris G, Reginaldi D, and others Rapid cyclers, temperament, and antidepressants. Compr Psychiatry 1983;24:249–58.
51. Tur vey CL, Coryell WH, Solomon DA, Leon AC, Endicott J, Keller MB, and others Long-term prognosis of bipolar I disorder. Acta Psychiatr Scand 1999;99:110–19.
52. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. The expert consensus guideline series: medication treatment of bipolar disorder. Postgrad Med 2000; Apr:1–104.
53. Altshuler LL, Kiriakos L, Calcagno J, Goodman R, Gitlin M, Frye M, and others The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: a retrospective chart review. J Clin Psychiatry 2001;62:612–6.
54. Post RM, Altshuder LL, Frye MA, Suppes T, Rush AJ, Keck PE, and others. An update on the Stanley Foundation Bipolar Network (SFBN). Bipolar Disorders 2001;3 (Suppl 1):13–4.

55. Ghaemi SN, Goodwin FK. Long-term natural istic treatment of depressive symptoms in bipolar illness with divalproex versus lithium in the setting of minimal antidepressant use. J Affect Disord 2001;65:281–7.

56. Goodwin FK, Ghaemi SN. An introduction to and history of affective disorders. In: Gelder MG, Lopez-Ibor JJ, Andreasen NC, editors. New Oxford Textbook of Psychiatry. New York: Oxford University Press; 2000. p 677–82.

57. Ghaemi SN, Ko JY, Goodwin FK. The bipolar spectrum and the antidepressant view of the world. Journal of Psychiatric Practice 2001;7:287–97.

58. Spitzer R, Endicott J, Robins E. Research diagnostic criteria for a selected group of functional disorders 2nd ed. New York: New York State Psychiatric Institute; 1975.

59. Ghaemi SN, Lenox ML, Baldessarini RJ. Efficacy and safety of antidepressants in long-term treatment of bipolar disorder. J Clin Psychiatry 2001;62:565–9.

Manuscript received and accepted February 2002.

[1] Director, Bipolar Disorder Research Program, Cambridge Hospital, Cambridge, Massachusetts; Assistant Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts.
[2] Research Coordinator, Bipolar Disorder Research Program, Cambridge Hospital, Cambridge, Massachusetts; Associate in Psychiatry, Harvard Medical School, Boston, Massachusetts.
[3] Director, Center on Neuroscience, Medical Progress, and Society; Professor, Department of Psychiatry and Behavioral Sciences, George Washington University, Washington, DC.
*Address for correspondence:* Dr SN Ghaemi, Department of Psychiatry, Cambridge Hospital, 1493 Cambridge Street, Cambridge, MA 02139
E-mail: ghaemi@hms.harvard.edu

**Résumé : La « maladie de Cade » et au-delà : erreur de diagnostic, utilisation des antidépresseurs et proposition d'une définition du trouble du spectre bipolaire**

Le diagnostic et le traitement du trouble bipolaire (TB) ont été incohérents et souvent mal compris ces dernières années. Pour trouver les causes de ce problème et suggérer des solutions possibles, nous avons entrepris une analyse critique des études concernant la nosologie du TB et les effets des agents antidépresseurs.

Le sous-diagnostic du TB et l'erreur fréquente qui consiste à le diagnostiquer comme un trouble dépressif majeur (TDM) unipolaire semblent faire problème chez les patients souffrant de TB. Le sous-diagnostic provient de la connaissance insuffisante des cliniciens des symptômes maniaques, des fausses notions qu'ont les patients de la manie et surtout du défaut d'inclure les membres de la famille ou les tiers dans le processus diagnostique.

Une partie, mais certainement pas la totalité du problème du sous-diagnostic peut aussi provenir de l'absence d'un consensus quant à l'ampleur du spectre bipolaire. Pour éliminer la confusion à propos des variétés moins typiques de la maladie bipolaire, nous proposons une définition heuristique, le « trouble du spectre bipolaire ». Ce diagnostic donnerait plus de poids aux antécédents familiaux et aux symptômes maniaques induits par les antidépresseurs, et s'appliquerait à la maladie bipolaire qui n'est pas de type I ou II.

Le rôle des antidépresseurs est aussi controversé. Notre examen des données probantes nous porte à conclure qu'on devrait moins insister sur l'utilisation d'antidépresseurs pour traiter les personne s