

## PREVALENCE AND IMPACT OF BIPOLAR DISORDERS IN PRIMARY CARE\*

Michael J. Ostacher, MD, MPH<sup>†</sup>ABSTRACT

Bipolar disorder is a lifelong illness marked by periods of mood changes, sometimes extreme and even psychotic, thus patients are persistently and frequently ill. Patients with a bipolar disorder face substantial burden, including social impairment, high divorce rates, and vocational disadvantages. The monetary cost of bipolar disorder is significant and includes medical expenses for the disorder, treatment of its comorbidities (psychiatric and medical), mental health service costs, and alcohol and drug treatment costs. Suicide rates and all-cause mortality are substantially higher for those with a bipolar disorder than the general population. Misdiagnosis is frequent; patients with bipolar disorder are most frequently diagnosed as having unipolar disorder and are thus likely to be started on antidepressant therapy. Although antidepressants are commonly used in bipolar disorder, it is unclear whether they are either effective or safe, especially when used without concurrent antimanic treatment. Inappropriate or delayed treatment may lead to induced mania or cycling, increased suicide risk, and prolonged morbidity. Given the established morbidity and mortality of bipolar disorder, especially when untreated, early recognition and correct diagnosis are required.

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**B**ecause bipolar disorder is one of the more serious forms of mental illness, it is not difficult to imagine the burden faced by patients experiencing it, including social impairment, high divorce rates, and vocational disadvantages. As reviewed by Dr Leibenluft later in this monograph, bipolar disorder is in reality a spectrum of disorders that range in severity and frequency of mood episodes (manic or depressive). However, as a whole, bipolar disorders begin fairly early in life, with the first episode usually presenting by the late teens or early 20s. It is a lifelong illness marked by periods of mood changes, sometimes extreme and even psychotic.

Although there are 3 phases in bipolar disorder (mania, depression, and euthymia), the phases are not always discrete. Patients can have mixed episodes (with manic and depressive symptoms) and euthymic periods are not always marked by a return to full functionality. Thus, patients with a bipolar disorder (even bipolar disorder-II [BP-II] or cyclothymia) are frequently and persistently ill.

The monetary cost of bipolar disorder is significant. One pharmacoeconomic analysis estimates that the total lifetime cost per case ranges from \$11 720 for people with a single manic episode to \$624 785 for people with nonresponsive chronic disease (Figure 1). The greatest share of direct costs is due to excess medical expenses (49%), followed by mental health service costs (46%) and alcohol and drug treatment costs (5%).<sup>1</sup>

Not surprisingly, those patients who screen positive for bipolar disorder use significantly more healthcare services than those who do not. Follow-up of 1167 adults in the United States who screened positive for bipolar disorder (using the Mood Disorders Questionnaire) showed that those who screen positive have greater use of psychiatric hospitals, emergency departments, and urgent care centers, and also had more outpatient visits to primary care physicians (PCPs), psychiatrists, and psychologists (Table 1).<sup>2</sup> As

\*This article by Dr Ostacher is based on a roundtable symposium held in Baltimore, Maryland, November 12, 2005.

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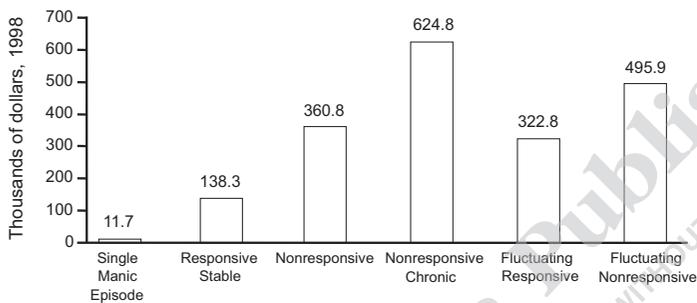
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**Table 1. Use of Healthcare Resources Among Patients Who Screen Positive for Bipolar Disorder**

Screening Result	Mean number of days in psychiatric hospital	Mean number of days in ED	Mean number of urgent care visits	PCP visits	Psychiatrist visits	Psychologist visits
Positive	0.42 ± 0.35	0.29 ± 0.13	0.05 ± 0.03	1.38 ± 0.47	1.21 ± 0.43	2.43 ± 0.79
Negative	0.01 ± 0.02	0.04 ± 0.04	0.01 ± 0.01	0.45 ± 0.31	0.16 ± 0.10	0.51 ± 0.42
P	.022	<.001	.024	.002	<.001	<.001

ED = emergency department; PCP = primary care physician.  
Data from Frye et al.<sup>2</sup>

**Figure 1. Estimated Total Lifetime Cost Per Case of Bipolar Disorder**



Shown here are results from a lifetime cost simulation model of bipolar disorder, based on 6 clinically defined prognostic groups. Total cost was estimated to be US \$24 billion, assuming onset of bipolar disorder in 1998. Data from Begley et al.<sup>1</sup>

in several other studies, misdiagnosis of bipolar disorder was common. Only 17.7% of those patients who screened positive for bipolar disorder reported receiving a diagnosis of a bipolar disorder. A total of 41.6% received a misdiagnosis and 40.7% did not receive any diagnosis. As shown in Figure 2, and in accord with other studies, the most frequent misdiagnosis was unipolar depression. This survey also confirmed that most patients who screen positive for bipolar disorder consult a PCP, as opposed to a psychiatrist or psychologist (Figure 3). However, misdiagnosis was not restricted to PCPs. Although PCPs misdiagnosed bipolar disorders 78% of the time, psychiatrists misdiagnosed 52.7% and psychologists 77.5% of the time.<sup>2</sup>

**A RISK OF MISDIAGNOSIS: ANTIDEPRESSANT-INDUCED MANIA AND HYPOMANIA**

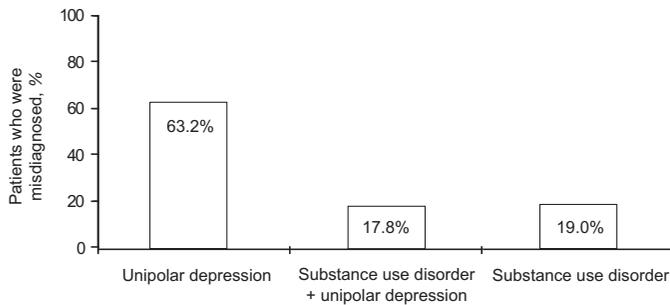
One of the most important hazards with misdiagnosing bipolar depression as unipolar depression is the effect on psychopharmacologic interventions. Although antidepressants are often first-line therapy for unipolar depression, these drugs may induce mania or rapid cycling in patients with bipolar disorder, especially if they are not administered with a concomitant mood stabilizer. (Rapid cycling is defined as at least 4 discrete mood episodes [of either pole] within 1 year.) The evidence for inducing a manic episode or cycling with antidepressants is more solidly established with older antidepressants (tricyclics and monoamine oxidase inhibitors); the data are not as clear with serotonin reuptake inhibitors and bupropion.

Goldberg and Truman have reviewed the literature on antidepressant-induced mania, noting that this type of switching has been reported in a large subgroup of patients with bipolar disorder (20%–40%).<sup>3</sup> A recent meta-analysis of randomized controlled trials of antidepressants for bipolar depression showed a switching rate (ie, antidepressant-induced switching to a manic episode) of 10% for tricyclic antidepressants but 3.2% for all antidepressants combined (and a rate of 4.7% for placebo).<sup>4</sup> However, Goldberg and Nassir Ghaemi later note that the literature on the use of antidepressants is unclear: “Decisions about the relative merits versus contraindications for antidepressant use should be made via more individualized, case-by-case profiling rather than by rigid prescribing practices.”<sup>5</sup>

Some patients will become manic only when taking antidepressants. In general, such patients are not con-

sidered to have BP-I or BP-II; some have referred to this phenomenon as BP-III, but it is diagnosed as bipolar disorder, not otherwise specified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV). However, many patients with BP-I and BP-

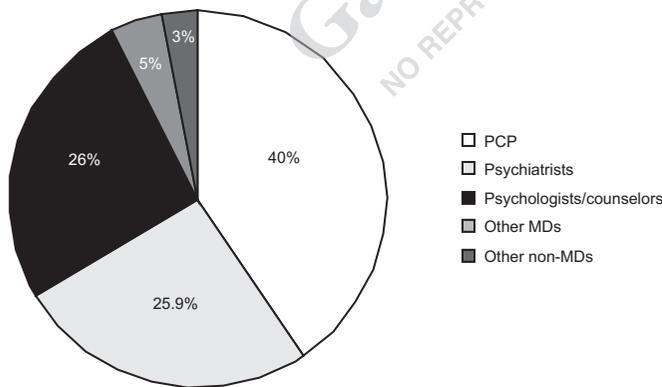
**Figure 2. Types of Misdiagnosis Among Those Screening Positive for Bipolar Disorder**



Patients ( $n = 1167$ ) were considered to screen positive for bipolar disorder if they reported the presence of 7 of 13 symptoms on the Mood Disorder Questionnaire, the co-occurrence of at least 2 symptoms, and moderate or severe symptom-related impairment.

Data from Frye et al.<sup>2</sup>

**Figure 3. Consulting Patterns by Those Who Screen Positive for a Bipolar Disorder**



Patients ( $n = 1167$ ) were considered to screen positive for bipolar disorder if they reported the presence of 7 of 13 symptoms on the Mood Disorder Questionnaire, the co-occurrence of at least 2 symptoms, and moderate or severe symptom-related impairment.

PCP = primary care physician.

Data from Frye et al.<sup>2</sup>

II will become “high” when on antidepressants without mood stabilizers. Patients who are most susceptible to antidepressant-induced euphorias are patients with previous antidepressant manias, a strong family history of bipolar disorder, an early onset of illness (in adolescence), and exposure to multiple antidepressant trials.<sup>3</sup> Depressed patients who report immediate resolution of symptoms with antidepressant therapy (ie, within the first few days) may be experiencing manic or hypomanic symptoms and should be evaluated for bipolar disorder. Finally, the delay in the initiation of mood stabilizer treatment appears to be associated with a higher likelihood of having made a suicide attempt.

**PROGRESSION OF BIPOLAR DISORDER AND THE CONCEPT OF EUTHYMIA**

In bipolar disorder, the majority of sick time is spent with depressive symptoms. Although manic episodes may be short lived, significant morbidity appears to continue even after resolution of the mood episode. Symptomatic recovery does not necessarily mean functional recovery. A 2- to 4-year follow-up of 166 patients first hospitalized for a manic or mixed episode showed that, although 98% of the patients achieved syndromal recovery fairly quickly (ie, no longer meeting DSM-IV episode criteria for a manic or mixed episode) and 72% had symptomatic recovery (ie, as assessed by rating scales for depression and mania), only 43% returned to their prior level of social and occupational functioning.<sup>6</sup> These results mirror an earlier, similar study that showed 48% syndromal recovery, 26% symptomatic recovery, and 24% functional recovery during a 12-month follow-up period after hospitalization for a manic or mixed episode.<sup>7</sup> Although these study patients were quite ill, the results suggest that patients with severe manic episodes have a high probability of not returning to their prior level of functioning.

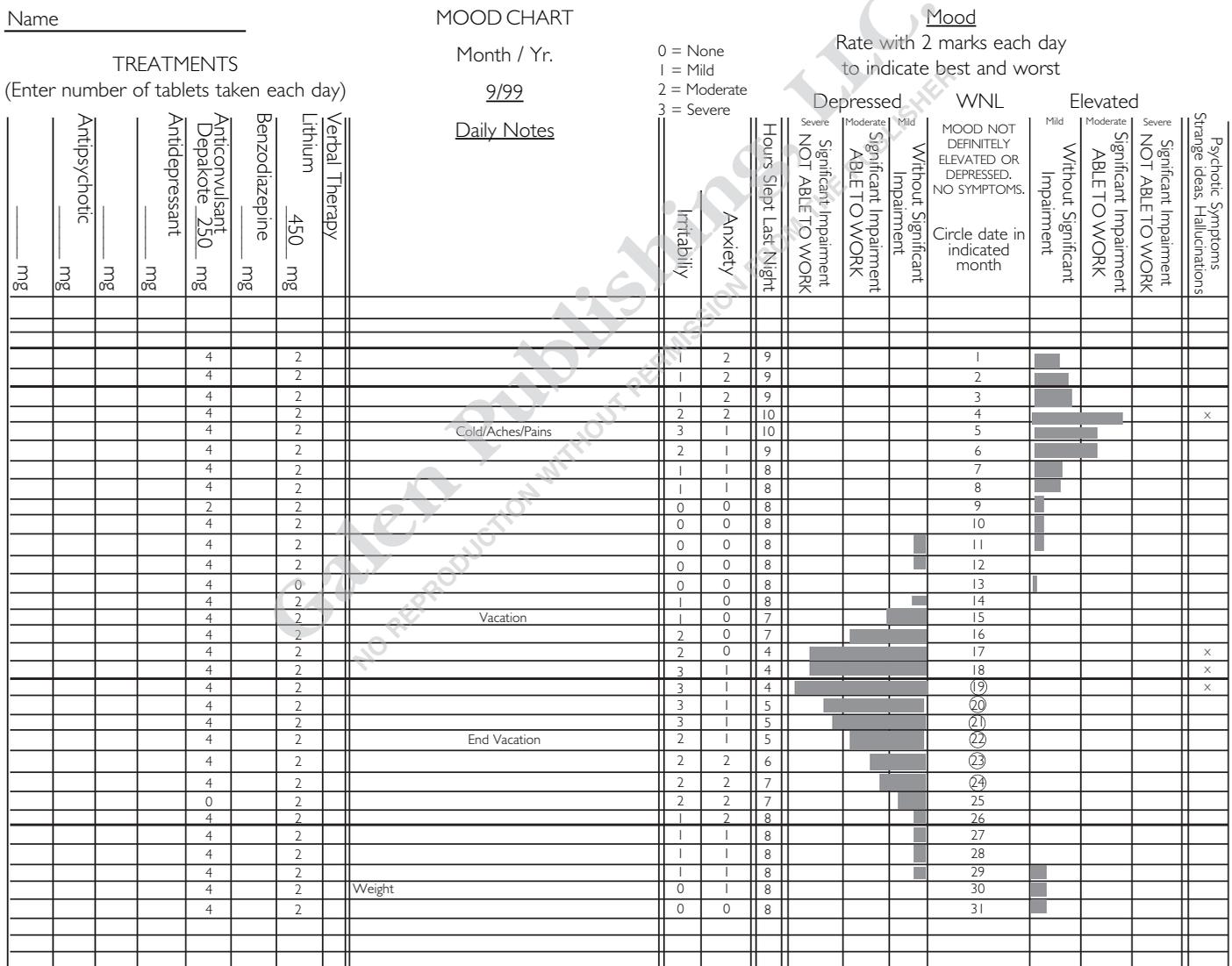
More recently, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is the largest, long-term outpatient treatment study ever conducted for bipolar disorder.<sup>8</sup> A subset of these patients were evaluated during a period of remission (ie, at least 4 weeks with no more than 2 depressive or manic symptoms). The 103 patients consisted of those patients with BP-I ( $n = 70$ ), BP-II ( $n = 24$ ), schizoaffective disorder–bipolar type ( $n = 4$ ), and BP-not otherwise specified ( $n = 5$ ). Their mean scores from the Work and Social Adjustment Scale showed significant functional impair-

ment, and the degree of functional impairment correlated with degree of depressive spectrum symptoms.<sup>9</sup>

In addition to cycling through extremes of mood during the course of bipolar disorder, patients will experience the full range of affective symptoms. A prospective natural history study of 146 patients with

BP-I showed that patients are ill nearly 50% of the time and most of the symptoms are depressive. Specifically, patients reported significant mood symptoms during 47.3% of weeks throughout a mean of 12.8 years of follow-up (based on weekly symptomatic status measures). Depressive symptoms (31.9% of total follow-up

Figure 4. Sample Mood Chart for Patients with Bipolar Disorder



Patients are asked to rate their mood and track hours slept and medication regimen daily.

WNL = within normal limits.

Reprinted with permission from Massachusetts General Hospital Web site and Dr Gary Sachs. Available at: <http://manicdepressive.org/images/samplechart.gif>. Accessed April 15, 2006.

weeks) were more common than manic/hypomanic symptoms (8.9% of weeks) or cycling/mixed symptoms (6% of weeks). Importantly, subsyndromal, minor depressive, and hypomanic symptoms combined were nearly 3 times more frequent than syndromal-level major depressive and manic symptoms (29.9% vs 11.2% of weeks, respectively).<sup>10</sup>

In a similar study of patients with BP-II ( $n = 86$ , follow-up 13.4 years), essentially 50% of the patients' time was spent ill with depressive symptoms (50.3% of weeks). Again, subsyndromal, minor depressive, and hypomanic symptoms combined were nearly 3 times more frequent than syndromal-level major depressive and manic symptoms, and poor previous social functioning predicted greater chronicity, suggesting a self-perpetuating phenomenon.<sup>11</sup>

During the long-term management of bipolar disorder, mood and life charting can be extremely useful. Such charts help to record symptoms, episodes, stressors, and treatments longitudinally. They are a valuable tool for patient and physician to monitor response to different treatments, particularly if care is managed across several providers (eg, PCP and psychiatrist or a change in PCP or psychiatrist in the future). An example of a daily mood chart and a life chart are shown in Figures 4 and 5.<sup>12</sup>

Figure 5. Sample Life Chart for Patients with Bipolar Disorder



Reprinted with permission from Bipolar.com Web site. Available at: <http://www.bipolar.com>. Accessed January 15, 2006.<sup>12</sup>

**BIPOLAR DISORDER: MORTALITY RISK**

Bipolar disorder also incurs a much higher all-cause mortality risk compared to the general population. The causes of death are varied and include suicide, violence, cardiovascular disease, and all-cause mortality. A study of Swedish patients with unipolar or bipolar depression showed that those with bipolar disorder had a standardized mortality ratio (SMR; ie, the death rate with bipolar disorder compared to the general population) of at least 2 for death from all natural causes (ie, excluding suicide, accidents, homicide, and undetermined), as shown in Table 2. With regard to suicide, the SMRs increased dramatically, and more so for women. For

Table 2. Bipolar Depression Increases All-Cause Mortality and Mortality from Suicide

Cause of Death	Males SMR	Females SMR
Infectious	3.4	2.4
Cancer	1.1	1.2
Endocrine	3.2	2.8
Mental*	3.7	4.8
Nervous system	1.6	2.3
Cardiovascular	1.9	2.6
Cerebrovascular	1.9	2.0
Respiratory	3.1	3.2
Gastrointestinal	2.0	1.9
Urogenital	3.7	4.3
Accidents	3.3	4.0
Traffic accidents	4.4	3.2
Suicide	15.0	22.4
Homicide	5.0	2.3
Undetermined†	10.3	14.2
Natural causes	1.9	2.1
Unnatural causes‡	8.6	12.7
All causes	2.5	2.7

95% confidence intervals not included.

SMR = standardized mortality ratio, calculated by dividing the observed number of deaths by the expected number of deaths.

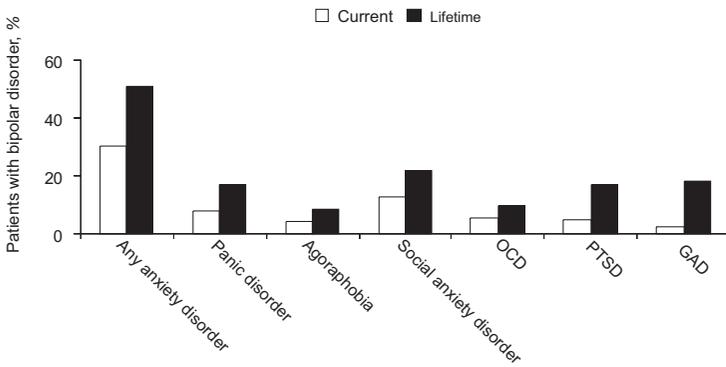
\*Mental causes of death for bipolar disorder are dementia, psychosis, depression, alcohol addiction/abuse, drug addiction, and developmental disorder. When the main cause of death is psychosis or depression, there is also an additional somatic cause.

†Undetermined deaths are unnatural (violent) deaths not classified by a specific cause.

‡Unnatural causes of death are accidents, suicide, homicide, and undetermined.

Adapted with permission from Osby et al. *Arch Gen Psychiatry*. 2001;58:844-850.<sup>13</sup>

**Figure 6. Current and Lifetime Anxiety Disorder Comorbidity in Patients with Bipolar Disorder Enrolled in the STEP-BD**

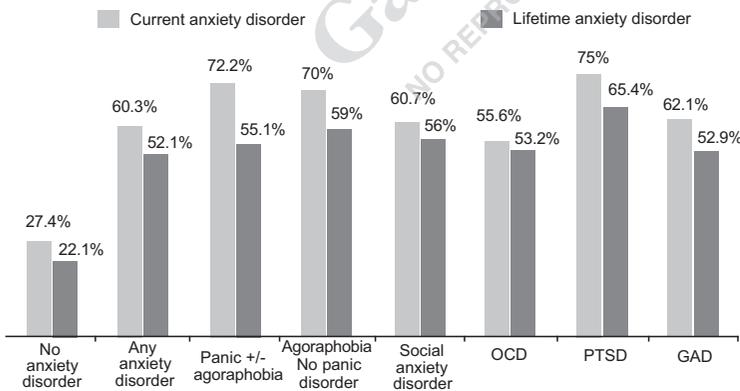


A cross-sectional sample from the first 500 patients with BP-I or BP-II enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a multi-center project funded by the National Institute of Mental Health designed to evaluate the longitudinal outcome of patients with bipolar disorder.

GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder.

Data from Simon et al.<sup>18</sup>

**Figure 7. Impact of Comorbid Anxiety Disorder on the History of Suicide Attempts in Patients with Bipolar Disorder**



A cross-sectional sample from the first 500 patients with BP-I or BP-II enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder.

Adapted with permission from Simon et al. *Am J Psychiatry*. 2004;161:2222-2229.<sup>18</sup>

bipolar disorder, most excess deaths were from natural causes, but in unipolar depression, they were from unnatural causes.<sup>13</sup>

Suicide is the most elevated mortality risk compared to the general population. In the STEP-BD, nearly 40% of patients had a prior suicide attempt.<sup>14</sup> Goodwin and Jamison initially reported a lifetime suicide risk of 12% to 19%; however, this may be an overestimation of the lifetime rate because younger patients tend to make more suicide attempts.<sup>15</sup> Nonetheless, a 22-year follow-up study of patients with affective disorders after an index hospitalization showed that those with untreated bipolar disorders had a standardized mortality ratio (ie, the death rate with bipolar disorder compared to the general population) of 29.2. With treatment, the SMR decreases to only 6.4. Thus, patients with untreated bipolar disorder are 12 times more likely to commit suicide and those who are treated are still 6.4 times more likely to commit suicide than the general population.<sup>16</sup>

Because there can be a long lag between the index episode and diagnosis (reported as up to 10 years), it is not surprising that the mean lag time from initial affective symptoms until first mood stabilizer treatment is also approximately 10 years (9.8 ± 9.4 years). Goldberg and Ernst have shown, in a small study, that a longer interval from symptom onset to first mood stabilizer was associated with poorer past year social functioning ( $P = .008$ ), more annual hospitalizations ( $P = .004$ ), and a greater likelihood for making a lifetime suicide attempt (odds ratio [OR] = 7.26; 95% confidence interval = 1.62–32.59).<sup>17</sup> For those patients who had made a suicide attempt, the delay in initiation of mood stabilizing treatment was 12.2 years versus 4.8 years in those who had never attempted suicide.<sup>17</sup>

Bipolar disorder is very often comorbid with anxiety disorders, as shown in Figure 6.<sup>18</sup> The STEP-BD study has also shown that patients with bipolar disorder and a comorbid anxiety disorder have a much higher rate of suicide attempts: 52.1% vs 22.1% for a lifetime prevalence of anxiety disorder; 60.3% vs 27.4% for those patients with a current anxiety disorder. Figure 7 shows these data, along with a comparison of suicide attempt rates by type of anxiety disorder.<sup>18</sup>

## BIPOLAR DISORDER AND SUBSTANCE ABUSE

Bipolar disorder is also highly comorbid with substance use and abuse. In the Epidemiologic Catchment Area study of mental illnesses, BP-I had one of the highest comorbidity rates with substance use of any mental illness at 61% (second only to antisocial personality disorder, 84%).<sup>19</sup> Nearly 50% (48.1%) of those patients with BP-II had comorbid substance abuse.<sup>19</sup> More recently, Grant et al showed that 21% of people in the general population with at least 1 current independent mood disorder had a comorbid substance use disorder.<sup>20</sup> Conversely, approximately 12% of people with alcohol dependence had mania or hypomania within the past 12 months.<sup>20</sup> In the STEP-BD, 48% of the first 1000 patients enrolled in this program had a substance use disorder; 36.2% met criteria for lifetime but not current substance use disorder.<sup>21</sup>

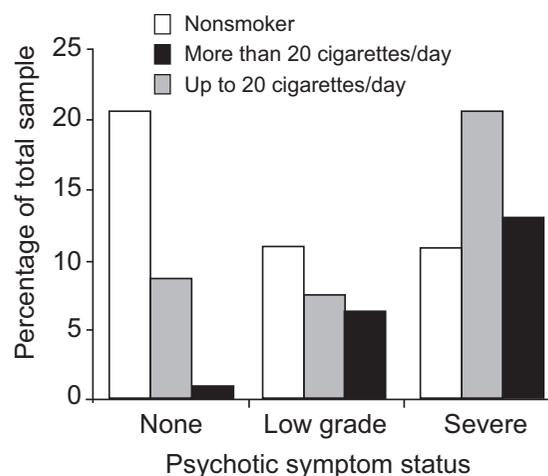
The presence of a comorbid substance use disorder is associated with a more severe course of illness: more suicide attempts (almost twice the rate: 39.5% vs 24% lifetime rate), more days sick, more severe symptoms, and more risk for violence.<sup>22-25</sup> The STEP-BD shows that current substance abuse is among the factors associated with the occurrence of a serious adverse psychiatric event among patients with bipolar disorder during 1 year of follow-up; the most frequent adverse event was hospitalization for suicidal ideation.<sup>26</sup> The first 1000 patients enrolled in the STEP-BD also provide insight into the functional outcomes of bipolar disorder with substance use disorders. Patients with a current or history of substance use disorder are less likely to be recovering from bipolar disorder and score worse on measures of role functioning and quality of life.<sup>21</sup> Thus, although substance use disorders may be intermittent in those patients with bipolar disorder, they are prevalent and have extended effects on patient clinical and personal outcomes.

## SMOKING AND BIPOLAR DISORDER

Although smoking is highly prevalent in those patients with bipolar disorder, the frequency is not as high as with schizophrenia. Grant et al observed smoking prevalence rates of 35% for those patients with BP-I (OR 3.9 compared to those without an Axis I disorder) and 33% for those with BP-II (OR

3.5).<sup>20</sup> As with other forms of substance use, smoking may predict future suicide attempts after a depressive episode and may be associated with a history of psychosis. In a study of 308 patients with major depressive disorder or bipolar disorder followed after an episode of major depression, cigarette smoking increased the risk of future suicide attempts by more than 2-fold. The exact relationship between smoking and suicide risk is unclear, as the investigators noted, but in this study, cigarette smoking was associated with other forms of substance use, including alcohol. Of note, the effect of smoking on suicide risk was additive to the other major risk factors (history of suicide and severity of depression).<sup>27</sup> In a small study of 92 unrelated patients with bipolar disorder, smoking (in particular, heavy smoking) was significantly related to psychosis (Figure 8). A total of 68.7% of study participants with a history of psychosis were smokers. Smoking was less prevalent in patients who were less symptomatic than in patients with a more severe psychosis (56.6% vs 75.7%). Also, the prevalence and severity of smoking predicted the severity of psychotic symptoms ( $P = .001$ ); this relationship was found to be independent of other variables ( $P = .0272$ ).<sup>28</sup>

**Figure 8. Relationship Between Smoking and Psychotic Symptoms in Patients with Bipolar Disorder**



$n = 92$ .

Reprinted with permission from Corvin et al. *Br J Psychiatry*. 2001;179:35-38.<sup>28</sup>

**OBESITY AND BIPOLAR DISORDER**

Bipolar disorder and schizophrenia also share obesity as a common comorbidity. In a study of 175 patients with BP-I who were treated for an acute affective episode, 35.4% of patients were clinically obese (as measured by body mass index). Obese patients with bipolar disorder were less likely to recover from a mood episode and more likely to relapse, especially to depression, as shown in Figure 9. Obesity was significantly correlated with lower education, more manic episodes, severity of depression, and more weeks in acute treatment (Table 3).<sup>29</sup> The mean body mass index of those patients with a history of suicide attempt versus no attempt is also significantly higher and reaches the level of obesity ( $30.21 \pm 6.67$  [29.92] vs  $27.89 \pm 6.35$  [26.63];  $P = .03$ ).<sup>29</sup>

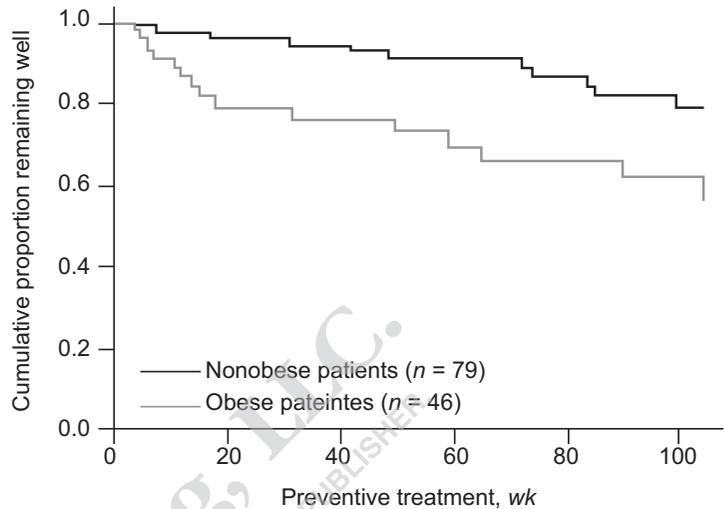
The metabolic syndrome, now considered a precursor to type 2 diabetes and which often involves overweight and obesity, is also highly prevalent in patients with bipolar disorder. A study of 171 consecutively recruited patients with bipolar disorder showed that 39% met the criteria for the metabolic syndrome: 49% met the criterion for abdominal obesity, 41% met the criterion for hypertriglyceridemia, 48% met the criterion for hypertriglyceridemia or were on a cholesterol-lowering medication, 23% met the criterion for low high-density lipoprotein cholesterol, 39% met the criterion for hypertension, and 8% met the criterion for high fasting glucose or antidiabetic medication use. Patients with the metabolic syndrome and patients with abdominal obesity were more likely to report a lifetime history of suicide attempts ( $P = .05$  and  $P = .004$ , respectively).<sup>30</sup>

Similar to smoking, the exact relationship is unknown. Obesity most likely adds to feelings of depression, but is also associated with lower socioeconomic status and educational level. Obesity is associated with other important health problems and is a significant side effect of some of the most effective drug treatments for bipolar disorder, thus it must be addressed early and aggressively.

**CONCLUSIONS**

Bipolar disorders incur high rates of morbidity and mortality. Depression and disability are com-

**Figure 9. Time to Depressive Illness Recurrence in Patients with BP-I**



Obese subjects had shorter time to depressive recurrence than nonobese subjects ( $P < .007$ ). BP = bipolar disorder. Reprinted with permission from Fagiolini et al. *Am J Psychiatry*. 2003;160:112-117.<sup>29</sup>

**Table 3. Mean Differences in Baseline Measures and Acute Treatment Duration Between Obese and Nonobese Patients with Bipolar Disorder**

Variable	Obese (n = 62)	Not Obese (n = 113)	P
Age (years)	36.5	34.5	.24
Education (years)	14.3	15.1	<.008
Duration of index episode	37.4	34.2	.06
Age at first manic episode	26.4	25.7	.66
Number of manic episodes	9.6	7.0	<.05
Number of years since first mania	10.1	8.9	.32
Age at first depressive episode (years)	21.9	22.4	.68
Number of depressive episodes	15.0	10.5	<.002
Number of years since first depression	14.6	12.5	.17
HAM-D-17 score	17.4	14.5	<.02
HAM-D-25 score	22.3	18.2	<.009
BRMS score	8.9	11.7	.16
GAF score	47.7	48.5	.55
Weeks in acute treatment	39.5	30.0	<.005

Standard deviations not included. Gray shading denotes statistical significance. BRMS = Bech-Rafaelsen Mania Scale; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale (17-item and 25-item). Adapted with permission from Fagiolini et al. *Am J Psychiatry*. 2003;160:112-117.<sup>29</sup>

mon, including comorbid medical illness, comorbid anxiety disorders, substance use, and obesity. Suicide rates and all-cause mortality are substantially higher for those patients with a bipolar disorder than in the general population, and treatment costs for bipolar disorder and its associated comorbidities are significant. Misdiagnosis is frequent; patients with bipolar disorder are most frequently diagnosed as having unipolar disorder and are thus started on antidepressant therapy. Although antidepressants are commonly used in bipolar disorder, it is unclear whether they are effective or safe, especially when used without concurrent antimanic treatment. Inappropriate or delayed treatment may lead to induced mania or cycling, increased suicide risk, and prolonged morbidity. Given the established morbidity and mortality with bipolar disorders (especially when untreated), earlier recognition, accurate diagnosis, and treatment with agents with established efficacy in different phases of the illness are essential.

## DISCUSSION

### INDUCING MANIA AND CYCLING

**Dr Manji:** Are mood elevation and cycle acceleration directly associated with antidepressant use, even if we don't see the mood elevation or don't detect it?

**Dr Ostacher:** We don't have enough long-term follow-up data with current antidepressants to know. There is one famous study by Wehr et al, in which patients who are on antidepressants are taken off the drugs and they stop cycling.<sup>31</sup> When they restart antidepressant treatment, they return to cycling. However, the study was small ( $n = 51$ ) and the antidepressants were tricyclics.<sup>31</sup> And, in the studies of acute depression, they didn't assess for manic symptoms, only for depressive symptoms.

**Dr Manji:** Do the STEP studies provide a hint as to whether the illness is destabilized or whether hypomanic episodes are triggered?

**Dr Ostacher:** Calabrese et al just published a randomized, controlled trial of divalproex sodium versus lithium.<sup>32</sup> They took a large number of patients ( $n = 254$ ) with a history of rapid cycling and tried to stabilize them on both drugs. Only 24% of the patients could ultimately be stabilized over a 6-month period. Almost all of the patients who weren't stabilized had recurrent or continuing depression. The investigators concluded that the hallmark of rapid cycling is highly recurrent refractory depression.<sup>32</sup>

It's a very pertinent question. Does cycling actually involve a mood elevation? It may well be that if the patient takes a drug that worsens their cycling, they may not experience mood elevation. They may be having more prolonged depressions, even if it's an antidepressant, and that's really the concern.

**Dr Leibenluft:** Lori Altshuler, MD, has published several studies of antidepressant-induced mania, but no one has really looked at the question of cycle acceleration with serotonin reuptake inhibitors (SSRIs). That's a huge gap in the literature. A recent meta-analysis of SSRIs did not find that SSRIs caused any more conversion to mania than placebo.<sup>33</sup> Of course, those were drug company trials, thus they would have used highly select patient populations, but we know remarkably little about this phenomenon in SSRIs. All of the data suggest it's less of an issue with SSRIs than it is with tricyclics, but how much less we really don't know, and where the cycle acceleration fits into it we really don't know.

**Dr Kaye:** From a clinician perspective, I would say there are probably 20% to 30% of patients with bipolar disorder who need a mood stabilizer and an antidepressant to maintain stability.

**Dr Treisman:** My toughest patients are the ones we've just talked about—the ones who, when you give them antidepressants, get worse, irrespective of whether you've ever seen mania in them. If you give them antidepressants, they get worse, but if you don't give them antidepressants, they're sick. They may be receiving numerous treatments—electroconvulsive therapy, lithium, and anticonvulsants—and they're not well. Thus, how do you treat them? Those are very tough patients. I now have a couple of those patients who are better on 300 mg of doxepin, when they failed several different SSRIs. With those tough patients, you've got to try everything, and you've got to be willing to haul stuff out of the closet that probably doesn't work in anyone except that person. For PCPs, a take-home message is: if you put someone on an SSRI and they say, "I got dramatically better in the first few days and then it started to wear off. I need more," or if they become hypomanic or manic, then you need to at least start thinking about bipolar disorder, and that's what a lot of people don't know to do. I get many patients who are referred to me who report that none of the antidepressants work for them because every time they take one, it works for a little while and then it doesn't work anymore.

**Dr Leibenluft:** Well, there's a placebo effect.

**Dr Adams:** Yes, that's true. However, it's important to remember that if a patient is looking a little better so quickly, the PCP should pay attention as to what that may mean, especially if they were pretty sure they'd made a diagnosis of depression. We go for a 4- to 6-week trial of a medication before we are willing to say whether it's efficacious. However, for patients who say, "I just spent \$5000 at Target," that should be a warning to look for bipolar disorder.

**Dr Kaye:** I agree with that. Remember, in the previous versions of the DSM, an antidepressant-induced elevated mood state was a criterion for bipolar disorder, but it ceased to be a criterion for DSM-IV. There are a lot of clinicians who still think that if we can induce mania or hypomania with an antidepressant trial, there's a pretty good likelihood that, even without an antidepressant, if we follow that patient prospectively, they are going to cycle and officially earn the diagnosis of bipolar disorder, even though DSM-IV doesn't allow us to diagnose them right now based on antidepressant-induced mania.

**Dr Leibenluft:** Absolutely. I think that there isn't anybody who would treat someone who became manic on an antidepressant with just another antidepressant, even if DSM-IV technically doesn't let you diagnose them as manic. Given the millions of people who take antidepressants and do perfectly well on them, what's different about the brains of those patients who become manic? We don't know how to categorize them, but clearly they're different from the patients who do very well with antidepressants.

Sleep deprivation can also precipitate mania in patients with bipolar disorder, although it doesn't do it every time. It can also make unipolar patients somewhat less depressed. Most people have some experience with being sleep deprived for a whole night, studying for examinations, a work deadline, or airplane flights. If the patient has a history of getting very "jazzed up" after having been up all night—euphoric, not being able to come down—this is another possible symptom of bipolar disorder.

**Dr Adams:** PCPs will often simply ask the patient, "Do you have any sleep problems?" You need to pin the patient down on the quality of the sleep, such as, "Do you have any trouble falling asleep or waking up early and finding you can't get back to sleep? And, when you don't get enough sleep, how do you feel?"

#### FAMILY BURDEN OF BIPOLAR DISORDER

**Dr Adams:** I'd also be interested in any data about how treating someone with bipolar disorder helps the quality of life of the family members. I've had female patients with bipolar disorder whose daughters become strippers and use cocaine, and I've seen others with teenage daughters who are attracted to boys with bipolar disorder, ostensibly because that's the kind of mood and emotions she's used to. She's attracted to it. Therefore, I tell people that in treating themselves they will help their children and their husbands.

**Dr Ostacher:** We don't have those data yet, but, as part of STEP, we were able to do an ancillary study. Deborah Perlick, PhD, a researcher at Yale, looked at burden on caregivers of people with bipolar disorder. We have 500 patients and 500 caregivers, and longitudinal data about burden in both over the course of treatment. We haven't analyzed the longitudinal data yet. Whether interventions that change outcomes also decrease caregiver burden is unclear, but I suspect that that will be the case. Clearly, the more depressed people are, and the more substances they use, the more burdened the family members are. It's an important question. We've studied it in schizophrenia and in Alzheimer's disease, but in bipolar disorder it's been overlooked, and I think there's a large impact.

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