

## Bipolar Disorder—Costs and Comorbidity

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### Abstract

Not only is bipolar disorder a chronic, severe psychiatric disorder, it is also expensive to treat and expensive to society. An estimate of the total cost of bipolar disorder made more than a decade ago was as high as \$45 billion per year. Most of this cost is accounted for by indirect costs related to reduced functional capacity and lost work. Patients with bipolar disorder have higher rates of utilization of healthcare resources compared with the general population and compared with patients with other types of psychiatric conditions. Comorbidity contributes to the heavy burden that bipolar disorder imposes on society. Bipolar disorder frequently occurs together with other psychiatric disorders, especially anxiety disorders and substance abuse. In addition, bipolar disorder has been associated with a variety of general medical conditions, which further complicate management of the psychiatric disorder.

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### Cost of Bipolar Disorder

Bipolar disorder is a recurrent and sometimes chronic psychiatric illness, which is characterized by episodes of mania or hypomania and depression. Bipolar disorder causes a significant impact on the patient's quality of life, as well as a considerable economic burden on both the individual and society as a whole. According to the World Health Organization report, bipolar disorder is ranked sixth in the top 10 causes of disability worldwide in the 15- to 44-year age group. Moreover, bipolar disorder is ranked third among mental illnesses after unipolar major depression and schizophrenia as the source of disease burden in established market economies.<sup>1</sup>

Until recently, much of the research in bipolar disorder has focused on bipolar I disorder, with a lifetime prevalence of about 1%

in the general population.<sup>2-4</sup> However, since epidemiologic studies started to use a broader definition of bipolar disorder, comprising a wider range of illnesses than pure mania, including hypomania, recurrent brief hypomania, sporadic brief hypomania, and cyclothymia,<sup>5,6</sup> the lifetime prevalence estimates of bipolar spectrum disorder are now placed at at least 5% of the general population,<sup>7</sup> with some authors producing even higher estimates.<sup>8</sup> In view of the high prevalence of bipolar spectrum disorder, it is important to assess the associated costs to society and to the afflicted individual.

**Direct and Indirect Costs of Bipolar Disorder.** Cost-of-illness studies typically assess direct and indirect costs of a particular disorder. Direct costs include direct medical expenditures, including cost of hospitalization, emergency department services, psychiatric visits, the cost of medications, and others. Indirect costs of illness assess the level of impairment, and the effect of the disorder on work productivity, as well as social welfare costs and criminal justice costs.<sup>9</sup>

The total economic burden of bipolar disorder in the United States was \$45 billion in 1991. Of that total, \$7 billion was a result of direct costs of inpatient and outpatient care, as well as nontreatment-related expenditures, such as costs of criminal justice. Indirect costs were estimated at \$38 billion and included the lost productivity of the patients and their caregivers. The lost productivity of patients who have committed suicide alone was assessed at \$8 billion.<sup>10</sup>

One key aspect of cost to society is the impact of bipolar disorder in the workplace. The recently completed National Comorbidity Replication study is a nationally representative survey of mental disorders

among US residents aged 18 and older.<sup>11</sup> Bipolar disorder was associated with 49.5 annual lost workdays per ill worker. Major depressive disorder (MDD) was associated with 31.9 annual lost workdays per ill worker. Projected losses for the total US labor force yielded an estimate of 180 million lost workdays per year and \$25.9 billion salary-equivalent lost productivity per year associated with bipolar disorder compared with 116.1 million workdays and \$19.4 billion salary-equivalent lost productivity per year associated with MDD.<sup>12</sup>

Many aspects of patients' lives are affected by their bipolar disorder, leading to an increase in the indirect costs of the disorder. Bipolar disorder is frequently associated with family discord, problems with the justice system, and workplace problems. One study has shown that only 50% of bipolar patients were employed 6 months after discharge from a psychiatric hospitalization. These findings have been corroborated (R. C. Kessler, MD, unpublished, 2005).

**Cost of Misdiagnosis.** Failure to recognize bipolar disorder in the early stages of the disease is also associated with increased costs. In fact, as many as 70% of patients who seek professional services are initially misdiagnosed, the most frequent misdiagnosis being unipolar depression.<sup>13</sup> The correct diagnosis of bipolar disorder is complicated by the fact that a majority of patients present to the physician while depressed. Misdiagnosis of bipolar disorder as unipolar depression can have significant economic consequences. The cost of bipolar disorder misdiagnosis was addressed in a study of paid claims of 3349 California Medicaid patients with bipolar disorder.<sup>14</sup> Of these patients, only 42% used a mood stabilizer during the first posttreatment year, and only 5.5% of patients used a mood stabilizer consistently for 1 year. Direct healthcare costs were significantly higher among the patients who failed to receive a mood stabilizer. Specifically, mood stabilizer treatment was associated with a decrease in the total cost of treatment of \$5044 per year, primarily because of the reductions in ambulatory costs and costs of hospitalizations.<sup>14</sup>

### Psychiatric Comorbidities of Bipolar Disorder

Psychiatric comorbidity, defined as the presence of a concurrent psychiatric syndrome in addition to the principal diagnosis, is common in psychotic and major affective disorders.<sup>15</sup> Epidemiologic studies have shown that between 25% and 50% of people with 1 mental disorder have at least 1 co-occurring mental disorder. High rates of comorbidity contribute to the cost of treatment of patients with psychiatric disorders, as comorbidity hinders diagnosis and complicates treatment.

Psychiatric and general medical comorbidity are especially common in patients with bipolar disorder.<sup>16</sup> The commonly reported rates of lifetime comorbidity in bipolar I samples are higher than 50%, and some authors report rates as high as 70%.<sup>17</sup> The rates of comorbidity are assessed in 2 types of studies: epidemiologic studies and general community, and clinical samples studies.

**Community Studies.** The Epidemiologic Catchment Area (ECA) study was a collaborative research effort conducted by the National Institute of Mental Health, which assessed the prevalence of psychiatric disorders in the combined community and institutional populations. The lifetime prevalence of any affective disorder was reported at 8.3%, and the lifetime prevalence of any bipolar disorder at 1.3% (0.8% for bipolar I and 0.5% for bipolar II). The ECA study further assessed the comorbidity of bipolar disorder with any substance abuse (ie, drug and alcohol), panic disorder, and obsessive-compulsive disorder (OCD). The ECA identified 168 individuals with bipolar disorder. Among them, 46% had comorbid alcohol abuse or dependence, 41% had drug abuse or dependence, 21% had panic disorder, and 21% had OCD.<sup>18-20</sup>

Strikingly high rates of comorbidity in patients with bipolar disorder were reported in the National Comorbidity Survey (NCS) study, a general population survey of *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)* disorders, conducted 1 decade after the ECA study. The lifetime prevalence rates

of bipolar disorder in the NCS study were lower than commonly reported, with the rate for manic episodes reported at 1.6% and dysthymia at 6.4%.<sup>2</sup> The lifetime prevalence of bipolar I disorder (euphoric-grandiose bipolar disorder, characterized by euphoria, grandiosity, and decreased need for sleep) was 0.45%.<sup>21</sup> Comorbidity rates of bipolar I disorder with other lifetime *DSM-III-R* disorders were further evaluated in a small clinical reappraisal study of 59 respondents of the NCS.<sup>22</sup> Twenty-nine manic patients with euphoria, grandiosity, and the ability to maintain energy without sleep were analyzed. All cases reported at least 1 other *DSM-III-R* disorder, and 95.5% of cases met criteria for 3 or more disorders. The episode of bipolar disorder (either mania or depression) for 59.3% occurred at a later age than at least 1 other NCS/*DSM-III-R* disorder.<sup>21</sup>

**Clinical Studies.** Bipolar disorder comorbidity with other mental disorders has also been evaluated in a number of clinic-based studies. A study from the Stanley Foundation Bipolar Treatment Outcome Network evaluated axis I psychiatric comorbidity in 288 patients with bipolar I and II disorder. The evaluation showed that 65% of the patients with bipolar disorder met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for at least 1 other lifetime axis I disorder. Lifetime and current axis I comorbidity were associated with earlier onset of affective symptoms and syndromal bipolar disorder.<sup>22</sup>

Forty-one patients admitted for a first psychiatric hospitalization were assessed for the presence of psychiatric and general medical comorbidities in a study conducted by Strakowski and colleagues.<sup>23</sup> Of these patients, comorbidities were found in 51% of patients, including 39% of psychiatric comorbidities and 22% of general medical comorbidities. More than 1 comorbid condition was found in 22% of the subjects. Women had a 2.7-fold higher rate of comorbidities than men; 56% of women admitted for mania had a comorbid psychiatric disorder compared with 12.5% of men.<sup>23</sup> Other studies specifically address

bipolar disorder comorbidities with specific other psychiatric disorders and will be discussed later.

*People with bipolar I disorder were more than 3 times as likely to have alcohol abuse or dependence and about 7 times more likely to have drug abuse or dependence than those in the general population.*

### Substance and Alcohol Abuse

**Community Studies.** Numerous studies have documented high rates of comorbid substance abuse in bipolar patients. Substance abuse is prevalent in the United States, with lifetime rates of alcohol and drug abuse reported at 13.5% and 6% respectively in the ECA study<sup>18</sup>; and at 23.5% and 11.9% in the NCS.<sup>2</sup> Both the ECA and NCS studies have shown that people with bipolar disorder have higher rates of comorbid substance use disorders than the population as a whole. Among individuals with bipolar disorder in the ECA study, 56.1% were dependent on substances; specifically, 46% had alcohol abuse or dependence, and 41% had drug abuse or dependence.<sup>18</sup> People with bipolar I disorder were more than 3 times as likely to have alcohol abuse or dependence and about 7 times more likely to have drug abuse or dependence than those in the general population.<sup>18</sup> Conversely, the ECA study found that 13.4% of alcoholics and 26.4% of nonalcohol drug abusers had an affective disorder.<sup>19</sup> Similarly, the NCS has reported that 6.5% of alcoholic men and 10.6% of alcoholic women have a lifetime history of mania.<sup>24</sup> Among the individuals diagnosed with bipolar I disorder in the NCS study, 71% reported at least 1 lifetime substance use disorder; 61% reported alcohol dependence; 64.2% reported alcohol abuse; 40.7% reported drug dependence; and 46.1% reported drug abuse.

**Clinical Studies.** In the report from the Stanley Foundation Bipolar Treatment Outcome Network, 42% of patients with bipolar I and II disorder also met the criteria for a lifetime substance use disorder. Alcohol was the most commonly abused substance, with 33% of bipolar patients meeting the criteria for alcohol abuse, followed by marijuana abuse (16%).<sup>23</sup>

Cassidy and colleagues<sup>25</sup> conducted a general review of the literature and demonstrated that estimates of comorbid substance abuse in bipolar patients range from 6% to 69%, with most authors reporting rates of 30% and greater. Estimates of comorbid drug abuse range from 14% to 60%.<sup>25</sup> In their own study of 392 hospitalized patients with manic or mixed episodes of bipolar disorder, Cassidy and colleagues found that 48.5% had a lifetime history of alcohol abuse and 43.9% had a lifetime history of drug abuse. Overall, nearly 60% of the patients had a history of some substance abuse.<sup>25</sup> Whether substance abuse follows bipolar disorder or vice versa remains unresolved.<sup>19,26</sup> Drug abuse may lead to misdiagnosis of bipolar disorder, because patients who are intoxicated with stimulants can appear manic.<sup>27</sup>

Complications of substance abuse in bipolar disorder include higher rates of mixed and rapid cycling, prolonged recovery time, higher prevalence of medical disorders, including liver disease, more suicide attempts, and suicide.<sup>27</sup> Comorbidity with alcohol and drug abuse is often associated with poor adherence and poor treatment response compared with patients without comorbidity.<sup>17</sup>

### Anxiety Disorders

**Community Studies.** Symptoms of anxiety often occur in patients with bipolar disorder. Therefore, the high rates of comorbidity of anxiety disorders in patients with bipolar disorder are not surprising. For example, the ECA study reported that 21% of patients with bipolar I and II disorder had comorbid lifetime panic disorder and 21% had comorbid lifetime OCD compared with 0.8% and 2.6%, respectively, in the general population.<sup>19,20</sup> In the NCS study, 92% of patients with bipolar I disorder also met the criteria for a lifetime anxiety disorder compared with 25% in the general population.<sup>2,21</sup>

**Clinical Studies.** As with substance abuse, comorbid anxiety hinders treatment response in patients with bipolar disorder. It has been reported that bipolar patients with anxiety have significantly poorer response to treatment, specifically to lithium therapy, than patients without anxiety.<sup>28,29</sup> In an analysis of 124 patients with bipolar I disorder, history of panic attacks proved to be significantly correlated with nonremission, whereas past or present anxiety was significantly correlated with longer time to remission.<sup>28</sup> Moreover, Young and colleagues<sup>29</sup> reported a trend for bipolar patients with high anxiety to be less likely to respond to lithium. Bipolar patients with high anxiety scores were more likely to have suicidal behavior (44% vs 19%), alcohol abuse (28% vs 6%), cyclothymia (44% vs 21%), and an anxiety disorder (56% vs 25%) with a trend toward lithium nonresponsiveness than bipolar patients with low anxiety scores.<sup>29</sup> In the report from the Stanley Foundation,<sup>22</sup> 42% of subjects diagnosed with bipolar I and II disorder also met the criteria for comorbid anxiety disorder, including panic disorder/agoraphobia (20%) and social phobia (16%).

### Other Comorbid Psychiatric Disorders

Other psychiatric disorders that have a high rate of comorbidity with bipolar disorder are eating disorders, sexual disorders, impulse-control disorders, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, conduct disorder, Tourette's syndrome (TS), and personality disorders.<sup>16,27</sup>

**Eating Disorders.** In the Zurich cohort study, individuals with *DSM-IV* hypomania and those with recurrent brief hypomania had higher lifetime prevalence rates of binge eating (12.8% and 22.2%, respectively) compared with controls (4.6%).<sup>5</sup> In another study of 61 adults with bipolar disorder, 13% met criteria for binge-eating disorder, whereas 25% more subjects exhibited partial binge-eating syndrome.<sup>30</sup> In the Stanley Foundation study of 288 patients with bipolar I and II disorder, the lifetime comorbidity of eating disorders with bipolar I or II disorder was estimated at 5% for bipolar I

and 12% for bipolar II disorder.<sup>22</sup> The rate of eating disorder comorbidity in 39 bipolar patients with first lifetime hospitalization was 15%. Notably, the diagnosis of bipolar disorder was antecedent to eating disorders in 13% of cases.<sup>15</sup>

**ADHD.** Childhood bipolar disorder is often comorbid with ADHD and conduct disorder. Features of bipolar disorder often overlap with those of ADHD, leading to misdiagnosis and consequent treatment with psychostimulants, which may induce mania or rapid cycling in bipolar patients. Systematic studies of pediatric patients with mania demonstrate rates of comorbidity with ADHD in the range of 60% to 90%.<sup>31</sup> In a study of 104 pediatric patients referred to a community mental health clinic for the treatment of ADHD, 60% met the criteria for a mood disorder; moreover, 13% of these referrals met the standard criteria for mania, and 41% of the children met the modified criteria for mania, which required the presence of euphoria and/or flight of ideas.<sup>32</sup>

**TS.** Although literature on the comorbidity of TS with bipolar disorder is limited, at least 1 study suggests co-occurrence of TS with bipolar disorder. In a study of 246 patients with TS, 17 patients with attention-deficit disorder, 15 patients with attention-deficit disorder associated with TS, and 47 controls, none of the control patients had above normal mania scores compared with 19% of the total patients with TS.<sup>33</sup>

**Personality Disorders.** Personality disorders may complicate the diagnosis and course of bipolar disorder, as well as impede treatment. Most studies report the rate of comorbid personality disorders in patients with bipolar disorder in the range of 30% to 45%, and as high as 65% in some studies.<sup>34-36</sup> Dramatic/emotionally erratic and fearful/avoidant personality disorders were more common than odd/eccentric disorders. Patients with bipolar disorder with personality disorders differed from patients with bipolar disorder without personality disorders in the severity of their residual mood symptoms, even during remission. The pres-

ence of comorbid personality disorders, specifically borderline personality disorder, may also significantly increase the utilization of mental health services, as it has been previously shown that patients with personality disorders tend to have more extensive histories of psychiatric outpatient, inpatient, and psychopharmacologic treatment than patients with affective disorders.<sup>37</sup>

### Conclusion

Bipolar disorder imposes a substantial economic burden on society. Much of the cost is indirect and related to factors such as work loss. Patients with bipolar disorder have higher rates of healthcare utilization compared with individuals without the disorder, and those higher rates of utilization are associated with higher healthcare costs. Appropriate treatment of bipolar disorder can help reduce the associated costs. Other psychiatric conditions frequently occur with bipolar disorder. Comorbid anxiety disorders and substance abuse are especially prevalent.

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