The Impact of Bipolar Depression

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Bipolar disorder is a chronic, intermittent illness that is associated with high morbidity and mortality. In addition, patients with bipolar disorder often have comorbid psychiatric conditions (such as anxiety disorders, alcohol or substance abuse, and eating disorders) or medical disorders (such as obesity), which result in increased burden of illness for the patients, family members, and treating clinicians. Although bipolar disorder consists of recurring episodes of mania and depression, patients spend more time depressed than manic. Bipolar depression is associated with a greater risk of suicide and of impairment in work, social, or family life than mania. This health burden also results in direct and indirect economic costs to the individual and society at large. Bipolar depression is often undiagnosed or misdiagnosed as unipolar depression, resulting in incorrect or inadequate treatment. Available treatments for bipolar depression include medications such as lithium, selected anticonvulsants, and the atypical antipsychotics. Traditional antidepressants are not recommended as monotherapy for bipolar depression as they can induce switching to mania. Early and accurate diagnosis, aggressive management, and earlier prophylactic treatment regimens are needed to overcome the impact of depressive episodes in patients with bipolar disorder. *(J Clin Psychiatry 2005;66[suppl 5]:5–10)*

Bipolar disorder is an intermittent to chronic psychiatric disorder characterized by recurring episodes of severe depressive illness and at least 1 episode of mania or hypomania. Episodes must meet diagnostic criteria for number and quality of symptoms and duration of a manic episode, hypomanic episode, or mixed episode.[1] After these acute episodes of illness are resolved, many patients are relatively well for variable periods of time. However, in carefully monitored cohorts, as many as 20% to 30% of patients have residual symptoms and impairment between episodes, despite intensive ongoing treatment.[2–6]

Bipolar disorders are a substantial public health problem. Recent estimates from a large, epidemiologic study indicate a lifetime prevalence for the spectrum of bipolar illnesses of approximately 3.7% in the United States.[7] A similar prevalence is seen in many other studies.[8] With an average onset at age 20, the prevalence of bipolar spectrum disorders in 1 survey was highest in younger adults (9.3% in the 18- to 24-year-old age group).[7] In a related analysis of subjects who screened positive for bipolar disorder in this study, these younger adults reported more disruption in daily activities than older adults and were more than twice as likely to have been incarcerated compared with older adults. In their study, Perlis et al.[9] found that 28% of adults with a definite diagnosis of bipolar disorder had an onset of illness prior to age 13. Severe psychiatric illness at this crucial period, by delaying or preventing normal social, educational, and economic advancement, may have lifelong consequences for patients with bipolar disorder.[10]

Unfortunately, bipolar disorder is often undiagnosed or misdiagnosed in the general population, leading to undertreatment and continuing disability.[11] Survey results indicated that accurate diagnosis may be significantly delayed: only 20% of patients who screened positive for bipolar disorder had received that diagnosis from a physician, whereas 31% had received a diagnosis of unipolar depression and 49% had received no diagnosis.[7] Of those diagnosed as bipolar in the community, most were not treated adequately and received antidepressants without a concomitant mood stabilizer. Since periods of hypomania occur in those with recurrent depression and depressive episodes are the presenting symptoms in many patients with bipolar disorder, bipolar disorder is often diagnosed as unipolar depression.[8,12] Findings of the study by Hirschfeld and colleagues[7] and Das et al.[13] indicate the need for a higher degree of vigilance for bipolar disorder in the general population and in primary medical care so that appropriate treatment can be instituted as soon as possible.

A major portion of the morbidity and mortality associated with bipolar disorder is derived from depressive epi-

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Table 1. Features of Bipolar Depression[a]

Affective	Cognitive	Physical	Chemical	Brain Alterations
Sadness	Poor self-esteem	Change in sleep	Hypercortisolism	Selective decrease in neurons or glia in prefrontal and anterior cingulate cortex and in amygdala
Apathy	Poor concentration	Change in appetite	Decreased somatostatin in CSF	Decreases in neuronal NAA in frontal cortex
Anhedonia	Indecisiveness	Decreased activity	Decreased intracellular calcium in blood elements	Decrease in prefrontal GFAP
Irritability	Suicidal ideas	Low energy		Decreases in reelin and GAD67
Anxiety	Self-blame	Change in weight		Frontal and hippocampal hypofunction on PET
				Amygdala and cerebellar hyperactivity on PET
				Loss of normal balance in positive and negative connectivity among brain regions

[a]Adapted with permission from Post et al.[46]
Abbreviations: CSF = cerebrospinal fluid, GFAP = glial fibrillary acidic protein, GAD67 = glutamic acid decarboxylase, NAA = N-acetylaspartate, PET = positron emission tomography.

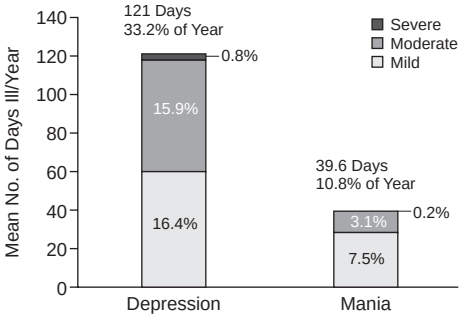
sodes and symptoms rather than manic characteristics. Although manic and hypomanic symptoms are usually the more conspicuous aspects of bipolar disorder, recent studies have shown that bipolar depression is associated with higher rates of dysfunction and more morbidity and mortality than bipolar mania. Patients experiencing acute depressive or mixed depressive episodes have been shown to be at significantly higher risk of suicide, panic disorder between episodes, and psychosis than patients with pure manic episodes.[14] In addition, subsyndromal depressive symptoms, which were found more often than hypomanic or mixed symptoms in longitudinal studies,[2–4,6,15] have been shown to correlate significantly with measurements of functional impairment.[5]

Bipolar depression may also impose a greater overall burden on patients and families than unipolar depression, due to an earlier age at onset, more frequent episodes, and a greater proportion of time spent ill.[16] Psychotic features, such as delusions or hallucinations, are more common, as are anger attacks, and the risk of suicide may be higher in bipolar depression than in unipolar depression.[17]

FEATURES OF BIPOLAR DEPRESSION

Bipolar depression is associated with a wide range of affective, cognitive, and physical symptoms as well as neurobiological abnormalities (Table 1). In addition to these disturbances, psychiatric comorbidities are common and include anxiety disorders, such as posttraumatic stress disorder, obsessive-compulsive disorder, panic disorder, and social phobia; substance abuse disorders; eating disorders, such as anorexia nervosa and bulimia; and attention-deficit/hyperactivity disorder (ADHD). Symptoms frequently lead to increased alcohol or substance abuse, which may magnify the severity of illness and increase hospitalizations. Women with bipolar disorder are at a more than 7-fold greater risk for alcohol use and abuse than are women in the general population.[18] Patients with bipolar disorder also have an increased risk of cardiovascular disease and a variety of other medical illnesses.[19,20]

Figure 1. Three Times Greater Amount of Treatment-Resistant Depression Than Mania in 258 Outpatients Rated Daily for 1 Year[a]



[a]Data from Post et al.[2]

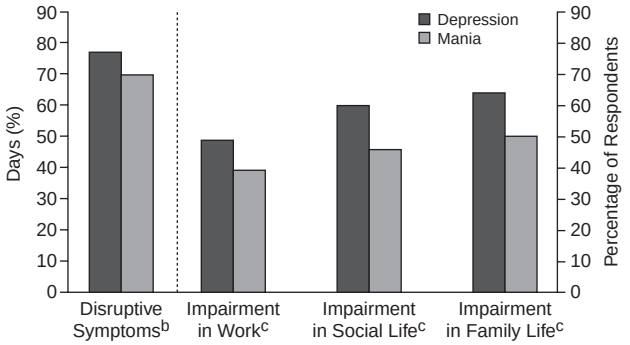
THE INDIVIDUAL BURDEN OF BIPOLAR DEPRESSION

Pattern of Illness

Recent longitudinal studies have revealed the preponderance of depressive features over manic features in patients with bipolar I and II disorder. In a prospective study of a cohort of 258 patients evaluated daily for 12 months, days depressed exceeded days manic by a factor of 3.[2] During the year, these patients had depressive symptoms for an average of 121 days (nearly one third of the year), compared with 40 days (one tenth of the year) for mania or hypomania (Figure 1). These differences in days of illness occurred even though the patients had more acute manic episodes (mean 4.9 episodes per year) than depressive episodes (mean 3.4 episodes per year).[2] Similar findings were reported by Judd and colleagues[3] in weekly evaluations of symptoms in patients with bipolar I disorder over an average of almost 13 years of follow-up.

In both studies,[2,3] on average, patients were symptomatic for almost half of the time, despite naturalistic treatment and close monitoring. Only 33% of patients could be considered relatively well and minimally impaired

Figure 2. More Dysfunction From Depression Than Mania in Outpatients Who Screened Positive for Bipolar Disorder on the Mood Disorder Questionnaire[a]



[a]Adapted with permission from Calabrese et al.[23]
[b]Within 12 months prior to survey.
[c]Within 4 weeks prior to survey.

by their illness during the follow-up year in the study of Post et al.[2] More severe symptoms of depression were predicted by an earlier age at onset of depression, 10 or more episodes of depression, a history of limited occupational functioning, and a depressed mood at entry into the network.[2,6]

Another important finding from these longitudinal studies was the extent of disability between episodes of acute illness in bipolar disorder. Two studies found that subsyndromal symptoms, including mild or minor depressive symptoms, were equally or more frequent than major depressive symptoms in patients with either bipolar I disorder[3] or bipolar II disorder.[4] These findings suggest that, in many patients with bipolar disorder, the pattern of treated illness is more chronic than previously thought. In the study by Post et al.,[2] 26.4% were ill more than three quarters of the year, 6.6% had chronic depression, and another 9.3% had virtually continuous depressive cycling, including very fast mood switching frequencies. Another 34.9% showed patterns of intermittent major depressions. Overall, about 47% of patients reported a past history of rapid cycling (4 episodes per year), and again, despite naturalistic treatment by specialists in bipolar illness, most continued to show rapid cycling as documented in the prospective year.[2,6]

Suicide

The disproportionately high association of bipolar depression with suicide is further proof of the magnitude of the individual burden of illness. Completed suicide is high in patients with bipolar I disorder, occurring in up to 20% of patients.[21] In a survey of patients with bipolar I or II disorder, a prior history of a medically serious suicide attempt was significantly associated with the number of hospitalizations for depression, as well as increasing rates of suicidal thoughts while depressed.[22] Suicide attempts in these patients were also significantly related to previous life events, such as a history of childhood adversities and stressors, and more current difficulties, such as loss of social or medical support. Lower educational and financial status, lack of a confidant or marital partner, as well as adverse characteristics of illness, such as more psychiatric and medical comorbidities and genetic vulnerability (family history of suicide or substance abuse), were also associated with attempted suicide.[22]

Work, Family, and Social Life

Disability related to bipolar depression affects many external and social aspects of patients' lives. Episodes of depression are associated with greater impairment in work, family, and social life than episodes of mania (Figure 2).[23] Similarly, the presence of subsyndromal depressive symptoms is strongly associated with functional disability in patients with bipolar disorder.[5]

COMPLEXITIES OF LONG-TERM TREATMENT

Bipolar depression has proved to be a complex syndrome to treat with available psychotropic agents, and use of unimodal antidepressants may further complicate the course. Traditional antidepressants, even when administered with a mood stabilizer, can result in a switch to treatment-emergent hypomania or mania.[24] In the latest analysis of the long-term outcome when an antidepressant (bupropion, sertraline, or venlafaxine) was added to a mood stabilizer for treating bipolar depression, only 16% of the intent-to-treat trials demonstrated both a good acute (10 week) and continuous (≈ 1 year) persistence of antidepressant response without a corresponding switch into full hypomania (≥ 7 days) or mania (associated with dysfunction).[25] These results are similar to the 15% response for at least 2 months when any antidepressant was added to a mood stabilizer.[26] However, in this very small subgroup of those who remained well (85% having already failed to sustain an antidepressant response or having switched), the discontinuation of the antidepressant may increase the risk of depressive relapse over the course of the subsequent year.[26,27]

Furthermore, long-term mood stabilizer therapy, which is necessary to avoid depressive and manic relapses, is associated with a range of side effects that may hinder treatment adherence. The appropriate choice and sequencing of the large array of agents available to treat bipolar depression (lithium, anticonvulsants, mood stabilizers, antidepressants, atypical antipsychotics, and a wide range of adjunctive treatments) have not been adequately studied.[28]

Studies have demonstrated that patients with bipolar mania were significantly more likely than patients with bipolar depression to achieve remission of symptoms with standard treatments.[29,30] In addition, median time to recov-

ery was significantly longer for patients with depressive episodes than for patients with manic episodes. Thus, there is a great need for new approaches and initiatives to better characterize the optimal acute, and especially the long-term, treatment approaches to bipolar depression.[24–29]

ECONOMIC BURDEN OF BIPOLAR DISORDER

The economic burden imposed by health care costs of bipolar disorder is high, although this area is not well studied. In an analysis of costs from a national database of health insurance plans, bipolar disorder was the most expensive behavioral health diagnosis for patients and for insurance plans.[31] Patients with bipolar disorder had a high overall rate of hospital admission for behavioral health care (39%), higher than the rate (35%) for patients with substance abuse diagnoses and a specific rate of admission for bipolar disorder of 13%.[31] Expenditures for hospitalization were 1.8 times higher than costs for outpatient care in this population.[31] In an earlier study, the total annual costs for bipolar disorder in 1991 in the United States were estimated to be $45 billion, including $7 billion in direct costs (inpatient and outpatient care) and $38 billion in indirect costs.[32] Indirect costs included lost productivity of wage earners, homemakers, caregivers, persons in institutions, and persons who committed suicide.[32]

FAMILY BURDEN OF BIPOLAR DEPRESSION

Support from family, significant others, and friends is integral to the successful treatment and well-being of patients with bipolar depression. However, studies of the burden on these individuals suggest that they often find their role difficult to sustain and detrimental to their own health and quality of life.[33–35] Relatives reported that their own employment was difficult because of responsibilities toward the patient and that household finances were impaired because of patients' inability to work. Social and leisure activities were often restricted as well.[33] Moreover, many first-degree relatives of patients with bipolar I disorder may also have bipolar disorder and other mood disorders, thus increasing the burden on family life and their own disability.

Traditionally, the role of caregivers in bipolar disorder has not been considered in a systematic way, and caregivers may not be given enough information about the patient's illness or advice about how to cope with it.[33] Efforts are needed to educate caregivers about practical coping mechanisms, approaches for enhancing treatment outcome, and ways to relieve some of their burden. Including caregivers in the therapeutic process has been shown to have a positive effect on the course of the patient's illness.[36]

EARLY-ONSET BIPOLAR DISORDER

Approximately one third of patients with bipolar disorder develop significant symptoms before the age of 15, and the prevalence in adolescence is approximately 1%.[8,37] In children, bipolar disorder has serious adverse effects on development, social functioning, and academic performance.

Several surveys document earlier ages at onset of bipolar disorder in successive generations since World War I (i.e., the cohort effect).[38] In addition, offspring of parents with bipolar disorder were shown to have earlier onset than their parents, by 6 to as many as 16 years (i.e., the anticipation effect).[38] In some studies, offspring also had more frequent episodes during the course of their illness compared with their parents.[38] These birth cohort and anticipation effects suggest the likelihood of even further increases in the occurrence of bipolar disorder in children and adolescents in the future.

These trends may also predict an increased burden of bipolar disorder on adults and on society in the future, due to correlations between an earlier age at onset and a more severe course of illness in later life. Earlier age at onset of the illness has been associated with greater rates of comorbidity and substance abuse in adults with bipolar disorder, as well as more frequent episodes of illness.[8,9] Further, adult patients with earlier age at onset may have diminished response to drug therapy and more suicide attempts than patients with a later onset.[22,39]

Although the diagnostic criteria for bipolar disorder in children are the same as for adults, it is more difficult to diagnose correctly, due to many symptoms and behaviors that overlap with ADHD and other common childhood psychiatric disorders, such as conduct and oppositional/defiant disorder. Bipolar disorder is often comorbid with ADHD or individual symptoms of ADHD may be present, resulting in more severe illness and disability.[40] However, some differences in patterns of onset and specific symptoms are beginning to be recognized. In very young children, there is now consensus that the illness can present with a bipolar disorder not otherwise specified (NOS) presentation. In these instances, rather than the classical discrete episodes of mania and depression with well intervals, as is the case in the majority of adults, youngsters present with extremes of mood lability and irritability without clear, prolonged well intervals. Behavior may be extreme, with early onset of poor frustration tolerance, tantrums, and aggression. Key early features that distinguish prepubertal-onset bipolar disorder from ADHD include the presence of brief or extended periods of euphoria and sleep disturbance. Later (after age 5) periods of withdrawal, change in appetite, somatic complaints, and suicidal ideation distinguish the 2 groups (Luckenbaugh DA, Findling RL, Leverich GS, et al.; unpublished data, 2005). Other symptoms precluding a diagnosis of pure ADHD

include homicidal thoughts or acts, psychosis (either delusions or hallucinations), decreased need for sleep, brief or extended periods of mood elevation, or increased sexual interest or acts in the absence of a history of sexual abuse.[41] Making an appropriate diagnosis is of considerable importance as treatment with antidepressants and stimulants in the absence of a mood stabilizer may exacerbate or destabilize the illness.[42,43]

These distinctions are important for early diagnosis and treatment of bipolar disorder in children and adolescents.[41,43] Although effective therapies in early-onset disease have the potential to greatly reduce the overall burden of bipolar illness, there are very few randomized clinical trials of treatments in this age group. More research is needed to identify effective therapies for children and adolescents with bipolar disorder, as well as those with prepubertal onset of dysthymia and depression, especially if the depression is associated with psychomotor retardation or psychosis, because these children are at considerable risk (30%–50%) for converting to bipolar disorder.[44,45]

CONCLUSIONS

Bipolar depression accounts for a large part of the morbidity and mortality associated with bipolar disorders. However, recognition, diagnosis, and treatment of bipolar depression are often delayed, resulting in long periods of functional disability for patients, a significant burden on caregivers, and, directly and indirectly, a substantial burden on the economy. Aggressive management and early effective pharmacologic therapies are needed to help overcome the impact of acute depressive episodes and persistent interepisodic subsyndromal symptoms.

While there is some consensus on how to treat an initial acute episode, i.e., the first goal, greater attention needs to be paid to the second goal, i.e., prevention of recurrence and perhaps disease progression; the third goal, i.e., treatment of breakthrough recurrent episodes; and the fourth goal, i.e., addressing and treating comorbidities and other causes of long-term disability.

Given the increasing recognition of the considerable morbidity of patients with bipolar disorder treated in clinical practice, the well-replicated brain neurobiological findings associated with the illness,[46] and the new appreciation of neurotrophic and neuroprotective effects of lithium and valproate,[47,48] bipolar illness should be fundamentally reconceptualized in 2 ways. First, it is a highly recurrent, potentially lethal, and progressive medical illness with diverse biochemical, physiologic, and structural changes in the brain, endocrine system, and other organ systems. Second, its adequate pharmacologic treatment helps not only to prevent episode recurrence, but may also reverse or prevent some of the neuropathologic changes of the illness itself. These conceptualizations should renew and propel efforts to recognize and treat bipolar disorders earlier in adults and children and support new research and public health paradigms to help improve the acute and long-term prophylactic treatment of bipolar illness.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol, Carbatrol, and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), sertraline (Zoloft), venlafaxine (Effexor).

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