

The Importance of Subsyndromal Symptoms in Bipolar Disorder

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Bipolar disorder continues to be characterized by poor clinical and functional outcomes in many patients. Poor outcomes may be related to subsyndromal symptoms, defined as symptoms that fail to meet the full diagnostic criteria for a mood episode. Several recent studies indicate that subsyndromal symptoms in bipolar disorder are strongly associated with deficits in both social and occupational functioning. Furthermore, subsyndromal symptoms appear to increase the risk of relapse. Combined, these factors emphasize the importance of aggressive treatment strategies at the onset of subsyndromal symptoms. In addition, the use of subsyndromal symptoms to broaden the diagnostic criteria for bipolar disorder is receiving increased attention. This article reviews and discusses these important issues. *(J Clin Psychiatry 2004;65[suppl 10]:24–27)*

Interest in subsyndromal symptoms, i.e., those that fail to meet the full diagnostic criteria for a mood episode, increased when, in 1989, Wells et al.¹ reported that patients with depressive symptoms (with or without a diagnosis of major depression or dysthymia) had significantly worse functioning than did patients with 8 other chronic medical conditions. Data were collected from 11,243 outpatients from 3 health care provision systems in the United States and revealed that patients who had either current depressive disorder or depressive symptoms in the absence of a depressive disorder tended to have worse physical, social, and role functioning; worse perceived current health; and greater bodily pain than did patients with no chronic conditions. Poor functioning, associated with depressive symptoms such as excessive number of days spent in bed, was comparable to or worse than that typically associated with 8 chronic medical illnesses that included hypertension, diabetes, and arthritis. Findings indicated that the considerable number of outpatients who experienced diminished functioning were likely experiencing subsyndromal symptoms, since their symptoms occurred in the absence of a diagnosable depressive disorder. More recently, the importance of subsyndromal mood symptoms within the context of a known mood disorder is becoming apparent. In bipolar disorder, subsyndromal

symptoms (especially depressive symptoms) are common, interfere with functioning and quality of life, and may increase the risk of relapse.

HOW COMMON ARE SUBSYNDROMAL SYMPTOMS IN BIPOLAR DISORDER?

Judd and colleagues² reviewed the long-term symptomatic status of a cohort of 146 patients with bipolar I disorder who had entered the National Institute of Mental Health Collaborative Depression Study from 1978 through 1981. Long-term follow-up revealed that patients with bipolar I disorder were symptomatically ill 47.3% of weeks throughout a mean of 12.8 years and that depressive symptoms (31.9% of total follow-up weeks) predominated over manic/hypomanic symptoms (8.9% of total weeks) or cycling/mixed symptoms (5.9% of total weeks). Notably, subsyndromal, minor depressive, and hypomanic symptoms were approximately 3 times more common than syndromal-level major depressive and manic symptoms (29.9% vs. 11.2%). Also in bipolar I disorder, Keitner and colleagues³ assessed 74 patients and reported that greater than half of the patients disclosed residual symptoms of depression (54%) and mania (68%).

More recently, Joffe and colleagues⁴ examined time spent in minor and subsyndromal mood states in a cohort of well-characterized bipolar I and II patients who were followed prospectively for an average of 3 years. Patients in the total sample and within each bipolar subtype spent about half of their time euthymic and the rest of the time in mood states of varying degrees of severity. However, the majority of time was spent with minor and subsyndromal symptoms, both manic and depressive. In patients with bipolar II disorder, Benazzi⁵ reported residual symptoms in 44.9% of patients. In total, these studies and others^{6,7}

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indicate that subsyndromal symptoms, while not well studied to date, appear to be common in patients with both bipolar I and II disorders.

RISK OF RELAPSE ASSOCIATED WITH SUBSYNDROMAL SYMPTOMS

Subsyndromal symptoms appear to be associated with an increased risk of relapse into subsequent episodes in bipolar patients.^{8,9} Goodnick and colleagues⁸ studied 98 patients who received lithium prophylaxis for a mean of 45 months. Most of these patients (N = 91) were diagnosed with a bipolar disorder. The investigators hypothesized that those patients who experienced more mood changes, even if those changes did not reach the level of a full-blown episode, would experience a higher rate of relapse. Their results supported their hypothesis—number of mood shifts was positively correlated with rate of relapse into both manic ($r = 0.56$) and depressive ($r = 0.58$) episodes ($p < .001$ for both). Subsyndromal manic symptoms predicted manic relapse, while depressive symptoms predicted depressive relapse.

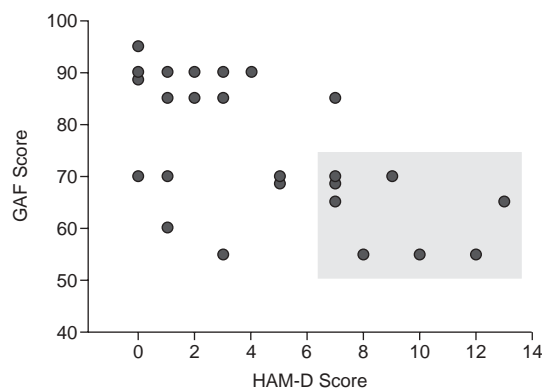
Tohen and coworkers¹⁰ prospectively followed 75 manic patients for 4 years to determine outcome and recovery after a manic episode. A variety of factors contributed to a negative outcome and relapse, including poor functioning prior to the index episode, history of previous episodes, and alcoholism, to name a few. The investigators also assessed presence of interepisode symptoms at 6 months. Patients with these symptoms had a significantly higher risk of relapse during the remainder of the study (odds ratio = 1.5, 95% confidence interval = 1.0 to 2.2, $p = .05$).

In a double-blind, prospective study⁹ of lithium maintenance therapy (N = 94), 68% of the major affective relapses occurred after a subsyndromal period. In fact, subsyndromal symptoms increased the risk of relapse 4-fold. Although more patients with hypomania (76%) than subsyndromal depressive symptoms (39%) had a major affective relapse, patients were 2 times more likely to develop depressive than hypomanic symptoms between acute episodes. Subsyndromal symptoms, as demonstrated by these studies, very often result in a relapse into a full episode of depression or mania.

IMPAIRMENT ASSOCIATED WITH SUBSYNDROMAL SYMPTOMS IN BIPOLAR DISORDER

In bipolar disorder, subsyndromal symptoms—particularly depressive symptoms—are positively correlated with deficits in both social and occupational functioning.^{11–17} Altshuler and coworkers¹² studied 25 male subjects with DSM-III-R bipolar I disorder and found that Global Assessment of Functioning (GAF) scale scores were nega-

Figure 1. Subsyndromal Depression (HAM-D score > 7) Predicts GAF Impairment in 25 Male Subjects^a



^aReprinted with permission from Altshuler et al.¹²
Abbreviations: GAF = Global Assessment of Functioning,
HAM-D = Hamilton Rating Scale for Depression.

tively correlated with depressive symptoms as measured by the Hamilton Rating Scale for Depression (HAM-D; $r = -0.61$, $df = 23$, $p = .001$). Interestingly, these subjects were euthymic for the previous 3 months, all were receiving treatment for bipolar disorder, and all had a HAM-D score ≤ 13 (i.e., symptoms were below the diagnostic threshold). Subjects who had HAM-D scores of 7 to 13 had more functional impairment than did patients who had HAM-D scores ≤ 3 (Figure 1).

In a 48-week longitudinal study, Bauer et al.¹⁸ investigated the degree to which disease outcome was correlated with functional outcome and direct treatment costs. They also examined whether similar demographic or clinical characteristics predicted disease and functional outcome and health care costs. Twice a month for 48 weeks, 43 outpatient veterans with bipolar disorder were given structured interviews to determine disease and functional outcome. Direct mental health treatment costs were estimated from the Veterans Affairs database and through patient interviews. Results indicated that poor functional outcome was correlated with depressive but not manic symptoms during follow-up. Additionally, several clinical but not demographic characteristics predicted symptom status. Ongoing depressive symptoms appeared to be strongly associated with functional outcome.

MacQueen and colleagues¹⁹ examined detailed life charting data from 138 patients with bipolar disorder and reported that patients with subsyndromal symptoms had high rates of comorbid anxiety disorders, eating disorders, and poor functioning compared with euthymic patients. In addition, patients with subsyndromal symptoms had as many clinic contacts and medication trials as patients with full episodes of illness. These studies suggest that the impact of subsyndromal symptoms on functioning and quality of life is comparable to that of full mood episodes.

Table 1. Lifetime Prevalence of Manic Symptoms Based on the Epidemiologic Catchment Area Community Sample^a

Lifetime Manic Spectrum Groups	N	Lifetime Prevalence (%)
Manic episode ^b	146	0.8
Hypomanic episode ^c	87	0.5
Subsyndromal manic/hypomanic symptoms ^d	940	5.1

^aData from Judd and Akiskal.²⁷^bPersons with a lifetime manic episode.^cPersons with 3 or more simultaneous symptoms of mania, but not qualifying for a manic episode.^dPersons who experienced 2 or more simultaneous symptoms of mania during their lifetime, but not qualifying for a manic or hypomanic episode.

SHOULD SUBSYNDROMAL SYMPTOMS BE USED TO DIAGNOSE BIPOLAR SPECTRUM DISORDERS?

Conventionally, prevalence rates of bipolar disorder have been cited at 1% based on the U.S. Epidemiologic Catchment Area (ECA) database^{20,21} and 1.6% according to the National Comorbidity Survey (NCS).²² Increasingly, however, the concept of a broader bipolar spectrum is being considered. For example, Akiskal et al.²³ proposed that hypomanic expressions with various admixtures of depression may be the most common manifestations of bipolar disorder. Community studies that utilize these broader definitions place the prevalence of bipolarity 3 to 5 times higher than conventionally thought.^{24–26}

Judd and Akiskal²⁷ recently conducted a study estimating rates of both manic/hypomanic and subsyndromal manic/hypomanic symptoms using national data derived from the ECA database. In their analysis, all respondents (N = 18,252) who participated in the lifetime prevalence interview of the ECA household sample were classified into 4 mutually exclusive categories based on the presence, severity, or absence of manic symptoms or episodes. Manic episode, hypomanic episode, and subsyndromal symptoms of mania were the 3 groups that constituted the manic spectrum, and subjects in these groups were compared with the comparison group that included individuals who reported no lifetime mental disorder or any manic/hypomanic or subsyndromal manic/hypomanic symptoms. Odds ratios were calculated on lifetime service utilization for measures of adverse psychosocial outcome, mental health problems, and suicidal behavior. Results revealed that although the lifetime prevalence for manic episode was 0.8% and 0.5% for hypomania, the inclusion of subthreshold subjects yielded a total lifetime prevalence of 6.4% for the bipolar spectrum (Table 1). Additionally, lifetime subsyndromal manic symptoms appeared to be 3 times more common than full manic or hypomanic symptoms. All 3 manic spectrum groups experienced greater marital disruption, increased lifetime use of health services, and increased need for welfare and disability benefits, as well as a higher incidence of suicidal behavior

when compared with the group without mental disorders or manic symptoms. In sum, subthreshold bipolar disorder appeared to be at least 5 times more prevalent than DSM-based syndromal bipolar disorder.

However, broader application of the diagnostic criteria is not without risk. Clinically, the fact that bipolar disorder includes symptoms of reckless behavior is problematic because the diagnosis has become appealing to individuals who are trying to escape personal responsibility for problematic behavior. Scientifically, dilution of the diagnosis may adversely affect research efforts to understand the neurobiology and genetics of the disorder.²⁸ While further refinement of the diagnosis to yield the most scientifically and clinically valid nosology is an important goal, especially if doing so will decrease patient morbidity, some degree of caution is warranted.

CONCLUSION

Subsyndromal depressive symptoms are common, interfere with functioning and quality of life, and may increase the risk of relapse. As such, aggressive evaluation and treatment at the onset of subsyndromal symptoms should be considered. A caveat worth considering is that medications used to treat bipolar disorder may induce side effects such as sedation and cognitive impairment, which can be difficult to distinguish from subsyndromal symptoms of bipolar depression. Some authors suggest that bipolarity may include subsyndromal hypomania with various admixtures of depression, thus increasing the incidence of bipolarity to a rate that is 3 to 5 times higher than conventionally thought. These and other challenges associated with subsyndromal symptoms underscore the need for further research into this area, including study in larger populations to ascertain which symptom clusters are most highly associated with clinical liability.

Drug name: lithium (Eskalith, Lithobid, and others).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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