Subsyndromal Depression Is Associated With Functional Impairment in Patients With Bipolar Disorder

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Background: The purpose of this study was to assess whether a relationship exists between mild depressive symptoms and overall functioning in subjects with bipolar disorder.

Method: Twenty-five male subjects with bipolar I disorder (DSM-III-R criteria), who had not experienced a DSM-III-R episode of mania, hypomania, or major depression for 3 months as determined using the Structured Clinical Interview for DSM-III-R, were evaluated for degree of depressive symptoms using the Hamilton Rating Scale for Depression (HAM-D) and for overall functional status using the Global Assessment of Functioning (GAF, DSM-IV Axis V).

Results: GAF scores were significantly negatively correlated with HAM-D scores ($r = -0.61$, $df = 23$, $p = .001$), despite the fact that no patient had a HAM-D score high enough to be considered clinically depressed.

Conclusion: The results of this study support a relationship between subsyndromal depressive symptoms and functional impairment in bipolar subjects, despite their not meeting threshold criteria for a major depressive episode. These findings raise the possibility that in some patients with bipolar disorder subsyndromal depressive symptoms might contribute to ongoing functional impairment.

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Subsyndromal depression has been operationalized as the presence of 2 or more symptoms of depression, for most or all of the time in a 2-week period, in persons who do not otherwise meet DSM-IV criteria for a current major depressive disorder or dysthymia.[1–4] Some studies[3–6] have concluded that the deficits in both occupational and psychosocial functioning associated with the presence of several depressive symptoms are nearly as severe as those associated with major depression. Decrements in functioning associated with subsyndromal depressive symptoms have been observed both in those individuals with a history of unipolar depressive disorder and in the general medical population with no such prior history.[3,5–13] The Medical Outcomes Study[8] reported that patients with depressive symptoms had significantly worse social functioning than patients with any of 8 other chronic medical conditions studied and significantly worse role functioning and current health than patients with every other condition except advanced coronary artery disease and angina. Another large-scale epidemiologic survey[9] found that patients with as few as 2 symptoms of depression had a 17.8% increased risk for work absenteeism. Further, subsyndromal depression has been linked to increased health service utilization and the need for public assistance.[9]

Patients with bipolar disorder are twice as likely to develop depressive rather than hypomanic symptoms between acute episodes of illness.[14] The relationship between subsyndromal depressive symptoms and functional impairment in the bipolar population has not been well studied. As in unipolar depressive disorder,[15] interepisode subsyndromal depressive symptoms in patients with bipolar illness are associated with an increased risk for relapse.[14,16–18] In the only study that assessed the relationship of subsyndromal depressive symptoms to work or role function in persons with bipolar illness,[19] the average severity of depressive symptoms (both syndromal and subsyndromal) was a better predictor of occupational outcome than the total number of threshold (e.g., syndromal) relapses. Similarly, a recent 48-week longitudinal study of 43 outpatients with bipolar disorder[20] determined that the presence of depressive symptoms during follow-up was the variable most consistently correlated with poor functional outcome.

To assess the relationship between subsyndromal depressive symptoms and functioning in bipolar subjects, we compared ratings on the Hamilton Rating Scale for Depression (HAM-D)[21] with ratings on the Global Assessment of Functioning (GAF, DSM-IV Axis V).[22] These ratings were obtained from subjects enrolled in a study that was not designed to explore this relationship, but rather one with a different purpose in which these variables were collected. Both ratings were obtained for subjects who had not experienced a DSM-III-R episode of mania, hypomania, or major depression for 3 consecutive months.

METHOD

Twenty-five male bipolar I subjects (DSM-III-R criteria) from the Bipolar Disorders Clinic, West Los Angeles (Calif.) VA Medical Center, gave informed consent to participate in a neuroimaging (magnetic resonance imaging [MRI]) study and to be interviewed using the Structured Clinical Interview for DSM-III-R (SCID), selected mood scales, and measures of overall functioning. Subjects included psychiatric outpatients from the West Los Angeles VA Medical Center who carried a diagnosis of bipolar disorder and who had no health problems that would exclude their participation in an MRI study. As part of the protocol, subjects could not meet DSM-III-R criteria for current major depression, hypomania, or mania as determined using the SCID–Patient Version (SCID-P),[23] mood module section, for 3 consecutive months. Subjects were interviewed using the SCID-P by a rater trained by the Diagnostic and Psychopathology Unit of the UCLA Research Center for Severe Mental Illnesses. Training included viewing videotapes of SCID-P interviews with accompanying "gold standard" ratings and conducting SCID-P interviews while an expert diagnostician co-rated the interview. Kappa statistics were used to compare the presence or absence of each symptom or critical SCID-P item rather than to evaluate classification of the diagnosis. Minimum standards of acceptable symptom agreement were an overall kappa of 0.75, kappa specificity of 0.75, and sensitivity of 0.75.

Once a subject's SCID-P results were below SCID-P criteria for a mood episode for 3 consecutive months, he underwent an MRI and was rated using a series of mood rating scales. On the day of the scan, subjects were evaluated for depressive symptoms using the HAM-D.[21] Manic symptoms were assessed using the Young Mania Rating Scale (YMRS).[24] Ratings of overall functional status were obtained using the GAF. Similar training as for the SCID-P (described above) was carried out for the use of each of these scales. The original GAF instructions call for rating symptoms *or* functioning. Since many other measures of mood symptoms were obtained as part of the evaluation, the rater was specifically instructed to use the GAF to measure psychosocial functioning in the month prior to rating. The final sample included 14 subjects with bipolar illness and no other Axis I disorder and 11 subjects with bipolar disorder and a history of comorbid alcohol dependence who had been sober for at least 9 months prior to the time of assessment (mean ± SD = 6.7 ± 5.9 years).

The majority of patients (23/25) were taking lithium as their primary mood stabilizer (1 took divalproex sodium, 1 took carbamazepine). Fourteen subjects were on treatment with at least 1 additional psychotropic medication (5 taking an antidepressant, 3 taking an additional mood stabilizer, 5 taking an antipsychotic, 1 taking a benzodiazepine). All ratings were obtained at the same time and were done by a single rater trained in using these measures. At the time of data collection, there was no plan to investigate the relationship of depression to GAF score. Given that the data existed, we chose for the purpose of the current study to explore the correlations, if any, between mood and role functioning.

RESULTS

The patient population at the time of the MRI scan had a mean ± SD YMRS score of 2.2 ± 3.3 and mean HAM-D score of 4.9 ± 4.5. HAM-D scores ranged from 0 to 13. In this small sample, the mean GAF for the entire sample was 75 ± 13.5. However, GAF distribution was clearly bimodal, with 1 group clustered around a mean ± SD of 64.3 ± 6.8 (range, 55–70) (N = 14, low GAF, "poorer functioning") and the other group clustered around a considerably higher mean of 88.6 ± 3.2 (range, 85–95) (N = 11, high GAF, "good functioning"). Subjects with bipolar disorder with and without a history of alcohol comorbidity were approximately equally distributed across the 2 groups. The difference between the highest in the "poorer functioning" group and the lowest in the "good functioning" group was almost 2 standard deviations and far outshadowed the clinical significance of within-cluster variation.

The demographic and illness characteristics of the high GAF and low GAF groups are shown in Table 1. The groups did not differ significantly on any variable. However, 55% of the high GAF group, compared with 29% of the low GAF group, had had no hospitalizations in the last 5 years.

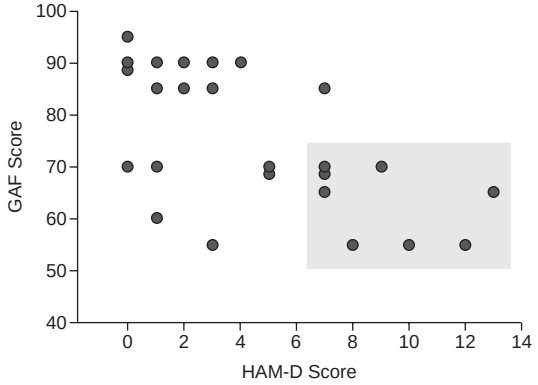
Figure 1 displays the relationship between GAF scores and HAM-D scores. GAF scores were significantly negatively correlated with HAM-D scores ($r = -0.61$, $df = 23$, $p = .001$). This correlation remained significant in the bipolar group without alcohol comorbidity ($r = -0.70$, $p = .005$; $N = 14$), and it approached significance in the bipolar group with a history of alcohol comorbidity ($r = -0.51$, $p = .11$; $N = 11$). The difference between the correlation in these subgroups is not significant ($z = 0.66$,

Table 1. Demographic, Illness, Age, Marital, and Educational Characteristics of the High and Low Functioning Bipolar Groups[a]

Variable	Low GAF[b] (N = 14)	High GAF[c] (N = 11)	F (df = 1,23)	χ^2	p Value
Age, y	51.6 ± 9.3	51.8 ± 16.7	3.2	…	.97
Education, y	15.1 ± 2.3	16.5 ± 2.6	1.21	…	1.0
Married, N (%)	2 (14)	5 (46)	…	2.97	.08
Hospitalization in last 5 y, N (%)	4 (29)	6 (55)	…	1.73	.19
History of psychosis, N (%)	6 (43)	2 (18)	…	1.72	.19
Duration of illness, y	26.1 ± 10.8	23.9 ± 12.9	1.43	…	.54
Age at onset of illness, y	25.5 ± 9.8	27.9 ± 10.6	1.17	…	.77
Duration of alcohol use, y	14.8 ± 12.1	18.3 ± 11.5	1.12[d]	…	1.0
Currently on antidepressant treatment, N (%)	5 (35.7)	1 (9.1)	…	2.39	.12

[a]Values shown as mean ± SD unless otherwise noted. Abbreviation: GAF = Global Assessment of Functioning.
[b]GAF score from 55 to 70.
[c]GAF score from 85 to 95.
[d]df = 1,9.

Figure 1. Subsyndromal Depression (HAM-D score > 7) Predicts GAF Impairment[a]



[a]Abbreviations: GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression.

p = .51). The "good functioning" group (N = 11) had a mean HAM-D score of 2.1 ± 2.1, whereas the mean HAM-D score for the "poorer functioning" group (N = 14) was 6.3 ± 4.0. Although 82% (N = 9) of the "good functioning" group had HAM-D scores of 3 or less, this was true for only 29% (N = 4) of the "poorer functioning" group. In the "poorer functioning" group, 57% (N = 8) had HAM-D scores ranging from 7 to 13.

DISCUSSION

In this study, the rater's evaluation of global functioning (GAF) in patients with bipolar disorder was significantly negatively correlated with ratings of patients' depressive symptoms (HAM-D), although no patient met SCID-P DSM-III-R criteria for major depression at the time of assessment or had HAM-D scores considered in the "syndromally depressed" range. Despite the relatively low mean and variance of HAM-D scores, many of the subjects who rated more poorly on the GAF had subthreshold HAM-D scores (7–13). Interestingly, scores of global functioning divided the subjects into 2 distinct groups, a "poorer functioning" cluster and a "good functioning" cluster. The majority of patients in the good functioning group had a score of 3 or less on the HAM-D, whereas a patient with a score of < 7 is usually considered euthymic. In the poorer functioning group, over half had scores of 7 or more, but substantially lower than 18, the usual HAM-D cut-off score suggesting clinical depression.

Several limitations of this study must be considered. First, because the study was not originally designed to assess functional outcome, only 1 crude overall global measure of functioning (GAF) was obtained. Second, one rater rated both the symptom (HAM-D, YMRS) and the function (GAF) scales. The GAF is a clinician-rated assessment of functioning and therefore might be unduly influenced by the clinician's view of the patients' affective symptoms.[25–27] However, the clinician rating the GAF understood first that all patients were not in a clinical threshold episode of depression, hypomania, or mania and second that the GAF was not to be used to rate mood symptoms since the other scales used would be assessing them. Further, because the idea to correlate HAM-D scores with GAF scores was not conceived until after data collection, rater bias in this regard was unlikely. Another limitation is that the bipolar population studied were male veterans; it is unclear whether these results would generalize to women or to other individuals with bipolar disorder not receiving their care at a Veterans Administration hospital.

Despite these limitations, the fact that higher HAM-D scores were associated with poorer functioning (as assessed using the GAF) in patients with bipolar illness, even though patients were not clinically depressed, is of note and has not previously been reported in the bipolar population. Our results suggest that, as in subjects with unipolar depressive disorder, subthreshold depressive symptoms in subjects with bipolar disorder are associated with some disability or functional impairment.

The DSM-IV[22(p377)] reports that in 20% to 30% of people suffering from a major depressive episode, depressive symptoms insufficient to meet full criteria for a major depressive episode may persist and may be associated with some disability. Documentation of recent psychiatric course (except for hospitalization over the last 5 years) was insufficient in the current study to accurately determine how many subjects had a recent episode of depression prior to study entry and therefore, despite being

euthymic by DSM-III-R criteria, may have been in the recovery phase following a recent major depressive episode. We imagine some of our patients were recovering from a threshold episode, while many had not experienced a recent threshold episode. Since subjects were euthymic by DSM-III-R SCID-P criteria for at least 3 months prior to the study, it is unlikely (but not impossible) that the symptoms for some represented a still-resolving depressive episode.

It has been documented that patients with bipolar illness often suffer from residual functional impairment and poor role function adjustment, despite mood stabilization after threshold episodes.[17,18,28–34] The etiology of this functional impairment is not well understood. However, functional impairment constitutes a major public health problem that imposes a profound economic burden on society. Although direct treatment costs for patients with bipolar disorder are estimated at $7 billion per year, the annual indirect costs (e.g., missed days from work, impaired work performance, work disability) are approximately $38 billion. Diminished annual productivity due to impaired work performance and absenteeism has been estimated at $17 billion and $11.7 billion, respectively.[35,36] Clearly, it is important to learn more about the etiology of residual functional impairment in order to formulate appropriate interventions and treatment strategies.

Our preliminary data suggest a relationship between subsyndromal depressive symptoms and role function. The direction of the relationship is as yet unclear. One possibility is that subsyndromal depressive symptoms are primary and contribute to the development of impairment in work/role function. If this is true, then a more aggressive approach to the treatment of subsyndromal depressive symptoms might be indicated and studies aimed at assessing whether pharmacologic or cognitive-behavioral approaches are helpful in improving subsyndromal depressive symptoms would be indicated. Currently, many clinicians hesitate to prescribe antidepressants to bipolar patients with subsyndromal depressive symptoms for fear of precipitating mania or cycle acceleration.[37,38] However, if subsyndromal depressive symptoms in fact have a significant influence on functional ability, then clinician reluctance to treat these symptoms may contribute to ongoing work impairment. Alternatively, a causality may exist in the opposite direction, whereby poor social/occupational functioning may contribute to the development of depressive symptoms. The direction of causality (that is, the reason[s] for the association of depressive symptoms with poor functioning) could not be teased apart in the present study.

Several possibilities that could not be adequately assessed in the current study might have contributed to differences between groups. First, it is possible that recency of a preceding episode is associated with poorer functioning. We do not have data on recency of outpatient episodes. However, our high and low GAF patient samples differed in that the group with low GAF scores had more persons (although not significantly) who had been hospitalized at least once in the past 5 years. It is possible that a consequence of hospitalization is difficulty with functional recovery and that this in turn contributes to demoralization and depressive symptoms. If that is true, vocational interventions and perhaps supportive psychotherapy interventions might be more appropriate than pharmacologic/cognitive behavioral strategies for the treatment of the depressive symptoms. Another possibility is that medications differentially impact cognition and function and that this in turn influences mood. Although we are exploring this possibility in other studies, we do not have sufficient data to adequately assess this possibility in the current study.

These very preliminary observations suggest that subthreshold depressive symptoms may contribute to poor functioning in some patients with bipolar disorder. It is possible that greater vigilance regarding treating patients with partial recoveries from depression or with no recent major depressive episode but ongoing subsyndromal depression may markedly impact their overall functioning. Further prospective studies using scales that measure role functioning with greater sensitivity are needed and may help determine causality in the subsyndromal depressive symptom–functional impairment relationship and thus guide appropriate treatment interventions. We are currently pursuing such studies.

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