Mixed Hypomania in 908 Patients With Bipolar Disorder Evaluated Prospectively in the Stanley Foundation Bipolar Treatment Network

A Sex-Specific Phenomenon

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Context: The prevalence of depressive symptoms co-occurring with hypomanic symptoms has not been quantified. Whether there is a greater likelihood for women to experience mixed symptoms has not been resolved.

Objectives: To determine whether mixed hypomania is observed more frequently than euphoric hypomania and whether a sex effect exists in patients with bipolar disorder.

Setting: Academic research settings in the United States (4 sites) and Europe (3 sites).

Participants: Subjects were enrolled in a naturalistic prospective study after providing written informed consent.

Main Outcome Measures: Mixed hypomania was defined at a given visit as a Young Mania Rating Scale score of 12 or higher and an Inventory of Depressive Symptomatology–Clinician-Rated Version score of 15 or higher. Given partial overlap of items from these scales, exploratory analyses were completed assessing instrument overlap affecting the findings.

Results: In 908 patients, 14,328 visits over 7 years were evaluated. Patients with bipolar I disorder were significantly more likely to experience hypomania than those with bipolar II disorder. Of all 1044 visits by patients with hypomanic symptoms, 57% met criteria for mixed hypomania. The likelihood of depression was significantly greater for women during hypomania (P < .001). For women, the probability of mixed symptoms increased with the severity of hypomania and then decreased at the most severe levels of hypomania or mania. When a modified Inventory of Depressive Symptomatology–Clinician-Rated Version was evaluated by removing the 5 overlapping Young Mania Rating Scale items, a significant sex effect persisted for women (P < .001) but not for men (P = .95), owing to the elimination of the items “irritability” and “agitation.”

Conclusions: Mixed hypomania is common in patients with symptoms of hypomania and particularly common in women. Potential overlap of clinical symptom scales should be assessed before study of patients with bipolar disorder symptoms is undertaken.
nia, sometimes called dysphoric hypomania or hypomania with co-occurring depressive symptoms. Few reports provide prospective, real-time, empirical data assessing patients with bipolar disorder, although a number of reports focus on hypomanic symptoms co-occurring during depression in naturalistic clinical settings.21-25

There are clear reasons why recognition of hypomanic symptoms co-occurring with depressive symptoms is clinically important. Patients with bipolar II disorder (BDII) may be misdiagnosed with unipolar depression because of lack of recognition of hypomanic periods.23,26 One contributor to misdiagnosis is the expectation that hypomania is predominantly euphoric.27 A patient may not report mixed hypomanic states (eg, “energized depression”) and may not be directly asked. Moreover, recognition of the presence of mixed symptoms in patients is important in making a treatment selection.10,14 Antidepressant monotherapy can be associated with an increased incidence of mood cycling or lack of response in patients with bipolar disorder.28,29 Appropriate recognition and management of all symptoms are crucial to improving the well-being of patients with bipolar disorder.

The Stanley Foundation Bipolar Treatment Network prospectively studied more than 900 patients for up to 7 years. The results of this report represent “real-time” prospective evaluation of well-characterized patients with bipolar disorder in a naturalistic follow-up study. The primary question was whether depressive symptoms were a rare or common event in those patients experiencing hypomanic symptoms. The hypothesis proposed was that mixed hypomania was more frequently experienced than euphoric hypomania by patients with bipolar disorder. The second hypothesis was whether more women would experience mixed hypomanic symptoms than men.

**METHODS**

Details of the Stanley Foundation Bipolar Treatment Network (1995-2002) are fully described elsewhere.30,31 Briefly, patients provided written informed consent and volunteered for a naturalistic follow-up study in which clinical state and medications were prospectively assessed. All patients were diagnosed using the **DSM-IV-TR**.32 All diagnoses were based on the **DSM-IV-TR** criteria set.9

Patients were seen at least monthly, and ongoing medication changes were made based on need. At each visit, the Young Mania Rating Scale (YMRS), the Inventory of Depressive Symptomatology—Clinician-Rated Version (IDS-C), the Clinical Global Impressions Scale for Bipolar Disorder,16 and the National Institutes of Mental Health Daily Life Chart17 were completed. Across 4 US and 3 international sites, interrater reliability was maintained (κ values: YMRS, 0.7 and IDS-C, 0.85). During the study, more than 900 patients enrolled in the naturalistic follow-up study; patients enrolled in separately defined, open, and double-blind clinical trials were not included.30,38 This decision was based on the possibility of biasing the likelihood of co-occurrence of symptoms owing to the inclusion/exclusion criteria for a given study.

In this study, clinical symptoms of mania and depression were collected prospectively in 908 patients with bipolar disorder. We included all naturalistic follow-up study visits at which both the YMRS and the IDS-C were completed, evaluating symp-
mania or mild mania. Repeated-measures logistic regression analyses were conducted evaluating both linear and quadratic (nonlinear) components of severity. The same statistical methods were applied to analyses of the modified IDS-C from which 5 overlapping items were removed. Because no generally accepted cut points for clinically significant depression exist for the modified IDS-C, analyses were done using several alternative thresholds to ensure that results presented herein were not artifacts of the chosen value.

RESULTS

PATIENT DEMOGRAPHICS AND DURATION OF FOLLOW-UP

A review of the database identified 908 naturalistic follow-up study outpatients (women = 507; men = 401) with bipolar I disorder (BDI) (n = 681); BDII (n = 187); bipolar disorder not otherwise specified (n = 18); or schizoaffective, bipolar type disorder (n = 22) who experienced a visit where the YMRS and IDS-C were both completed. The mean ± SD age was 41.16 ± 11.61 years. Over a period of almost 7 years, the median follow-up was 16 months and the mean ± SD was 22.9 ± 20.9 months. The sample by diagnosis, type of visit, and sex is shown in the Table.

PATIENT VISITS

The portion of the Stanley Foundation Bipolar Treatment Network database used for these analyses was made up of 14,328 patient visits. The median number of visits was 28 and the mean ± SD was 22 ± 17.7. Examining the 25% to 75% middle quartiles of the population, the mean was 17 and the mean ± SD was 22.9 ± 20.9 months. The sample by diagnosis, type of visit, and sex is shown in the Table.

VISITS BY PATIENT NUMBER

Of all visits by patients with hypomania, 596 visits by 277 patients met criteria for mixed hypomania (i.e., 57% of all visits by patients with hypomania or 4.2% of total visits). Only 5 of this group of 277 patients contributed more than 10 visits with mixed hypomania to the total; thus, no single or small group of individuals determined the outcome. In total, these 277 patients contributed 5671 visits to the database; of these visits, 44% involved depression; 5%, hypomania without depression; 11%, mixed hypomania; and 41%, euthymia.

PATIENT DISTRIBUTION BY VISIT TYPE

The Table provides information on the types of visits this group of 908 patients experienced. Five hundred sixteen patients (57%) experienced no visits where hypomanic symptoms were reported or observed, and 392 patients (43%) experienced a visit where hypomanic symptoms were reported or observed. Over the course of follow-up, a majority of patients who experienced a visit where hypomanic symptoms were reported or observed had at least 1 visit where mixed symptoms were reported or observed (277/392 or 71%).

Table. Incidence of Mixed Hypomania and Depressive Symptoms During Hypomania*

<table>
<thead>
<tr>
<th></th>
<th>No Visits With Hypomania Symptoms (n = 516 [57%])</th>
<th>Visits With Hypomania Symptoms (YMRs score ≥12; IDS-C score ≥15) (n = 392 [43%])</th>
<th>Total (N = 908 [100%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>358 (53)</td>
<td>323 (47)</td>
<td>681 (75)</td>
</tr>
<tr>
<td>BDII</td>
<td>132 (71)</td>
<td>55 (29)</td>
<td>187 (21)</td>
</tr>
<tr>
<td>BD NOS</td>
<td>15 (83)</td>
<td>3 (17)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>SABD</td>
<td>11 (50)</td>
<td>11 (50)</td>
<td>22 (2)</td>
</tr>
<tr>
<td>Female</td>
<td>305 (60)</td>
<td>202 (40)</td>
<td>507 (56)</td>
</tr>
<tr>
<td>Male</td>
<td>211 (53)</td>
<td>190 (47)</td>
<td>401 (44)</td>
</tr>
</tbody>
</table>

Abbreviations: BD, bipolar disorder; BDI, bipolar I disorder; BDII, bipolar II disorder; IDS-C, Inventory of Depressive Symptomatology–Clinician-Rated Version; NOS, not otherwise specified; SABP, schizoaffective, bipolar type disorder; YMRS, Young Mania Rating Scale.

*Values are expressed as number (percentage) of patients.
†Mean ± SD age for total, 41.16 ± 11.61 years (range, 17-81 years).

Figure 1. Affective states in 908 patients during 14,328 visits. IDS-C indicates Inventory of Depressive Symptomatology–Clinician-Rated Version; YMRS, Young Mania Rating Scale.

Percentage of Total Visits

- Depression (YMRS score <12; IDS-C score <15) = 34.4%
- Hypomania (YMRS score ≥12; IDS-C score <15) = 3.1%
- Mixed Hypomania (YMRS score ≥12; IDS-C score ≥15) = 4.2%
- Euthymia (YMRS score <12; IDS-C score ≥15) = 58.3%
BDI VS BDII

Reviewing the Table, of 681 patients with BDI, 358 experienced no visits with a YMRS score of 12 or higher. For 187 patients with BDII, 132 experienced no visits with a YMRS score of 12 or higher. Comparing patients with BDI vs BDII, about an equal number of patients with BDI had visits with or without hypomanic symptoms reported or observed, whereas patients with BDII had a greater number of visits without hypomanic symptoms. The likelihood of experiencing a visit with hypomanic symptoms was higher for patients with BDI ($\chi^2 = 19.4; P < .001$; odds ratio, 2.2).

Among patients with BDI, 323 experienced at least 1 visit with a YMRS score of 12 or higher and 223 of these individuals also experienced a visit with mixed symptoms reported or observed, while for patients with BDII, 55 experienced a visit with hypomanic symptoms reported or observed and 42, a visit with mixed symptoms reported or observed (Table). If a patient experienced hypomanic symptoms, having BDI or BDII did not predict an increased likelihood of mixed symptoms ($\chi^2 = 1.2; P = .27$). Thus, when hypomanic, the probability of experiencing mixed symptoms was the same for patients with BDI or BDII.

RELATIONSHIP OF DEPRESSION TO HYPOMANIA SEVERITY

To evaluate if the frequency of depressive symptoms changed with increasing severity of hypomanic symptoms, a frequency chart was constructed. The frequency of depressive symptoms was generally similar across all categories of hypomanic symptom severity. For the total 1044 visits with a YMRS score of 12 or higher, for patients with mild hypomania (YMRS score of 12-14), concurrent depressive symptoms made up 53% (293/553) of visits; of those with moderate hypomania (YMRS score of 15-20), 66% (207/314) had visits with concomitant depressive symptoms; and of those with severe hypomania or mild mania (YMRS score >20), 54% (96/177) had visits with depressive symptoms. Depressive severity and hypomanic symptom distribution were not significantly related. Thus, the severity of depressive symptoms was not significantly greater as a function of more severe hypomanic or manic symptoms for the group overall.

THE EFFECTS OF SEX ON MIXED HYPOMANIA AND DEPRESSION

Figure 2 shows the likelihood of depression was significantly greater for women (72%) than men (42%) experiencing hypomanic symptoms ($\chi^2 = 11.46; P < .001$). For women in 7244 visits with no hypomanic symptoms (YMRS score <12), the probability of depressive symptoms (IDS-C score ≥15) was 41%. For women in 515 visits with hypomanic symptoms, the probability of concurrent depressive symptoms was 72% ($\chi^2 = 36.6; P < .001$). For men in 6040 visits with no hypomanic symptoms, the probability of concurrent depressive symptoms was 32% and in 529 visits with hypomanic symptoms, 42% ($\chi^2 = 5.8; P = .02$).

SEX RELATIONSHIP OF DEPRESSIVE SYMPTOMS TO HYPOMANIC SEVERITY

For women, the probability of experiencing depressive symptoms (IDS-C score ≥15) varied with the severity of hypomania: no hypomania, 41%; mild hypomania, 66% (YMRS score 12-15); moderate hypomania, 81% (YMRS score 15-20), and severe hypomania/mania, 67% (YMRS score ≥21). Because of the increase of mixed symptoms through moderate hypomania followed by a decrease at more severe hypomania levels, this bell shape was analyzed using a quadratic equation to model the nonlinear change ($\chi^2 = 13.1; P < .001$). Thus, for women, the probability of a depressive component increased significantly with the severity of the hypomania, then decreased during the most severe symptoms.

For men, the probabilities of experiencing depressive symptoms at a given level of hypomania were: no hypomania, 33%; mild hypomania, 38%; moderate hypomania, 44%; and severe hypomania/mania, 48%. This relatively shallow increase could be modeled linearly, supporting a symptom-related increase in mixed symptoms ($\chi^2 = 6.7; P = .01$). The overall test for sex x severity (4 levels) interaction was significant ($\chi^2 = 12.09; P = .007$).

EFFECT OF SYMPTOM SCALE OVERLAP ON SEX DIFFERENCES

To evaluate if the identification of mixed symptoms could be an artifact of overlapping identical items on the YMRS and IDS-C, analyses were done with 5 questions eliminated (modified IDS-C, see “Methods” section). Using the same threshold of 15, the finding of a sex-specific association of mixed hypomania in women remained significant ($P < .001$). As illustrated in Figure 3, for women, the probability of depressive symptoms, using a cut point of 12 or greater on the modified IDS-C, was 41.8% when the YMRS score was lower than 12 and 64.1% when the YMRS score was 12 or higher ($\chi^2 = 21.58; P < .001$). Assessing the distribution of symptoms using the modified IDS-C, for no hypomania, there was a 42% chance of experiencing depressive symptoms; for mild hypomania, 59%; for moderate hypomania, 70%; and for severe hypomania or mania, 61%. Because of the non-
linear changes in depressive symptoms with increasing hypomania, a nonlinear model was used to model the whole curve ($\chi^2=6.81; P=.009$). The probability of women experiencing mixed symptoms was also significant for threshold cut points on the modified IDS-C of 11, 9, and 6.

A factor analysis was conducted to assess which IDS-C items on the full scale were associated with an elevated YMRS score for women. The result found no specific item(s) responsible for the mixed hypomanic symptoms of depression. Women endorsed items throughout the IDS-C when experiencing hypomania vs endorsing only a few specific items when experiencing hypomania. This suggests for women an overall higher likelihood of depressive symptoms during periods of hypomania.

Similar analyses were carried out for men to assess for scale overlap effects. For a modified IDS-C threshold of 12, no association was found between depressive symptoms and an elevated YMRS score for men ($\chi^2=0; P=.95$). A similar pattern was observed using the modified IDS-C with cut points of 15, 12, 11, 9, and 6. For men, using the modified IDS-C, for no hypomania, there was a 33% chance of experiencing depressive symptoms; for mild hypomania, 34%; for moderate hypomania, 35%; and for severe hypomania or mania, 34%. Thus, for men, this relationship was linear and flat, showing no evidence of greater or lesser likelihood of mixed symptoms with increasing severity of hypomanic or manic symptoms.

In contrast to women, a factor analysis found that for men, only 2 of the IDS-C items on the full scale were associated with the elevated YMRS score. These 2 items, item 6 on irritability and item 24 on agitation, were eliminated on the modified IDS-C because of direct overlap with the YMRS. Thus, for men, unlike women, there were limited and specific items responsible for the mixed hypomanic symptoms of depression. The result of this factor analysis illustrates why men did not show evidence of greater or lesser likelihood of mixed hypomania when the modified IDS-C was used. These results suggest that for men there is overall no significant association with hypomanic and depressive symptoms, but men are likely to be irritable and agitated when hypomanic.

A significant interaction by sex was found when evaluating the clinical symptoms of women and men using the YMRS and the modified IDS-C threshold of 12 ($\chi^2=12.89; P<.001$). While men had more visits overall with a YMRS score of 12 or higher (529/6569 or 8.1%), men had a lower number of visits with both a YMRS score of 12 or higher and a modified IDS-C score of 12 or higher (183/529 or 35%). While women had only 6.6% (515/7759) of all visits with a YMRS score of 12 or higher, a higher percentage included visits with an elevated modified IDS-C score of 12 or higher (330/515 or 64%). Assessing all visits with a YMRS score less than 12, men experienced 33.1% (1998/6040) of visits with a modified IDS-C score of 12 or higher, while women experienced 41.8% (3026/7244). These results support that women are more prone to depressive symptoms as well as mixed symptoms.

**OTHER FINDINGS**

The database was evaluated for other evident trends. There was a linear trend of decreasing likelihood of observing depression over time ($\chi^2=39.2; P<.001$). In other words, in earlier visits for a given patient, depressive symptoms were generally more likely to be observed. A similar trend was observed for hypomanic symptoms where lower symptom scores were noted in later months of observation ($\chi^2=15.2; P<.001$). This decline was linear and interaction of the trend with fixed effects (eg, sex) was nonsignificant ($P>.20$). Thus, the effect of time was modeled as a covariate only.

**COMMENT**

In this sample of naturally treated patients with bipolar disorder, at visits where hypomania or mania was observed, 596 (57% of hypomanic visits) met the a priori criteria for mixed hypomania. The results presented herein, encompassing more than 14,000 visits, indicate that prominent depressive symptoms can occur during hypomania. The results suggest that mixed hypomania is a common, identifiable, and significant component of the bipolar spectrum and that it should be within the differential diagnosis of patients with either depressive or hypomanic symptoms. To our knowledge, this study shows for the first time the co-occurrence of hypomanic or manic and depressive symptoms collected prospectively in a large cohort of well-characterized patients with bipolar disorder.

Patients with BDI were significantly more likely to experience hypomania than patients with BDII. Though a diagnosis of BDI or BDII did not predict a greater likelihood of experiencing mixed symptoms at a given hypomanic visit, these results support the overall clinical impression that patients with BD I experience hypomania and mania more frequently than those patients with BDII. Evaluating those patients (n = 277) who experienced a mixed hypomanic visit, it was observed that they were generally more likely to experience mixed visits than purely hypomanic visits. This observation is in line with other prospective studies suggesting a degree of consistency from episode to episode.18–20

To assess potential subpopulations more susceptible to mixed vs classic hypomania, sex analyses were com-
In the present study, the probability for women of experiencing mixed symptoms was greater than 70% when a woman experienced hypomania (P<.001). For a man, the probability was greater than 40% when he experienced hypomania (P<.02). The interaction of depression during hypomania by sex was highly significant (P<.001). Our results support data from others reporting that more women than men were diagnosed with mixed symptoms.8,9,11,13,16-18 However, other studies have not found this sex bias.40,41 To our knowledge, this is the first study to definitively show a significant predominance of mixed symptoms for women.

While a female predominance has been observed for full mixed episodes, the majority of previous studies focused on full manic or mixed episodes, not mild and moderate hypomanic states. Using the full IDS-C scale, our results showed a linear increase for men with severity of hypomania (P=.01) and a nonlinear increase of mixed symptoms for women (P<.001). In this prospectively observed cohort, the rates of mixed symptoms for women actually increased with the severity of hypomania and then decreased at the most severe symptom levels consistent with severe hypomania or mild mania. As might be expected with the greater likelihood for women to experience mixed states, the sex interaction by level of hypomanic severity was significant (P<.007).

To assess potential confounds of instrument overlap, 5 overlapping items of the YMRS and the IDS-C were identified a priori and analyses of sex differences were conducted. When these items were removed from the IDS-C for assessment of women and men, the significant finding of the co-occurrence of hypomanic and depressive symptoms in men was no longer present. This significant finding for men was not found when thresholds lower than 15 for the IDS-C were also analyzed. In contrast, the finding for women of a high probability of co-occurring hypomanic and depressive symptoms continued to be significant with the relatively high threshold of 15 and at lower thresholds as well (eg, YMRS score ≥15 and modified IDS-C score ≥12; P<.001).

Further item analysis showed the cross-instrument items of irritability and agitation accounted for the initial significant finding of an increased probability of depressive symptoms co-occurring during hypomania/mania for men. When these overlapping items were removed, there was no longer an association of hypomania and development of mixed symptoms for men (P=.95). For women, item analysis found no specific items supported the finding but rather depressive symptoms were weighted throughout all items. The association for women of hypomania and development of mixed symptoms was significant with overlapping items removed (P<.001). Similar to findings using the full-scale IDS-C, assessment using the modified IDS-C found that women experienced mixed symptoms increasingly with more severe hypomania and then at a somewhat lower level at the most severe hypomanic or mild manic symptoms levels (P=.009).

These results suggest further consideration of item overlap is needed before results from 1 scale are judged independent from another in the same study; scoring high on a depression scale for a man experiencing mania may only reflect the severity of the mania and not the presence of a mixed state. Recent acute mania treatment studies have reported on mixed populations without consideration of this potential confound.

In sum, results using all mania and depression scale items to assess symptoms found an elevated probability for both sexes of experiencing mixed symptoms when hypomanic. A significant interaction by sex was noted, supporting that women are particularly likely to experience mixed symptoms. Further assessment of cross-instrument interaction found the probability of mixed symptoms for women was significant regardless of depressive symptom threshold, and for men, the phenomenon was based on elevated irritability and agitation only.

**DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS**

The results of this study support the observations by others that the presence of mixed symptoms in patients with bipolar disorder is common and often underrecognized.11,13,15,23 Mixed hypomania must be considered in the diagnostic criteria for a number of psychiatric conditions, and particularly major depression. Although a link between hypomanic and mixed symptoms is less obvious in men, the presence of hypomanic symptoms in women and irritability or agitation in men should raise the possibility that the patient with depression may diagnostically fall in the bipolar spectrum.

Mixed hypomania exists on a spectrum of severity continuous with DSM-IV-TR criteria for a mixed episode.27 The prognosis in patients with mixed episodes is less favorable. The duration of episode is longer and rate of recurrence is higher across a number of studies assessing mixed episodes meeting DSM-IV criteria.20,39,40,42,43 Patients with mixed symptoms may also be at an increased risk for suicide. Goldberg et al44 reported that suicidality is linked with dysphoric mania and may be, in fact, a marker for the disorder. In 1 study, Dilsaver et al45 reported that 54.5% of patients with mixed mania were suicidal vs only 2% of those without dysphoria. Furthermore, other Stanley Foundation Bipolar Treatment Network data suggest that a patient who has a history of suicidal ideation or attempts should be assessed for the possibility of a mixed state.36

The DSM-IV-TR defines bipolar disorder, mixed, as having met criteria both for a manic episode and for a major depressive episode nearly every day for a 1-week period.4 Bauer and colleagues13 noted that the DSM-IV criteria for mixed episode have become more restraining, limiting the diagnostic criteria to those who meet criteria for a full major depressive episode and mania, such that the possible occurrence of dysphoria (mixed symptoms) during hypomania was not recognized. Essentially, the current criteria set does not include the large number of patients described in this study who endorse subthreshold depressive symptoms during a hypomanic episode and, importantly, DSM-IV-TR does not highlight the possibility of mixed hypomania. Recent studies have also focused on the co-occurrence of subsyndromal manic or hypomanic symptoms during predominantly depressed episodes in patients with bipolar disorder (depressive mixed states).21,23 The concept that mixed...
states are a continuum of complex symptoms warrants further study.

LIMITATIONS OF THIS STUDY

Results presented in this report were collected prospectively and subject to analyses retrospectively. While hypotheses were stated a priori, retrospective analyses may limit generalizability. Additionally, because of the different time frames of the symptom scales assessment (YMRS, 3 days; IDS-C, 7 days), we could not distinguish symptoms occurring simultaneously vs in close juxtaposition.

CONCLUSION

Despite naturalistic treatment of patients with bipolar disorder in mood disorder specialty clinics, prospectively assessed symptoms of depression, hypomania, and mixed hypomania were frequent. This study of 908 patients in 14 328 clinical visits found that mixed hypomania is common in patients with bipolar disorder experiencing hypomania. This study provides definitive data supporting that mixed hypomania is significantly more likely to occur in women. The incidence of depressive symptoms increases in women, in general, with hypomania severity, but this weaker relationship in men is attributable to the specific overlapping scale items of irritability and agitation. These data support that more systematic attempts should be made to identify depressive symptoms in patients with hypomania. It also cautions us to carefully assess for the presence of hypomania in patients with depressive symptoms. Analyses of the scales used to identify mania and depression indicate the need to carefully consider instruments used to identify and define complex mood states in patients with bipolar disorder.

Submitted for Publication: October 6, 2004; final revision received January 31, 2005; accepted February 2, 2005.

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Previous Presentation: This study was presented at the Second European Stanley Foundation Conference on Bipolar Disorder; September 21-22, 2001; Amsterdam, Holland, and the Fourth European Stanley Foundation Conference on Bipolar Disorder; September 23-24, 2004; Aarhus, Denmark.

Acknowledgment: We would like to acknowledge the generous support of the Stanley Medical Research Institute, Bethesda, Md.

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