Incidence and Time Course of Subsyndromal Symptoms in Patients With Bipolar I Disorder: An Evaluation of 2 Placebo-Controlled Maintenance Trials

Mark A. Frye, M.D.; Lakshmi N. Yatham, M.D.; Joseph R. Calabrese, M.D.; Charles L. Bowden, M.D.; Terence A. Ketter, M.D.; Trisha Suppes, M.D., Ph.D.; Bryan E. Adams, Ph.D.; and Thomas R. Thompson, M.D.

Background: Subsyndromal symptoms in bipolar disorder can cause significant functional impairment and are associated with relapse.

Method: In this post hoc analysis from 2 randomized, double-blind, 18-month, placebo-controlled maintenance trials for bipolar I disorder (both trials were conducted between August 1997 and August 2001 and used DSM-IV criteria), the incidence, time course, and impact of pharmacotherapy on subsyndromal symptoms were examined.

Results: Subsyndromal symptoms occurred in approximately 25% of all visits. Compared with placebo (54.8%), a significantly higher mean percentage of visits in remission were observed with lamotrigine treatment (63.0%, p = .020) but not with lithium treatment (60.0%, p = .165). The median time to onset of subsyndromal symptoms for lamotrigine (N = 223), lithium (N = 164), and placebo (N = 188) was 15, 15, and 9 days, respectively. Compared with placebo, both lamotrigine and lithium significantly delayed the time from randomization to onset of subsyndromal symptoms (p = .046, lamotrigine vs. placebo; p = .033, lithium vs. placebo; p = .763, lamotrigine vs. lithium) and the time from onset of subsyndromal symptoms to subsequent mood episode (p = .037, lamotrigine vs. placebo; p = .023, lithium vs. placebo; p = .845, lamotrigine vs. lithium). Agreement between the polarities of the first-observed subsyndromal symptom and subsequent intervention for mood episode was statistically significant (p < .001).

Conclusion: Subsyndromal symptoms are common during maintenance treatment and appear to be associated with relapse into an episode of the same polarity. Both lithium and lamotrigine delayed the onset of subsyndromal symptoms and the time from onset of subsyndromal symptoms to subsequent relapse. Further study to assess whether treatment intervention can minimize subsyndromal symptoms or prevent relapse is encouraged.

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Received Jan. 23, 2006; accepted April 11, 2006. *From the Mood Disorders Research Program, University of California at Los Angeles (Dr. Frye); the Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada (Dr. Yatham); the Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio (Dr. Calabrese); the Department of Psychiatry, University of Texas Health Science Center at San Antonio (Dr. Bowden); the Stanford University School of Medicine, Stanford, Calif. (Dr. Ketter); the University of Texas Southwestern Medical Center, Dallas (Dr. Suppes); GlaxoSmithKline, Research Triangle Park, N.C. (Dr. Thompson); and Clinforce, Research Triangle Park, N.C. (Dr. Adams). Dr. Adams is now with GlaxoSmithKline, Research Triangle Park, N.C.*

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Corresponding author and reprints: Mark A. Frye, M.D., Department of Psychiatry and Psychology, Mayo Clinic, 200 First St., S.W., Rochester, MN 55905 (e-mail: mfrye@mayo.edu).

A growing body of evidence suggests that subsyndromal mood symptoms in bipolar disorder are common and have significant clinical impact from the standpoint of functional disability and as a prodrome to relapse. In prospective, naturalistic studies, hypomanic and minor depressive symptoms were 3 times more common than syndromal manic or depressive symptoms.[1–3] In a study that used life-charting methods to follow 138 patients with bipolar I or II disorder for an average of 3 years, patients experienced subsyndromal depressive symptoms approximately 25% of the time.[3]

The incidence of subsyndromal mood symptoms in bipolar disorder and their association with impaired function and quality of life have become increasingly clear.[4–6] Yatham et al. found that patients with subsyndromal depressive symptoms had a significant impairment in function and quality of life, and there was a direct correlation between severity of depressive symptoms and impairment in quality of life.[4] In a study of 25 patients with bipolar I disorder, subsyndromal depressive symptoms were associated with poorer global function as measured by the Global Assessment of Functioning (GAF); none of the patients in this study met criteria for major depressive disorder or had Hamilton Rating Scale for Depression (HAM-D) scores reflecting syndromal depression sug-

gesting that the functional disability present may be related to subsyndromal symptoms.[5] Similarly, in the 138-patient sample described above,[3,6] patients with subsyndromal symptoms scored significantly worse than euthymic patients on the GAF. Subsyndromal symptoms were also associated with rates of medication use and physician consultation equal to those of full syndromal mood episodes. Subsyndromal manic symptoms have also been associated with significant health care utilization and disability as reported from a reanalysis of the Epidemiological Catchment Area database.[7]

Subsyndromal mood symptoms are also clinically significant because they are associated with an increased risk of syndromal relapse.[6,8,9] A subsyndromal period preceded approximately two thirds (68%) of relapses to mood episodes in a double-blind study of 94 patients with bipolar disorder.[8] Patients with subsyndromal symptoms were approximately 4 times more likely to relapse than patients without subsyndromal symptoms.

In light of the high incidence rate, their functional impact, and their association with relapse, it has been suggested that better recognition and more aggressive management of subsyndromal symptoms could improve the well-being and functioning of patients with bipolar disorder.[3,5,9] However, relatively little work has been undertaken to understand subsyndromal mood symptoms; the vast majority of studies in bipolar disorder focus on the full syndrome. This current investigation—a post hoc analysis of data from 2 randomized, double-blind, 18-month clinical trials of maintenance therapy for bipolar I disorder—was undertaken to (1) ascertain the incidence, time course, and polarity of subsyndromal symptoms in patients with bipolar I disorder treated with lithium, lamotrigine, or placebo; (2) identify any relationship between subsyndromal symptoms and the polarity of the subsequent mood episode; and (3) determine the impact of treatment with lamotrigine, lithium, or placebo on the time to onset of subsyndromal symptoms and on the time from onset of subsyndromal symptoms to a mood episode.

METHOD

The methods and primary results of the studies upon which this post hoc analysis were based are fully described elsewhere.[10–12] The studies enrolled patients aged 18 years or older with a diagnosis of bipolar I disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[13] criteria who were currently manic or had been manic within 60 days of the screening visit (study 1; GlaxoSmithKline protocol GW606/SCAB2006) or who were currently depressed or had been depressed within 60 days of the screening visit (study 2; GlaxoSmithKline protocol GW605/SCAB2003). Both trials were conducted between August 1997 and August 2001. Each study comprised an 8- to 16-week open-label phase during which lamotrigine was titrated to a target dose of 200 mg/day with a minimum dose of 100 mg/day while other psychotropic drugs that could have been added to treat acute symptoms were discontinued. The open-label phase was followed by a 76-week, double-blind phase during which patients received lamotrigine, lithium, or placebo as maintenance therapy. Only those patients who reached a stable lamotrigine dose by week 8 and who met response criteria as defined by a Clinical Global Impressions-Severity of Illness (CGI-S) scale[14] score less than or equal to 3 (mildly ill) maintained for at least 4 continuous weeks were randomly assigned to treatment. In the original protocol, response criteria utilized the CGI-Improvement (CGI-I) scale[14] score (1 or 2, very much or much improved, respectively), and this resulted in a low number of subjects who met the clinical response criterion at time of entry into the open-label, stabilization phase. Therefore, the protocol was revised to be recently, not currently, manic or depressed and used a response criteria defined by the CGI-S score. This subgroup still required a minimum of 6 to 8 weeks open trial with lamotrigine prior to randomization.

During the double-blind phase, lamotrigine was dosed at 100 to 400 mg/day depending on clinical response (target dose of 200 mg/day) in study 1 and at 50, 200, or 400 mg/day in study 2. Lithium was titrated to serum levels of 0.8 to 1.1 mEq/L during the double-blind phase of both studies. Due to slow enrollment, recruitment of patients into the lithium arm of study 1 was stopped prematurely, and the protocol for study 2 was amended to reduce the number of lamotrigine groups from 3 to 1 (200 mg/day). The 17-item HAM-D (HAM-D-17)[15] and the subset of items from the Schedule for Affective Disorders and Schizophrenia-Change Version,[16] which comprised the 11-item Mania Rating Scale (MRS) in addition to other scales, were completed at randomization and at clinic visits occurring during double-blind treatment. Postbaseline clinic visits were scheduled every week for the first 4 visits (weeks 1, 2, 3, and 4), every 2 weeks for the next 2 visits (weeks 6 and 8), and every 4 weeks for the remaining 17 visits (weeks 12 through 76) for a potential total of 23 visits.

Data Analysis

The analytic approach was modeled after that of a previous assessment of subsyndromal symptoms in bipolar disorder.[8] In this analysis, due to inherent heterogeneity in the study designs for GW605 and GW606 (e.g., index episode and dosing), all pooled statistical analyses were adjusted for study whenever possible and are indicated when relevant. For each patient at each clinic visit, clinical status was categorized on the basis of HAM-D-17 and MRS scores as symptom free (symptom free: HAM-D-17 score of 0 to 7 and MRS score of 0 to 7), with subsyndromal symptoms (subsyndromal: HAM-D-17 score

of 8 to 14 or MRS score of 8 to 13), or with syndromal symptoms (syndromal: HAM-D-17 score ≥ 15 or MRS score ≥ 14). Note that some patients may have had both depressive and manic symptoms at the same visit.

First-observed subsyndromal symptoms were examined with regard to both polarity and time to onset from randomization. For these analyses, subsyndromal symptoms were defined by the first visit during which either subsyndromal or syndromal symptoms were observed (HAM-D-17 score ≥ 8 or MRS score ≥ 8).

Incidence of subsyndromal symptoms. The incidence of subsyndromal symptoms was assessed by determining the number of visits during which subsyndromal criteria were met and the percentage of total visits during which patients had subsyndromal manic symptoms or subsyndromal depressive symptoms. The number of visits spent in each clinical status category was determined for each patient by evaluating, sequentially, each HAM-D-17 or MRS assessment and adding each visit to the cumulative total number of visits for the particular clinical status category in which it fell. To obtain the percentage of visits in a clinical status category, the cumulative total number of visits in a clinical status category was divided by the cumulative total number of visits spent in all clinical status categories (symptom free, subsyndromal, syndromal) and multiplied by 100.

Incidence of subsyndromal depressive symptoms was examined separately and independently of manic symptoms, and conversely, incidence of subsyndromal manic symptoms was examined separately and independently of depressive symptoms. The (composite) percentage of visits during which patients had subsyndromal symptoms of either or both polarities was also examined. In this composite setting, the most severe symptoms (manic or depressive) determined the severity state for a given visit; remission required meeting the criteria for remission on both poles.

These analyses were undertaken with observed data and excluded any visit having missing HAM-D-17 or MRS data and any assessment occurring after the time of recurrence/withdrawal from the study. Pairwise differences between treatment groups in the percentage of visits during which patients were in remission, subsyndromal, or syndromal were tested with an analysis of covariance (ANCOVA) adjusted for study.

Polarity of subsyndromal symptoms relative to subsequent time to intervention for mood episode. The primary outcome measure of the 2 maintenance studies was time to intervention for a mood episode (TIME). The percentage of patients with first-observed subsyndromal manic/mixed or depressive symptoms and the polarity of the subsequent mood episode (manic/mixed or TIME manic, depressed or TIME depressed) associated with study discontinuation were examined. These measures were calculated for the sample as a whole and for each treatment group separately. The polarity of the onset of subsyndromal symptoms was determined by the scale (HAM-D-17 for depression and MRS for mania) on which scores first fell within the subsyndromal (or worse) range. If subsyndromal symptoms were first observed concurrently for HAM-D-17 and MRS scales, then the subsyndromal symptoms were considered to be mixed.

The degree to which first-observed subsyndromal symptoms and subsequent mood episode agreed was assessed using Cohen's kappa measure of agreement.[17] This statistic is designed to detect a concentration of data in the diagonal elements of a table with matching rows and columns, thereby measuring agreement between the categories beyond that due to chance alone. Values of the kappa statistic near zero indicate agreement as would be expected by chance; as values approach 1, the level of agreement becomes stronger with values equal to 1 indicating perfect agreement (i.e., all off-diagonal cells have zero counts). Note that due to sparse cell counts this analysis was not stratified by study.

Effect of pharmacotherapy. The impact of pharmacotherapy on the onset of subsyndromal symptoms was assessed by determining for each treatment group the time from randomization to the onset of subsyndromal symptoms. The onset of subsyndromal symptoms was defined as the first visit with a HAM-D-17 score greater than or equal to 8 for depression or an MRS score greater than or equal to 8 for mania, whichever occurred first, unless subsyndromal-range scores were first observed concurrently for HAM-D-17 and MRS scales, in which case the subsyndromal symptoms were considered to be mixed.

The impact of pharmacotherapy on the occurrence of a mood episode following subsyndromal symptoms was assessed by determining the time from onset of subsyndromal symptoms to a subsequent mood episode (defined as the first intervention of additional treatment for a mood episode or an emerging mood episode) for each treatment group. The time from onset of subsyndromal symptoms to a subsequent mood episode was determined for mood episodes of the same polarity as the subsyndromal symptoms, for any mood episode (depressive/manic/mixed) following either depressive or manic subsyndromal symptoms, and for mood episodes regardless of the polarity of the subsyndromal and subsequent syndromal symptoms.

For each of the time-to-event measures, Kaplan-Meier survival curves were constructed, medians with 95% confidence intervals were computed, and differences between pairs of treatments were tested with log-rank tests adjusted for study. Patients who withdrew prior to a mood episode were censored at the time of withdrawal. Data from the 200-mg, 400-mg, and flexible doses of lamotrigine were pooled for analysis. Data from patients

Table 1. Incidence of Subsyndromal Symptoms Among Patients With Bipolar I Disorder

Variable	Lamotrigine (N = 223)	Lithium (N = 164)	Placebo (N = 188)
Composite (either polarity)			
Visits in remission, mean ± SE, %[a]	63.0 ± 2.5[b]	60.0 ± 2.8	54.8 ± 2.6
Visits with subsyndromal symptoms, mean ± SE, %	21.1 ± 1.9	25.6 ± 2.2	26.1 ± 2.0
Visits with syndromal symptoms, mean ± SE, %	15.9 ± 1.6	14.4 ± 1.9	19.1 ± 1.7
Depression (HAM-D-17)			
Visits in remission, mean ± SE, %	68.5 ± 2.4	65.2 ± 2.8	61.9 ± 2.6
Visits with subsyndromal symptoms, mean ± SE, %	19.8 ± 1.9	23.9 ± 2.2	22.6 ± 2.0
Visits with syndromal symptoms, mean ± SE, %	11.7 ± 1.6	10.9 ± 1.8	15.5 ± 1.6
Mania (MRS)			
Visits in remission, mean ± SE, %	88.3 ± 1.4	89.8 ± 1.6	86.4 ± 1.5
Visits with subsyndromal symptoms, mean ± SE, %	6.6 ± 1.1	5.5 ± 1.2	8.3 ± 1.1
Visits with syndromal symptoms, mean ± SE, %	5.1 ± 0.9	4.7 ± 1.0	5.3 ± 0.9

[a]Means are based on an analysis of covariance adjusted for study.
[b]Indicates a statistically significant difference versus placebo ($p < .05$).
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MRS = Mania Rating Scale.

receiving lamotrigine 50 mg/day, which, based on clinical data, is thought not to be therapeutic for bipolar disorder, were excluded.

RESULTS

Sample

Data from 575 patients (N = 223 lamotrigine, N = 164 lithium, N = 188 placebo) who took at least 1 dose of study medication and had at least 1 postrandomization efficacy assessment were included in the analyses. The mean ± SD number of days in the open-label phase was 89.9 ± 21.9, 86.9 ± 21.4, and 89.4 ± 30.9 for the lamotrigine, lithium, and placebo groups, respectively. At randomization, the mean ± SD HAM-D-17 and MRS scores were 5.2 ± 4.4 and 1.9 ± 3.1 for lamotrigine, 4.9 ± 4.5 and 1.9 ± 3.1 for lithium, and 4.5 ± 3.9 and 1.8 ± 2.9 for placebo. The mean ± SD number of postrandomization visits (of a total of 23 possible visits) per patient for which HAM-D-17 and MRS data were available was 9.2 ± 6.7 for the sample as a whole and 10.1 ± 7.1, 9.6 ± 6.6, and 7.8 ± 6.1 in the lamotrigine, lithium, and placebo groups, respectively.

Incidence of subsyndromal symptoms. As presented in Table 1, the mean percentage of visits (adjusted for study) during which patients were in remission on both poles was 63.0%, 60.0%, and 54.8% in the lamotrigine, lithium, and placebo groups, respectively ($p = .020$, lamotrigine vs. placebo; $p = .165$, lithium vs. placebo; $p = .416$, lithium vs. lamotrigine).

The mean percentage of visits with subsyndromal symptoms (either polarity) was 21.1%, 25.6%, and 26.1% in the lamotrigine, lithium, and placebo groups, respectively ($p = .067$, lamotrigine vs. placebo; $p = .872$, lithium vs. placebo; $p = .109$, lamotrigine vs. lithium). The mean percentage of visits with subsyndromal depressive symptoms was 19.8%, 23.9%, and 22.6% in the lamotrigine, lithium, and placebo groups, respectively ($p = .305$, lamotrigine vs. placebo; $p = .649$, lithium vs. placebo; $p = .143$, lamotrigine vs. lithium). The corresponding percentages for subsyndromal manic symptoms were 6.6%, 5.5%, and 8.3% in the lamotrigine, lithium, and placebo groups, respectively ($p = .231$, lamotrigine vs. placebo; $p = .078$, lithium vs. placebo; $p = .497$, lamotrigine vs. lithium).

Polarity of first-observed subsyndromal symptoms relative to subsequent mood episode. As presented in Table 2, first-observed subsyndromal symptoms more often preceded a subsequent mood episode associated with study discontinuation of the same polarity in the sample as a whole and in the treatment groups separately. Of the 255 patients with subsyndromal depressive symptoms, 160 patients (63%) had a subsequent depressive mood episode. Of the 91 patients with subsyndromal manic/mixed symptoms (N = 54 [59%] subsyndromal mania, N = 37 [41%] subsyndromal mixed), 59 (65%) had a subsequent manic/mixed mood episode. Of the 57 patients with no subsyndromal symptoms, 41 patients (72%) completed the study without a subsequent syndromal episode. Within the lamotrigine, lithium, and placebo treatment groups, 55 (55%) of 100, 48 (71%) of 68, and 57 (66%) of 87 patients with subsyndromal depressive symptoms had a subsequent depressive episode, respectively, while 25 (66%) of 38, 9 (53%) of 17, and 25 (69%) of 36 patients with subsyndromal manic/mixed symptoms had a subsequent manic/mixed episode, respectively. Of the 22 (lamotrigine), 20 (lithium), and 15 (placebo) patients with no subsyndromal symptoms, 17 (77%), 16 (80%), and 8 (53%) completed the study without a subsequent syndromal episode, respectively. Agreement between first-observed subsyndromal symptom polarity and subsequent syndromal episode polarity, evident in Table 2, was statistically significant for all patients ($\kappa = 0.41$, $p < .001$), as well as for patients taking lamotrigine ($\kappa = 0.38$, $p < .001$), lithium ($\kappa = 0.47$, $p < .001$), and placebo ($\kappa = 0.40$, $p < .001$), indicating fair to moderate agreement.[18]

Table 2. Polarity of First-Observed Subsyndromal Symptoms Relative to Polarity of the Subsequent Intervention for Mood Episode Among Patients With Bipolar I Disorder[a,b]

Variable	Subsequent Mood Episode Depression	Subsequent Mood Episode Mania/Hypomania/Mixed	Completed Study With No Subsequent Mood Episode
Subsyndromal symptoms depressive, N (%)[c]			
All patients (N = 255)	**160 (63)**[d]	41 (16)	54 (21)
Lamotrigine (N = 100)	**55 (55)**[e]	16 (16)	29 (29)
Lithium (N = 68)	**48 (71)**[f]	8 (12)	12 (18)
Placebo (N = 87)	**57 (66)**[g]	17 (20)	13 (15)
Subsyndromal symptoms manic/mixed, N (%)[h]			
All patients (N = 91)	24 (26)	**59 (65)**	8 (9)
Lamotrigine (N = 38)	10 (26)	**25 (66)**	3 (8)
Lithium (N = 17)	5 (29)	**9 (53)**	3 (18)
Placebo (N = 36)	9 (25)	**25 (69)**	2 (6)
No emergent subsyndromal symptoms, N (%)			
All patients (N = 57)	5 (9)	11 (19)	**41 (72)**
Lamotrigine (N = 22)	0 (0)	5 (23)	**17 (77)**
Lithium (N = 20)	3 (15)	1 (5)	**16 (80)**
Placebo (N = 15)	2 (13)	5 (33)	**8 (53)**

[a]Bold values indicate statistically significant agreement between first-observed subsyndromal symptoms and subsequent intervention for a mood episode.
[b]Data not shown for patients with depressive, manic/mixed, or no emergent subsyndromal symptoms who had a subsequent premature discontinuation (38, 6, and 19 lamotrigine patients; 35, 8, and 16 lithium patients; 26, 11, and 13 placebo patients, respectively). Reasons for premature discontinuation included adverse events, being lost to follow-up, withdrawing consent, and protocol violation.
[c]Subsyndromal depressive symptoms defined as HAM-D-17 score ≥ 8.
[d]All patients, $\kappa = 0.413$ and $p < .001$.
[e]Lamotrigine, $\kappa = 0.381$ and $p < .001$.
[f]Lithium, $\kappa = 0.466$ and $p < .001$.
[g]Placebo, $\kappa = 0.403$ and $p < .001$.
[h]Subsyndromal symptoms mania/mixed defined as an MRS score ≥ 8 with or without a HAM-D-17 score ≥ 8.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MRS = Mania Rating Scale.

Note that due to sparse cell counts this analysis was not stratified by study.

Effects of Pharmacotherapy

Median numbers of days between randomization and the onset of subsyndromal symptoms and between the onset of subsyndromal symptoms and subsequent mood episodes are shown in Table 3 along with the log-rank test of the difference in survival distributions between treatments adjusted for study.

Time from index randomization to the onset of subsyndromal symptoms. Both lamotrigine and lithium significantly delayed the time from randomization to the onset of subsyndromal symptoms (either polarity) compared with placebo (p = .046, lamotrigine vs. placebo; p = .033, lithium vs. placebo; p = .763, lamotrigine vs. lithium) (Table 3).

Time from the onset of subsyndromal symptoms to subsequent mood episode.

Any subsyndromal symptoms preceding any mood episode. Both lamotrigine and lithium significantly delayed the time from onset of any subsyndromal symptoms to any subsequent mood episode compared with placebo (p = .037, lamotrigine vs. placebo; p = .023, lithium vs. placebo; p = .845, lamotrigine vs. lithium) (Table 3).

Subsyndromal symptoms preceding a mood episode of the same polarity. Lamotrigine, but not lithium, significantly delayed the time from onset of subsyndromal depressive symptoms to a subsequent depressive episode compared with placebo (p = .016, lamotrigine vs. placebo; p = .467, lithium vs. placebo; p =.178, lamotrigine vs. lithium) (Table 3). Lithium, but not lamotrigine, nonsignificantly delayed the time from onset of subsyndromal manic/mixed symptoms to a subsequent manic/mixed episode compared with placebo (p = .084, lithium vs. placebo; p = .801, lamotrigine vs. placebo; p = .050, lithium vs. lamotrigine) (Table 3).

Subsyndromal symptoms of either depression or manic/mixed preceding any mood episode. Lamotrigine, but not lithium, significantly delayed the time from onset of subsyndromal depressive symptoms to any subsequent mood episode compared with placebo (p = .007, lamotrigine vs. placebo; p = .247, lithium vs. placebo; p = .303, lamotrigine vs. lithium) (Table 3). Lithium, but not lamotrigine, significantly delayed the time from onset of subsyndromal manic/mixed symptoms to any subsequent mood episode compared with placebo (p = .024, lithium vs. placebo; p = .746, lamotrigine vs. placebo; p = .020, lithium vs. lamotrigine) (Table 3).

DISCUSSION

These findings corroborate previous observations that subsyndromal symptoms are common in patients with bipolar I disorder. Over an 18-month period of double-blind treatment, patients experienced subsyndromal symptoms at approximately one fourth of the clinic visits in the sample as a whole. Subsyndromal depression was more

Table 3. Summary of Median Survival Estimates and Comparison of Survival Distributions Across Treatment Groups of Patients With Bipolar I Disorder

Variable	Median Days to Event (95% CI)			p Value[a]		
	Lamotrigine (N = 223)	Lithium (N = 164)	Placebo (N = 188)	Lamotrigine vs Placebo	Lithium vs Placebo	Lamotrigine vs Lithium
Randomization → subsyndromal (either polarity)[b]	15 (8 to 22) (N = 182)	15 (8 to 18) (N = 128)	9 (8 to 14) (N = 160)	.046	.033	.763
Subsyndromal (either polarity) → intervention (either polarity)[c]	72 (41 to 154) (N = 138)	84 (57 to 137) (N = 103)	43 (23 to 78) (N = 113)	.037	.023	.845
Subsyndromal depression → intervention for depression[d]	431 (154 to NC)	115 (57 to NC)	82 (55 to 307)	.016	.467	.178
Subsyndromal depression → intervention (either polarity)[e]	155 (72 to 431) (N = 44)	79 (57 to 165) (N = 25)	64 (34 to 106) (N = 47)	.007	.247	.303
Subsyndromal manic/mixed → intervention for mania[f]	35 (8 to 153)	258 (124 to NC)	79 (8 to 195)	.801	.084	.050
Subsyndromal manic/mixed → intervention (either polarity)[g]	23 (8 to 43)	101 (23 to NC)	18 (8 to 76)	.746	.024	.020

[a]Difference in survival distributions between treatments tested with a log-rank test adjusted for study.
[b]Time between randomization (recovery from index episode either polarity) and onset of subsyndromal symptoms (either polarity).
[c]Time between onset of any subsyndromal symptoms and intervention for any mood episode.
[d]Time between onset of depressive subsyndromal symptoms and intervention for a depressive mood episode.
[e]Time between onset of depressive subsyndromal symptoms and intervention for any mood episode.
[f]Time between onset of manic/mixed subsyndromal symptoms and intervention for a manic mood episode.
[g]Time between onset of manic/mixed subsyndromal symptoms and intervention for any mood episode.
Abbreviation: NC = not calculable.

common than subsyndromal mania and was present in approximately 20% of the study visits. This incidence rate is similar to that reported in other naturalistic and cross-sectional studies.[1–3] Despite the lack of operationalized subsyndromal criteria, the literature has suggested that these subsyndromal symptoms significantly impair functional ability and health-related quality of life.[4–6,9]

To our knowledge, this is the first report from a controlled, comparative maintenance study to assess the incidence and time course of subsyndromal symptoms. These data would suggest that, in addition to a significant incidence rate, subsyndromal symptoms may develop soon after randomization from an index episode. The criteria for randomization for this study (4 continuous weeks with a CGI-S score less than or equal to 3) is shorter than the stabilization criteria of 6 weeks in the more recent maintenance study of aripiprazole[19] but longer than the stabilization criteria of 2 weeks for the maintenance study of olanzapine.[20] This shorter response criterion may be a limitation to this study. However, though it was not criteria for randomization, the mean HAM-D-17 and MRS (11-item) scores by treatment were clearly consistent with recovery from index episode at time of randomization. As such, the reported symptoms and subsequent interventions for a mood episode during the randomized phase of the studies were not likely residual symptoms from the index episode. It would be valuable to examine the time course of subsyndromal symptoms in the other controlled trials to assess the generalizability of these findings.

A second limitation to this study is that our criteria for subsyndromal symptoms were based on clinical rating scales, which is different from the investigator-evaluated primary outcome variable TIME. As the clinician clearly would use the rating scales as a guide in the investigator assessment to the need for intervention, it is unlikely this would negatively impact our overall incidence rate and time course to first subsyndromal symptoms. Nonetheless, the high incidence of subsyndromal symptoms from this monotherapy maintenance trial might suggest that other interventions, such as combinations of these medications with one another or with psychosocial interventions, ought to be explored to minimize subsyndromal symptoms and decrease the risk of relapse.

In these data, first-observed subsyndromal symptoms were associated with a subsequent mood episode of the same polarity. These data are consistent with previous results showing that polarity of symptoms or polarity of index episode predict subsequent relapses or recurrences of the same polarity.[21–23] The relationship between polarity of first-observed subsyndromal symptoms and polarity of subsequent relapses or recurrences may help to tailor pharmacotherapy given at the time of onset of subsyndromal symptoms. For example, maximizing the dose of mood stabilizer or mood stabilizer/antidepressant at time of subsyndromal mania or subsyndromal depression onset, respectively, may decrease the relapse rate into a full syndromal episode.

Both the time from randomization to the onset of subsyndromal symptoms and the time from the onset of

subsyndromal symptoms to a relapse or recurrence were delayed by pharmacotherapy. Lamotrigine and lithium each delayed the time from randomization to the onset of subsyndromal symptoms (either polarity) compared with placebo. Likewise, lamotrigine and lithium each significantly delayed the time from onset of subsyndromal symptoms to any subsequent mood episode compared with placebo. Lamotrigine, but not lithium, significantly delayed the time from onset of subsyndromal depressive symptoms to any subsequent depressive episode compared with placebo, whereas lithium, but not lamotrigine, numerically delayed the time from onset of subsyndromal manic/mixed symptoms to any subsequent manic/mixed episode compared with placebo. This observation may potentially be clinically relevant when considering treatment combinations on the basis of the emergence of subsyndromal symptoms (i.e., augmentation of lithium with lamotrigine with the emergence of subsyndromal depression or augmentation of lamotrigine with lithium with the emergence of subsyndromal mania). It would be valuable for future controlled studies to consider these types of combination, complimentary strategies.

These results are consistent with the primary results of the studies considered individually and in a pooled analysis.[10–12] In the pooled analysis, both lamotrigine and lithium delayed the time to intervention for any mood episode compared with placebo.[12] In recently manic, hypomanic, or depressed patients with bipolar I disorder, lamotrigine delayed the time to intervention for a depressive episode, and lithium, and to a lesser extent, lamotrigine, delayed the time to intervention for a manic episode compared with placebo.[12]

In summary, subsyndromal mood symptoms were common—present in about one fourth of the clinic visits—among patients with bipolar I disorder in a pooled analysis of two 18-month studies. The majority of patients who required an intervention for a mood episode during the study experienced symptoms prior to intervention. Depressive subsyndromal symptoms were associated with subsequent relapses or recurrences of the same polarity, and manic/mixed subsyndromal symptoms were associated with relapses or recurrences of the same polarity. Both lamotrigine and lithium significantly delayed the time from the index mood episode to the onset of subsyndromal symptoms. Even after the onset of subsyndromal symptoms, lamotrigine and lithium each significantly delayed the time to intervention for a mood episode.

Drug names: aripiprazole (Abilify); lamotrigine (Lamictal and others); lithium (Eskalith, Lithobid, and others); olanzapine (Zyprexa).

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