Morbidity in 258 Bipolar Outpatients Followed for 1 Year With Daily Prospective Ratings on the NIMH Life Chart Method

Robert M. Post, M.D.; Kirk D. Denicoff, M.D.; Gabriele S. Leverich, M.S.W.; Lori L. Altshuler, M.D.; Mark A. Frye, M.D.; Trisha M. Suppes, M.D.; A. John Rush, M.D.; Paul E. Keck, Jr., M.D.; Susan L. McElroy, M.D.; David A. Luckenbaugh, M.A.; Chad Pollio, M.S.; Ralph Kupka, M.D.; and Willem A. Nolen, M.D.

Background: A number of recent longitudinal outcome studies have found substantial long-term morbidity in patients with bipolar disorder. The detailed course and pattern of illness emerging despite comprehensive treatment with mood stabilizers and adjunctive agents have previously not been well delineated.

Method: 258 consecutive outpatients admitted from 1996 to 1999 to the Stanley Foundation Bipolar Network who had a full year of prospective daily clinician ratings on the National Institute of Mental Health-Life Chart Method were included in the analysis. Patients were diagnosed by the Structured Clinical Interview for DSM-IV, with the majority (76%) having bipolar I disorder. They completed a questionnaire on demographics and prior illness course, and variables associated with outcome were examined in a hierarchical multinomial logistic regression analysis. Patients were treated naturalistically with a mean of 4.1 psychotropic medications during the year.

Results: Despite comprehensive pharmacologic treatment, mean time depressed (33.2% of the year) was 3-fold higher than time manic (10.8%); 62.8% of patients had 4 or more mood episodes per year. Two thirds of the patients were substantially impacted by their illness; 26.4% were ill for more than three fourths of the year, and 40.7% were intermittently ill with major affective episodes. After logistic regression analysis, those who were ill most of the year, compared with the largely well group, had a significantly greater family history of substance abuse, 10 or more depressive episodes, and limited occupational functioning prior to Network entry.

Conclusion: A majority of outpatients with bipolar illness, even with intense monitoring and treatment in specialty clinics, have a considerable degree of residual illness-related morbidity, including a 3-fold greater amount of time spent depressed versus time spent manic. A personal or family history of substance abuse, 10 or more prior depressions, and limited occupational functioning predicted the poorest outcomes. Additional interventions, particularly those targeted at treating depressive phases of bipolar illness, are greatly needed.

(J Clin Psychiatry 2003;64:680–690)

Received May 28, 2002; accepted Oct. 1, 2002. *From the Stanley Foundation Bipolar Network and Biological Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Md. (Drs. Post and Denicoff, Ms. Leverich, Mr. Luckenbaugh, and Mr. Pollio); UCLA Ambulatory Clinical Research Center and VA Medical Center, Los Angeles, Calif. (Drs. Altshuler and Frye); University of Texas Southwestern Medical Center, Dallas, Tex. (Drs. Suppes and Rush); University of Cincinnati College of Medicine, Cincinnati, Ohio (Drs. Keck and McElroy); and the University Medical Center and Altrecht Institute for Mental Health Care, Utrecht, the Netherlands (Drs. Kupka and Nolen).*

Supported by the Stanley Medical Research Institute, Bethesda, Md.

Financial disclosure statements appear at the end of the article.

Corresponding author and reprints: Robert M. Post, M.D., NIMH, Biological Psychiatry Branch, 10 Center Drive MSC 1272, Bldg. 10, Room 3S239, Bethesda, MD 20892-1272 (e-mail: robert.post@nih.gov).

A number of studies have described the limited response to lithium and a variety of other therapeutic agents in patients with bipolar disorder.[1–8] Cross-sectional ratings performed in some of these studies have revealed the severity of persisting mood symptoms, but few systematic studies have used validated longitudinal rating instruments to document the precise course of illness in individuals with bipolar disorder.[9,10]

Kraepelin,[11] in a large sample of untreated patients, carefully depicted the pattern and fluctuations of manic and depressive symptoms and described the illness' overall pleomorphic and highly variable course among and within subjects. However, within this variability, he observed a general tendency for more frequent recurrences, cycle acceleration, and autonomy from psychosocial precipitants. Using the National Institute of Mental Health (NIMH)-Life Chart Method (LCM), we have modified Kraepelin's method to include the provisions for daily ratings of mania and depression at 4 levels of severity, as well as noting medications and psychosocial events.[12,13] This prospective longitudinal methodology has been validated against more widely used cross-sectional measures[14,15] and is the core instrument for providing mood ratings of patients in the Stanley Foundation Bipolar Network (SFBN, or Network).[16,17]

The major aims of the current study were to determine the detailed pattern and severity of illness in the first 258 outpatients in the Network who had 1 year of continuous prospective ratings. Furthermore, we intended to define the proportions of patients who remained (1) severely and almost continuously ill (75%–100% of the time), (2) intermittently ill (less than 75% of the time), or (3) only mildly or briefly ill over the course of the year, including those who were essentially well. These patients were treated with accepted mood stabilizers (lithium, carbamazepine, and valproate) and a variety of adjunctive agents including novel approaches to clinical therapeutics. Therefore, this study represents the most detailed continuous assessment of the naturalistic course of illness in a large population of treated outpatients with bipolar illness. Note: Following the acceptance of this article, the study of Judd et al.[8] was published and reported many findings convergent with the current study.

METHOD

Patients provided written informed consent to be enrolled, assessed, and treated in the Network, as previously described.[16,17] Patients were recruited from 1996 to 1999 from the local community at each Network site (Los Angeles VA Hospital and University of California at Los Angeles Ambulatory Clinical Research Center, Los Angeles, Calif.; University of Texas Southwestern Medical Center, Dallas, Tex.; University of Cincinnati Medical Center affiliated hospitals and clinics, Cincinnati, Ohio; University Medical Center and Altrecht Institute for Mental Health Care, Utrecht, the Netherlands; and the NIMH outpatient clinic for patients with bipolar disorder in Bethesda, Md.) with few restrictions or exclusions for comorbid illness. Patients were required to participate in regular and intensive assessments and in naturalistic treatment of their illness. They were asked to consider participation in treatment protocols and randomized controlled clinical trials as their emerging symptoms might warrant.[16,17]

All 258 patients met DSM-IV criteria for bipolar disorder based on a formal Structured Clinical Interview for DSM-IV (SCID),[18] including 196 bipolar I patients (76.0%), 53 bipolar II patients (20.5%), and 9 patients with bipolar disorder not otherwise specified (NOS) or schizoaffective disorder, bipolar type (3.5%) (Table 1). They could enter the Network in any mood phase or state, depressed, manic, cycling, or euthymic. They were not excluded on the basis of comorbid illness, with 2 exceptions: (1) major medical conditions that would preclude participation in clinical trials or (2) current substance abuse that would require separate or adjunctive treatment in another facility.

The present sample of 258 patients overlaps with that of the Network described by Suppes et al.,[19] McElroy et al.,[20] and Kupka et al.,[21] although it represents a slightly different population based on the requirement of at least 1 year of continuous LCM measurements. These were the first consecutive patients to have complete prospective rating data for 1 year. Patients who dropped out of the Network prior to 1 year were not included, and the 258 patients thus represent the completer rather than the intent-to-treat sample. Patients completed a questionnaire on demographics and prior illness course variables.[18,20]

As previously described in detail,[12,13] clinicians rated patients on the prospective LCM, characterizing each day for its severity of manic or depressive symptomatology based on the degree of mood-related functional impairment in patients' usual social, educational, or occupational roles. Symptom severity was characterized as (1) none (not symptomatic, i.e., euthymic), (2) mild (little or no functional impairment), (3) low moderate (requiring some extra effort to maintain usual activities with some degree of dysfunction), (4) high moderate (exerting much extra effort and barely getting by), or (5) severe (unable to perform or essentially incapacitated).

Clinicians interviewed patients approximately every 2 to 4 weeks and, whenever possible, also used the patient's daily self-rated prospective LCM[12,13] to facilitate recall of the details of mood fluctuations and the associated degree of incapacitation. All raters in the Network participated in detailed training on the LCM and showed good reliability (single-measure intraclass correlation coefficient = 0.82) based on ratings of taped interviews and ratings of standardized prototypes or real mood charts.[15]

LCM ratings have been validated.[14,15] Briefly, LCM mania ratings correlated highly ($r = 0.656$, $p < .001$) with the Young Mania Rating Scale; LCM depression ratings correlated highly with the 17-item Hamilton Rating Scale for Depression ($r = 0.86$, $p < .001$) and the 30-item Inventory of Depressive Symptomatology-clinician rated ($r = –0.785$, $p < .001$); and overall LCM severity ratings correlated highly with the Global Assessment of Functioning scale ($r = –0.732$, $p < .001$).

LCM ratings of mild depression (i.e., without functional incapacity) in the absence of ratings of moderate depression within the same episode were not counted as an episode. In contrast, LCM ratings of only mild mania were counted as a hypomanic episode if symptoms lasted at least 4 days because of the higher threshold for many bipolar patients to report any hypomanic symptoms. Mean severity ratings of depression and mania were calculated from the LCM over the 365 days.

Episodes of mania and depression were counted in 2 ways by a computer program. The first uses DSM-IV criteria[22] and requires 2 weeks' duration for a depressive episode and 4 days for a manic episode. The second does not set an arbitrary durational criterion, but conservatively attaches days of intermittent symptomatology to the previous episode by the "leapfrog" rule[23]—that is, an episode ends with (1) a change in mood polarity (i.e., a swing

Table 1. Demographics of 258 Bipolar Patients With 1-Year Prospective Life Chart Method Ratings in the Stanley Foundation Bipolar Network[a]

Variable	Bipolar I (N = 196; 76.0%)	Bipolar II (N = 53; 20.5%)	Bipolar NOS and SA (N = 9; 3.5%)	Total (N = 258; 100%)
Age at entry, mean ± SD, y	42.4 ± 11.2	46.4 ± 12.2	43.5 ± 7.8	43.2 ± 11.4
Gender, %				
Male	44.9	43.4	55.6	45.0
Female	55.1	56.6	44.4	55.0
Ethnic group, %				
White	91.5	95.7	100	92.7
Nonwhite	8.5	4.3	…	7.3
Marital status, % married or cohabitating	56.6*	36.2*	66.7	53.1
Income level < $20,000, %	41.5*	17.0***	33.3	36.5
Education level, %				
< High school graduate	0.7	7.4	…	1.7
High school graduate	41.3	25.9	42.9	39.0
College graduate	58.0	66.7	57.1	59.3
Self-report of limited occupational functioning, %	42.0	34.0	44.4	40.6
Family history positive for:				
Depression, %	64.4	66.0	100.0	65.8
Bipolar disorder, %	57.1	53.2	87.5	57.4
Age, mean ± SD, y				
Onset of symptoms	20.1 ± 9.9	23.8 ± 12.7	20.3 ± 11.8	20.8 ± 10.6
First medication	29.2 ± 10.0	35.2 ± 11.2	31.6 ± 13.0	30.5 ± 10.6
First hospitalization	29.9 ± 10.2	37.4 ± 11.7	29.1 ± 11.5	30.7 ± 10.6
History of drug or alcohol abuse, %	41.8*	25.5	22.2	38.0
History of alcohol abuse, %	29.1	21.3	…	26.5
History of 1 or more suicide attempts, %	28.3	25.5	44.4	28.4
Episodes, %				
4 or more manic	82.8	74.5	87.5	81.3
4 or more depressed	74.1**	93.6***	77.8	78.0
Hospitalized, %				
4 or more times for mania	26.1***	…	22.2	20.9
4 or more times for depression	13.6	6.4	55.6***	13.8
History of any cycling, %	50.0	54.0	44.4	50.6
(rapid, ultra, or ultradian)				
History of ultra-rapid cycling	25.0	21.3	33.3	24.6
History of ultradian cycling	20.3	16.7	22.2	19.7

[a]All values represent percentage of patients except where stated otherwise.
*p < .05.
**p < .01.
***p < .001.
Abbreviations: NOS = not otherwise specified, SA = schizoaffective disorder, bipolar type, … = none.

from mania to depression or the converse), (2) 2 weeks of euthymia, or (3) a well interval between 2 successive manic or 2 successive depressive periods that was at least 1 day greater than the longest duration of the adjacent episode. For example, if a patient had 8 consecutive days of moderate-to-severe mania, any residual or intermittent days of mania ratings immediately thereafter would be associated with that prior episode if the following well interval was 8 days or less. The same rule would apply to several days of intermittent mania ratings immediately preceding a full-blown episode. In this fashion, the total number of episodes would not be artificially inflated by premonitory or residual symptoms of a given mood phase, while, at the same time, distinct periods of a pathologic mood state would be counted even if they were not followed by an arbitrarily set period of, for example, 2 months well. Episode data based on the "leapfrog" rule are presented in this article.

Rapid cycling was defined as the traditional 4 episodes/year,[24] whereas ultra-rapid cycling was defined as 4 episodes/month.[13] Periods of ultradian cycling[25] consisted of sudden fluctuations in mood occurring rapidly within the course of a 24-hour period, as distinct from normal diurnal variations in mood. The number of days during which these occurred and the number per day were recorded. These fluctuations within a day were not included in the total episode count, however. Thus, dramatic mood fluctuations and dysphoric mania, which are often subsumed under "mixed states," could be differentiated. A check-box was provided for indicating if a mania was dysphoric as opposed to euphoric.

Each patient's LCM for the entire year was printed out and sorted for its overall pattern of illness into 1 of 12 categories, ranging from chronically ill for more than three fourths of the year to virtually well for the entire period. These included 3 groups:

Table 2. Intensive Drug Treatment During 1 Year of Prospective Follow-Up of 258 Outpatients With Bipolar Disorder[a]

Treatment	N	%	Mean Days Taken
Mood stabilizers	250	97	261.7
Lithium	165	64	299.5
Valproate	135	52	264.6
Carbamazepine	68	26	278.7
Gabapentin[b]	43	17	196.9
Lamotrigine	28	11	174.4
Topiramate[b]	29	11	168.3
Antidepressants	136	53	164.4
Venlafaxine	34	13	113.9
Bupropion	45	17	202.2
Sertraline	30	12	186.9
Fluoxetine	26	10	177.9
AD1 blind medication[c]	22	9	
Paroxetine	19	7	153.3
Tranylcypromine	11	4	139.7
Nefazodone	6	2	134.5
Moclobemide	5	2	172.0
Fluvoxamine	4	2	67.8
Phenelzine	1	0.4	304.0
Neuroleptics	85	33	148.8
Atypical	54	21	165.9
Olanzapine	31	12	139.2
Risperidone	13	5	163.5
Clozapine	12	5	306.3
Quetiapine	9	4	62.5
Typical	43	17	126.9
Thioridazine	13	5	74.8
Perphenazine	10	4	179.1
Thiothixene	6	2	212.7
Haloperidol	6	2	47.5
Chlorpromazine	5	2	40.4
Trifluoperazine	4	2	173.8
Fluphenazine	2	0.8	365.0
Pimozide	1	0.4	74.0
Molindone	1	0.4	188.0
Prochlorperazine	1	0.4	4.0
Benzodiazepines	126	49	101.5
Clonazepam	49	19	113.2
Temazepam	34	13	89.6
Lorazepam	33	13	85
Oxazepam	26	10	108.7
Alprazolam	15	6	123.3
Diazepam	5	2	80.4
Clorazepate	1	0.4	184.0
Thyroid			268.3
Levothyroxine	67	26	279
Liothyronine	16	6	207.9

[a]Mean number of psychiatric medications per patient was 4.1.
[b]Gabapentin and topiramate are no longer classified as mood stabilizers.
[c]This medication would be bupropion, sertraline, or venlafaxine.
Abbreviation: AD = antidepressant.

Group I: Ill for 75% to 100% of the year. This group included 4 categories: (A) those ill almost the whole year with marked rapid and ultradian cycling, (B) those with a predominance of recurrent depressions, (C) those with a predominance of recurrent manias, and (D) those with persistent chronic depression with little cycling.

Group II: Intermittent illness occupying less than 75% of the year. The 4 categories in this group were those with (E) intermittent isolated depressions predominating, with full-blown manias; (F) intermittent isolated depressions predominating, with hypomanias; (G) intermittent isolated depressions predominating, with no manias; or (H) a predominance of manias or hypomanias.

Group III: Not markedly impaired by illness. The 4 categories in this group included those (I) initially having 1 or more manic or depressive episodes of at least moderate severity, but resolving so that the last two thirds of the year was essentially free of illness; (J) with only isolated periods of mild hypomania; (K) with only isolated periods of mild depression; or (L) virtually well the entire year.

All assignments of these LCM patterns were completed independently by 2 separate raters. In the few instances where there were discrepancies, they were resolved by consensus of the 2 investigators. To demonstrate the internal validity of the groupings (I, II, III) and the relative contribution of a patient's mean depression severity, manic severity, and number of episodes to the clinical categories, these variables derived from the LCM were treated as predictors of the groups of illness patterns in a multinomial logistic regression.

Patients were treated in a naturalistic study according to the prevailing academic standards in the community, except in 22 instances when patients were entered into a comparative double-blind trial of 3 second-generation antidepressants.[26] However, because this trial was designed to mirror clinical practice based on the physician's assessment of the need to treat breakthrough depressive symptoms, the entire data set can be considered to be based on naturalistic treatment.

These patterns of mood fluctuations were examined independently of medication status. The types and numbers of medications are listed in Table 2 and included at least 1 mood stabilizer in 97% of patients. The mean ± SD number of psychotropic medications per patient was 4.1 ± 2.1 and included a large variety of agents in each medication class. The mean duration of treatment with each drug during the year is also listed in Table 2.

Chi-square and group t tests were applied to demographic and illness variables as appropriate. Those variables from the patient questionnaire[16,19] that were significantly intercorrelated with clinical outcome in a univariate analysis (W.A.N., D.A.L., L.L.A., et al., unpublished manuscript) were entered into a hierarchical multinomial logistic regression analysis. In addition, mood state in the first prospective week (manic, depressed, cycling, or euthymic) was noted and entered into the last sequence of the hierarchical analysis.

RESULTS

Patients were euthymic a mean 52.6% of the year and experienced symptoms almost half (47.4%) of the year, with manic symptoms 10.8% of the time, depressed symptoms 33.2% of the time, and ultradian cycling 3.4% of the time. Ratings with moderate or severe depression

Table 3. Days of Manic and Depressive Morbidity and Number of Episodes at Each Level of Severity for 1 Year as a Function of Outcome Group (N = 258)

Outcome Group	N (%)	Days Manic, Mean ± SD				Days Depressed, Mean ± SD				No. of Episodes, Mean	
		Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Manic	Depressive
Ill $^{3}/_{4}$ of the year											
A Ill virtually whole year, cycling predominates	17 (6.6)	55.1 ± 30.4	25.9 ± 19.3	0.9 ± 2.1	81.8 ± 39.9	68.8 ± 35.3	73.9 ± 47.5	2.2 ± 3.6	144.9 ± 69.0	20.6	12
B Ill ≥ $^{3}/_{4}$, depression predominates	24 (9.3)	28.8 ± 25.0	20.3 ± 22.5	1.6 ± 4.7	50.8 ± 43.1	98.1 ± 55.2	139.0 ± 48.1	10.1 ± 19.6	247.1 ± 42.9	6.5	5.5
C Ill ≥ $^{3}/_{4}$, cycling, mania predominate	10 (3.9)	142.0 ± 53.0	56.3 ± 31.5	…	198.3 ± 36.2	38.6 ± 16.7	39.5 ± 27.7	2.6 ± 5.5	80.7 ± 41.2	8.3	3.9
D Chronic depressions most of the year	17 (6.6)	7.9 ± 15.9	4.1 ± 12.1	…	12.0 ± 18.6	91.4 ± 75.7	218.0 ± 82.1	6.2 ± 13.5	315.6 ± 38.0	0.9	1.8
Subtotal	68 (26.4)	46.8 ± 52.4	23.0 ± 26.3	0.8 ± 3.0	70.5 ± 68.9	80.4 ± 56.4	127.8 ± 84.0	6.0 ± 13.9	214.2 ± 96.0	8.9	5.99
Intermittently ill											
E Episodic, major depression w/full-blown mania	26 (10.1)	23.8 ± 19.9	16.0 ± 15.6	0.5 ± 1.4	40.4 ± 25.2	59.5 ± 32.4	64.5 ± 36.8	7.7 ± 15.4	131.7 ± 46.9	6.7	5.2
F Episodic, major depression w/hypomania	49 (19.0)	23.9 ± 21.9	1.6 ± 2.3	…	25.5 ± 22.9	69.7 ± 42.1	57.4 ± 39.7	1.5 ± 4.3	128.9 ± 58.3	5.1	4.2
G Episodic, major depression w/no mania	15 (5.8)	0.8 ± 1.4	…	…	0.8 ± 1.42	71.1 ± 53.7	68.0 ± 49.3	5.1 ± 8.7	144.2 ± 73.3	0.4	2.5
H Episodic, hypomania/mania	15 (5.8)	45.9 ± 25.3	51.5 ± 42.0	6.8 ± 12.5	104.2 ± 44.5	29.9 ± 32.9	15.5 ± 19.0	…	45.4 ± 38.3	4.8	1.2
Subtotal	105 (40.7)	23.7 ± 23.5	12.1 ± 24.5	1.1 ± 5.2	36.9 ± 39.6	61.7 ± 42.4	54.7 ± 41.3	3.3 ± 9.2	119.8 ± 63.1	4.8	3.8
Predominantly well											
I Ill first $^{1}/_{3}$, well last $^{2}/_{3}$ of the year	18 (7.0)	12.1 ± 16.5	5.4 ± 8.7	1.3 ± 4.7	18.7 ± 21.7	37.3 ± 26.2	21.2 ± 20.0	0.4 ± 1.9	59.2 ± 37.7	1.6	1.2
J Mild hypomania only	12 (4.6)	78.8 ± 29.6	1.7 ± 2.6	…	80.4 ± 29.9	51.0 ± 34.2	6.3 ± 9.6	…	57.3 ± 40.2	6.2	0.7
K Mild depression only	26 (10.1)	7.9 ± 9.2	0.1 ± 0.3	…	8.0 ± 9.4	80.0 ± 58.6	4.0 ± 4.5	…	84.1 ± 58.3	1.4	1.1
L Virtually well	29 (11.2)	1.3 ± 2.5	0.2 ± 0.8	…	1.4 ± 2.7	4.2 ± 8.2	0.3 ± 0.7	…	4.5 ± 8.2	0.4	0.1
Subtotal	85 (32.9)	16.5 ± 29.3	1.5 ± 4.6	0.3 ± 2.2	18.3 ± 30.4	41.0 ± 47.9	6.7 ± 12.7	0.1 ± 0.9	47.9 ± 51.3	1.8	0.7
Total	258 (100)	27.4 ± 36.9	11.4 ± 22.3	0.7 ± 3.9	39.6 ± 50.8	59.8 ± 50.4	58.2 ± 68.9	3.0 ± 9.5	121.0 ± 94.5	4.9	3.4
Percentage of year		7.5%	3.1%	0.2%	10.8%	16.4%	15.9%	0.8%	33.2%		

Symbol: … = none.

(i.e., associated with dysfunction) occupied 16.7% (61.2 days) of the year (Table 3). The rating with mild depressive symptoms occupied a mean of 59.8 days/year or almost another 2 months in addition to the 2 months of more severe depression.

Figure 1 represents the frequency distribution of patients with a given number of episodes in the prospective year classified by the leapfrog method. For all manic and depressive episodes combined, only 8.9% of the patients had no episodes, 28.3% had 1 to 3 episodes, 32.2% had 4 to 8 episodes, and 30.6% of the population had more than 8 episodes in the year. The number of manic and depressive episodes was highly correlated within individuals ($r = 0.73$; $N = 258$; $p < .001$).

Patient reports of a past history of rapid and ultradian cycling were generally prospectively validated (Table 4). For example, of the patients who reported a prior history of rapid cycling, 79.3% of these showed rapid cycling in the observed prospective year, compared with 44.9% in those without a prior history. Similarly, of those patients who reported a prior history of ultradian cycling, 82.6% showed this pattern in the prospective year compared with 23.9% in those without a prior history. Surprisingly, those with bipolar I versus bipolar II diagnostic subtype showed no difference in the mean percentage of days with mania, depression, ultradian cycling, or euthymia. A greater percentage of females (61.3%) had at least 30 days of moderate or more severe depression, compared with 47.4% of males.

As illustrated in Table 3, two thirds of the patients (Groups I and II) were moderately to severely affected by their illness in the prospective year. In Group I, 26.4% were ill more than three fourths of the year, and these included (A) 6.6% who were essentially ill the entire year with prominent components of ultra-rapid and ultradian cycling, (B) 9.3% who showed a pattern of predominant depressive episodes, (C) 3.9% who had a relative predominance of manic episodes, and (D) 6.6% who had long periods of chronic and persistent depression with very little cycling.

Group II consisted of 40.7% of patients who showed more intermittent patterns of illness, with 3 types of depressive patterns and 1 manic pattern. Of those with intermittent depressions, (E) 10.1% were associated with intervening full manias, (F) 19.0% were associated with intervening hypomanias, and (G) 5.8% were associ-

Figure 1. Frequency Distribution of the Number of Manic and Depressive Episodes Observed in 1 Year in 258 Outpatients Treated for Bipolar Disorder

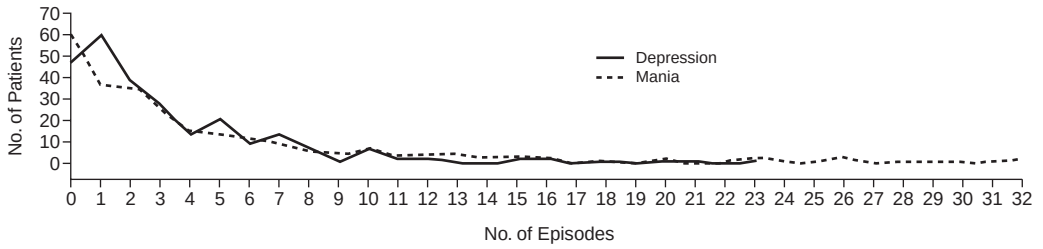


Table 4. Retrospective Self-Reports of Rapid and Ultradian Cycling Are Prospectively Validated and Are Negative Prognosticators

Patient Characteristic	N	Rapid Cycling in Prospective Year N (%)	Ultradian Cycling in Prospective Year N (%)	Percent Time Depressed	Percent Time Manic
All patients	258	162 (62.8)	91 (35.3)	33.2	10.8
Male	116	67 (57.8)	33 (28.4)*	31.2	11.1
Female	142	95 (66.9)	58 (40.8)	34.7	10.6
Bipolar I	196	125 (63.8)	72 (36.7)	32.8	11.8
Bipolar II	53	32 (60.4)	16 (30.2)	33.5	7.6
Bipolar NOS	4	3 (75.0)	3 (75.0)	58.4	6.1
Schizoaffective	5	2 (40.0)	0 (0.0)	22.6	12.7
History of rapid cycling[a]	121	96 (79.3)***	60 (49.6)***	36.3*	12.5
No history of cycling	118	53 (44.9)	25 (21.2)	29.1	9.0
History of ultradian cycling	46	42 (91.3)**	38 (82.6)***	41.0**	13.8
No history of ultradian cycling	188	104 (55.3)	45 (23.9)	30.2	10.2

[a]From retrospective patients questionnaire.
*p ≤ .05.
**p ≤ .01.
***p ≤ .001.
Abbreviation: NOS = not otherwise specified.

ated with no manias (i.e., only depressions); 5.8% of patients showed a pattern of (H) predominantly intermittent manias or hypomanias and fewer or no depressions.

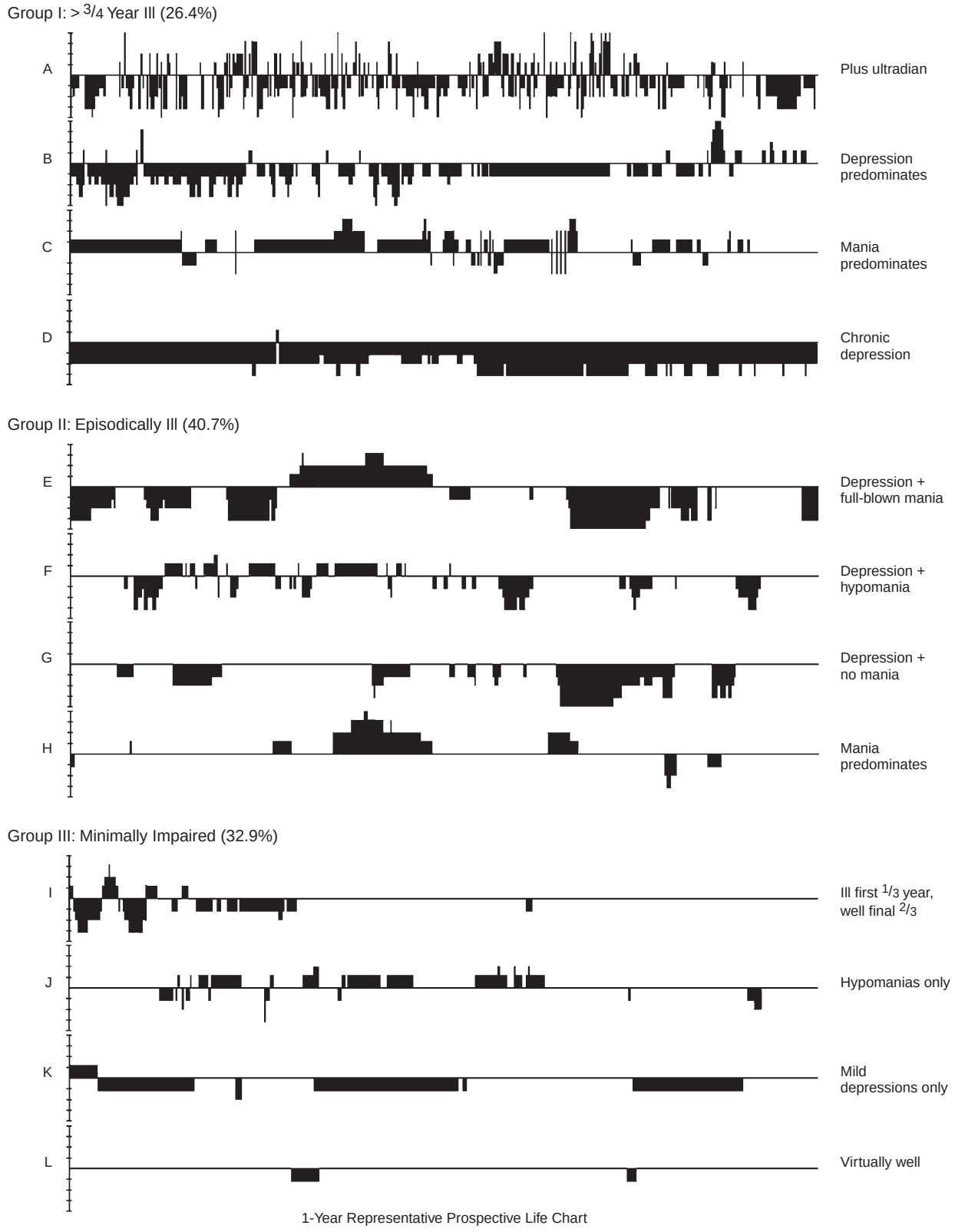
Only 32.9% of the patients (Group III) could be characterized as being relatively well over most of the prospective year. Of these, (I) 7.0% of the patients had moderate-to-severe episodes of mania or depression at the beginning of the year, followed by relative euthymia for the last two thirds of the year; (J) 4.6% displayed isolated periods of hypomania, rarely exceeding mild severity; (K) 10.1% showed isolated periods of depression, rarely exceeding mild severity; and (L) only 11.2% were essentially well for the entire year with only very rare periods (several days) of any symptoms. A representative patient's entire 1-year LCM illustrating the pattern typical of each of the above 12 categories is presented in Figure 2.

Differential use of antidepressants and other medications did not appear related to these morbidity outcomes. For example, in Group I, 72.4% of patients were on antidepressants for a mean of 6.4 months; Group II included 51.5% of patients on antidepressants for a mean of 8.5 months; and in Group III, 45.2% of patients were given antidepressants for a mean of 7.6 months.

Consistent with Figure 2, the multinomial logistic regression analysis indicated that greater mean severity of depression on the LCM would tend to place one in the mostly ill Group I (odds ratio [OR] = 34.4) or in the episodic Group II (OR = 10.6) compared with the largely well Group III. Similarly, the mean severity of mania on the LCM yielded an OR of 31.4 for Group I versus Group III and an OR of 7.9 for Group II versus Group III. An individual's total number of episodes was significantly but only weakly related to these global categorizations of outcome (OR = 1.27 for Group I versus III; OR = 1.21 for Group II versus III).

The hierarchical multinomial logistic regression (Table 5) showed that the most severely ill patients (Group I) were differentiated from those who were relatively well (Group III) by a positive family history of drug abuse in first-degree relatives, 10 or more prior depressive episodes, and a history of limited occupational functioning prior to Network entry. It should be noted that the initial significant relationship of family history of drug abuse was ultimately subsumed by the other historical and illness variables (in models 2–4) that were subsequently entered. Mood state in the first week (particularly

Figure 2. Patterns of Illness Among 258 SFBN Patients Treated Prospectively and Rated Daily for 1 Year[a]



[a]Each line represents a modal patient rated for 1 year. Line = baseline (euthymia); above = mania; below = depression. Severity of each phase is rated mild, low and high moderate, and severe according to distance from baseline.
Abbreviation: SFBN = Stanley Foundation Bipolar Network.

Table 5. Predictors of Outcome Categories From Hierarchical Multinomial Logistic Regression

		Well (Group III) vs Sick (Group I)[a]				Well (Group III) vs Episodic (Group II)			
Hierarchical Entries	Variables Entered	1	2	3	4	1	2	3	4
1 Familial	Family history of drug abuse	3.19*	2.61	2.18	2.45	1.84	1.48	1.29	1.49
2 Early stressors	Physical abuse as a child		1.86	1.71	1.01		2.12	2.14	1.41
	Verbal abuse as a child		1.78	1.62	1.45		1.62	1.50	1.16
3 Onset and comorbidity	Age at onset of mania			0.98	0.99			1.00	1.02
	Comorbid substance abuse			1.93	2.48			2.41*	2.97*
4 Retrospective illness course	Prior cycling				1.51				1.99
	10 or more prior manic episodes				1.50				1.52
	10 or more prior depressed episodes				3.13*				2.38*
	Limited occupational functioning				1.59*				1.47*
Mood state at network entry	Manic				4.51*				1.04
	Depressed				16.39*				2.86
	Cycling				4.50*				1.85

[a]Numbers 1 through 4 represent sequential steps in the regression analysis entering the variables numbered in the left column. Cox and Snell Pseudo-r^2 for steps 1–4 of well (Group III) vs. sick (Group I) were 0.03, 0.06, 0.10, and 0.36, respectively; likewise, the % correctly classified for steps 1–4 in the same group comparison was 42.9, 43.3, 46.7, and 60.8, respectively.
*Significant odds ratio values; $p < .05$.

depression) placed patients in Group I (versus Group III) but did not discriminate for the intermittent (Group II) versus largely well (Group III) categorization.

Only prior depressed episodes and limited occupational functioning differentiated Group II from Group III. A positive family history of drug abuse was not significant for Group II, but a personal history of comorbid substance abuse did contribute significantly.

DISCUSSION

Two hundred fifty-eight outpatients with bipolar disorder treated naturalistically were followed for 1 year using clinician-rated prospective daily LCM assessments so that the precise course and patterns of residual or treatment-resistant illness could be elucidated. Despite treatment with a range of routine and novel agents, two thirds of the patients (N = 173) had clinically substantial manic or depressive symptoms during the year (Groups I and II). In the entire 258-patient cohort, patients were functionally impaired (greater than mild severity on the daily LCM) a mean of almost 2.5 months/year (only 12.1 days of moderate or greater mania, but 61.2 days of moderate or greater depression).

The majority of patients (62.8%) had 4 or more episodes/year, and 30.6% had more than 8 episodes/year. In addition, 91 patients (35%) had ultradian cycling, which was displayed for a mean of 12.5 days (range, 1–335 days). As might be expected, those with a self-reported history of rapid and/or ultradian cycling on entry into the Network also experienced a greater percentage of prospectively observed and clinician-rated rapid cycling and ultradian cycling, respectively. These relationships provide some internal validation of the patient questionnaire reports of the experience of these cycle frequencies in the past.

Of the 258 patients, 26.4% of the patients (Group I) were extremely ill for almost the entire year. Approximately 40.7% of the patients (Group II) showed patterns of intermittent major depressive (34.9%) or manic (5.8%) episodes. The remaining one third of the patients (Group III) were relatively well for most of the year, although only 11.2% were virtually illness-free, as illustrated in Figure 2. The highly significant ORs for the mean severity of depression (OR = 34.4) and mean severity of mania (OR = 31.4) in the likely categorization of the most ill (Group I) versus most well (Group III) outcomes show their greater contribution than the total number of episodes, demonstrating the internal consistency of the clinical global categorization used. Using just 3 LCM variables (manic and depressive severity and frequency of episodes) would correctly classify 79% of the patients to 1 of the 3 groups.

Clinical variables that significantly differentiated those with the poorest outcome (Group I) from those with the best outcome (Group III) were a positive family history of drug abuse, 10 or more prior depressive episodes, limited occupational functioning prior to Network entry, and mood state at entry in any state. Only prior depressive episodes and limited occupational functioning discriminated those who showed intermittent illness patterns (Group II) from the largely well (Group III), with an additional contribution of a personal history of comorbid substance abuse. Average severity of depression and mania on the LCM were most closely associated with the clinical global categorizations reported here, whereas the number of episodes was a weak contributor when the other variables were accounted for. However, it should be emphasized that the ultradian fluctuations prominent in Group I, categories A, B, and C, were not included in the episode count. Taken together, these data are consistent

with the view that emergent depression is a greater problem in this cohort than mania and lend credence to the global clinical characterizations we used, because there were meaningful differences in severity of LCM depression and mania ratings by category (Table 3). To some extent, presentation in a manic, depressed, or cycling state during the first week of prospective follow-up would increase the likelihood that the patient would be in the most ill (Group I) compared with the most well (Group III) group.

A number of caveats are necessary to the interpretation of these data. Although the patients were almost exclusively recruited from the community and not from an inpatient population, this group is not representative of a nonselective epidemiologically derived population with bipolar illness. It is also likely that this cohort has included a greater percentage of outpatients with treatment resistance than in general clinical practice, thus attracting patients to treatment centers with a record of excellence in the study and treatment of bipolar illness. Conversely, selectivity toward less ill, more highly motivated patients may have occurred on the basis of patients' initial willingness to invest a considerable amount of time in the detailed documentation and rating of their illness. Moreover, this study included only those individuals committed enough to remain in the Network for a minimum of 1 year. Finally, the preponderance of bipolar I compared with bipolar II patients probably also reflects some nonrepresentativeness of the cohort, given the new estimates of a large percentage of unipolar patients that may have bipolar II disorder on closer inspection.[27]

On the other hand, this population is probably representative of many clinical populations at tertiary care centers. As noted in the introduction, recent reports on long-term follow-up from a variety of centers have also indicated a substantial degree of residual illness despite the use of a wide range of potential therapeutic agents.[1–8] In addition, patients in the Network were not a population solely chosen for either a recent episode[28] or treatment resistance[29] requiring hospitalization. Of these outpatients, 23.3% of the patients had never had a prior hospitalization.

Another caveat relates to the use of the clinician-rated LCM as the longitudinal rating instrument in this study, although the LCM has been validated against a variety of cross-sectional measures.[14,15] LCM euthymia, which is defined as the lack of ratings of either mild mania or depression, does not necessarily imply complete recovery and ability to work or work up to an individual's full potential. For example, a number of reports raise the distinction between syndromal as opposed to functional recovery.[30–33]

Although we have used the "leapfrog" episode criteria derived from a practical clinical approach to severity and duration of symptoms,[23] it is clear that neither these nor the DSM-IV criteria for an episode accurately describe the pleomorphic presentations of bipolar disorder and the continua of both severity and duration possible for any given episode within or between individuals (Figure 2). As in unipolar depression,[34] subsyndromal and episodic presentations do not appear to represent separate conditions, but are related parts of a clinical continuum. On the other hand, however, the definition of a sufficient euthymic period to end an episode is, in part, a function of the cycle frequency. Perhaps the detailed daily illness template provided here will lead to a reevaluation of the episode and recovery criteria for bipolar disorder that have been derived from a confusing legacy[35] and based largely on criteria for unipolar depression[36] toward those based on more naturally and empirically based divisions. In addition, given this detailed depiction, one can more precisely examine how incompletely treated subsyndromal or dysthymic symptoms and more periodic breakthrough minor episodes[37] or "flurries"[38] may herald the onset of more severe exacerbations and relapses.

Although there are a number of caveats about the interpretation of the current data and the clinical population from which they are derived, the findings are, nonetheless, highly convergent with those of a number of recently reported clinical outcomes from a variety of other academic centers as reviewed by Goldberg et al.[39] These data suggest that, despite wide use of a range of well-accepted mood stabilizers (such as lithium, valproate, and carbamazepine), clinical exploration of promising new agents (such as lamotrigine[40] and topiramate[41]) in small numbers of subjects, and substantial use of adjunctive antipsychotics, antidepressants, and benzodiazepines, some two thirds of these outpatients remain intermittently (Group II) to continuously (Group I) affected by treatment-nonresponsive aspects of their illness. A subsequent report on this same cohort will explore demographic and clinical correlates of outcomes based on ratings on the LCM or manic and depressive severity and numbers of episodes rather than the global clinical characterization used here (W.A.N., D.A.L., L.L.A., et al., manuscript in preparation).

The emerging consensus view of the considerable morbidity remaining in a large percentage of intensively followed and treated bipolar outpatients in academic centers contrasts with the relative lack of studies on bipolar disorder in general, and clinical trials in particular, conducted and reported in the literature over the past 2 decades.[42–44] Our data suggest that even with the current expanding array of potential therapeutic agents, bipolar disorder (especially its depressive components) remains a severe public health problem, particularly given the perspective that persistent depression predicts depressive morbidity 15 years later.[10] New and more effective agents are needed to begin to make initial 60% to 80% response rates for lithium observed in formal clinical trials[45] a clinical reality in more typical and less restrictively recruited outpatients with bipolar illness.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin and others), clorazepate (Tranxene and others), clozapine (Clozaril and others), diazepam (Valium and others), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), fluvoxamine (Luvox and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), levothyroxine (Synthroid and others), liothyronine (Cytomel and others), lorazepam (Ativan and others), molindone (Moban), nefazodone (Serzone), olanzapine (Zyprexa), oxazepam (Serax), paroxetine (Paxil), perphenazine (Trilafon and others), phenelzine (Nardil), pimozide (Orap), prochlorperazine (Compazine and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), temazepam (Restoril), thiothixene (Navane and others), topiramate (Topamax), tranylcypromine (Parnate), trifluoperazine (Stelazine and others), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, alprazolam, bupropion, carbamazepine, chlorpromazine, clonazepam, clorazepate, clozapine, diazepam, fluoxetine, fluphenazine, fluvoxamine, gabapentin, haloperidol, lamotrigine, levothyroxine, liothyronine, lorazepam, molindone, nefazodone, oxazepam, paroxetine, perphenazine, phenelzine, pimozide, prochlorperazine, quetiapine, risperidone, sertraline, temazepam, thiothixene, topiramate, tranylcypromine, trifluoperazine, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Altshuler is a consultant for Abbott, Eli Lilly, Forest, Janssen, Parke-Davis, and Solvay; has received research support from Abbott, Eli Lilly, Forest, Glaxo-Wellcome, SmithKline Beecham, and Solvay; is a member of the speakers' bureau for Abbott, Glaxo-Wellcome, and Solvay; and is a member of the advisory board for Abbott, Eli Lilly, and Forest; Dr. Frye has received grant/research support from the Stanley Foundation; Dr. Suppes has received research/grant support from Abbott, AstraZeneca, Bristol-Meyers Squibb, GlaxoSmithKline, Janssen, National Institutes of Mental Health, Novartis, Robert Wood Johnson, and The Stanley Medical Research Institute; and is a consultant for or is a member of the speakers/advisory board for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, and Pharmaceutical Research Institute (PRI); Dr. Keck is a consultant for and a member of the speakers/advisory board for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Ortho-McNeil, Pfizer, and Shire Richwood; and has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, Organon, Pfizer, Forest, and Elan; Mr. Nolen is an employee of Altrecht; and Drs. Post, Denicoff, Rush, McElroy, and Kupka and Ms. Leverich, Mr. Luckenbaugh, and Mr. Pollio have no significant commercial relationships to disclose relative to the presentation.

REFERENCES

1. Benazzi F. Prevalence and clinical correlates of residual depressive symptoms in bipolar II disorder. Psychother Psychosom 2001;70:232–238
2. O'Connell RA, Mayo JA, Flatow L, et al. Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 1991;159:123–129
3. Gelenberg AJ, Kane JM, Keller MB, et al. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989;321:1489–1493
4. Goldberg JF, Harrow M, Leon AC. Lithium treatment of bipolar affective disorders under naturalistic followup conditions. Psychopharmacol Bull 1996;32:47–54
5. Maj M, Pirozzi R, Magliano L, et al. Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998;155:30–35
6. Gitlin MJ, Swendsen J, Heller TL, et al. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995;152:1635–1640
7. Vestergaard P. Treatment and prevention of mania: a Scandinavian perspective. Neuropsychopharmacology 1992;7:249–259
8. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
9. Keller MB, Lavori PW, Friedman B, et al. The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987;44:540–548
10. Coryell W, Turvey C, Endicott J, et al. Bipolar I affective disorder: predictors of outcome after 15 years. J Affect Disord 1998;50:109–116
11. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh, Scotland: ES Livingstone; 1921
12. Leverich GS, Post RM. Life charting the course of bipolar disorder. Curr Rev Mood Anxiety Disord 1996;1:48–61
13. Leverich GS, Post RM. Life charting of affective disorders. CNS Spectrums 1998;3:21–37
14. Denicoff KD, Smith-Jackson EE, Disney ER, et al. Preliminary evidence of the reliability and validity of the prospective life-chart methodology (LCM-p). J Psychiatr Res 1997;31:593–603
15. Denicoff KD, Leverich GS, Nolen WA, et al. Validation of the prospective NIMH-Life-Chart Method (NIMH-LCM-p) for longitudinal assessment of bipolar illness. Psychol Med 2000;30:1391–1397
16. Leverich GS, Nolen WA, Rush AJ, et al. The Stanley Foundation Bipolar Treatment Outcome Network, 1: longitudinal methodology. J Affect Disord 2001;67:33–44
17. Post RM, Nolen WA, Kupka RW, et al. The Stanley Foundation Bipolar Network, 1: rationale and methods. Br J Psychiatry 2001;178:S169–S176
18. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1996
19. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network, 2: demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45–59
20. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426
21. Kupka RW, Nolen WA, Altshuler LL, et al. The Stanley Foundation Bipolar Network, 2: preliminary summary of demographics, course of illness and response to novel treatments. Br J Psychiatry 2001;178: S177–S183
22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
23. Denicoff KD, Blake KD, Smith-Jackson EE, et al. Morbidity in treated bipolar disorder: a one year prospective study using daily life chart ratings. Depression 1994;2:95–104
24. Dunner DL, Fieve RR. Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 1974;30:229–233
25. Kramlinger KG, Post RM. Ultra-rapid and ultradian cycling in bipolar affective illness. Br J Psychiatry 1996;168:314–323
26. Post RM, Altshuler LL, Frye MA, et al. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. Bipolar Disord 2001;3:259–265
27. Allilaire JF, Hantouche EG, Sechter D, et al. Frequence et aspects cliniques du trouble bipolaire II dans une etude multicentrique francaise: EPIDEP. [Frequency and clinical aspects of bipolar II disorder in a French multicenter study: EPIDEP.] Encephale 2001;27:149–158
28. Coryell W, Endicott J, Maser JD, et al. The likelihood of recurrence in bipolar affective disorder: the importance of episode recency. J Affect Disord 1995;33:201–206
29. Frye MA, Ketter TA, Leverich GS, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J Clin Psychiatry 2000;61:9–15
30. Tohen M, Hennen J, Zarate CM Jr, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am J Psychiatry 2000;157:220–228
31. Keck PE Jr, McElroy SL, Strakowski SM, et al. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. Am J Psychiatry 1998;155:646–652
32. Tohen M, Strakowski SM, Zarate C Jr, et al. The McLean-Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. Biol Psychiatry 2000;48:467–476
33. Robb JC, Cooke RG, Devins GM, et al. Quality of life and lifestyle disruption in euthymic bipolar disorder. J Psychiatr Res 1997;31:509–517
34. Judd LL, Akiskal HS. Delineating the longitudinal structure of depressive

illness: beyond clinical subtypes and duration thresholds. Pharmacopsychiatry 2000;33:3–7
35. Kendell RE. The classification of depressions: a review of contemporary confusion. Br J Psychiatry 1976;129:15–28
36. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48:851–855
37. Post RM, Weiss SRB, Leverich GS, et al. Sensitization and kindling-like phenomena in bipolar disorder: implications for psychopharmacology. Clin Neurosci Res 2001;1:69–81
38. Keller MB, Lavori PW, Kane JM, et al. Subsyndromal symptoms in bipolar disorder: a comparison of standard and low serum levels of lithium. Arch Gen Psychiatry 1992;49:371–376
39. Goldberg JF, Harrow M, Sands JR. Lithium and the longitudinal course of bipolar illness. Psychiatr Ann 1996;26:651–658
40. Suppes T, Brown ES, McElroy SL, et al. Lamotrigine for the treatment of bipolar disorder: a clinical case series. J Affect Disord 1999;53:95–98
41. McElroy SL, Suppes T, Keck PE, et al. Open-label adjunctive topiramate in the treatment of bipolar disorders. Biol Psychiatry 2000;47:1025–1033
42. Prien RF, Potter WZ. NIMH workshop report on treatment of bipolar disorder. Psychopharmacol Bull 1990;26:409–427
43. Prien RF, Rush AJ. National Institute of Mental Health Workshop report on the treatment of bipolar disorder. Biol Psychiatry 1996;40:215–220
44. Goodwin G. Perspectives for clinical research on bipolar disorders in the new millennium. Bipolar Disord 2000;2:302–304
45. Baldessarini RJ, Tondo L. Does lithium treatment still work? evidence of stable responses over three decades. Arch Gen Psychiatry 2000;57: 187–190

For the CME Posttest for this article, see pages 738–739.