Are Antidepressants Associated With New-Onset Suicidality in Bipolar Disorder? A Prospective Study of Participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

Mark S. Bauer, M.D.; Stephen R. Wisniewski, Ph.D.; Lauren B. Marangell, M.D.; Cheryl A. Chessick, M.D.; Michael H. Allen, M.D.; Ellen B. Dennehy, Ph.D.; David J. Miklowitz, Ph.D.; Michael E. Thase, M.D.; and Gary S. Sachs, M.D., for the STEP-BD Investigators

Objective: Depressive episodes are common in bipolar disorder, and the disorder is characterized by high suicide rates. Recent analyses indicate a possible association of antidepressant treatment and suicidality in children and adults with depressive or anxiety disorders. However, few data are available to inform the suicidality risk assessment of antidepressant use specifically in bipolar disorder.

Method: Of the first 2000 participants followed for 18 months in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), 425 experienced a prospectively observed, new-onset major depressive episode without initial suicidal ideation. Standardized ratings of suicidality and antidepressant exposure at index depressive episode and next evaluation were used to investigate the primary hypothesis that new-onset suicidality was associated with increased antidepressant exposure (antidepressant initiation or dose increase). Secondary analysis investigated correlates of new-onset suicidality and antidepressant exposure. Data were collected from November 8, 1999, to April 24, 2002.

Results: Twenty-four participants (5.6%) developed new-onset suicidality at follow-up, including 2 suicide attempts. There was no association of new-onset suicidality with increased antidepressant exposure or any change in antidepressant exposure, and no association with initiation of antidepressant treatment. New-onset suicidality was associated with neuroticism, prior attempt, and higher depressive or manic symptom ratings at index episode. Increased antidepressant exposure was negatively associated with higher manic symptom rating at index episode; control for this sole empirically identified confound did not alter the primary results.

Conclusions: Although careful monitoring for suicidality is always warranted in bipolar disorder, this cohort study provides no evidence that increased antidepressant exposure is associated with new-onset suicidality in this already high-risk population. Correlates of both suicidality and antidepressant exposure indicate directions for further research.

(J Clin Psychiatry 2006;67:48–55)

Received March 18, 2005; accepted June 1, 2005. *From Providence Veterans Affairs Medical Center and the Department of Psychiatry and Human Behavior, Brown University, Providence, R.I. (Dr. Bauer); School of Public Health, University of Pittsburgh, Pittsburgh, Pa. (Dr. Wisniewski); Baylor College of Medicine, Houston, Tex. (Dr. Marangell); Department of Psychiatry, University of Colorado, Denver (Drs. Chessick, Allen, and Miklowitz); Department of Psychological Science, Purdue University, West Lafayette, Ind. (Dr. Dennehy); Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, Pa. (Dr. Thase); and Massachusetts General Hospital and the Department of Psychiatry, Harvard Medical School, Boston, Mass. (Dr. Sachs).*

This project has been funded in whole or in part with federal funds from the National Institute of Mental Health (NIMH), National Institutes of Health, under contract N01 MH80001.

Financial disclosure appears at the end of this article.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sites and principal investigators are listed at the end of the article.

The authors wish especially to express their appreciation for the statistical programming work by Mako Araga, M.S., that made this work possible.

Any opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the NIMH. This article was approved by the publication committee of the STEP-BD.

Corresponding author and reprints: Mark S. Bauer, M.D., VAMC-116R, 830 Chalkstone Ave., Providence, RI 02908-4799 (e-mail: mark_bauer@brown.edu).

Individuals with bipolar disorder may spend over 30% of their course in depressive episodes.[1] Cross-sectional and prospective studies indicate that depressive symptoms are the strongest predictor of social role dysfunction.[2] Those with bipolar disorder comprise a population at particularly high risk for suicide.[3–8] Thus, adequate treatment of depressive episodes is critical for optimal outcome in this disorder.

However, recent warnings by the U.S. Food and Drug Administration (FDA) suggest that antidepressants may be associated with increased suicidality, based on pooled analyses of 24 placebo-controlled trials of antidepressants in children and adolescents with depressive or anxiety disorders.[9] A database study of 24,119 U.S. adolescents also demonstrated increased risk of suicide attempts with 6 months of antidepressant use.[10] A mixed-age, mixed-diagnosis, case-control study of 159,810 individuals in the United Kingdom also indicated an increased risk of suicidal behaviors with the use of antidepressants within 90 days of the event.[11] A Cochrane Collaboration meta-analysis of clinical trials of antidepressants across all ages indicated a significant association between serotonin reuptake inhibitors and suicide attempts compared to placebo,[12] although another meta-analysis[13] and a correlational study of county-level U.S. data[14] failed to do so. This potential increased risk of suicidality due to antidepressants has sparked substantial discussion in both professional[15] and lay[16] publications.

Thus, if antidepressant medications increase suicidality in the already vulnerable bipolar population, their use should be minimized or avoided. On the other hand, if depressive episodes are undertreated, risk for social dysfunction and suicidality increases.

The only data on the antidepressant-associated suicidality risk specifically for bipolar disorder derive from 1 cross-sectional analysis, which indicated no association between suicidality and paroxetine use in individuals with this disorder.[17] Thus, there is little evidence to guide the clinician's suicide risk assessment of antidepressant use for such individuals. Moreover, few evidence-based alternatives to antidepressant medications exist for the treatment of acute bipolar depressive episodes.[18,19]

We therefore utilized prospective data from the National Institute of Mental Health–funded multisite Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[20] to investigate the primary hypothesis that increased exposure to antidepressant medications in a prospectively observed major depressive episode is associated with new-onset suicidality in individuals with bipolar disorder. Secondarily, we investigated correlates of suicidality and of antidepressant exposure that might modulate such an association.

METHOD

Study Overview

This cohort study analyzed the first 2000 participants enrolled in STEP-BD who completed 18 months of follow-up across 21 clinics. Program treatment is evidence-based and determined by physician and patient choice, while all participants receive the same structured assessments of treatment and outcome.[20] The STEP-BD participants are required to be at least 15 years of age and to meet DSM-IV criteria for bipolar I, bipolar II, cyclothymia, bipolar not otherwise specified, or schizoaffective manic or bipolar subtypes by semistructured interview. Exclusion criteria for STEP-BD are minimal, including unwillingness or inability to comply with study assessments, or inability to give informed consent. Thus, STEP-BD emphasizes recruiting an effectiveness sample[21,22] representative of patients seen in similar clinical practice venues. All participants provided written informed consent as approved by each institution's investigation review board. Data were collected from November 8, 1999, to April 24, 2002.

Assessments and Procedures

At STEP-BD intake, bipolar disorder characteristics and comorbidities were identified using the Mini-International Neuropsychiatric Interview (MINI)[23] for Axis I comorbidity. The Affective Disorders Evaluation (ADE),[20,24] a modification of the mood and psychosis modules from the Structured Clinical Interview for DSM-IV (SCID),[25] determined episode status at STEP-BD intake.

The Clinical Monitoring Form (CMF)[26] is administered to every STEP-BD participant at every clinic visit. The CMF assesses manic and depressive symptom status, including suicidal ideation, based on the SCID current mood modules. It also includes standardized assessment of stressors, comorbid substance abuse and anxiety symptoms, current medications, medication adherence, adverse effects of treatment, and relevant laboratory data. Participants are assigned at each visit to one of 8 clinical states including DSM-defined episodes (major depressive, manic, hypomanic, mixed); recovering (for those with ≤ 2 criteria for, respectively, 1–8 weeks) or recovered (for those with ≤ 2 criteria for more than 8 weeks); or 2 subsyndromal states, continued symptomatic or roughening, depending on whether they have transitioned from, respectively, an acute episode or recovery. Intraclass correlation coefficients (ICC) for CMF depression and mania items have been excellent (ICC = 0.83–0.99).

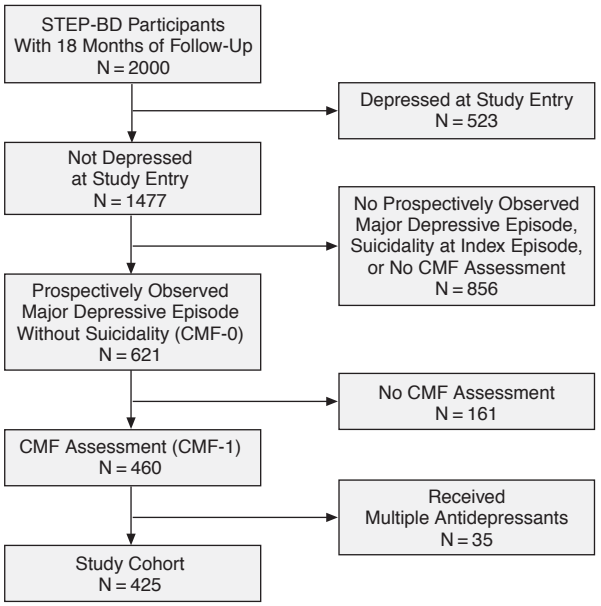
Among other relevant assessments, quality of life was assessed at STEP-BD intake using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[27] a 16-item self-report. Social role function at intake was assessed with the Range of Impaired Functioning Tool (LIFE-RIFT),[28] a 4-item clinician-administered semistructured interview in which work, recreation, interpersonal relations, and global satisfaction are rated from 1 (no impairment) to 5 (severe impairment). Neuroticism and extraversion were assessed at intake with the Neuroticism Extraversion Openness Five Factor Inventory (NEO-FFI).[29]

Study Cohort Definition

The cohort definition is summarized in Figure 1. We identified among the first 2000 participants in STEP-BD

who completed 18 months of prospective follow-up those participants who were not in a major depressive episode at STEP-BD intake according to the ADE (N = 1477). From these, we identified participants who subsequently experienced a prospectively observed major depressive episode without initial suicidality using CMF-0 assessment (N = 621; see Classification of Outcome for definition of suicidality) and who had at least one subsequent clinic visit with CMF-1 assessment within the prospective follow-up period (N = 460). For those participants who experienced more than one prospectively observed depressive episode, the episode that occurred first was chosen. Our initial design called for utilizing a cohort not taking antidepressants at intake who were then prescribed antidepressants for this first prospectively observed, nonsuicidal major depressive episode. However, this stringent criterion identified only 253 individuals. We therefore included participants whether or not they were taking antidepressants at index depressive episode, excluding those receiving multiple antidepressants[11] (N = 35), resulting in the study cohort of 425. To summarize: cohort participants experienced a prospectively observed index depressive episode without clinically significant suicidality and had a subsequent standardized clinical assessment with CMF within the prospective follow-up period.

Figure 1. Participant Flow From the First 2000 STEP-BD Participants to the Study Cohort



Abbreviations: CMF = Clinical Monitoring Form, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

Classification of Outcome

Since Angst and coworkers[7] found that both suicidal thoughts and behavior were associated with eventual suicide in their long-term follow-up study, we treated suicidal ideation/behavior as one construct (*suicidality* hereafter). Suicidality was therefore defined as either or both of the following. (1) Clinically significant suicidal ideation by CMF rating. This item is scored 0 to 2, with clinically significant suicidal ideation (rating ≥ 1) defined as thoughts that life is not worth living most of the day nearly every day, thoughts of death without planning, suicidal planning without action or urges for even brief periods over several days, or suicidal action or urges for persistent periods nearly every day. The ICC for interrater reliability for the CMF suicidality rating was 0.99. (2) Documented serious adverse event involving self-harm since the index depressive episode clinic visit according to study monitoring of best available data including death due to suicide, hospitalization for a suicide attempt, hospitalization for suicidal ideation, reported suicide attempt without hospitalization, or suicidal ideation reported outside of the clinic visit requiring clinician intervention.

Since the outcome of interest was the development of new-onset suicidality, we required a CMF rating at the index depressive episode of no suicidal ideation (rating ≤ 0.5, no more than "rare, fleeting thoughts of life not worth living") and no suicidal behavior since index episode CMF rating.

To summarize: cohort participants, who were all suicidality-negative at index CMF assessment, were classified as positive for new-onset suicidality at the next CMF if they met either of the above 2 criteria; all others were classified as negative. Median time between index depressive episode CMF assessment and next CMF assessment was 21 days (quartiles: 13, 35).

Antidepressant Exposure Classification

We applied an a priori antidepressant exposure categorization describing whether or not each participant had experienced a clinically significant increase in antidepressant dosage between the index assessment and next CMF assessment (available on request from L.B.M.). On the basis of recent studies showing no difference in suicidality risk among classes of antidepressants,[11,12,30] all antidepressant classes were combined, including serotonin reuptake inhibitors, tricyclic antidepressants, newer serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, bupropion, nefazodone, and trazodone in doses > 250 mg/day.

Statistical Methods

Descriptive statistics are presented as mean ± standard deviation for continuous variables and as percentages for discrete variables. Because of occasional small cell sizes, Fisher exact test (FET) and exact logistic regression models were used to assess potential bivariate asso-

Table 1. Characteristics of 425 STEP-BD Participants Who Experienced a Prospectively Observed Major Depressive Episode Without Initial Suicidality[a]

Characteristic	Value
Demographic characteristic	
Gender, male, N (%)	167 (39.3)
Age, mean ± SD, y	39.76 ± 11.99
Aged ≤ 20 years, N (%)	17 (4.0)
Minority status, N (%)	33 (7.8)
Marital status N (%)[b]	
Married or living as married	158 (39.6)
Divorced/separated	105 (26.3)
Widowed	5 (1.2)
Never married	131 (32.8)
Bipolar characteristic	
Age at onset, mean ± SD, y	17.10 ± 8.50
Bipolar type I, N (%)	298 (70.1)
History of psychosis, N (%)	164 (38.6)
History of suicide attempt, N (%)	180 (42.4)
Family history of suicide attempt, N (%)	89 (20.9)
Comorbidity and associated features	
Lifetime substance use disorder, N (%)	193 (45.4)
Current anxiety disorder, N (%)	152 (35.8)
Lifetime conduct disorder, N (%)	
Probable	15 (3.5)
Definite	12 (2.8)
NEO-FFI score, mean ± SD	
Extraversion	43.52 ± 11.6
Neuroticism	65.11 ± 8.6
Functional status at intake to STEP-BD	
Employment status, N (%)[c]	
Employed	123 (31.1)
Unemployed	87 (22.0)
Other than gainfully employed	185 (46.8)
LIFE-RIFT total score, mean ± SD	11.8 ± 3.7
Q-LES-Q total score, mean ± SD	188.7 ± 174.8
Clinical and treatment characteristics at index episode	
No. of CMF-identified manic symptoms, mean ± SD	1.2 ± 1.2
No. of CMF-identified depressive symptoms, mean ± SD	8.3 ± 2.0
Taking lithium, N (%)	23 (5.4)
Taking anticonvulsant (valproate, carbamazepine, or lamotrigine), N (%)	52 (12.2)
Taking second-generation antipsychotic, N (%)	159 (37.4)
Taking lithium, anticonvulsant, or second-generation antipsychotic, N (%)	220 (51.8)
Taking benzodiazepine, N (%)	20 (4.7)
Total number of psychotropics, mean ± SD	2.4 ± 1.4

[a]These characteristics were assessed for association with new-onset suicidality and with change or increase in antidepressant exposure between the index depressive episode and subsequent visit.
[b]N = 399 with available marital status data.
[c]N = 395 with available occupational status data.
Abbreviations: CMF = Clinical Monitoring Form, LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool, NEO-FFI = Neuroticism Extraversion Openness Five Factor Inventory, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

ciations between patient characteristics and antidepressant exposure or suicidal ideation. Odds ratios were calculated to estimate the magnitude of the associations.

Exact logistic regression was also used to assess the independent association of antidepressant exposure status and suicidal ideation after controlling for confounding characteristics identified in bivariate analyses. Confounds were defined[31] as characteristics associated ($p < .05$) with both the exposure (antidepressant increase) and the outcome (new-onset suicidal ideation).

Table 2. Antidepressant Exposure and Suicidality in STEP-BD Participants Who Experienced a Prospectively Observed Major Depressive Episode Without Initial Suicidality[a]

Antidepressant Exposure Increase	New-Onset Suicidality, N (%)	No Suicidality, N (%)	Total, N (%)
Yes	4 (0.9)	87 (20.5)	91 (21.4)
No	20 (4.7)	314 (73.9)	334 (78.6)
Total	24 (5.6)	401 (94.4)	425 (100)

[a]For association of new-onset suicidality with any change in antidepressant exposure (increase, decrease, or no change), Fisher exact test = 0.032, p = .46. For association of new-onset suicidality with increase in antidepressant exposure (vs. no change or decrease), Fisher exact test = 0.183, p = .80.
Abbreviation: STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

RESULTS

Primary Analysis

Relevant cohort characteristics (N = 425) are described in Table 1. Twenty-four participants (5.6%) developed new-onset suicidality between the index episode evaluation and subsequent clinical evaluation (Table 2). Of these, 2 made suicide attempts. During this interval, 91 (21.4%) were prescribed an increase in antidepressant, while 27 (6.4%) were prescribed a decrease in dose, and 307 (72.2%) had no net change.

Participants who received an increase in antidepressant exposure were no more likely to develop new-onset suicidality than participants with a decrease or no change in antidepressant exposure (FET = 0.183, p = .80). There was also no association of new-onset suicidality with any change in antidepressant exposure (increase [4/91, 4.4%] vs. decrease [0/27, 0%] vs. no change [20/307, 6.5%]; FET = 0.032, p = .46).

The specific category of antidepressant taken at intake and at follow-up is summarized in Table 3. As can be seen from the last row, the low event rate for new-onset suicidality across subtype of antidepressant precludes analysis by subtype.

Limiting the analysis to the 253 participants who entered their index depressive episode without any antidepressant treatment, there was no association of antidepressant initiation with new-onset suicidality. Specifically, 2 (4.4%) of 46 who had an antidepressant initiated experienced new-onset suicidality, while 12 (5.8%) of 207 who did not have an antidepressant initiated experienced new-onset suicidality (FET = 0.060, p = .99).

Characteristics Associated With New-Onset Suicidality

Among putative correlates (Table 1), bivariate analyses revealed several significant associations with new-

Table 3. Antidepressant Subtype Taken at Index Evaluation and at Follow-Up Evaluation and Development of New-Onset Suicidality, N

	Antidepressant at Follow-Up Evaluation											
Variable	Missing Data	None	SRI	TCA	Venlafaxine	Mirtazapine	Bupropion	Nefazodone	Trazodone	MAOI	Other	Total
Antidepressant at index evaluation												
Missing data	2	7	1	0	0	0	0	0	0	0	0	10
None	4	203	25	0	4	3	13	1	0	0	0	253
SRI	0	5	57	0	2	0	2	1	0	0	0	67
TCA	0	0	0	1	0	0	0	0	0	0	0	1
Venlafaxine	0	2	1	0	32	0	0	0	0	0	0	35
Mirtazapine	0	0	0	0	0	7	0	0	0	0	0	7
Bupropion	0	4	1	0	0	0	38	0	0	0	0	43
Nefazodone	0	1	0	0	0	0	0	7	0	0	0	8
Trazodone	0	0	0	0	0	0	0	0	1	0	0	1
MAOI	0	0	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0	0	0
Total	6	222	85	1	38	10	53	9	1	0	0	425
New-onset suicidality	0	13	5	0	3	0	2	1	0	0	0	24

Abbreviations: MAOI = monoamine oxidase inhibitor, SRI = serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

onset suicidality. The odds for new-onset suicidality were higher in participants with higher NEO-FFI neuroticism scores (OR = 1.12, p = .004), higher depression symptom ratings at index depressive episode (OR = 1.22, p = .042), and higher mania symptom ratings at index depressive episode (OR = 1.62, p = .002) and those who had a prior suicide attempt (OR = 3.42, p = .009). A trend was seen for those with new-onset suicidality to have higher (worse) LIFE-RIFT total scores at STEP-BD intake (OR = 1.11, p = .085). No other characteristics were associated with new-onset suicidality at the $p \leq .10$ level, including any association with lithium, anticonvulsants, second-generation antipsychotics, antimanic agents, or number of psychotropics.

Characteristics Associated With Increased Antidepressant Exposure

The odds of receiving an increase in antidepressant exposure were lower among those with higher manic scores at index depressive episode evaluation (OR = 0.72, p = .003). No other characteristics were associated with antidepressant exposure increase at the $p \leq .10$ level, including any association with history of prior suicide attempt (OR = 0.92, p = .380). After adjusting for manic symptoms at index depressive episode, the sole empirically identified potential confound, there was still no association between increased antidepressant exposure and suicidal ideation (OR = 0.92, p > .99).

DISCUSSION

New-Onset Suicidality and Antidepressant Exposure

This cohort study identified 425 individuals from the first 2000 STEP-BD participants followed for at least 18 months who experienced a prospectively observed major depressive episode without suicidal ideation or behavior. Uniform STEP-BD assessment procedures allowed the documentation of suicidality, antidepressant and other treatment, and other clinical characteristics at this index depressive evaluation and the subsequent structured clinical evaluation.

Ninety-one participants (21.4%) in this cohort received an increase in antidepressant exposure, and 24 (5.6%) developed new-onset suicidality, including 2 with suicide attempts. Analyses indicated no association of new-onset suicidality with increased antidepressant exposure or with any change in antidepressant exposure and no association with the initiation of antidepressant treatment in this large cohort of individuals with bipolar disorder in a major depressive episode treated under naturalistic conditions. Outcome of this primary analysis should be reassuring to those treating such individuals, whose depressive episodes are so common,[1] so frequently characterized by suicidality,[3–8] and so strongly associated with social dysfunction.[2]

Correlates of New-Onset Suicidality or Antidepressant Exposure

In secondary analyses, we did find that several variables were associated with development of new-onset suicidality, including higher neuroticism ratings, a history of prior suicide attempts, and higher manic and depressive symptom ratings at index depressive episode. In contrast, only higher manic symptom ratings were associated with a lesser likelihood of receiving an increase in antidepressants, making this characteristic the sole empirically identified confound. Controlling for this confound did not change the lack of association between antidepressant dose increase or initiation and new-onset suicidality. To our knowledge, correlates of increased antidepressant ex-

posure among individuals with bipolar disorder have not been previously reported.

Other clinical studies of bipolar disorder have demonstrated an association between suicidality, variously defined, and the correlates identified in this study, including higher neuroticism ratings, a history of prior suicide attempts, and higher manic and depressive symptom ratings.[32–35] In an earlier report describing the STEP-BD sample,[36] we examined a number of characteristics possibly associated with suicidal ideation in a cross-sectional analysis of participants who had versus had not attempted suicide previously. Of 243 participants, logistic regression models achieved positive predictive values of 55% and 59% for the attempter (N = 92) and nonattempter groups (N = 151), respectively. Depression was associated with suicidal ideation in both the attempter and nonattempter groups but made a smaller contribution among attempters. Poor psychosocial adaptation and the NEO-FFI factor openness were stronger contributors to suicidal ideation among prior attempters, while anxiety and extraversion appeared protective against ideation. Among nonattempters, depression, anxiety, and neuroticism were the predominant influences on suicidal ideation. No associations were found between suicidality and agitation or psychosis.

Limitations

Several limitations should be kept in mind in interpreting these data. First, only 24 of 425 cohort participants experienced new-onset suicidality, including only 2 suicide attempts, despite 43.2% having had a prior attempt and 20.9% having a family history of suicide attempt (Table 1). This equates to a suicide attempt rate of 0.31% per person-year (2 attempts per 425 participants per 1.5 years). Suicide attempt rates reported in person-years are limited in the bipolar population literature. Most studies[37–42] reporting suicide attempts are cross-sectional; thus, reporting is retrospective. In addition, many studies are of hospitalized patient populations with unclear treatment histories, and few take into account confounding variables. Angst and coworkers[43] reported a 36% suicide attempt rate over 44 years of follow-up in their initially hospitalized bipolar population. A mean year of follow-up was not reported, preventing a person-year calculation. Coryell and coworkers[44] did report measures that permit a person-year calculation. In the overall study group, 116 attempts per 354 patients per 13.7 mean year follow-up time = 2.4% person-year rate. Unfortunately, the treatment history is somewhat unclear. Thus, while this suicide attempt rate is lower than that expected from population studies of bipolar disorder, a comparatively low rate of suicidality in research samples with bipolar disorder has been demonstrated by others.[45]

Notably, it has been estimated that the sample size of clinical trials necessary to detect even a 2-fold antidepressant/placebo difference in nonfatal self-harm would have to exceed 30,000.[13] It is therefore not likely that adequately powered clinical trials of antidepressant harm avoidance will be done in the foreseeable future. As an alternative, multiple studies, including both population-based database studies and prospective clinical studies of large samples, such as this one, will be needed to characterize risk.

Second, the interval between clinical evaluations was variable; accordingly, it is possible that suicidality of shorter duration was missed. However, the interval between CMF evaluations was brief (21 days, quartiles: 13, 35) and reflects a monitoring interval that is clinically relevant; use of serious adverse event reports also decreased the likelihood that significant instances of suicidality were missed.

Third, it is possible that the CMF did not identify lesser but still clinically relevant levels of suicidal ideation. Although we cannot definitively rule this out, the CMF was explicitly designed to standardize clinical practice and reduce the likelihood of such occurrences,[26] and item interrater reliability has been excellent.

Finally, this study was not designed to test for effects of psychotropics other than antidepressants on suicidality, but rather to identify potential confounds with any antidepressant-suicidality associations. Thus, conclusions cannot be drawn from this analysis regarding putative protective effects of lithium,[46] anticonvulsants,[47] or other agents. Similarly, even this large study was not of sufficient size to test for differences among specific antidepressants.

CONCLUSIONS

In summary, in this prospective follow-up study of a large number of individuals with bipolar disorder treated under naturalistic conditions and assessed with structured instruments, we found no association of increased antidepressant exposure and new-onset suicidality. While careful monitoring for suicidality is clearly required in all situations in which antidepressants are administered, these data provide no evidence that antidepressants increase suicidal risk in this already high-risk population.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Equetro, Carbatrol, and others), lamotrogine (Lamictal), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), trazodone (Desyrel and others), venlafazine (Effexor).

Financial disclosure: Dr. Marangell has received grant/research support from Bristol-Myers Squibb, Eli Lilly, Cyberonics, Neuronetics, the National Institute of Mental Health (NIMH), and the Stanley Foundation and has served as a consultant to or received honoraria from Eli Lilly, GlaxoSmithKline, Cyberonics, NIMH, Pfizer, and Medtronics. Dr. Chessick has received honoraria from Forest and has served on the speakers or advisory boards of Forest, Abbott, and Janssen. Dr. Miklowitz has served on the speakers or advisory boards of Eli Lilly. Dr. Sachs has served as a consultant to Abbott,

AstraZeneca, Janssen, Bristol-Myers Squibb, GlaxoSmithKline, Solvay, Wyeth, Pfizer, and Eli Lilly; has received grant/research support from Abbott; and has served on the speakers or advisory boards of Abbott, AstraZeneca, Janssen, GlaxoSmithKline, Bristol-Myers Squibb, Wyeth, Solvay, and Eli Lilly. Drs. Bauer, Wisniewski, Allen, Dennehy, and Thase report no additional financial or other relationships relevant to the subject of this article.

Investigators for the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) are as follows: STEP-BD Contract. Gary S. Sachs, M.D. (principal investigator), Michael E. Thase, M.D. (co-principal investigator), Mark S. Bauer, M.D. (co-principal investigator). *STEP-BD Sites and Principal Investigators*. Baylor College of Medicine (Lauren B. Marangell, M.D.); Case University (Joseph R. Calabrese, M.D.); Cornell University (Joseph F. Goldberg, M.D.)*; Massachusetts General Hospital and Harvard Medical School (Andrew A. Nierenberg, M.D.); Medical University of South Carolina (R. Bruce Lydiard, M.D.)*; New York University School of Medicine (James C.-Y. Chou, M.D.)*; Portland VA Medical Center (Peter Hauser, M.D.); Rush-Presbyterian St. Luke's Medical Center (John Zajecka, M.D.)*; Stanford University School of Medicine (Terence A. Ketter, M.D.); State University of New York at Buffalo (Uriel Halbreich, M.D.)*; University of Arizona (Alan J. Gelenberg, M.D.)*; University of California, San Diego (Mark Rapaport, M.D.)*; University of Colorado Health Sciences Center (Marshall Thomas, M.D.); University of Louisville School of Medicine (Rif S. El-Mallakh, M.D.)*; University of Massachusetts Medical Center (Jayendra Patel, M.D.); University of Missouri (Kemal Sagduyu, M.D.)*; University of Oklahoma College of Medicine (Mark D. Fossey, M.D.); University of Pennsylvania Medical Center (Laszlo Gyulai, M.D.); University of Pittsburgh Western Psychiatric Institute and Clinic (Michael E. Thase, M.D.); University of Texas Health Science Center at San Antonio (Charles L. Bowden, M.D.). *No longer an active site participating in STEP-BD. Additional details on past and current participants in STEP-BD can be located at http://www.stepbd.org/research/STEPAcknowledgementList.pdf.

REFERENCES

1. 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
2. Bauer MS, Kirk G, Gavin C, et al. Determinants of functional outcome and healthcare costs in bipolar disorder: a high-intensity follow-up study. J Affect Disord 2001;65:231–241
3. Guze SB, Robins E. Suicide and primary affective disorders. Br J Psychiatry 1970;117:437–438
4. Harris E, Barraclough B. Suicide as an outcome for mental disorders: a meta-analysis. Br J Psychiatry 1997;170:205–228
5. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press Inc; 1990:227–244
6. Baldessarini RJ, Tondo L, Hennen J. Treating the suicidal patient with bipolar disorder: reducing suicide risk with lithium. Ann NY Acad Sci 2001;32:24–43
7. Angst F, Stassen HH, Clayton PJ, et al. Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord 2002;68:167–181
8. Rihmer Z, Kiss K. Bipolar disorders and suicidal behaviour. Bipolar Disord 2002;4(suppl 1):21–25
9. Antidepressant Use in Children, Adolescents, and Adults. U.S. Food and Drug Administration Web site. Available at: http://fda.gov/cder/drug/antidepressants. Accessibility verified October 21, 2005
10. Valuck RJ, Libby AM, Sills MR, et al. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. CNS Drugs 2004;18: 119–132
11. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA 2004;292:338–343
12. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 2005;330:396–403
13. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ 2005;330:385–390
14. Gibbons RD, Hur K, Bhjaumik DK, et al. The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 2005;62:165–172
15. Culpepper L, Davidson JRT, Dietrich AJ, et al. Suicidality as a possible side effect of antidepressant treatment (commentary). J Clin Psychiatry 2004;65:742–749
16. Mahler J. The antidepressant dilemma. New York Times Sunday Magazine. November 21, 2004
17. Bauer MS, Wisniewski SR, Kogan JN, et al. Paroxetine in a high-risk population. Psychopharmacol Bull 2005. In press
18. Bauer MS, Mitchner L. What is a "mood stabilizer"? an evidence-based response. Am J Psychiatry 2004;161:3–18
19. Otto MW, Reilly-Harrington N, Sachs GS. Psychoeducational and cognitive-behavioral strategies in the management of bipolar disorder. J Affect Disord 2003;73:171–181
20. Sachs GS, Thase M, Otto MW, et al. Rationale, design, and methods of STEP-BD. Biol Psychiatry 2003;53:1028–1042
21. Wells K. Treatment research at the crossroads: the scientific interface of clinical trials and effectiveness research. Am J Psychiatry 1999;156: 5–10
22. Bauer MS, Williford W, Dawson E, et al. Principles of effectiveness trials and their implementation in VA Cooperative Study #430, "Reducing the Efficacy-Effectiveness Gap in Bipolar Disorder." J Affect Disord 2001;67: 61–78
23. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
24. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. Acta Psychiatr Scand 2004; 110(suppl 422):7–17
25. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P), version 2.0. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1994
26. Sachs GS, Guille C, McMurrich S. A clinical monitoring form for mood disorders. Bipolar Disord 2002;4:323–327
27. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29:321–326
28. Leon AC, Solomon DA, Mueller TI, et al. A brief assessment of psychosocial functioning of subjects with bipolar I disorder: the LIFE-RIFT. Longitudinal Interval Follow-up Evaluation-Range Impaired Functioning Tool. J Nerv Ment Dis 2000;188:805–812
29. Costa PT, McCrae RR. Normal personality assessment in clinical practice: the NEO Personality Inventory. Psychol Assess 1992;4:5–13
30. Martinez C, Rietbrock S, Wise L, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ 2005;330:389–396
31. Meinart CL. Clinical Trials: Design, Conduct, and Analysis. New York, NY: Oxford University Press; 1986:285
32. Dilsaver SC. Suicidality in patients with pure and depressive mania. Am J Psychiatry 1994;151:1312–1315
33. Dilsaver SC. Suicidality, panic disorder and psychosis in bipolar depression, depressive-mania and pure-mania. Psychiatry Res 1997;73:47–56
34. Goldberg JF. Correlates of suicidal ideation in dysphoric mania. J Affect Disord 1999;56:75–81
35. Oquendo MA. Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. J Affect Disord 2000; 59:107–117
36. Chessick CA, Allen MH, Goldberg J. Bipolar disorder with/without suicidal ideation/behavior. In: Abstract Book, Fifth International Conference, International Society for Bipolar Disorder; June 13, 2003; Pittsburgh, Pa. Abstract NRP41
37. Vieta E. Suicidal behavior in bipolar I and bipolar II disorder. J Nerv Ment Dis 1997;185:407–409
38. Wu LH. Suicide attempts in rapid cycling bipolar disorder patients. J Affect Disord 1993;29:57–61
39. Chen YW. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. Biol Psychiatry 1996;39:896–899

40. Leverich GS, Altshuler LL, Frye MA, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. J Clin Psychiatry 2003;64:506–515
41. Endicott J, Nee J, Andreasen N, et al. Bipolar II: combine or keep separate? J Affect Disord 1985;8:17–28
42. Goldring N. Attempted suicide in manic-depressive disorder. Am J Psychother 1984;38:373–383
43. Angst J, Angst F, Gerber-Werder R, et al. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res 2005;9:279–300
44. Coryell W, Solomon D, Turvey C, et al. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 2003;60:914–920
45. Rucci P, Frank E, Kostelnik B, et al. Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. Am J Psychiatry 2002;159:1160–1164
46. Goodwin FK, Fireman B, Simon GE, et al. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003;290: 1467–1473
47. Yerevanian BI, Koek RJ, Mintz J. Lithium, anticonvulsants, and suicidal behavior in bipolar disorder. J Affect Disord 2003;73:223–238