Case-Control Analyses of the Impact of Pharmacotherapy on Prospectively Observed Suicide Attempts and Completed Suicides in Bipolar Disorder: Findings From STEP-BD

Lauren B. Marangell, M.D.; Ellen B. Dennehy, Ph.D.; Stephen R. Wisniewski, Ph.D.; Mark S. Bauer, M.D.; Sachiko Miyahara, M.S.; Michael H. Allen, M.D.; Melissa Martinez, M.D.; Rayan K. Al Jurdi, M.D.; and Michael E. Thase, M.D.

Objective: Given high rates of suicide and suicide attempts in bipolar disorder and the data suggesting a suicide-protective effect of lithium, we evaluated the impact of pharmacotherapy on prospectively observed suicides and suicide attempts in subjects in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

Method: The STEP-BD study enrolled 4360 participants with DSM-IV bipolar disorder diagnoses from September 1998 through November 2004. There were 270 suicide events in STEP-BD (8 completed suicides, 262 attempts). These occurred in 182 of STEP-BD participants (cases). Inclusion criteria required cases to be white or Caucasian, have at least 1 postbaseline visit, and have prescription information within 30 days of the suicide event. This reduced the available cohort to 106 cases. Matching included age, gender, history of previous suicide attempt, and a propensity score that considered bipolar subtype, marital status, age at onset, and history of psychosis, resulting in 93 matched pairs. A secondary analysis added mood state status within 30 days of the suicide event to the propensity score (N = 54 pairs). The association of drug prescriptions with suicide attempts/completions was assessed using a conditional logistic regression model.

Results: The results do not indicate a relationship between lithium use and suicide attempts or completions ($p = .41$). Similar findings were found for exposure to valproate, carbamazepine, lamotrigine, and the atypical antipsychotic medications. An association between selective serotonin reuptake inhibitor (SSRI) prescription and suicide events was observed ($p < .0001$). Findings were similar in a secondary analysis that controlled for mood state.

Conclusion: Our data are not consistent with a suicide-protective effect of lithium. The association between suicide events and SSRI prescriptions requires cautious interpretation due to complex relationships between treatment, severity, and suicidality.

Trial Registration: clinicaltrials.gov Identifier: NCT00012558

(J Clin Psychiatry 2008;69:916–922)

Received July 26, 2007; accepted Dec. 7, 2007. From the Mood Disorders Center, Menninger Department of Psychiatry, Baylor College of Medicine and South Central Mental Illness Research and Education Core, Department of Veterans Affairs, Houston, Tex. (Drs. Marangell, Martinez, and Al Jurdi); Department of Psychological Sciences, Purdue University, West Lafayette, Ind. (Dr. Dennehy); Epidemiology Data Center (Dr. Wisniewski and Ms. Miyahara) and Department of Psychiatry, Western Psychiatric Institute (Ms. Miyahara), University of Pittsburgh, Pittsburgh, Pa.; Harvard Medical School and the Veterans Affairs Boston Healthcare System, Boston, Mass. (Dr. Bauer); University of Colorado Health Sciences Center, Denver (Dr. Allen); and Department of Psychiatry, University of Pennsylvania School of Medicine and Philadelphia Veterans Affairs Medical Center, Philadelphia, and Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, Pa. (Dr. Thase). Dr. Marangell is now with Eli Lilly and Co., Indianapolis, Ind.

This project was funded by an Independent Investigator Award from the National Alliance for Research in Schizophrenia and Depression (NARSAD) (L.B.M.) and a grant from the American Foundation for Suicide Prevention (L.B.M.). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study was conducted with federal funds from the National Institute of Mental Health (NIMH), National Institutes of Health, under contract N01MH80001.

This article was approved by the publication committee of the STEP-BD study. Additional details on STEP-BD can be located at http://www.stepbd.org/research/STEPAcknowledgementList.pdf.

Any opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of NARSAD, the American Foundation for Suicide Prevention, the Department of Veterans Affairs, NIMH, or Eli Lilly.

Financial disclosure appears at the end of this article.

Corresponding author and reprints: Lauren B. Marangell, M.D., Lilly Corporate Center, Indianapolis, IN 46285 (e-mail: drlauren@lilly.com).

The risk of suicide in bipolar disorder is estimated to be at least 15 times higher than that of the general population[1] and may account for almost a quarter of all completed suicides.[2] Several factors have been reported to be associated with suicide in persons with bipolar disorder; however, most studies to date have been retrospective and have not accounted for the redundant association among variables submitted for analysis. We recently examined the association between baseline clinical and demographic variables and subsequent suicide attempts and completions through 2 years of follow-up of participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).[3] Several variables predicted suicide when considered alone—including base-

© Copyright 2008 Physicians Postgraduate Press, Inc.

© Copyright 2008 Physicians Postgraduate Press, Inc.

line suicidal ideation, age, gender, marital status, and the percent of days spent either anxious or irritable in the year prior to baseline—but after controlling for redundant associations from other baseline characteristics, only history of suicide attempt (OR = 4.52, p < .0001) and percent of days spent depressed in the past year (OR = 1.16, p = .036) were significantly associated with suicide attempts or completions. Pharmacotherapy was not considered in our previous report.

There is a growing literature supporting the use of lithium as a suicide-protective agent in bipolar disorder. In a pooled analysis of 34 studies, the rate of suicide attempts and completions with lithium treatment was 0.210 per 100 person years (95% CI = 0.172 to 0.253), compared to the baseline rate (non-lithium) of combined attempts and completed suicides of 3.10 per 100 person years (95% CI = 2.80 to 3.42). This represents a 14.8-fold (95% CI = 8.84 to 25.6, p < .0001) risk reduction associated with lithium treatment.[4] However, these studies are mostly retrospective and may reflect a selection bias for positive lithium responders and/or more adherent patients. Goodwin and colleagues[5] evaluated data from a retrospective cohort study of 20,638 health plan members with diagnosed bipolar disorders. They report that the risk of death by suicide was 2.7 times higher (95% CI = 1.1 to 6.3) with valproate treatment compared to lithium treatment, and the risk for nonfatal suicide attempts was 1.7 (95% CI = 1.2 to 2.3) times higher with valproate treatment. During the time patients were exposed to combination treatment, the risk of nonfatal suicide attempts and completions was comparable to valproate alone, but with more variance in the data. In addition, because the subjects were not randomly assigned, a selection bias at the level of the prescriber once again cannot be ruled out. Cipriani et al.[6] completed a systematic review and meta-analysis of evidence from 32 randomized controlled trials comparing long-term treatment (≥ 3 months) of mood disorders (unipolar, bipolar, schizoaffective, dysthymia, or rapid cycling) with lithium (total N = 1377) versus either placebo or other compounds (total N = 2052), on the risk of suicide, deliberate self-harm (including suicide attempts), and all-cause mortality. This group concluded that lithium appears to reduce the risk of death and suicide by approximately 60%, and to reduce the risk of a composite of suicide and deliberate self-harm by about 70%. However, most of the studies included in the Cipriani report did not include a generalizable population, such as participants with comorbid substance use and anxiety disorders.

In contrast, Coryell and colleagues[7] applied a case-control design to data from the National Institute of Mental Health Collaborative Depression Study, a naturalistic, long-term follow-up study of patients with major affective disorders, in which they matched patients who completed suicide (N = 15) or made suicide attempts (N = 41) while receiving treatment during follow-up to nonsuicidal patients (controls, N = 57). These findings are more relevant to major depressive disorder, as only 6 of the 57 cases were diagnosed with a bipolar spectrum disorder. Given this caution, their findings did not support a suicide-protective effect of lithium treatment.

The current article employs a case-control design to assess the suicide-protective effect of lithium and other psychotropic medications in a cohort of patients with bipolar disorders. This sample is similar to the more general case-control study of patients with all affective disorder diagnoses described above,[7] and represents an advance over several prior case-control studies in that data were collected prospectively with a uniform assessment battery established a priori that included standardized assessment of pharmacotherapy and suicidality. The cohort includes persons with bipolar disorder who experienced a suicide or suicide attempt during the course of their participation in STEP-BD. Specifically, we were most interested in evaluating the suicide-protective effect of lithium, expecting that cases with suicide events would be less likely to be prescribed lithium in the months before the event.

METHOD

Study Overview

Subjects participated in STEP-BD, a multicenter study designed to evaluate longitudinal outcomes in patients with bipolar disorder.[8,9] The overall study combines a large, prospective, naturalistic study utilizing a common disease-management model and a series of randomized, controlled trials, which share a battery of common assessments. Over the course of the study, STEP-BD recruited from 21 geographically diverse academic psychiatry centers. STEP-BD clinicians are certified in model practice and assessment procedures, with relevant training in the implementation of evidence-based treatment. STEP-BD was approved by the institutional review boards of all participating treatment centers and coordinating centers, and oral and written informed consent was obtained from patients prior to any study-related procedures. For subjects 15 to 17 years of age, written assent was obtained, with written informed consent obtained from a parent or legal guardian.

Participants

From September 1998 through November 2004, STEP-BD enrolled a total of 4360 patients. STEP-BD inclusion criteria were broad and required patients to be at least 15 years of age and to meet diagnostic criteria for bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, or schizoaffective disorder, bipolar subtype, as set forth in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[10] Exclusion criteria were lim-

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

ited to unwillingness or inability to comply with study assessments, inability to give informed consent, and being an inpatient at time of enrollment (although hospitalized patients could enter STEP-BD following discharge).

Assessments and Procedures

The Mini-International Neuropsychiatric Interview (MINI, Version 5.0.0)[11] was used to confirm bipolar diagnosis and establish comorbid Axis I illness, and was administered by MINI-certified study clinicians on study entry. The MINI has acceptable validity and reliability.[11] Clinical course characteristics were obtained from baseline administration of the Affective Disorders Evaluation (ADE),[9] an assessment tool that utilizes versions of the mood and psychosis modules from the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition[12] modified for routine use by practicing clinicians. A consensus diagnosis of one of the eligible bipolar disorders was required on both the ADE and MINI for study entry. The ADE also included systematic assessment of lifetime and recent course of illness, including age at onset. Age at onset was defined as younger than 13 years, 13 through 18 years, and older than 18 years for consistency with other reports from this study.[13]

Demographic data and family history data were collected at baseline. Use of services was recorded on the Care Utilization form, a semistructured interview administered quarterly over the first year of participation and biannually after that point. The Care Utilization Form includes information about use of different services in the prior period, including hospitalization or suicide attempts that might not have otherwise been reported. Serious Adverse Event forms are completed in the event of death, suicide attempts, hospitalizations, or other serious adverse events. Suicide events include completed suicides, as well as suicide attempts (defined as self-injurious behaviors serious enough to be categorized as a serious adverse event and with some potential for lethality).

Prescription information is entered on the Clinical Monitoring Form (CMF),[14] a 1-page standardized record-keeping form designed for use as a routine progress note. Simple recording conventions are used to record medication dose. The CMF also includes a categorical assignment of *clinical status* at each visit.[14] On the basis of the presence or absence of DSM-IV–based criteria, 1 of 8 operationally defined clinical states is assigned at each clinic visit. Four clinical states correspond to the DSM-IV definitions for major depressive episode and manic, hypomanic, or mixed episodes. Patients achieving relative euthymia (≤ 2 moderate symptoms) for at least a week are assigned a status of *recovering* or *recovered*, depending on whether this status has been sustained for at least 8 weeks. Two subsyndromal states (≥ 3 moderate symptoms, but not full criteria for a mood episode) categorize patients as either *continued symptomatic (*a subsyndromal state follows an acute episode without an intervening full recovery) or *roughening (*a subsyndromal state occurs after recovery from the last full mood episode). These bipolar state categories and interrater reliability training are further discussed by Sachs et al.[14] In the current analysis, clinical states of hypomanic, manic, and mixed episodes; roughening and continued symptomatic; and recovering and recovered are combined, resulting in these 4 potential categories of clinical status: (1) major depressive episode; (2) hypomanic, manic, and mixed episodes; (3) roughening and continued symptomatic; and (4) recovering and recovered.

Intervention

Since STEP-BD was designed as an effectiveness study, subjects received pharmacologic interventions as clinically indicated. Study clinicians completed training in the principles of evidence-based treatment, and pharmacotherapy guidelines based on published treatment guidelines were supplied in an annually updated Clinicians' Handbook (STEP-BD Clinicians' Handbook, unpublished). This approach did not demand strict compliance to a specific treatment algorithm. Instead, it emphasized application of evidence-based treatments at every decision point in treatment, according to the current priorities for a given patient.

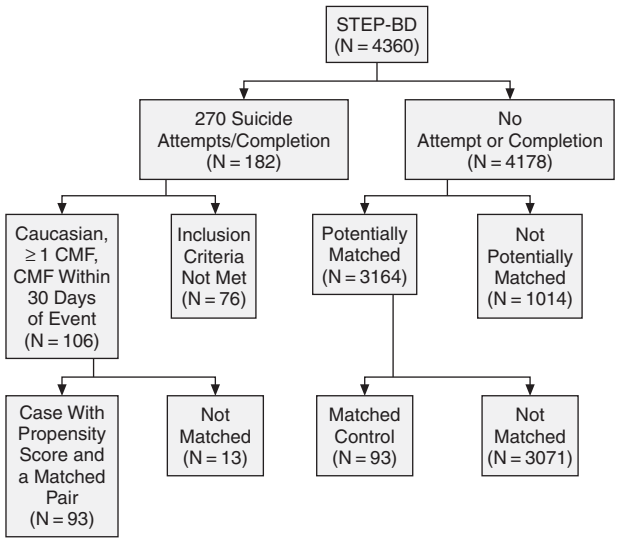
Case-Control Cohort

Over the course of STEP-BD, there were 8 completed suicides and 262 suicide attempts documented on the Serious Adverse Event form and/or Care Utilization form. These events, collectively, are referred to as *suicide events* throughout this article. The 270 events occurred within 182 persons, the pool of potential cases. From this group, we applied the following inclusion criteria: must have self-identified as white or Caucasian, must have a baseline assessment (ADE) and at least 1 follow-up (CMF) while in STEP-BD, and must have a follow-up (CMF) within 30 days of the suicide event. These criteria resulted in an available cohort of 106 cases.

The cases were then matched to controls. Eligible controls were defined as whites or Caucasians who did not have a suicide attempt or completion and had an ADE and at least 1 CMF while in STEP-BD. Cases were matched on history of past suicide attempt, gender, and age (< 21, 21–40, 41–60, and > 60 years). In addition, for each case and control, a propensity score was created using bipolar subtype, marital status, age at onset, and history of psychosis. Cases and controls were also matched on propensity score (± 0.02 points). The best possible case-control match was defined as those matching on all of the hard-matching characteristics (history of past suicide attempt, gender, age) and having the smallest squared case-control difference in propensity scores. In one instance, a given control was the best match for 2 different cases. In this

© COPYRIGHT 2008 PHYSICIANS POSTGRADUATE PRESS, INC.

Figure 1. CONSORT Chart for the Case-Control Study of the Impact of Pharmacotherapy on Suicide Events in Bipolar Disorder



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

Table 1. Characteristics of Cases and Controls in the Study of the Impact of Pharmacotherapy on Prospectively Observed Suicide Events in Bipolar Disorder

Variable	Cases, N = 93	Controls, N = 93
Variables used to match cases and controls		
History of past suicide attempt, N (%)	68 (73.1)	68 (73.1)
Gender, male, N (%)	26 (28.0)	26 (28.0)
Age, mean (SD), y	35.3 (10.6)	36.4 (12.5)
Age distribution, N (%)		
< 21 y	9 (9.7)	9 (9.7)
21–40 y	52 (55.9)	52 (55.9)
41–60 y	30 (32.3)	30 (32.3)
61+ y	2 (2.2)	2 (2.2)
Variables used in propensity score		
Age at onset of bipolar symptoms, mean (SD), y	15.4 (7.8)	12.0 (5.4)
Bipolar subtype, N (%)		
Bipolar I	61 (65.6)	72 (77.4)
Bipolar II	24 (25.8)	17 (18.3)
Other	8 (8.6)	4 (4.3)
Married, N (%)	33 (35.5)	30 (32.3)
History of psychosis, N (%)	40 (43.0)	70 (75.3)
Other clinical characteristics, N (%)		
Current alcohol use/dependence[a]	20 (26.3)	13 (16.9)
Current drug use/dependence[a]	12 (15.8)	9 (11.7)

[a]N = 76 for cases, N = 77 for controls.

instance, the best match was randomly assigned to 1 case, and the second best match was assigned to the other case. An additional 13 cases were lost due to the inability to calculate a propensity score or failure to find a matched control. A total of 93 pairs were formed for the final case-control cohort (see Figure 1 for consort diagram).

Given the established association between depressive symptoms and suicidality, we conducted a secondary analysis that controlled for mood state at the visit just prior to the suicide event. The propensity score also included category of clinical status at the visit just prior to the suicide event. We expanded the range of scores required to match cases and controls to ± 0.05 points, and repeated the analysis in this cohort of 54 matched pairs.

With respect to medication exposure, the time frame of interest was the 6 months prior to the suicide event for cases. For those patients who were not enrolled in STEP-BD for 6 months prior to the event, previous medication exposure (as recorded on the ADE) was used to supplement study records. CMFs and the ADE (if applicable) from the pertinent time period were examined, and cases were classified into 1 of 3 categories: all of the sources indicate continuous prescription of the medication of interest, some of the sources indicate exposure (i.e., the medication was prescribed for only part of the 6-month period), and none of the sources indicate exposure to the medication of interest. The same method was used to define exposure to lithium, carbamazepine, valproate, lamotrigine, selective serotonin reuptake inhibitor (SSRI) medications, and atypical antipsychotic medications.

For cases with more than 1 suicide event, the last suicide event documented during STEP-BD participation was chosen as the point of analysis, assuming that event allowed clinicians the best opportunity to learn individual patient needs and optimize pharmacotherapy. As controls did not have a suicide event, we designed an alternate method to define the 6-month time interval for medication exposure. The time interval from enrollment in STEP-BD to the last clinic visit (CMF) was defined. A date in this interval was randomly selected, and the 6 months prior to this random point was examined for medication exposure. Medication exposure was then classified using the same methods described above.

Statistical Methods

Descriptive statistics are reported as means and standard deviations for continuous variables and as percentages for discrete variables. The association of drug prescriptions with suicide attempts/completions was assessed using a logistic regression model that looks at the case/control dyad referred to as conditional logistic regression model. A 2-sided p value less than .05 was used to indicate statistical significance.

RESULTS

The characteristics of the cases and controls are presented in Table 1. As the pairs were matched on these variables, each group included 73.1% with a history of a prior suicide attempt, 28.0% male, and 55.9% between

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

Table 2. Association of Medication Prescriptions With Suicide Attempt/Completion

Lithium				
	Cases, N			
Controls, N	No Lithium	Some Lithium	All Lithium	p Value
No lithium	32	5	9	.4131
Some lithium	8	6	4	
All lithium	13	7	9	
Valproate				
	Cases, N			
Controls, N	No Valproate	Some Valproate	All Valproate	p Value
No valproate	48	8	10	.9089
Some valproate	7	3	3	
All valproate	10	1	3	
Carbamazepine, Oxcarbazepine				
	Cases, N			
Controls, N	No CBZ, OXC	Some CBZ, OXC	All CBZ, OXC	p Value
No CBZ, OXC	77	6	2	.1808
Some CBZ, OXC	2	1	0	
All CBZ, OXC	5	0	0	
Atypical Antipsychotics[a]				
	Cases, N			
Controls, N	No AAP	Some AAP	All AAP	p Value
No AAP	20	15	10	.1513
Some AAP	7	13	6	
All AAP	7	8	7	
Selective Serotonin Reuptake Inhibitors[b]				
	Cases, N			
Controls, N	No SSRI	Some SSRI	All SSRI	p Value
No SSRI	43	16	20	< .0001
Some SSRI	3	2	1	
All SSRI	5	1	2	
Lamotrigine				
	Cases, N			
Controls, N	No Lamotrigine	Some Lamotrigine	All Lamotrigine	p Value
No lamotrigine	36	10	12	.8599
Some lamotrigine	10	2	2	
All lamotrigine	14	3	4	

[a]Atypical antipsychotics: olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole.
[b]SSRIs: paroxetine, citalopram, sertraline, fluoxetine, fluvoxamine, escitalopram.
Abbreviations: AAP = atypical antipsychotic, CBZ = carbamazepine, OXC = oxcarbazepine, SSRI = selective serotonin reuptake inhibitor.

21 and 40 years of age. As expected, the groups were relatively similar on all variables that were included in the propensity score. Among cases, 65.6% were diagnosed with bipolar I disorder, compared to 77.4% of controls. The mean (SD) age at onset of bipolar symptoms was 15.4 (7.8) years in the cases and 12.0 (5.4) years in the controls, while 35.5% of the cases were married, compared to 32.3% of the controls. Finally, there was more history of psychosis in the control group (75.3%) compared to cases (43.0%).

Of the 53 cases with no lithium in the 6 months prior to the event, 32 matched controls also had no lithium in the 6 months prior, 8 had some lithium use, and 13 had lithium on all CMFs. Of the 18 cases with some lithium use, 5 matched controls had no lithium use, 6 had some, and 7 had lithium on all CMFs. Lastly, of the 22 cases with lithium use on all CMFs, 9 had matched controls with no lithium use, 4 with some, and 9 with lithium use on all CMFs (Table 2). These results do not indicate a relationship between lithium use and suicide attempts or completions ($p = .41$). Similar findings were found for exposure to valproate, carbamazepine, lamotrigine, and the atypical antipsychotic medications.

Analyses also examined exposure to the antidepressant medication, specifically those in the class of SSRIs. For those 51 cases with no SSRI exposure in the 6 months prior to a suicide event, 43 of the matched controls also had no exposure, 3 had some exposure, and 5 had exposure. Nineteen cases had some SSRI exposure in the 6 months prior to a suicide event and were matched to 16 controls with none, 2 with some, and 1 with exposure. Twenty-three cases had exposure to SSRI documented on all sources in the 6 months prior to an event. Within their matched controls, 20 had no exposure to an SSRI medication, 1 had some, and 2 had exposure in a 6-month period. These findings suggest that exposure to an SSRI medication is associated with a suicide event over a 6-month period prior to the event ($p < .0001$).

Secondary analysis controlled for mood state just prior to the suicide event and included 54 matched pairs. The majority of cases were in a depressed (33.8%) or recovered/recovering (39.0%) clinical status at the visit prior to their suicide event. The majority of controls were in a depressed episode (62.3%). The conditional logistic regression for the impact of pharmacotherapy was repeated, yielding very similar findings. There was no indication of differential exposure to lithium across cases and controls ($\chi^2 = 2.86$, df = 2, $p = .24$). Similar to the initial analyses, there was no difference between groups in exposure to divalproex, carbamazepine, lamotrigine, or atypical antipsychotic medications. There continued to be a significant difference between groups in exposure to SSRI medications ($\chi^2 = 5.94$, df = 2, $p = .05$), with cases more likely to have some exposure to an SSRI medication in the 6 months prior to the suicide event.

DISCUSSION

This case-control analysis assessing the protective effects of lithium in a cohort of bipolar patients indicated no differences in lithium exposure between patients who experienced a suicide event and those who did not. The findings were similar in a secondary analysis that controlled for mood state within 30 days of the suicide

© Copyright 2008 Physicians Postgraduate Press, Inc.

event. Interestingly, this result corresponds to the only other case-control analysis of lithium in suicidality, which included patients with all affective disorder diagnoses.[7] These results differ from larger reports that used differing methodologies; most often those studies computed a standardized mortality ratio in a large sample, and then compared the mortality of persons exposed to lithium to a control group.

We find it noteworthy that relatively few patients in the current study were prescribed lithium throughout the 6-month period of observation. Fifty-three of the cases (57.0%) and 46 of the controls (49.5%) had no documented lithium exposure during the 6-month observation period. Many characteristics associated with increased risk for suicide, like substance use disorders and unstable illness with mixed states and/or frequent episodes, are also associated with poor response to lithium. Given the broad inclusion criteria and heterogeneity of the STEP-BD sample, it may be that this group had sufficient chronicity and severity that lithium wasn't often offered as a treatment option, which creates an inherent bias. Regardless, in this cohort, there were no differences in lithium exposure between those with suicide events and those without.

It is important to note the limitations of our report. The study included over 4000 patients who were treated and assessed with consistent methods, hence creating a unique sample that warrants study of important issues, such as suicide and suicide attempts. However, there were a relatively small number of patients who experienced a suicide event in STEP-BD. Further, most events were attempts and not completed suicides, and there may be differences between these groups that cannot be addressed in the current sample. It is also notable that while there were 182 individuals with observed suicide events, only 93 cases were matched in current analyses. When mood state prior to the suicide event was added to the propensity score, the number of matched pairs was reduced even further (N = 54 pairs). However, we felt that it was essential to have documentation of medication prescriptions relatively close to the event (within 30 days) to minimize the likelihood that events were attributed to medications that the subject was no longer taking.

Furthermore, it would have been optimal to control for the overall burden of symptoms over time, for each patient. In STEP-BD, this information was collected retrospectively at baseline and may not be relevant to the time of the suicide event. After STEP-BD entry, clinical information was recorded at each clinical visit, which occurred at irregular and varying intervals across patients. We chose to include classification of clinical status at the visit just prior to the suicide event in our secondary analysis, understanding that this is neither a direct reflection of clinical mood state at the time of the event nor a measure of the overall burden of symptoms and chronicity of illness.

Another limitation of the current study is our inability to draw conclusions about the association of pharmacotherapy and risk for suicide events in nonwhite persons. Once other inclusion criteria were applied, there were only 11 nonwhite potential cases, distributed across several ethnic categories. Given the poor likelihood of matching them to a control participant, and our concern about drawing inappropriate conclusions about suicide and pharmacotherapy in minority samples, we chose to exclude nonwhite subjects.

One of the weaknesses of population studies such as Baldessarini et al.[4] and Goodwin et al.[5] is confounding by indication. Other authors[15] have observed that in Goodwin's analysis, subjects receiving no treatment had fewer suicidal events than lithium-treated patients. Similarly, in the Goodwin et al. study,[5] subjects receiving combination treatment had a comparable risk of suicidal events compared to those taking valproate alone, suggesting that more seriously ill patients may have been prescribed valproate rather than lithium if monotherapy was chosen. Angst et al.[16] found that there was an advantage to lithium and antidepressants but not to lithium alone. Assuming appropriate matching, case-control studies are better able to account for such factors. Interestingly, there were no differences in exposure to the other medications studied and suicide events, with one exception. In the current study, the observed association between exposure to SSRI medications and suicide events is consistent with confounding by indication.

There has been much debate and concern about a potential increased risk of suicide with exposure to SSRI medications, particularly in children and adolescents, prompting a U.S. Food and Drug Administration (FDA) warning to this effect. While other meta-analyses and pooled studies suggest that this relationship is true for adults as well,[17–18] other studies provide conflicting results.[19–20] More recent FDA data indicate that suicidality in association with the onset of SSRI treatment is seen in adults aged 18 to 24 years, but not in older adults. We previously reported results from a study utilizing the first 2000 entrants into STEP-BD that found no association between new-onset suicidality and increased or changed antidepressant exposure in a large cohort of individuals with bipolar disorder who were experiencing a major depressive episode.[21] However, the methodology used in that report differed from the current methodology, as the fundamental questions differed. While the current analysis suggests an association between exposure to SSRI medications and suicide events ($p < .0001$), it was not designed to assess the association of SSRIs and suicide risk. For example, we matched on age, and hence cannot comment on an interaction with age, SSRI exposure, and suicidality in the current study. The association between SSRI exposure and suicide risk was still statistically significant, but less robust ($p = .05$), when mood state at the visit prior to the suicide

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

event was included in the matching. We plan to further assess this issue in a separate analysis. At this juncture, we urge cautious interpretation of the association between suicide events and SSRIs in this dataset.

In conclusion, our data are not consistent with a suicide-protective effect of lithium, which is in contrast to studies using different methodologies. STEP-BD was a longitudinal study, the suicide events were observed prospectively, and data were gathered systematically utilizing standardized methods. If the question of a possible suicide-protective effect of lithium is deemed important to the field, it may be necessary to consider a prospective randomized trial in a generalizable population with suicidality as a primary outcome variable.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), divalproex (Depakote), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), ziprasidone (Geodon).

Financial disclosure: **Dr. Marangell** is currently employed by Eli Lilly; has received grant/research support from Bristol-Myers Squibb, Eli Lilly, Cyberonics, Neuronetics, National Institute of Mental Health, Stanley Foundation, National Alliance for Research in Schizophrenia and Depression (NARSAD), American Foundation for Suicide Prevention, Aspect Medical Systems, and Sanofi Aventis; and is a consultant for or has received honoraria from Eli Lilly, GlaxoSmithKline, Cyberonics, Pfizer, Medtronics, Forest, Aspect Medical Systems, Novartis, and Sepracor. Several companies have given educational grants for Continuing Medical Education programs at Baylor College of Medicine. These checks are made payable to Baylor College of Medicine and handled through the Office of Continuing Medical Education. **Dr. Wisniewski** is or has been a consultant for Cyberonics, ImaRx Therapeutics, Bristol-Myers Squibb, and Organon. **Dr. Thase** is a consultant for AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, GlaxoSmithKline, Janssen, MedAvante, Neuronetics, Novartis, Organon, Sepracor, Shire, Supernus, and Wyeth; is a member of the speakers bureau for AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Organon, Sanofi Aventis, and Wyeth; has given consultation in legal matters to attorneys representing Wyeth and GlaxoSmithKline and has given formal disposition in a matter concerning GlaxoSmithKline; has equity holdings in MedAvante; and has received royalties/patents/other income from American Psychiatric Publishing, Guilford Publications, and Herald House. Dr. Thase's spouse is the Senior Medical Director for Advogent (formerly Cardinal Health). **Drs. Dennehy**, **Bauer**, **Allen**, **Martinez**, and **Al Jurdi** and **Ms. Miyahara** report no additional financial or other relationships relevant to the subject of this article.

REFERENCES

1. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a meta-analysis. Br J Psychiatry 1997;170:205–228
2. Rihmer Z, Kiss K. Bipolar disorders and suicidal behaviour. Bipolar Disord 2002;4(suppl 1):21–25
3. Marangell LB, Bauer MS, Dennehy EB, et al. Prospective predictors of suicide and suicide attempts in 1556 patients with bipolar disorders followed for up to 2 years. Bipolar Disord 2006;8:566–575
4. Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: update and new findings. J Clin Psychiatry 2003;64(suppl 5):44–52
5. Goodwin FK, Fireman B, Simon GE, et al. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003;290(11): 1467–1473
6. Cipriani A, Wilder H, Hawton K, et al. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005; 162(10):1805–1819
7. Coryell W, Arndt S, Turvey C, et al. Lithium and suicidal behavior in major affective disorder: a case-control study. Acta Psychiatr Scand 2001;104(3):193–197
8. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2003;53:1028–1042
9. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. Acta Psychiatr Scand 2004;110(suppl 422):7–17
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
11. 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):22–57
12. First MB, Gibbon M, Spitzer RL, et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press; 1997
13. Perlis R, Miyahara S, Marangell LB, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2004;55:875–881
14. Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. Bipolar Disord 2002;4(5):323–327
15. Bowden C, Fawcett J. Pharmacotherapy and risk of suicidal behaviors among patients with bipolar disorder. JAMA 2004;291(8):939
16. 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
17. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA 2004;292:338–343
18. Fergusson D, Doucette S, Glass KC, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomized controlled trials. BMJ 2005;330:396–403
19. Gunnell D, Sapeira J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised trials submitted to the MHRA's safety review. BMJ 2005;330:385–390
20. Gibbons RD, Hur K, Bhjaimik DK, et al. The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 2005;62:165–172
21. Bauer MS, Wisniewski SR, Marangell LB, et al. 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). J Clin Psychiatry 2006;67(1): 48–55

 © Copyright 2008 Physicians Postgraduate Press, Inc.