Lithium Treatment and Risk of Suicidal Behavior in Bipolar Disorder Patients

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Background: Lithium may exert an antisuicidal effect in bipolar disorder patients, but this hypothesis requires further testing by direct comparison of patients with and without lithium treatment.

Method: Risk of life-threatening suicidal acts over time and associated factors were analyzed in 310 patients with DSM-IV bipolar I (N = 186) or II (N = 124) disorder evaluated for a mean of 8.3 years before, and prospectively during, a mean of 6.4 years of lithium maintenance in a mood disorder clinic; 185 were also followed for a mean of 3.7 years after clinically discontinuing lithium.

Results: In 5233 patient-years of observation, 58 patients made 90 suicide attempts (8 were fatal). Survival analyses with Weibull modeling with adjustments for covariates indicated a highly significant 6.4-fold adjusted hazard ratio during versus before and 7.5-fold ratio after versus during lithium maintenance. Suicidal acts were more common early in the course of illness before lithium and were associated with prior suicide attempts, greater proportion of time depressed, and younger age. After the discontinuation of lithium, suicidal acts were more frequent in the first year than at later times or before start of lithium treatment. Fatalities were 9 times more frequent after versus during treatment.

Conclusion: Lithium maintenance was associated with marked reduction of life-threatening suicidal acts, the number of which sharply increased after discontinuing lithium. Suicidal behavior was strongly associated with prior suicide attempts, more time depressed, and younger age or recent onset. Greater attention to suicidal risk in patients with bipolar depression and assessment of all proposed mood-stabilizing agents for antisuicidal effects are strongly encouraged.

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"One of the more interesting questions in preventive medicine today is the impact of lithium on suicide rates. There are no current and systematic data available. . . ."
—Goodwin and Jamison (1990:237–238).[1]

Mortality risk is greatly elevated in major affective disorders owing to suicide and probably also to comorbid substance abuse and cardiovascular or other presumably stress-related somatic disorders associated with affective illness.[1,2] Suicidal risks may be even higher in bipolar manic-depressive illness than in unipolar major depression.[1,3] Of the estimated $45 billion annual economic burden of bipolar manic-depressive disorders in the United States, at least $8 billion is accounted for by suicide.[4] The specific impact of contemporary treatment on suicidal behavior remains unclear, and available research on suicide prevention by treatment interventions remains insufficiently developed to guide public health policy.[5] For example, although suicidal acts are commonly associated with depression, evidence is lacking that treatment with an antidepressant actually reduces rates of suicidal acts (attempts or fatalities) in persons with affective illness.[6,7]

Some mood-altering agents may have antisuicidal effects, however, and studies of possible antisuicide effects of lithium [1,8–11] have reported some positive [9,10,12–21] or sug-

gestively supportive observations [22–31] and relatively few unsupportive findings.[32–35] Many of these studies are limited by small numbers, inclusion of subjects with unipolar and schizoaffective as well as bipolar diagnoses, lack of indication of severity of suicidal behavior, indirect comparisons to potentially unreliable suicide rates in general populations, and a nearly universal lack of direct comparison with alternative treatments.[9,10] In addition, inconsistent compliance with maintenance treatments probably limits antisuicide or other mortality-limiting benefits that may exist, whereas highly compliant study samples may be unrepresentative and thus limit generalization of benefits.[31,36,37] Well-designed, controlled prospective studies of suicide prevention are unlikely to be carried out owing to ethical constraints when fatality is a potential outcome, and they are further constrained by recent recognition of high risks of early recurrences of affective illness after discontinuing lithium maintenance.[38–42] Moreover, since long-term research on antisuicidal effects of other mood-stabilizing drugs is virtually nonexistent, it is not known whether alternatives to lithium may provide antisuicidal effects. One rare direct comparison found much less protection from suicide with carbamazepine or with amitriptyline plus neuroleptics than with lithium.[21]

In order to evaluate relationships between treatment with lithium and suicidal behaviors, a large series of types I and II bipolar manic-depressive patients followed in a mood disorders clinic were studied for risk of life-threatening acts before, during, and after discontinuation of lithium maintenance treatment. Data on time to a life-threatening act under different treatment conditions in the same subjects were evaluated with survival analysis, including adjustments for important covariates, using Weibull regression models. Poisson models, with and without adjustment for significant time-based covariates, were used to compare suicidal rates between treatment conditions, using random effects models to adjust for observing the same subjects in different treatment conditions.

The principal hypothesis to be tested, based on meta-analyses of previous relevant observations,[9,10] was that lithium maintenance treatment is associated with reduced risk of life-threatening suicidal behavior. A second hypothesis was that discontinuation of lithium would be associated with a sharp rise in suicidal risk, particularly soon after stopping lithium, in accord with recent findings of markedly increased affective morbidity under such conditions.[38–42]

METHOD

Risk of suicidal behavior was evaluated among 310 consecutive bipolar disorder patients evaluated between July 1977 and May 1997 at the Lucio Bini Center, a mood disorders research clinic affiliated with the University of Cagliari in Sardinia. Diagnoses of bipolar disorder were updated by clinical consensus, which relied on clinical records and current semistructured interviews based on current DSM-IV criteria. Patients were selected as having been followed prospectively during continuous lithium maintenance therapy for bipolar disorders of type I (with mania) or type II (with hypomania). Confidentiality of subjects' psychiatric records and identity was assured, in accord with ethical standards of the treating institution, and patients provided informed consent to anonymous participation and reporting. The study was approved by the Institutional Review Board (IRB) of McLean Hospital (Belmont, Mass.) and equivalent officials in Cagliari.

Descriptors recorded included gender, onset age, family psychiatric history, education and current employment status, and diagnostic subtype—all at the start of lithium treatment—as well as clinical history (DSM-IV manic or depressive episodes/year and percentage of time ill) and the occurrence and timing of suicidal behaviors before, during, and after discontinuing lithium maintenance treatment. Information was acquired in nonblinded clinical assessments during follow-up visits averaging 6 per year during periods of active treatment, and every 3 to 6 months during follow-up. Patients were evaluated, treated, and followed-up by research psychiatrists (L.T., G.F., F.S.). Assessments and records were clinical in focus but were systematic and protocol-guided, and they were recorded on forms designed to provide data for clinical research.[9,11,39,42,43] In addition, detailed life charts of the course of illness have been used in the Bini Center since 1977 and are updated at least annually. Past history of illness and suicidal behavior was determined clinically and retrospectively and, when reliability was uncertain (< 10% of cases), was verified by semistructured interview of at least 1 family member with the patient's consent. Data collection was prospective during and after lithium treatment. The present analyses were unanticipated during clinical data collecting and were carried out by blinded investigators not involved in data collection (R.J.B., J.H., M.T.). Suicidal events were defined as fatal acts (during or after lithium maintenance) or as serious and potentially life-threatening acts requiring hospital treatment; suicidal threats, minor self-injuries, and drug overdoses that did not require hospitalization were excluded.

All 310 reported subjects were maintained on lithium treatment continuously for a minimum of 6 months. Serum lithium assays typically were obtained quarterly to verify compliance and dosing, at 10 to 14 hours after a day's final dose. Lithium treatment was considered effective or "satisfactory" if patients experienced a greater-than-50% reduction in the proportion of time in manic or depressive illness meeting DSM-IV criteria for an episode during versus before lithium treatment. Treatment was not specifically initiated in response to suicidal behavior. Pa-

tients exposed to other mood-stabilizing, antidepressant, or antipsychotic drugs, other than for brief periods (≤ 8 weeks), as well as sustained psychotherapy, were excluded, as were patients whose cases involved abuse of alcohol or other psychoactive substances, and those with comorbid DSM-IV anxiety or personality disorders. A subgroup (N = 185) of the 310 subjects discontinued lithium treatment clinically, not under experimental control, and were followed up and offered supportive care as needed, but did not receive regular medication or psychotherapy. Subjects who changed to maintenance treatment with alternative mood-stabilizing agents after discontinuing lithium were excluded. Reasons for stopping lithium included prolonged clinical stability and uncomfortable side effects (46.5% of cases), emergence of clinically significant adverse effects (15.1%), and pregnancy (3.24%); remaining patients (35.1%) refused to continue taking lithium based on dissatisfaction with their progress or a desire to rely on intermittent treatment of future episodes of acute illness.

Rates of suicidal acts were compared between the phases of lithium maintenance: (A) before treatment, (B) during treatment, and (C) after discontinuation. Times to suicidal events or to the end of observations (time of censoring) were recorded for each subject, as months from (A) illness onset, (B) the start of lithium maintenance, or (C) the last day of lithium maintenance. All suicidal acts per subject were recorded, with time intervals defined as months to the first act, or months between subsequent acts in each treatment phase.

Contrasts of rates of suicidal acts between treatment phases were made by computing incidence risk ratios, using the Poisson distribution for counts of infrequent suicidal events in random effects models to provide for repeated observations on the same subjects in different treatment conditions.[44] This approach permits calculation of incidence rates and estimates of the incidence risk ratio when 2 phases of treatment of the same subjects are compared.[44,45] Additional contrasts compared suicidal events in the first 12 versus the next 60 months of time at risk in the phases before (A_1 vs. A_2) and after discontinuing lithium (C_1 vs. C_2), to test the hypotheses that there are disproportionately high suicidal risks early in the illness before treatment, as well as soon after discontinuing lithium.

Risk assessments included Kaplan-Meier product-limit survival analyses of the distribution of times to first suicidal events in the 3 phases (A, B, and C) with 95% confidence intervals (CI); survival functions between treatment phases were compared initially with Wilcoxon chi-square statistics for non-independent samples.[46] The hazard functions for the 3 treatment phases were not proportional over the entire risk periods, especially when multiple events were included; because hazard functions were proportional when only first events were considered and observations in each phase were limited to 72 months (censored for later times), these conditions were applied to subsequent analyses by proportional hazards methods.

On the basis of analyses considered in the Results section, previous suicidal acts, presence of severe depression at any time, being above the median for proportion of time depressed in each treatment phase, and age at the start of each phase were found to be significant covariates and were included in Weibull regression models comparing survival functions between treatment phases A versus B and C versus B, and regression coefficients were adjusted for clustering on the number of subjects in each phase.[44,45] Interactions among these main effects were found not to be significant (not shown). This modeling procedure provided acceptable goodness-of-fits.[44] Differences in survival functions in these covariate-modeled comparisons were assessed by changes in log-likelihood (doubled and referred to a chi-square distribution with 1 degree of freedom). In this modeling, "robust" variance-covariance estimation methods [45,46] were used because of a lack of independence between phases due to the inclusion of the same 310 subjects before (A) and during (B) lithium treatment, and of 185 of them in all 3 periods (A, B, C).

Other comparisons employed standard statistical methods as specified in Results. Statistical analyses used Statview-4.5 (Abacus Corp., Berkeley, Calif.) and Stata (Stata Corp., College Station, Tex.) programs. Data are presented as percentages or means ± SD unless stated otherwise; confidence intervals (CI) are at 95%. Comparisons were considered statistically nonsignificant (NS) at $p > .05$ in 2-tailed tests, at defined degrees of freedom (df).

RESULTS

Three hundred ten DSM-IV bipolar manic-depressive patients of type I (N = 186) or type II (N = 124) were entered in this study, of whom 198 (63.9%) were women and 112 (36.1%) were men. Mean age was 29.4 ± 12.1 (range, 12–66) years at illness onset, 38.7 ± 14.8 (range, 15–75) years at start of lithium treatment, and 40.8 ± 15.5 (range, 17–76) years at lithium discontinuation. Time from illness onset to starting lithium averaged 8.28 ± 8.38 years (range, 1 month–42.3 years). Patients were maintained on lithium for a mean of 6.36 ± 4.98 years (range, 0.5–22.4; 98.4% were treated for at least 1 year) at a mean serum level of 0.624 ± 0.134 mEq/L, consistent with standard international practice.[19,47] Serum lithium concentrations were somewhat lower with advancing age ($r = –0.311$, df = 308, $p < .001$), averaging 0.670 ± 0.140 mEq/L in the youngest quartile and 0.570 ± 0.110 in the eldest ($F = 19.9$, df = 1,154; $p < .001$). Of the 310 subjects treated with lithium, 185 were also followed for an average of 3.70 ± 3.71 years (range, 1 month–16.7 years) after discontinuing lithium.

A total of 90 life-threatening suicidal acts occurred among 58 of the 310 patients; 8 of those that occurred during or after discontinuation of lithium treatment were fatal; of the 90 suicidal acts, 69 were first events within a treatment phase, and 21 were second or third acts. Overall suicidal rates were 1.72 acts per 100 patient-years (or percentage of patients/year) and 0.301 fatalities per 100 patient-years. Suicidal behavior in each treatment phase is summarized in Table 1. Concurrent depression (73.3%) or, less commonly, a mixed-dysphoric state (15.6%) was associated with 88.9% of the 90 suicidal acts and all 8 fatalities in both type I and II patients; only 11.1% of suicidal acts were associated with mania, and none occurred in a euthymic state.

Before lithium maintenance (phase A) started, 59 suicide attempts occurred in 46 of the 310 patients (11 made more than one) over an average of 8.28 years, yielding rates of 1.79 suicidal persons and 2.30 acts per 100 patient-years of risk (see Table 1). Since lithium treatment was a selection criterion, fatalities in phase A were an exclusion criterion. A disproportionately large number of suicidal acts (27.1%) occurred during the first year at risk, and the majority (54.2%) occurred within the first 5 years, suggesting an association with early illness itself, or with younger age (Figure 1). Suicidal risk in year 1 versus years 2 through 6 (A_1 vs. A_2) yielded a highly significant risk ratio of 12.3 (95% CI = 18.5 to 70.5; overall model $\chi^2 = 110$, df = 1, $p < .0001$).

During lithium maintenance (phase B), 7 suicidal acts (2 were fatal) occurred in 7 of the 310 subjects over 6.36 years (no patient made more than 1 attempt during lithium treatment), yielding 0.355 persons and acts per 100 patient-years, or a reduction of crude risk (compared with phase A) by 5.04-fold (persons) or 6.48-fold (acts); the apparent fatality rate was 0.101 per 100 patient-years on lithium treatment (see Table 1).

After 185 of the subjects discontinued lithium (phase C), 24 suicidal acts occurred in 16 patients (3 with > 1) over 3.70 years of follow-up, yielding crude rates of 2.34 suicidal persons (6 died) and 3.51 suicidal acts per 100 patient-years of risk (see Table 1). The fatality rate was 0.877 per 100 patient-years after discontinuation versus 0.101 during lithium maintenance—an 8.68-fold difference in crude risk. In the first year after discontinuing lithium, more persons became suicidal (3.24 per 100 patient-years) than at later times after discontinuation (2.00/100) or before lithium was started (1.79/100). Moreover, there was a much higher risk of suicidal acts (7.11 per 100 patient-years) than at later times (2.29/100) or in the period before lithium was started (2.73/100). These various crude rates (see Table 1) are compared in Figure 2. We found a 1.96-times greater suicidal risk within 1 year of stopping lithium rapidly versus gradually (4.96 vs. 2.55 acts per 100 patient-years), but this trend was not statistically significant.

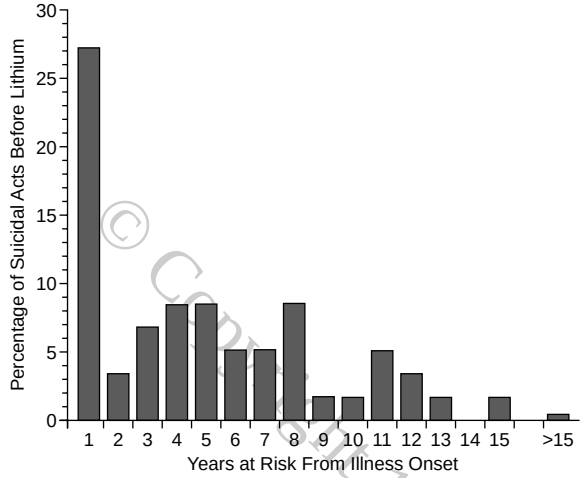
Table 1. Suicidal Risk Rates in Patients With Bipolar Disorder*

Variable	Value
Overall risk rate	
Persons with suicidal events (proportion = 58/310)	0.187
Suicidal acts per suicidal patient (ratio = 90:58)	1.55
Suicidal acts per 100 patient-years[a]	1.72
Fatalities per 100 persons (proportion = 8/310)	2.58
Fatalities per 100 patient-years[a]	0.301
Severity (% of 90 suicidal acts)	
Nonfatal attempts (N = 82)	91.1
Fatalities (N = 8)	8.90
Violent acts (N = 36)	40.0
Risk of suicidal act per 100 patient-years	
Before lithium treatment	
Persons	1.79
Acts	2.30
During lithium treatment	
Persons	0.355
Acts	0.355
Fatalities	0.101
After lithium treatment	
Total	
Persons	2.34
Acts	3.51
Fatalities	0.877
First year following discontinuation	
Persons	3.24
Acts	7.11
After first year following discontinuation	
Persons	2.00
Acts	2.29
Age and time factors at time of first suicidal act	
Duration of illness, y (mean ± SD)	7.95 ± 9.20
Current age, y (mean ± SD)	33.6 ± 12.0
Mood during suicidal acts (% of 90 acts)	
Depression	73.3
Mixed (bipolar) mood	15.6
Mania	11.1

*Three hundred ten subjects before and during lithium treatment and 185 after discontinuation were at risk for an overall mean total of 18.3 years.
[a]Risk for suicide attempts calculated using 5233 patient-years (all phases of treatment), but risk for fatal suicides calculated using 2656 patient-years (during and after lithium treatment).

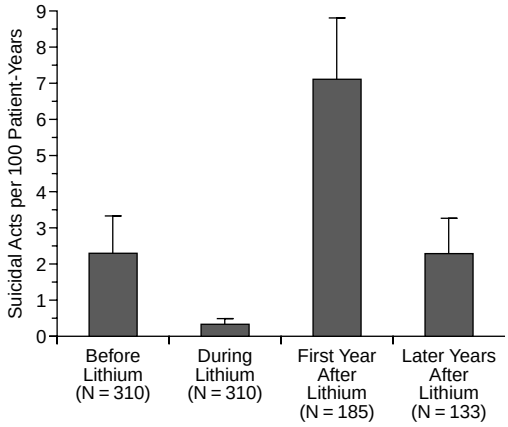
Incidence rate contrasts before versus during (A vs. B) and after versus during lithium treatment (C vs. B) were statistically significant as evaluated by Poisson random effects analysis using robust SE estimation.[44] These methods indicated highly significant differences in suicidal rates between before versus during (phases A vs. B), and after versus during lithium treatment (C vs. B), with computed risk ratios that were similar to those based on crude rates (A/B = 6.48; C/B = 9.89; see Table 1 and Figure 2): the adjusted, Poisson modeling-based incidence of suicidal acts (risk ratio A/B) was 5.62-fold greater before versus during lithium maintenance (95% CI = 2.15 to 14.5; z = 3.96, $p < .001$); the risk ratio for after discontinuing versus during lithium treatment (C/B) was 9.10 (95% CI = 3.47 to 23.4; z = 4.57, $p < .001$). In addition, the rate of suicidal acts in the first year after discontinuing lithium was significantly higher than before starting lithium (C_1/A; crude risk ratio = 3.09; computed ra-

Figure 1. Distribution of 59 Suicidal Acts Following the Onset of Bipolar Illness and Before the Start of Lithium Maintenance Treatment*



*The latest point (> 15 years) indicates a mean of acts/year for years 16–42. Note that 27.1% of the total occurred within the first 12 months at risk, 54.2% within the first 5 years, and that suicidal acts were uncommon after 10 years. A test of the difference in risk in the first vs. next 5 years based on random-effects Poisson modeling yielded a risk ratio of 12.3 (95% CI = 18.5 to 70.5, with a highly significant partial-likelihood ratio test statistic = 77.0, $p < .0001$, based on reference to a chi-square distribution with 1 degree of freedom).

Figure 2. Crude Rates (Acts per 100 Patient-Years) of Suicidal Behavior (A) Before, (B) During, and (C) After (in the [C_1] First and [C_2] Later Years) Discontinuing Lithium Maintenance Treatment in Patients With Bipolar Disorder*



*A 95% CI suggests that $C_1 > C_2 = A > > B$. Indicated variances are based on random-effects Poisson models with robust variance estimates. Computed risk ratios (limiting follow-up to 72 months) ± robust SE, in rank-order of magnitude, are as follows: $C/B = 9.10 \pm 4.40$ ($z = 4.57$, $p < .0001$); $A/B = 5.62 \pm 2.44$ ($z = 4.78$, $p < .0001$); $C_1/A = 4.76 \pm 1.55$ ($z = 3.96$, $p < .001$). Based on random-effects Poisson modeling, an additional test of the difference between the first year after discontinuation vs. the subsequent 5 years (C_1/C_2) yielded a risk ratio = 4.79 (95% CI = 1.83 to 12.3); the partial likelihood test statistic for this ratio = 53.1 (based on reference to a chi-square distribution with df = 1 and $p < .001$).

tio = 4.76 [95% CI = 1.82 to 12.1]). In addition, based on the model applied to Figure 1, a within-treatment phase comparison of the rate in the first year off lithium treatment versus the next 5 years (C_1/C_2) yielded a crude risk ratio of 3.10, and a computed ratio of 4.79 (95% CI = 1.83 to 12.3; $\chi^2 = 54.6$, df = 1, $p < .0001$). These ratios did not differ appreciably with or without adjusting for past history of a suicide attempt, presence of severe depression, or age at the start of each phase (data not shown).

Exploratory analyses were made with random effects methods to identify factors associated with suicidal events. Preliminary consideration of a large number of descriptive, demographic, diagnostic, family history, and morbidity factors eliminated many potential associations with the presence/absence of suicidal acts at any time (Table 2). Four factors were initially found to be associated with suicidal behavior. In rank-order of their significance, these factors were (1) previous history of a suicidal act (present [72.2%] > absent [27.8%]; $\chi^2 = 34.6$, df = 1, $p < .0001$), (2) proportion of time depressed above the median (76%–100% if suicidal versus 47%–49% if nonsuicidal in each phase; all $\chi^2 \geq 7.16$, df = 1, $p \leq .007$), (3) previous depression severity (severe [21.9%] > mild or moderate [8.06%]; $\chi^2 = 6.13$, df = 1, $p = .013$), and (4) age at onset of illness and at the start of each treatment phase (younger > older; e.g., for onset age: 25.7 ± 7.92 versus 30.2 ± 12.7 years; $F = 6.60$; df = 1,308; $p = .01$; see Table 2). After Weibull multivariate, proportional hazards analysis with robust estimation of the variance-covariance parameters (SE), factors 1, 2, and 4 remained significant (hazard ratios ≥ 4.61, $p < .001$) and consistent with requirements for modeling, and so were included as covariates in subsequent modeling of times to suicidal events.[44]

Initial Kaplan-Meier survival analyses compared the times to first suicidal events in the 310 subjects before versus during lithium maintenance (A vs. B), as well as during treatment versus after its discontinuation (B vs. C) by 185 of the subjects (Figure 3). These analyses indicated a highly significant difference in suicidal risk over time between treatment conditions A and B (Wilcoxon $\chi^2 = 19.7$, $p < .0001$), as well as between B and C (Wilcoxon $\chi^2 = 16.4$, $p < .0001$), but not between C and A (Figure 3).

Weibull regression modeling of the times to suicidal events, stratified by treatment phase, showed an acceptable fit to the actual data, and consistency with a common shape parameter, for comparisons of before versus during (A vs. B) and after versus during (C vs. B) lithium treatment (not shown). In Weibull analyses, treatment phase was defined as the principal explanatory factor and adjustment was made for presence/absence of past suicidal history, presence/absence of severe depression, and age at the start of each phase. These analyses indicated that the

Table 2. Comparisons of Suicidal and Nonsuicidal Patients With Bipolar Disorder*

Factor	Nonsuicidal	Suicidal
Proportion of cases		
Female	63.5	65.5
Single	49.6	51.7
Educated > 8 years	62.3	56.9
Unemployed	14.3	19.0
Affective family history	54.8	60.3
Unsatisfactory lithium response[a]	30.6	34.5
Diagnostic type		
Bipolar-I	78.0	22.0
Bipolar-II	86.3	13.7
Depression severity[b]		
Severe	78.1	91.9
Mild	21.9	8.06
Values before lithium treatment (mean ± SD)		
Onset age[c]	30.2 ± 12.7	25.7 ± 7.9
Years	8.41 ± 8.39	7.71 ± 9.3
Episodes/year	2.05 ± 2.47	1.42 ± 1.03
Admissions/year	0.32 ± 0.98	0.47 ± 0.56
Percent time ill	46.6 ± 31.2	43.7 ± 27.4
Severe depression (%)[d]	46.9	75.8
Values during lithium treatment (mean ± SD)		
Age started[c]	38.7 ± 14.8	33.3 ± 11.6
Years	6.30 ± 4.95	6.60 ± 5.14
Episodes/year	0.70 ± 1.02	0.67 ± 0.71
Admissions/year	0.04 ± 0.17	0.08 ± 0.19
Percent time ill	15.1 ± 18.9	18.1 ± 19.3
Severe depression (%)[d]	48.8	100.0
Values after lithium treatment (mean ± SD)		
Age at discontinuation[c]	42.1 ± 16.3	36.2 ± 11.3
Years of follow-up	3.11 ± 2.51	3.86 ± 3.97
Episodes/year	2.01 ± 2.71	1.72 ± 1.93
Admissions/year	0.38 ± 0.65	0.26 ± 0.71
Percent time ill	39.7 ± 34.0	34.0 ± 29.4
Severe depression (%)[d]	46.8	87.5

*The study included 252 nonsuicidal and 58 suicidal patients before and during lithium treatment, and 145 nonsuicidal and 40 suicidal patients after discontinuation. Proportions were compared by random-effects regression analysis; continuous measures were compared by random-effects ANOVA; with Bonferroni-correction for multiple comparisons, no difference was statistically significant, except as noted.
[a]Unsatisfactory = < 50% reduction of proportion of time ill during vs. before lithium maintenance.
[b]$\chi^2 = 6.13$, df = 1, p = .013.
[c]F = 4.36–6.78, df = 1,308 or df = 1,183; all p < .05.
[d]Severe depression = proportion of persons above median for percentage of time depressed in each phase; all $\chi^2 \geq 7.16$, all p ≤ .007.

risk of suicidal acts before versus during lithium treatment (A vs. B) differed highly significantly, with an adjusted hazard ratio ± robust SE[44] of 6.36 ± 3.42 (95% CI = 2.21 to 18.3; $\chi^2 = 9.05$, df = 1, p = .003). Similarly, the suicidal risk after discontinuing versus during lithium treatment (C vs. B) also differed highly significantly, with an adjusted hazard ratio of 7.48 ± 3.62 (95% CI = 2.90 to 19.3; $\chi^2 = 10.4$, df = 1, p = .001). These results indicate a 6.4-fold difference in adjusted risk of suicidal behavior during versus before lithium treatment and a 7.5-fold increase after discontinuation of lithium. When Weibull analyses were restricted to the 185 subjects observed under all 3 treatment phases, the reported results changed

Figure 3. Survival Analysis for 310 Patients With Type I or II Bipolar Disorder (A) Before and (B) During Lithium Maintenance Treatment and (C) for 185 of the Subjects After Discontinuing Lithium*

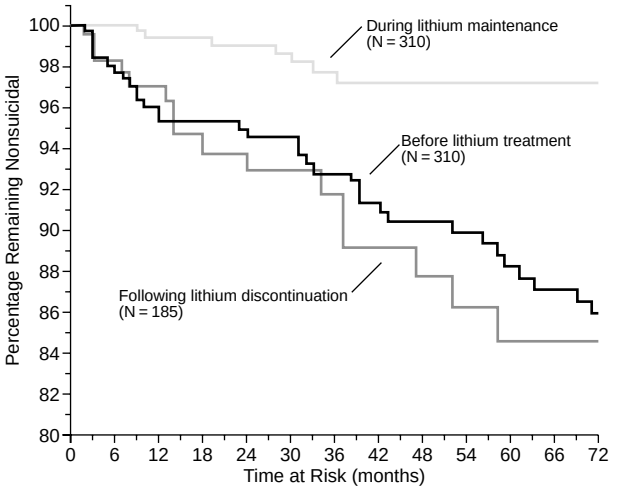


*Figure shows the proportion of persons remaining free of life-threatening suicidal acts over time, limited to 6 years of risk for graphical convenience. Cumulative suicidal risks (with 95% CI) over 5 years at risk were A = 10.8% (5.54 to 14.8), B = 2.78% (0.72 to 4.81), and C = 13.8% (6.90 to 20.7) of patients. Differences in survival functions A vs. B and B vs. C are highly significant (Wilcoxon $\chi^2 = 19.7$ and 16.4, respectively; both p < .0001), but A and C are not significantly different ($\chi^2 = .03$).

trivially. Analyses of times to multiple suicidal acts in each treatment phase, and extension of the survival analyses beyond 72 months, also did not appreciably change the results reported (not shown).

DISCUSSION

This clinical study of relationships of lithium treatment to suicidal acts found that 58 of 310 bipolar I or II disorder patients made 90 suicide attempts (8 were fatal) during a total of 5233 patient-years of observation before, during, and after lithium maintenance treatment, with 1.72% of patients making at least 1 suicide attempt per year, and 0.301 fatal suicides occurring per 100 patient-years (see Table 1). It is also important to emphasize that there was little difference in risk of life-threatening suicidal acts between the bipolar I and II subtypes (see Table 2), tending to challenge the view that type II disorders are of lesser severity or lethality.[11,43] The present observation that more than half of all suicidal acts from illness onset to the start of lithium maintenance occurred within the first 5 years of illness (see Figure 1) is consistent with reports from previous studies of a disproportionately high suicidal risk found relatively early in bipolar [48,49] as well as in nonbipolar major depressive disorders.[50]

Risks of life-threatening suicidal acts as well as affective morbidity were much lower during long-term maintenance treatment than at other periods of observation (see

Tables 1 and 2), and survival analyses of time to a suicidal act further indicated marked differences between treatment phases A (before) or C (after discontinuing) and B (during lithium maintenance; see Figure 3). Crude rates of suicidal acts before starting (phase A) and after discontinuing (C) versus during lithium treatment (B) were 2.30 and 3.51 (average for time not taking lithium = 2.90) versus 0.355 per 100 patient-years, respectively (see Table 1); computed corrected risk or hazard ratios (by Poisson modeling of crude rates or Weibull survival modeling to adjust effects due to treatment condition for covariates, respectively) were 5.62 or 6.37 (A/B) and 9.10 or 7.46 (C/B) to compare pre-lithium and post-lithium phases to the period on lithium treatment. These rates and risk ratios are strikingly similar to the mean of 3.58 ± 6.80 suicide attempts or fatalities per 100 patient-years found in 12 studies of untreated bipolar subjects versus 0.367 ± 0.681 during lithium treatment in 22 studies—a 9.75-fold difference.[9,10] These comparisons thus support our principal initial hypothesis that lithium has a protective effect against suicidal behavior.

An important additional finding was that, in the first year after the discontinuation of lithium nonexperimentally for various clinical reasons, the crude rate of suicidal acts (7.11) was nearly 3-times greater than at later times (2.29) or before treatment (2.30 per 100 patient-years; see Table 1 and Figure 2). Moreover, the fatality rate was 8.7-times lower during versus after discontinuing lithium (0.101 vs. 0.877 deaths per 100 patient-years at risk). It is important to emphasize that previous comparisons of patient-subjects from the same clinic population who did and did not discontinue lithium maintenance treatment revealed few and minor differences in demographic or clinical factors,[42] suggesting that the observation of an elevated suicidal risk after discontinuing lithium may have some generalizability. In addition, patients included in the present analysis after lithium discontinuation were not maintained on alternative psychotropic medicines (including antidepressants or antipsychotics) or in psychotherapy, although they were followed up and received short-term clinical treatment for acute recurrences of affective illness for not more than 8 weeks at a time.

The relatively high mortality rate found here and in other studies after discontinuing lithium, along with increased morbidity (see Table 1 and Figure 2),[10,11,38–42,51] may not simply represent the natural history of untreated bipolar illness, but may include a contribution of stopping treatment itself. Such responses may be related to central pharmacodynamic changes induced by long-term lithium therapy, followed by time-dependent readjustments after drug removal.[52,53] They may be modified or prevented by gradual discontinuation of lithium to allow time for neuropsychological readaptation to the unmedicated state.[39–42] We found, suggestively, a 1.96-times greater risk of suicidal acts after stopping lithium rapidly versus gradually (4.96 vs. 2.55 acts per 100 patient-years), but this difference was not statistically significant. Although additional data are required to test the hypothesis that slow discontinuation of lithium may limit risk of suicidal behavior, clinical prudence indicates that this is the safer option when clinically feasible, particularly since it can limit affective morbidity, including potentially lethal bipolar depression.[42]

Suicidality was consistently associated with concurrent, severe affective disturbance. Current depression (73.3%) or a mixed-dysphoric manic-depressive state (15.6%) was associated with 88.9% of the 90 suicidal acts and all 8 fatalities in both type I and II patients; only 11.1% of suicidal acts were associated with mania and, not surprisingly, none occurred in a euthymic state. This overwhelming association makes it difficult to separate reduction in risk of suicidality from the mood-stabilizing effects of lithium treatment. It has been suggested that lithium may exert antisuicidal or antiaggressive actions more-or-less independent of its antimanic and mood-stabilizing effects, perhaps by enhancing central serotonergic neurotransmission.[2,42,54–59] However, the evidently close association of mood stabilization and lowered suicide risk makes the testing of this hypothesis difficult. Nevertheless, there are some provocative recent suggestions that other agents with mood-altering actions may have less antisuicide effect than lithium, including carbamazepine in bipolar disorder cases not involving lithium discontinuation (B. Müller-Oerlinghausen, written communication to R.J.B., June 1997), or combinations of a tricyclic antidepressant and neuroleptic,[21] and use of adrenergic versus mixed or serotonergic antidepressants in major depression.[60] These unexpected results seem to suggest either a superior antisuicide effect of lithium or a lesser mood stabilizing effect of the alternative treatments, and these possibilities require further study.

Other descriptive and clinical factors, including sex, marital, educational and employment status, family history, and diagnostic subtype, as well as measures of overall illness frequency or severity at any phase of treatment and responsiveness to lithium maintenance treatment, were insignificantly or minimally associated with suicidal behavior (see Table 2). However, a past history of suicide attempts, a higher-than median proportion of time in depression within each phase, and relatively younger age in this sample of mainly young adults (only 2.58% of the 310 illnesses began at age ≥ 60 years) were associated with suicidal behavior. Only these 3 factors (prior suicide attempts, severe depression, and younger age) were sustained in multivariate analyses and so were incorporated into statistical models controlling for covariates other than treatment status. Associations with severe depression and previous suicide attempts are not unexpected. The apparent effect of youth may reflect a relatively higher risk of aggression and impulsivity in adolescent or young

adult bipolar patients, or other factors associated with the impact of early adjustment to severe affective illness.[1,10,61–64]

The comparisons involved in this study have clear methodological limitations. These include having to reconstruct much of the prelithium course of illness on retrospectively gathered data, and having only a subsample of patients (59.7%) followed after discontinuing lithium. On the other hand, the close similarity of suicidal risk before lithium and that based on prospectively gathered data following its discontinuation, and particularly at times later than the first year (see Figure 2), tends to support the reliability of the information reported. Selection bias may, however, be introduced by requiring nonlethality of suicidal acts up to the start of lithium treatment. Additional bias may be inherent in selecting relatively treatment-compliant bipolar disorder patients and by excluding patients with additional proposed risk factors for suicidality, particularly comorbid abuse of alcohol or drugs.[1] That is, the present results do not provide a full picture of suicidal behavior in untreated populations of bipolar disorder patients, nor do they deal with the important problem of risk associated with erratic treatment or poor compliance, which may worsen at times of elevated suicidal risk because of emerging affective illness (e.g., with either nihilistic despair or grandiose or psychotic denial).[1,42,64] Finally, although the present study is based on clinically acquired data, the design of a scientifically ideal, randomized, blind, prospective study involving life-threatening behavior as the explicit dependent variable would be ethically and clinically daunting, and probably not feasible given current knowledge of the risks involved.[9–11,41,42] These risks include suicidal behavior (see Table 1 and Figure 2) as well as severe affective morbidity following discontinuation of lithium treatment, with a several-month period of markedly elevated risk of recurrences of mania or depression after discontinuing lithium, particularly when doing so abruptly.[39–42]

The strong association between suicidality and current or past severe depression in bipolar disorder patients highlights the need for improved methods of diagnosing, treating and managing depression in both type I and II bipolar disorders, as well as distinguishing bipolar from nonbipolar forms of depression to minimize the potentially destabilizing effects of treating bipolar depression without adequate mood-stabilization.[1,52,64–66] While the treatment of mania has improved greatly over the past several decades, and several innovative antimanic agents have been introduced in recent years, bipolar depression largely remains an "orphan syndrome" in contemporary psychiatric research.[1,6,11,19,52,66,67] In modern studies of the treatment of major depression, bipolar depression has been systematically excluded or not analyzed separately,[52,63,64,67] in part, no doubt, owing to widely recognized clinical and liability risks involved in treating bipolar patients without adequate mood-stabilization. More generally, despite recent advances toward antidepressants with greater safety in acute overdoses, suicide rates in mood-disordered populations seem not to have diminished, and causes of death may be shifting to other, more lethal alternatives.[10,43,68–70] Other related therapeutic questions remaining to be studied further include (1) the possibility that newer antidepressants may have less risk of inducing mood instability or rapid cycling in bipolar disorders, (2) the potential risk of inducing depression with long-term antipsychotic drug use, and (3) the potential antisuicide effect of lithium or other mood stabilizing agents in nonbipolar depression, and of anticonvulsants in bipolar depression.[1,3,21,52,59,63,71–75]

Overall, the quality and quantity of data to define treatment interventions that might limit suicidal risk in all major mood disorders remain insufficient as a basis for establishing secure clinical policies. Moreover, prospective, controlled studies of treatment effects on suicidality would be ethically and clinically very difficult.[9,10,40,42,43] Nevertheless, the present and previous findings reviewed above indicate a substantial, and possibly rather specific, beneficial effect of lithium on suicidal risk in bipolar disorders, provided that it is taken consistently over prolonged periods.[1,9,10,12–31] From a public health, clinical practice, risk-management, and research perspective, we conclude that an appropriate and compelling practical emphasis should be placed on preventing suicide or minimizing its risk in patients with depression or mixed dysphoric states in bipolar disorders, in which suicidal risk appears to be especially great, diagnosis challenging, and treatment difficult.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others).

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