Effects of Lithium Treatment and Its Discontinuation on Suicidal Behavior in Bipolar Manic-Depressive Disorders

Ross J. Baldessarini, M.D.;
Leonardo Tondo, M.D.; and John Hennen, Ph.D.

Background: Whether mood-altering treatments reduce risk of suicidal behavior remains largely unproved. ***Method:*** We compared suicidal rates in published studies of patients treated with lithium with those who were not, and in a mood disorders clinic before, during, and after discontinuing lithium. ***Results:*** Published reports indicate a 7.0-fold lower rate of suicidal acts with lithium treatment of manic-depressive patients. In new findings in over 300 bipolar patients, latency from illness onset to lithium maintenance averaged 8.3 years (from 11.0 years in women with bipolar II disorder to 6.9 years in men with bipolar I disorder), but half of all suicidal acts occurred in the first 7.5 of 18.3 years at risk. Most acts (89%) occurred during depressive (73%) or dysphoric-mixed (16%) mood states and were associated with previous severe depression, prior attempts, and lower age at onset. Morbidity was reduced 2.7-fold and suicidal acts per year 6.5-fold during lithium treatment, with 8.3-fold cumulative sparing of risk by 15 years on lithium. In the first year off lithium, affective illness recurred in 67% of patients, and suicidal rates rose 20-fold but were much lower thereafter; fatalities were 14 times more frequent after discontinuation of lithium. Early morbidity was 2.5-fold lower, and suicidal risk was 2.0-fold lower after slow versus rapid discontinuation. ***Conclusion:*** Lithium maintenance is associated with sustained reduction of suicidal acts in manic-depressive disorders. Treatment discontinuation, particularly abruptly, led to early affective morbidity and suicidal behavior. Improved diagnosis and treatment as well as earlier intervention for potentially lethal bipolar depression are urgently needed, as are studies of all mood-altering agents for effects on suicidal behavior.

(J Clin Psychiatry 1999;60[suppl 2]:77–84)

From the International Consortium for Research on Bipolar Disorders; the Department of Psychiatry & Neuroscience Program, Harvard Medical School, Boston, and the Bipolar & Psychotic Disorders and Psychopharmacology Programs, McLean Division of Massachusetts General Hospital, Belmont, Mass. (all authors); and the Departments of Psychiatry & Psychology, University of Cagliari and Lucio Bini Psychiatric Center, A Stanley Foundation European Research Center, Cagliari, Sardinia (Dr. Tondo).

Supported by grant MH-47370 from the National Institutes of Health, Bethesda, Md., and awards from the Bruce J. Anderson Foundation, and by the McLean Private Donors Neuropharmacology Research Fund (Dr. Baldessarini), and awards from the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Theodore & Vada Stanley Foundation, the American Foundation for Suicide Prevention, and the Italian National Research Council (Dr. Tondo).

Presented at the symposium "Effects of Medical Interventions on Suicidal Behavior," which was held February 26–28, 1998, Miami, Fla., cosponsored by the American Foundation for Suicide Prevention, the Johns Hopkins University School of Medicine, and the Long Island Jewish Medical Center, with the cooperation of the Suicide Prevention Advocacy Network, and supported by an educational grant from Solvay Pharmaceuticals, Inc.

Correspondence to: Ross J. Baldessarini, M.D., Mailman Research Center–McLean Hospital, 115 Mill St., Belmont, MA 02478.

Depressive phases of major affective disorders are strongly associated with suicidal acts in persons of all ages.[1–10] Bipolar disorders occur in over 2.0% of the general population if type II cases are included,[11,12] and they carry a very high risk of suicide that accounts for 15% to 25% of all deaths in relatively severely ill bipolar patients.[3] Excess mortality other than that due to suicide is also found in patients with bipolar disorders as an outcome of highly prevalent comorbid substance abuse as well as cardiovascular and other medical disorders worsened by long-term emotional distress.[13–16] In addition to high levels of mortality,[6] morbidity, and disability,[3,5] bipolar disorders produce extraordinarily high financial costs to individuals, families, and society. These amount to several tens of billions of dollars per year in the United States alone, of which about 20% can be ascribed to suicide.[17]

Major affective disorders, including bipolar syndromes, are highly treatable across the age spectrum,[3,5,12,18,19] but their diagnosis and timely, effective treatment reach only a minority of persons affected.[3–5,20–24] Specifically, rates of psychiatric treatment for mood disor-

ders among persons dying of suicide are low, suggesting low levels of detection and lack of appropriate interventions among those at risk for suicide.[22–24] Moreover, with the exception of lithium, remarkably little is known about specific contributions of mood-altering treatments to minimizing mortality rates in persons with major mood disorders in general, and bipolar depression in particular.[3–5,18–26] Ironically, suicidal, bipolar, and psychotic forms of depression have been excluded from most contemporary studies of antidepressant treatment—virtually precluding systematic studies of bipolar depression.[18,26] Antidepressant treatment has not led to securely demonstrated reductions in suicide rates in at-risk populations,[27] although suggestive evidence is starting to appear.[22–24] It is also not clear whether risk of suicide is reduced with newer antidepressants that are much safer on overdose, because more lethal alternative methods are often chosen.[28,29] There is also little support for earlier proposals that certain types of antidepressants may even increase suicidal risks, aside from the potential lethality of many older antidepressants in acute overdose.[25,30]

In general, well-designed research on the effectiveness of treatment to prevent suicide or other causes of early mortality in patients with mood disorders is rare.[3,9,12–15,26] This state of current knowledge reflects severe ethical problems in withholding or removing mood-altering treatments when fatality is a potential outcome. Clinical and ethical limitations to such research are now further compounded by the recently recognized high risk of recurrences of affective illness after discontinuation of maintenance treatment with lithium,[31–36] antidepressants,[37] and other psychotropic agents.[38]

Despite the severe constraints on research on the therapeutics of suicide, some encouraging information specifically pertinent to the effectiveness of lithium in reducing risk of suicidal behavior is considered here, based on research carried out by the International Consortium for Research on Bipolar Disorders, much of which is presented elsewhere in greater detail.[9,39,40]

PREVIOUS STUDIES OF LITHIUM AND SUICIDE

Computerized literature searches and references cited in reports so identified, including an important earlier review,[41] yielded studies from 1974 through 1997, with data permitting estimates of annual rates of suicide attempts or fatalities in patients with major affective illnesses treated with lithium.[39] Methodological problems can arise in such pooling of data across diagnostically and otherwise heterogeneous studies.[39] However, comparisons of risks with and without lithium maintenance treatment could be made in many of the studies involving matched conditions of diagnosis, follow-up, and assessment of patients with and without lithium treatment.

Table 1. Reported Rates of Suicidal Acts With and Without Lithium Maintenance*

Measure	Value
Rate of suicidal acts, mean ± SD % of subjects/y	
Without lithium	1.778 ± 1.444
With lithium	0.255 ± 0.403
Apparent risk-reduction with lithium	6.97-fold

*Findings are based on studies involving several thousand bipolar, schizoaffective, and some unipolar major depression cases, as well as unselected groups of major affective disorders, and include both life-threatening and fatal suicidal acts, in persons at risk for a mean ± SD of 8.22 ± 4.53 years. Mean rates differ highly significantly ($t = 3.43$, $df = 34$, $p < .001$). Data are adapted from a meta-analysis by Tondo et al.[39] based on 22 studies.

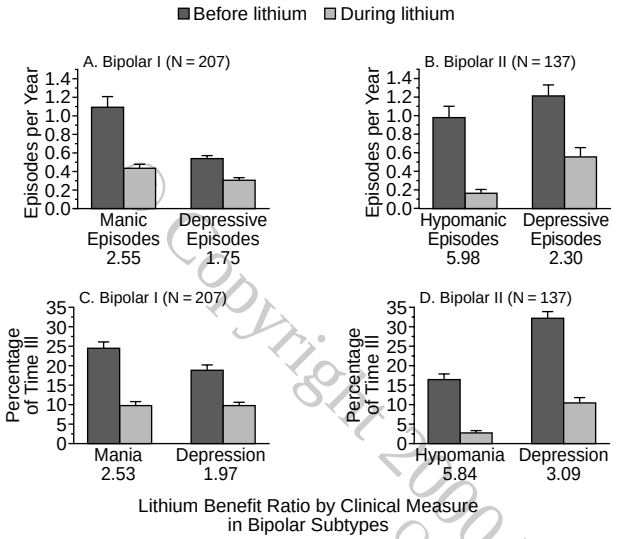
In the reports reviewed, the mean ± SD overall rate of suicide attempts or deaths with lithium treatment was 0.255% ± 0.403% of subjects per year during lithium treatment in 22 studies, compared with 1.778% ± 1.444% per year without lithium treatment in 13 of the reports (Table 1). This 7-fold difference in crude rates is highly statistically significant ($t = 3.73$, $df = 34$, $p < .001$). Moreover, all 13 reports involving direct comparisons within the same study found annual rates of suicidal behavior to be substantially lower during maintenance treatment with lithium than in comparison groups of patients with severe affective illnesses who were not so treated.[39] It is not clear whether the residual risk found with lithium treatment reflects limited effectiveness, inappropriate dosing, variable compliance, or the type of illness treated in this broad assortment of patients with disorders that include nonbipolar depression and schizoaffective syndromes as well as bipolar disorders.

In addition to the mortality-sparing effects of lithium due to reducing risk of suicide, there is also some evidence that long-term treatment with lithium may reduce risks of premature fatalities due to all causes in manic-depressive patients.[42,43] Similar results are emerging in an ongoing study of various treatment interventions in patients who have a range of major affective illnesses.[44]

DEPRESSION-LIMITING EFFECTS OF LITHIUM TREATMENT

The evident benefit of lithium treatment against suicidal acts may represent a distinct action on suicidal or other aggressive behaviors.[45,46] Alternatively, it may be a manifestation of general clinical benefits associated with the prevention of manic and especially depressive morbidity that result from an effective treatment, along with additional supportive effects of remaining in a stable treatment program. Resolution of these alternative possibilities awaits additional information about the effectiveness of emerging mood-stabilizing agents against both depressive and manic illness, and against suicidal behavior specifically. Currently, mood-stabilizing effects are far better established for lithium than for any other treatment for

Figure 1. Reduction of Depressive and Manic Morbidity With Lithium Maintenance Treatment for at Least 1 Year in 344 Sardinian Patients (222 Women, 122 Men) With Bipolar I Disorder (N = 207; left panels A and C) or Bipolar II Disorder (N = 137; right panels B and D)*



*Data (means ± SEM) are shown as episodes per year meeting DSM-IV criteria (upper panels A and B) or percentage of time with such illness (lower panels C and D), with the reduction of morbidity as a ratio of morbidity before versus during lithium maintenance treatment. Overall, numerical data for a similar but larger pooled bipolar I and II sample are shown in Table 2. These expanded results are based on methods reported by Tondo et al.[13] All before versus during lithium differences are highly significant (paired t = 4.9–14.9, df = 343, all p < .0001).

Table 2. Effect of Lithium Maintenance on Morbidity in 344 Patients With Bipolar I or II Disorders*

	Before Lithium		During Lithium			
Morbidity Measure	Mean	SD	Mean	SD	Percent Difference	Effect Ratio
Total episodes/y	1.879	2.237	0.746	1.120	60.3	2.52
Manic episodes/y	1.049	1.622	0.334	0.550	68.2	3.14
Depressive episodes/y	0.828	1.048	0.413	0.841	50.1	2.00
Hospitalizations/y	0.340	0.880	0.053	0.235	84.4	6.42[a]
% Time ill	45.32	30.53	17.01	22.36	62.5	2.66
% Time manic	21.39	22.62	7.183	12.10	66.4	2.98
% Time depressed	23.93	22.23	9.828	16.85	58.9	2.43

*Data are mean ± SD. All differences in morbidity between 8.25 ± 8.24 years before vs. 4.54 ± 3.98 years during lithium maintenance are highly significant (paired t = 5.86–15.0, df = 343, all p < .0001), with similar effects in both diagnostic subtypes (not shown).
[a]Reduction of hospitalizations was 2.84 times greater among bipolar II than bipolar I subjects in this Sardinian sample. Methods and comparable results for some of the subjects are reported elsewhere by Tondo et al.[12]

bipolar disorders,[3,5,18] whether or not treatment discontinuation stress may inflate differences between continued and discontinued lithium therapy in some studies.[47,48]

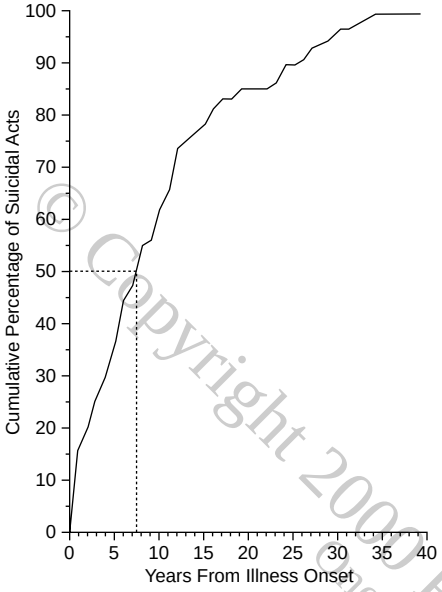
Lithium has short-term and powerful long-term antimanic effects, but its ability to protect against recurrences of bipolar and unipolar depression, and to reduce suicidal risk in nonbipolar disorders, is less well demonstrated. In previous studies in bipolar disorder patients, the reduction of episodes of mania by lithium has been greater, on average, than for depression, but the number of episodes of depression and mania have been very similar *during* lithium treatment.[3,5,18] Our recent findings indicate highly significant reductions in both manic (or hypomanic) and depressive phases of bipolar disorders in both diagnostic subtypes (Figure 1; Table 2).[12]

Thus, among 317 Sardinian patients with bipolar disorders, we found that lithium maintenance was effective in both depressive and manic phases of illness, with somewhat greater benefits in patients with type II versus type I disorders (see Figure 1). Results were obtained by analyses of episode frequency and of the proportion of time ill and showed a particularly large cost-saving reduction in the rate of rehospitalization. As in earlier studies, the proportional reduction in manic episodes was larger than for depressive episodes, but depressive and manic morbidity during treatment were very similar in type I cases.[3,5] Lithium also produced substantial reductions of both depressive and hypomanic morbidity in type II disorders.[12]

It is far from clear that proposed mood-stabilizing agents other than lithium provide similar protection against both depression and mania,[5,18] and even less certain that proposed mood-stabilizing treatments yield reductions of suicidal behavior similar to those found with lithium treatment. Some long-term studies indicate substantial long-term protective effects of carbamazepine against mania and bipolar depression in bipolar and related disorders, but strongly suggest lesser antisuicidal effects than those of lithium. Notably, in recent observations in Germany, carbamazepine treatment of bipolar or schizoaffective disorder patients who apparently had not been refractory to or discontinued from lithium was associated with suicidal behavior in 1% to 3% of the subjects, compared with none of those receiving lithium.[49,50] These findings appear to support the hypothesis that specific benefits may be associated with some but not all effective mood-stabilizing treatments.

Lithium may exert relatively selective antiaggressive actions, perhaps owing to enhancement of central serotonergic activity, including increased release of serotonin in the limbic forebrain.[8,45,46] If carbamazepine and valproic acid share such serotonin release–enhancing effects, they appear to be weak,[51,52] and their contribution to clinical effects is not clear. Another observation suggesting separation of mood-altering and antisuicidal effects is that the serotonin-enhancing agent paroxetine was found to have some beneficial effects on suicidal behavior even in persons not found to be clinically depressed.[53] On the other hand, clozapine can reduce mortality rates in schizophrenic patients despite its potent antagonistic actions on at least one class of serotonin receptors (type 2A).[54] This effect may merely accompany the superior antipsychotic benefits of clozapine or may reflect antiaggressive actions of

Figure 2. Temporal Distribution of 104 Reported Life-Threatening Suicidal Acts Among 346 Sardinian Bipolar I and II Disorder Subjects, at Risk for up to 40 Years From Illness Onset*



*Note that half of the suicidal acts occurred within the first 7.5 years (dotted lines). The time from illness onset to the start of lithium maintenance treatment in the same population averaged 8.28 ± 8.38 years, indicating that much of the suicide risk occurred early and prior to sustained lithium treatment. Some of the later apparent falloff in risk reflects the inclusion of time in maintenance treatment. These expanded results are based on methods reported by Tondo et al.[9]

clozapine that are not yet well explained pharmacodynamically.[54]

Clarification of the hypothesis that antisuicidal and mood-stabilizing effects may not always be closely linked awaits further studies of the effects of various treatment interventions on suicidal behavior. Specifically, evidence is required to clarify whether treatments with little effect on central serotonergic function, but clear long-term efficacy against bipolar depression as well as mania, are also associated with reduced suicidal behavior.

NEW FINDINGS ON LITHIUM AND SUICIDE

The striking overall difference in rates of suicidal behavior between the presence and absence of lithium treatment in published reports[39] (see Table 1) encouraged additional studies of patients who were evaluated, treated, and followed at the collaborating Lucio Bini mood disorder research center in Cagliari, Sardinia. We recently carried out an extensive clinical study of life-threatening suicidal acts over time in 310 DSM-IV bipolar I (N = 186) and II (N = 124) disorder patients in that center.[9] Suicidal events were recorded for the period before and, under observation, during clinically indicated treatment, and following its discontinuation. Although data analyzed were acquired primarily for clinical purposes, methods employed for clinical assessment and data gathering and recording have been of research quality since the founding of the clinic in the 1970s. The subjects studied provided informed consent for anonymous research use of their clinical records.

Changes in treatment, and particularly lithium discontinuation, occurred clinically and were never investigator-initiated for research purposes, for obvious ethical reasons. Discontinuation was medically recommended for clinical indications (typically for adverse effects or pregnancy) or represented a unilateral decision by the patient to stop without medical consultation, usually after remaining stable for prolonged periods.[9,34–36] Suicidal acts considered were fatal or potentially fatal without medical intervention; fatalities prior to lithium treatment were excluded to permit comparisons of the same patients before and during lithium treatment.

The 310 bipolar I and II patients studied included 198 (63.9%) women and 112 (36.1%) men, ill for a mean ± SD of 8.28 ± 8.38 years, from the onset of bipolar illness at age averaging 29 ± 12 years (range, 12–66 years) to the start of lithium maintenance. Subjects were followed prospectively thereafter during 6.36 ± 4.98 years of lithium maintenance treatment given essentially as a monotherapy as described elsewhere.[9,12,34–36] Serum lithium concentrations averaged 0.62 ± 0.13 mEq/L, consistent with standard international practice aimed at optimizing compliance.[9,12,49,50,55–57] A subgroup of 128 of the same subjects were also followed prospectively for an average of 3.70 ± 3.72 years after discontinuing lithium, with no other maintenance treatments given.

In the 8.28 years before regular lithium treatment had been initiated, the rate of life-threatening suicidal acts was 2.30 per 100 patient-years. The majority of suicide attempts arose early in the illness, and 53% of the 60 acts noted before the start of lithium maintenance treatment occurred within the first 5 years of illness (median latency = 4.79 years from illness onset), a period in which 55.5% of the 310 subjects at risk had not yet entered regular maintenance treatment with lithium. On the basis of an expanded group of 346 patients in the same clinic, we also computed the cumulative temporal distribution of a total of 104 suicide attempts over a total of 40 years (average = 18.3 years; Figure 2); half of these potentially fatal events occurred within 7.50 years of illness onset, well before the mean time to lithium maintenance, and 74% of all suicidal events occurred before lithium treatment. Latency from illness onset to lithium maintenance was shortest in bipolar I men (mean ± SD = 6.87 ± 7.54) and longest in bipolar II women (11.0 ± 9.51 years; $t = 3.32$, $df = 186$, $p < .001$), possibly reflecting differences in the social impact of manic versus depressive illness and misdiagnosis of the type II syndrome as depression, particularly in women. That the majority of life-threatening suicidal acts occurred in the years before sustained maintenance treat-

Table 3. Suicidal Risk in Bipolar Disorder Patients Before Versus During Lithium Maintenance Treatment*

Years at Risk	Cumulative Percentage Suicidal (95% CI) Before Lithium	During Lithium	Risk Ratio
1	4.71 (2.30 to 7.11)	0.65 (0.00 to 1.54)	7.25
2	5.49 (2.87 to 8.11)	1.01 (0.00 to 2.14)	5.44
3	7.26 (4.16 to 10.4)	2.76 (0.72 to 4.80)	2.63
4	9.69 (6.02 to 13.4)	2.76 (0.72 to 4.80)	3.51
5	11.8 (6.02 to 13.4)	2.76 (0.72 to 4.80)	4.28
10	18.5 (13.0 to 24.1)	2.76 (0.72 to 4.80)	6.70
15	22.9 (16.1 to 29.6)	2.76 (0.72 to 4.80)	8.30

*Data are derived from Kaplan-Meier actuarial survival functions for 310 Sardinian bipolar I and II patients and represent the cumulative proportion of patients with a life-threatening suicidal act over time, with 95% confidence intervals (CI), as well as the risk ratio of rates for the 2 treatment conditions. The differences are highly significant (Wilcoxon χ^2 for paired samples = 22.1, df = 1, $p < .0001$ for the overall survival functions). Most of the risk on lithium treatment occurred in the first 2 to 3 years, with a rising ratio of protection thereafter. Data are adapted from Tondo et al.[9] and Baldessarini and Tondo.[36]

Table 4. Rates of Suicidal Acts and Treatment Status in Bipolar Patients*

Treatment	Suicidal Acts Per 100 Patient-Years
A. Before lithium treatment	2.30
B. During lithium maintenance	0.355
A/B Ratio	6.48
C. After discontinuing lithium	4.86
C/B Ratio	13.7
D. First year off lithium	7.11
D/B Ratio	20.0
E. Later years off lithium	2.29
A/E ratio	1.00

*N and time at risk were as follows: A (310 for 8.28 years), B (310 for 6.36 years), and C–E (128 for 3.70, 1.00, or 2.70 years). Differences for A versus B, C versus A, C versus B, D versus A, and D versus B are statistically significant (all $p \leq .001$). Results are based on methods detailed in Tondo et al.[9]

ment with lithium suggests that lithium treatment was protective, but also emphasizes the need for early intervention to limit suicidal risk.[9]

During lithium maintenance treatment of the 310 subjects evaluated both during and before lithium maintenance treatment, 7 suicidal acts (2 were fatal) occurred in 7 subjects over 6.36 years, to yield 0.355 acts per 100 patient-years. This crude risk rate is 6.59-fold lower than that encountered before lithium started (0.355 vs. 2.34) and is very similar to the 6.97-fold difference found in other studies (see Table 1).[39] Suicidal risk during lithium treatment was also evaluated by Kaplan-Meier survival analyses to compare the times to first suicidal events in the 310 subjects before versus during lithium maintenance. This analysis yielded a highly significant difference in suicidal risk over time (Wilcoxon $\chi^2 = 22.1$, df = 1, $p < .0001$). Comparisons of yearly risks of suicidal acts provided by this analysis indicated that by 15 years of follow-up the cumulative annual risk rate differed by 8.3-fold (Table 3). Most of the risk was encountered within the first 2 to 3 years of lithium maintenance, suggesting somewhat greater benefits with longer treatment or earlier suicidal behavior in persons who were more prone to suicide (see Table 3).

Table 5. Rate of Fatal Suicidal Acts*

Treatment Condition	Value
During lithium treatment, acts per 100 patient-years	0.101
After discontinuing lithium, acts per 100 patient-years	1.270
Difference	12.6-fold

*Data based on methods in Tondo et al.[9] for 310 Sardinian bipolar I or II disorder patients at risk for 6.36 years during and, in 128 cases, for 3.70 years following discontinuation of lithium maintenance treatment; the difference is highly significant ($\chi^2 = 15.9$, df = 1, $p < .0001$).

Table 6. Effect of Lithium Discontinuation Rate on 12-Month Risk of Suicidal Acts*

Measure	Value
Discontinuation rate, suicidal acts per 100 patient-years	
Rapid (1–14 d)	4.96
Gradual (15–30 d)	2.55
Difference	1.95-fold

*Risk is for life-threatening acts within the first 12 months after discontinuing lithium in 128 Sardinian bipolar disorder patients; the trend is statistically nonsignificant. Adapted from Tondo et al.[9]

After 128 of the patients discontinued lithium, 23 suicidal acts occurred among 16 persons (13.0% incidence), including 6 fatalities, over an average of 3.70 years of follow-up, to yield a crude rate of 4.86 suicidal acts per 100 patient-years of risk. After discontinuation of lithium, the rate of suicidal acts was 13.7 times (4.86 vs. 0.355 per 100 patient-years) greater than the risk during lithium treatment (Table 4). Moreover, in the first year after discontinuation of lithium, the rate of suicidal acts rose especially sharply, 20-fold (7.11/0.355) compared with the time on lithium therapy. A much lower rate was found at times later than 12 months after discontinuation (2.29 per 100 patient-years), and was virtually identical to that found before lithium maintenance had started (2.30 per 100 patient-years). These observations indicate that the first months after discontinuation of lithium may carry a particularly high risk of suicidal behavior and included multiple attempts and fatalities, sometimes in persons without previous suicidal acts. Moreover, the fatality rate due to suicide was 1.27 per 100 patient-years after discontinuation of lithium compared with 0.101 during lithium maintenance—an alarming 12.6-fold increase (Table 5). There was a nearly 2-fold numerically greater risk after abrupt or rapid discontinuation of lithium (within 14 days of tapering) versus more gradual discontinuation (15–30 days). This trend (Table 6) was not statistically significant, but power is limited by the infrequency of suicidal acts in available subjects.[9,40]

Concurrent depression (73%) or, less commonly, mixed-dysphoric mood states (16%) were associated with 89% of the 90 suicidal acts and all 8 fatalities in the 310

type I and II patients; only 11% of suicidal acts were associated with mania, and, as expected, none occurred in a euthymic state. Additional analyses, based on multifactorial statistical modeling reported elsewhere,[9] identified 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 or absence of suicidal acts at any time. However, 3 factors were significantly more frequently found in patients who manifested suicidal behavior, compared with those who did not. In rank-order of their significance, they were (1) having a previous history of a suicidal act, (2) being depressed for a proportion of time above the median, and (3) being younger at illness onset. In addition, in a new Sardinian multisite clinical sample involving over 500 patients with either unipolar major depressive and bipolar disorders, comorbid substance use disorders also represented a significant risk factor for suicide attempts among hospitalized affectively ill patients.[57]

Increased depression is almost certainly a crucial intervening variable contributing to the marked increase in suicidal risk after discontinuing lithium (see Tables 4 and 5), and slow discontinuation of lithium may limit suicidal risk by limiting risk of recurrences of bipolar depression or dysphoric-mixed states (see Tables 6 and 7). However, consideration of the rates of suicidal acts per depressive episode raises the possibility that the relationships among depression, suicide, and lithium treatment are probably complex. In the years before lithium treatment, this rate averaged 3.68 acts per episode. The rate fell 2.30-fold, to 1.60 acts/episode during lithium maintenance, suggesting a beneficial effect against suicidal acts that is disproportionate to that against depressive recurrences. In contrast, within 12 months after discontinuation of lithium, this rate rose 7.88-fold, to 12.6 suicidal acts per depressive episode (not shown). The last observation suggests that discontinuing lithium treatment increased the risk of suicide more than that of depression, or that post-lithium depressive recurrences were particularly severe or potentially life-threatening.

Table 7. Effect of Lithium Discontinuation Rate on Morbidity During First 12 Months Off Lithium Treatment*

	Rapid (N = 109)		Gradual (N = 66)		Risk
Measure	Mean	SD	Mean	SD	Ratio
Episodes/y					
All	1.303	1.110	0.515	0.881	2.53[a]
Manic	0.734	0.647	0.242	0.498	3.03[a]
Depressive	0.569	0.762	0.273	0.570	2.08[b]
Hospitalizations	0.174	0.427	0.061	0.240	2.87[c]
Percentage time ill					
All	28.29	25.57	11.49	20.66	2.46[a]
Manic	14.98	17.64	5.05	11.41	2.97[a]
Depressive	13.30	19.91	6.44	13.85	2.07[b]

*In this sample of 196 patients discontinued from lithium, 66.8% had a recurrence within 12 months; only 175 are analyzed above because the discontinuation rate was not certain in 21 cases. These risks contrast with a mean ± SD at 0.726 ± 1.103 episodes per year and 16.70% ± 22.10% time ill during lithium maintenance treatment. The risk of relapse after rapid (1–14 days), uncertain, and gradual (5–30 days) discontinuation differed as 88.1%, 57.1%, and 34.8%, respectively ($\chi^2 = 53.5$, df = 2, $p < .0001$).
[a]All $F \geq 16.7$, df = 1,173; $p < .0001$.
[b]All $F \geq 6.1$, df = 1,173; $p \leq .01$.
[c]$F \geq 3.9$, df = 1,173; $p < .05$.

DISCUSSION AND CONCLUSIONS

The findings summarized here indicate that lithium maintenance treatment is associated with a highly clinically important and long-sustained reduction of risk of suicidal acts that has not been demonstrated for alternative treatments. In 22 published studies providing quantitative data pertaining to several thousand patients with major affective illnesses, the overall risk of suicidal acts was 7 times lower during lithium maintenance treatment than without it (see Table 1).[39]

In our recent long-term analysis of clinical data of over 300 bipolar I and II disorder patients in a Sardinian mood disorders center, we also found a nearly 7-fold lower rate of suicidal acts during lithium maintenance monotherapy in comparison to the time at risk before this treatment was begun in the same persons (see Table 4).[9] Methodological limitations of this clinical study are reviewed elsewhere.[9,40] The cumulative risk of a life-threatening suicide attempt was reduced more than 8-fold over 15 years of follow-up with lithium maintenance. Current depression or dysphoric-mixed mood states were associated with nearly 90% of suicidal acts. Long-term lithium treatment was also associated with a marked reduction in depressive (as well as mixed, manic, and hypomanic) illness, and this effect presumably contributes to the sharply reduced frequency of suicidal acts (see Figure 1; Table 2). However, the increase of suicidal acts following discontinuation of lithium was much greater than the rate of recurrence of depressive episodes, indicating a disproportionately high suicidal risk under such circumstances. Suicidality was predicted by a history of severe depression and prior attempts, relatively early illness onset, as well as comorbid substance abuse. Suicidal acts occurred with an alarmingly high frequency in the first several years of illness, before lithium maintenance had begun (Figure 2).[9,40,57]

Rates of suicidal acts and fatalities increased sharply shortly after discontinuation of lithium and fell back to pretreatment levels after 12 months of follow-up (see Table 4). The rate of suicidal behavior rose 20-fold within the first year after discontinuation of lithium maintenance to levels several times above later risks and the similar rates found before the start of lithium treatment (see Table 4). Moreover, fatalities increased nearly 13-fold in the year after discontinuation of lithium (see Table 5). There was a tendency for risks to be greater following abrupt or rapid discontinuation of lithium than after gradual taper-

ing over several weeks. Slow tapering of lithium might reduce suicidal risk, particularly since it can sharply reduce rates of early recurrence of bipolar depression as well as mania (Table 7).[32–36]

These increased suicidal rates were associated with increased recurrences of bipolar depressive illness, although the increase in suicidal acts (20-fold in the year after discontinuation of lithium; see Table 4) was proportionally much greater than an approximately 2-fold increase in depressive morbidity (as new episode rates or proportion of time ill; see Table 7). On the other hand, more than two thirds of patients suffered recurrences of affective illness after stopping lithium, whereas only 13% of the same persons became suicidal during that time. These disparities may suggest some separation of mood-stabilizing and antisuicidal actions of lithium but, at least, indicate that determinants of suicide include more than the current affective and treatment status.

It is important to emphasize that there was a prolonged latency of more than 8 years between the onset of bipolar illness and initiation of regular maintenance treatment. Nearly three quarters of all life-threatening suicidal acts recorded in more than 40 years at risk in a large population of Sardinian bipolar I and II disorder patients occurred during this delay. Many of these cases involved young persons, and delays in women with bipolar II disorders were particularly prolonged, probably owing in part to misdiagnosis as cases of nonbipolar depression. Multiyear delays from illness onset to treatment have also been reported recently for patients with major depressive disorders.[58]

The long latency to protective mood-stabilizing treatment underscores the need for earlier recognition of major affective disorders and their appropriate long-term treatment. Timely and sustained interventions may limit mortal risks associated with medical and substance abuse disorders as well as suicide in persons with mood disorders. Further studies are required to test for both depression- and suicide-limiting actions of all proposed mood-stabilizing agents for obvious clinical reasons and to help resolve the question of whether antisuicide effects are somewhat specific to lithium or a general property of all effective therapies for major affective illness. Finally, the close association of suicidality with depression and dysphoria in bipolar disorders emphasizes the need for experimental studies to define safe and effective treatments for bipolar depression and mixed-dysphoric states that can improve on the substantial but imperfect depression-preventing effects found with lithium.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), paroxetine (Paxil), valproic acid (Depakene and others).

REFERENCES

1. Taube CA, Barrett SA, eds. Mental Health: United States. Washington, DC: US Government Printing Office; 1985. NIMH publication 1378
2. Roy A. Suicide. In: Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry, vol 2, 5th ed. Baltimore, Md: Williams & Wilkins; 1989: 1414–1427
3. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
4. Faedda GL, Baldessarini RJ, Suppes T, et al. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. Harv Rev Psychiatry 1995;3:171–195
5. Baldessarini RJ, Tondo L, Suppes T, et al. Pharmacological treatment of bipolar disorder throughout the life-cycle. In: Shulman KI, Tohen M, Kutcher S, eds. Bipolar Disorder Through the Life-Cycle. New York, NY: John Wiley & Sons; 1996:299–338
6. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a meta-analysis. Br J Psychiatry 1997;170:205–228
7. Hirschfeld RMA, Russell JM. Assessment and treatment of suicidal patients. N Engl J Med 1997;337:910–915
8. Stoff DM, Mann JJ, eds. The Neurobiology of Suicide. Ann N Y Acad Sci 1997;836:1–365
9. Tondo L, Baldessarini RJ, Floris G, et al. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. J Clin Psychiatry 1998;59: 405–414
10. Jacobs D, ed. Harvard Medical School Guide to Assessment and Intervention in Suicide. New York, NY: Simon & Shuster; 1998. In press
11. Kessler RC, McGonigle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the US: results from the national comorbidity study. Arch Gen Psychiatry 1994;51:8–19
12. Tondo L, Baldessarini RJ, Hennen J, et al. Lithium maintenance treatment: depression and mania in bipolar I and II disorders. Am J Psychiatry 1998; 155:638–645
13. Weeke A. Causes of death in manic-depressives. In: Schou M, Strömgren E, eds. Prevention and Treatment of Affective Disorders. New York, NY: Academic Press; 1979:289–299
14. Angst J, Stassen HH, Gross G, et al. Suicide in affective and schizoaffective disorders. In: Marneros A, Tsuang MT, eds. Affective and Schizoaffective Disorders. Berlin, Germany: Springer-Verlag; 1990:168–185
15. Nilsson A. Mortality in recurrent mood disorders during periods on and off lithium: a complete population study in 362 patients. Pharmacopsychiatry 1995;28:8–13
16. Sharma R, Markar HR. Mortality in affective disorder. J Affect Disord 1994;31:91–96
17. Wyatt RJ, Henter I. An economic evaluation of manic-depressive illness. Soc Psychiatry Psychiatr Epidemiol 1995;30:213–219
18. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: antimanic and antidepressant agents. In: Hardman JG, Limbird LE, Molinoff PB, et al, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill 1996:431–459
19. Avery D, Winokur G. The efficacy of electroconvulsive therapy and antidepressants in depression. Biol Psychiatry 1977;12:507–523
20. Keller MB, Lavori PW, Klerman GL, et al. Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. Arch Gen Psychiatry 1986;43:458–466
21. McCombs JS, Nichol MB, Stimmel GL, et al. Cost of antidepressant drug therapy failure: a study of antidepressant use patterns in a Medicaid population. J Clin Psychiatry 1990;51(6, suppl):60–69
22. Isacsson G, Boëthius G, Bergman U. Low level of antidepressant prescription for people who later commit suicide: 15 years of experience from a population-based drug database in Sweden. Acta Psychiatr Scand 1992;85: 444–448
23. Isacsson G, Bergman U, Rich CL. Epidemiological data suggest antidepressants reduce suicide risk among depressives. J Affect Disord 1996;41: 1–8
24. Isacsson G, Holmgren P, Druid H, et al. The utilization of antidepressants—a key issue in the prevention of suicide: an analysis of 5281 suicides in Sweden during the period 1992–1994. Acta Psychiatr Scand 1997;96: 94–100
25. Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. Drug Saf 1993;3:186–212
26. Zornberg GL, Pope HG Jr. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993;13:397–408
27. Gunell D, Frankel S. Prevention of suicide: aspirations and evidence. BMJ 1994;308:1227–1233
28. Freemantle N, House A, Song F, et al. Prescribing selective serotonin reuptake inhibitors as strategy for prevention of suicide. BMJ 1994;309:

249–253
29. Öhberg A, Lonqvist J, Sarna S, et al. Trends and availability of suicide methods in Finland: proposals for restrictive measures. Br J Psychiatry 1995;166:35–43
30. Montgomery SA, Pinder RM. Do some antidepressants promote suicide? Psychopharmacology 1987;92:265–266
31. Suppes T, Baldessarini RJ, Suppes T, et al. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991;48:1082–1088
32. Faedda GL, Tondo L, Baldessarini RJ, et al. Outcome after rapid vs. gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry 1993;50:448–455
33. Baldessarini RJ, Suppes T, Tondo L. Lithium withdrawal in bipolar disorder: implications for clinical practice and experimental therapeutics research. Am J Therapeutics 1996;3:492–496
34. Baldessarini RJ, Tondo L, Faedda GL, et al. Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders. J Clin Psychiatry 1996;57:441–448
35. Baldessarini RJ, Tondo L, Floris G, et al. Reduced morbidity after gradually discontinuing lithium in bipolar I and II disorders: a replication study. Am J Psychiatry 1997;154:548–550
36. Baldessarini RJ, Tondo L. Effects of discontinuing lithium treatment in bipolar manic-depressive disorders. Clin Drug Invest 1998;15:337–351
37. Viguera AC, Baldessarini RJ, Friedberg J. Risks of interrupting continuation or maintenance treatment with antidepressants in major depressive disorders. Harv Rev Psychiatry 1998;5:293–306
38. Viguera AC, Baldessarini RJ, Hegarty JM, et al. Risk of discontinuing maintenance medication in schizophrenia. Arch Gen Psychiatry 1997;54: 49–55
39. Tondo L, Jamison KR, Baldessarini RJ. Effect of lithium on suicide risk in bipolar disorder patients. Ann N Y Acad Sci 1997;836:339–351
40. Baldessarini RJ, Tondo L. Antisuicidal effect of lithium treatment in major mood disorders. In: Jacobs D, ed. Harvard Medical School Guide to Suicide Assessment and Intervention. San Francisco, Calif: Jossey-Bass; 1998:355–371
41. Crundwell JK. Lithium and its potential benefit in reducing increased mortality rates due to suicide. Lithium 1994;5:193–204
42. Coppen A, Standish-Barry J, Bailey J, et al. Does lithium reduce the mortality of recurrent mood disorders? J Affect Disord 1991;23:1–7
43. Ahrens B, Müller-Oerlinghausen B, Schou M, et al. Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. J Affect Disord 1995;33:67–75
44. Angst J, Sellaro R, Angst F. Long-term outcome and mortality of treated vs untreated bipolar and depressed patients: a preliminary report. Int J Psychiatr Clin Pract. In press
45. Wickham EA, Reed FV. Lithium for the control of aggressive and self-mutilating behavior. Int Clin Psychopharmacol 1977;2:181–190
46. Cappiello A, Sernyak MJ, Malison RT, et al. Effects of acute tryptophan depletion in lithium-remitted manic patients: a pilot study. Biol Psychiatry 1997;42:1076–1078
47. Moncrieff J. Lithium revisited: a re-examination of the placebo-controlled trials of lithium prophylaxis in manic-depressive disorder. Br J Psychiatry 1995;167:569–573
48. Baldessarini RJ, Tondo L, Viguera LC. Forty years of lithium treatment: commentary. Arch Gen Psychiatry 1998;55:92–93
49. Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, et al. Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Pharmacopsychiatry 1996;29:103–107
50. Greil W, Ludwig-Mayerhofer W, Erazo N, et al. Lithium vs. carbamazepine in the maintenance treatment of bipolar disorders—a randomized study. J Affect Disord 1997;43:151–161
51. Yan QS, Mishra PK, Burger RL, et al. Evidence that carbamazepine and antiepilepsirine may produce a component of their anticonvulsant effects by activating serotonergic neurons in genetically epilepsy-prone rats. J Pharmacol Exp Ther 1992;261:652–659
52. Biggs CS, Pearce BR, Fowler LJ, et al. Regional effects of sodium valproate on extracellular concentrations of 5-hydroxytryptamine, dopamine, and their metabolites in the rat brain: an in vivo microdialysis study. J Neurochem 1992;59:1702–1708
53. Verkes RJ, Van der Mast RC, Hengeveld MW, et al. Reduction in suicidal behavior by paroxetine in patients with repeated suicide attempts but not major depression. Am J Psychiatry 1998;155:543–547
54. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183–190
55. Coppen A. Depression as a lethal disease: prevention strategies. J Clin Psychiatry 1994;55(4, suppl):37–45
56. Maj M, Starace F, Nolfe G, et al. Minimum plasma lithium levels required for effective prophylaxis in DSM-III bipolar disorder: a prospective study. Pharmacopsychiatry 1986;19:420–423
57. Tondo L, Baldessarini RJ, Hennen J, et al. Suicide attempts in major affective disorder patients with comorbid substance use disorders. J Clin Psychiatry 1999;60(suppl 2):63–69
58. Kessler RC, Olfson M, Berglund PA. Patterns and predictors of treatment contact after first onset of psychiatric disorders. Am J Psychiatry 1998; 159:62–69