Effects of the Rate of Discontinuing Lithium Maintenance Treatment in Bipolar Disorders

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Background: Gradual discontinuation of lithium may reduce high risk of early morbidity in bipolar disorder patients discontinuing successful long-term maintenance on lithium, but previous small samples have limited analyses of subgroups.

Method: DSM-IV bipolar disorder patients (N = 161) were pooled from similar samples maintained on lithium for 4.2 ± 3.1 years. Effects of discontinuing treatment abruptly (1–14 days) or gradually (15–30 days) were compared by survival analysis in clinically closely similar groups.

Results: After gradual versus rapid discontinuation, the overall median time to recurrence ± SE differed by 5.0-fold (20.0 ± 5.8 vs. 4.0 ± 0.7 months; $p < .0001$). After rapid discontinuation, the median time in remission was 2.3 times shorter than the mean cycling interval before lithium (6.3 vs. 14.6 months; $p < .0001$). The proportion of subjects falling ill/month (recurrence rate) was much higher in the first year after rapid discontinuation (6.5% vs. 2.3%), but similar thereafter (0.4% vs. 0.6%); patients remained stable for 3 years when off lithium treatment 20 times more frequently after gradual than rapid discontinuation (37% vs. 1.8%; $p < .0001$). Ratios of median survival times after gradual/rapid lithium discontinuation were similar for a first recurrence of mania and depression (4.4- vs. 3.4-fold), insignificantly higher (34%) with rapid or continuous cycling before lithium, and greater in Type II than Type I disorder (9.8- vs. 4.0-fold). The polarity of first off-lithium and first lifetime episodes matched in 70% of cases.

Conclusion: These pooled results strengthen the concept of a pharmacodynamic stress factor in early relapse after stopping lithium maintenance and support the conclusion that early recurrence risk can be minimized by discontinuing maintenance treatment gradually in both Type I and II bipolar disorders.

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After lithium maintenance treatment of bipolar disorders is discontinued, affective morbidity and suicidal risk are reported to increase markedly for at least several months.[1–9] The existence of an early period of high recurrence risk and, specifically, its dependence on the speed of discontinuing lithium maintenance treatment in manic-depressive disorders have been questioned.[10] However, we found the median latency to a recurrence of mania or depression in 64 bipolar disorder patients to be 4.7 times greater after gradual (2–4 weeks) than after rapid (< 2 weeks) removal of lithium.[11] These initial results were replicated recently with an independent sample of 78 new cases, finding a 5.6-fold longer median time to a first recurrence, with a sustained 6.3-fold greater chance of remaining stable for 2 years after stopping lithium gradually (Baldessarini RJ, Tondo L, Floris G, et al. Manuscript submitted). Due to the clinical and theoretical importance of a possible relationship of recurrence risk to the rate of discontinuing lithium, we now provide a comprehensive analysis of the effects of rapid versus gradual discontinuation of lithium on subsequent affective morbidity, based on pooling previous and new data and considering diagnostic subtypes, courses of illness, and both mania and bipolar depression. Hypotheses tested were that (1) gradual removal of lithium reduces subsequent morbid risk of both mania and bipolar depression for at least several months after discontinuation of lithium, (2) bipolar I and II patients experience similar risks of rapid removal of lithium, (3) greater morbidity before lithium indicated by rapid or continuous cycling predicts greater morbid risks after discontinuing lithium, (4) the time to a recurrence of illness after stopping lithium abruptly is

shorter than cycling intervals before lithium treatment, and (5) the polarity of the first recurrence after stopping lithium is predicted by that of the first lifetime episode.

METHOD

Consecutive adults (104 women, 57 men) were evaluated by research psychiatrists (L.T. and G.F.) at the Lucio Bini Center for mood disorders affiliated with the University of Cagliari in Sardinia, Italy. Data include 141 previously reported cases[11,*] plus 20 new observations. The total of 161 subjects with Type I (N = 96) or II (N = 65) bipolar disorders stopped clinically based lithium maintenance treatment that had been sustained without interruption for at least 1 year. Diagnoses were based on semistructured examination protocols and followed DSM-IV criteria. Diagnostic subtyping before starting lithium required at least one episode of mania or hypomania, either spontaneously or during treatment for depression; rediagnosis from Type II to I due to new emergence of mania during or after lithium treatment was not necessary in any case. Illness onset was defined as a time of first treatment or determined by consensus from historical information from the subject and family members. Each course of illness was characterized prior to analysis (as reported previously[12]) and included rapid cycling (≥ 4 episodes of mania or depression within the year before lithium treatment), continuous cycling (lacking a month of euthymia between episodes of opposite polarity from illness onset to the start of lithium maintenance), and an irregular course (inconsistent relations among periods of mania, depression, and euthymia) versus regular, slower cycling (discrete episodes of mania followed by depression or vice versa, at fewer than four episodes/year). Excluded were patients exposed to antidepressant or antipsychotic drugs other than for brief periods (≤ 8 weeks), receiving anticonvulsants, or abusing drugs or alcohol, as well as those who responded poorly to lithium (< 25% reduction of time ill during lithium maintenance compared with their course before lithium) and subjects (9.1% of those initially screened) who were acutely ill or in emerging hypomanic or depressive episodes when stopping lithium.

While assessments were clinical, all evaluations were done by research psychiatrists during follow-up visits (averaging once monthly) and recorded on forms and lifecharts designed for use in major mood disorders.[9,11,*] All instances of treatment discontinuation were clinically determined and not based on a research protocol. Reasons for stopping lithium included elective, or patient-decided, discontinuation due to prolonged well-being and a disinclination to tolerate side effects, or by medical recommendation due to clinically significant adverse effects or pregnancy. Confidentiality was assured, and patients provided informed consent for such anonymous use of their records. This retrospective analysis of clinically acquired data was reviewed and approved by the Institutional Review Board of McLean Hospital and conforms to the ethical requirements of the University of Cagliari Medical Center.

Time after the last day of lithium use to a first DSM-IV-defined episode of depression or mania was determined as the primary dependent variable in this retrospective clinical study. Subjects were divided into those undergoing rapid (< 2 weeks) versus gradual (2–4 weeks) discontinuation of lithium for comparability with our previous findings.[11,*] These two subgroups, as well as the three subsamples (from our two previous reports[11,*] and new observations), all were first compared by contingency tables (χ^2) or ANOVA (F) for their matching on salient clinical variables (listed in the Results section) before entry into a pooled dataset. Kaplan-Meier survival analysis was used to compute median latency (time to 50% recurrence risk ± SE), with actuarial survival analysis used to compute the percentage surviving to 1 to 3 years of follow-up; survival functions between subgroups were compared by Mantel-Cox log-rank tests (χ^2), as reported previously.[11,*] Relapse rates (percentage of subjects falling ill/month ± SE) were estimated from survival functions for the first 12 months and for later times (13–60 months) using regression of survival versus time and compared with 99% confidence intervals (CI). Other data are mean ± SD unless stated otherwise. Nonsignificance (N.S.) is at $p \geq .10$ in two-tailed tests at defined degrees of freedom (df); trends involve $p \geq .05$ but $< .10$. Computations were carried out with the Statview 4 and Survival Tools programs (Abacus Concepts Inc., Berkeley, Calif.).

RESULTS

Descriptive and clinical characteristics of the subject pool are summarized in Table 1. Note that the bipolar disorder patients studied were relatively well functioning, cooperative, and lithium-responsive. Their mean ± SD age was 28.4 ± 12.3 years at illness onset and 36.1 ± 14.9 at the start of continuous lithium maintenance treatment, which lasted a mean of 4.18 ± 3.06 years at a moderate mean serum lithium concentration of 0.611 ± 0.123 mEq/L (range, 0.5–1.2). Lithium maintenance reduced morbidity by an average of 80% relative to pretreatment levels, as measured by episodes/year (paired $t = 8.3$, $df = 160$, $p < .0001$) and the proportion of time ill (paired $t = 13.7$, $df = 160$, $p < .0001$ [Table 1]). The mean overall time of observation was 16.5 years.

Subjects undergoing rapid (N = 85), gradual (N = 59), or uncertain (N = 17) periods of discontinuing lithium did not differ in the following: gender ratio, educational level, employment, marital status, history of mood disorder in a

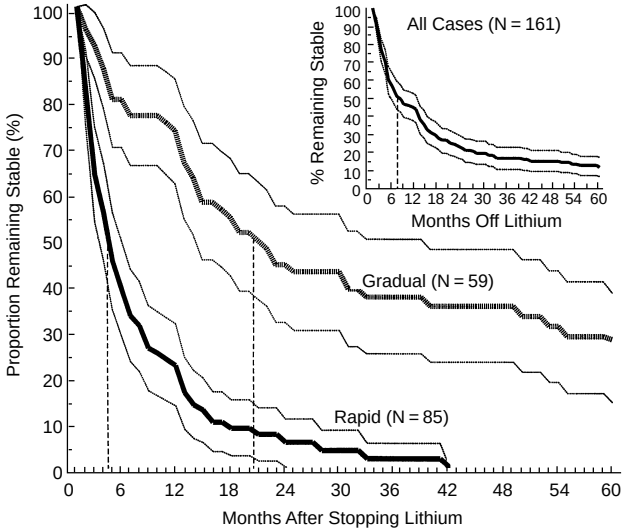
*Baldessarini RJ, Tondo L, Floris G, et al. Manuscript submitted.

Table 1. Characteristics of Subjects

Characteristic	Measure
Total number	161
Diagnosis: Bipolar I/II	96/65
Descriptive factors (%)	
Women	64.6
Educated > 12 years	40.4
Employed[a]	81.4
Married	52.2
Family history[b]	60.9
First episode (%)	
Depression	63.4
Mania or hypomania	36.6
Course (%)	
Continuous or rapid cycling	38.5
Mania before depression	25.5
Depression before mania	13.0
Irregular	23.0
Age (y), mean ± SD	
Onset	28.4 ± 12.3
Starting lithium	36.1 ± 14.9
Stopping lithium	40.3 ± 15.5
At last follow-up	44.9 ± 15.7
Duration (y), mean ± SD	
Onset to lithium start	6.39 ± 6.91
On lithium	4.18 ± 3.06
Follow-up off lithium	5.92 ± 4.38
Total time observed	16.5 ± 4.78
Episodes/y	
Before lithium, mean ± SD	2.29 ± 2.73
On lithium, mean ± SD	0.480 ± 0.728
Percent change	79.0
Percentage of time ill	
Before lithium, mean ± SD	53.63 ± 37.95
On lithium, mean ± SD	10.32 ± 13.91
Percent change	80.8
Serum lithium (mEq/L)	0.611 ± 0.123

[a]Employment includes students and homemakers and is for periods on lithium when not acutely ill.
[b]History of major affective illness or suicide in at least one first-degree relative.

Figure 1. Survival Analysis Showing the Proportion of Bipolar I and II Disorder Patients Remaining Clinically Stable Over Time in Months After Stopping Lithium Either Rapidly (< 2 wk) or Gradually (2–4 wk)*



*Light thin lines indicate the 95% confidence intervals; dashed vertical lines indicate the time to 50% recurrence risk (see Table 2). Inset indicates the time to 50% recurrence for all subjects (N = 161).

first-degree relative, bipolar subtype (I or II) (all $\chi^2 \leq 2.1$, df = 2, N.S.), or course of illness (regular episodes of mania or depression, irregular, or continuous or rapid cycling; $\chi^2 = 1.8$, df = 3, N.S.). The rapid and gradual discontinuation subgroups also did not differ in onset age, time from illness onset to start of lithium maintenance, age when lithium was started or stopped, months on lithium treatment, or either their mean (based on within-subject mean concentrations typically determined at 3-month intervals) or final serum lithium concentrations (all $F \leq 1.1$, df = 2,158; N.S.). Discontinuation subgroups were also closely matched by the number of episodes/year, proportion of time ill with mania or depression, and hospitalizations/year before and during lithium maintenance treatment (all $F \leq 2.1$, df = 2,158; N.S.; not shown). Finally, the distribution of reasons for stopping treatment was similar among those who discontinued treatment rapidly or gradually ($\chi^2 = 5.28$, df = 2, N.S.); 77.6% of patients elected to discontinue lithium because of prolonged well-being, and 22.4% discontinued because of side effects or pregnancy. These comparisons indicate the clinical comparability of subjects withdrawn from lithium rapidly versus gradually. In addition, subsamples emerging from two smaller studies[11,*] and 20 new cases did not differ among themselves on any of these variables in similar comparisons (not shown), thus supporting pooling of the three datasets.

Survival analysis indicated that the time to 50% risk of a first recurrence of mania or depression (median latency to a recurrence, or median time remaining in remission ± SE) was 7.00 ± 2.38 months overall for the total pool of 161 subjects (Figure 1, Table 2). This median latency was 5.00-fold shorter after rapid (4.00 ± 0.69 months) than gradual (20.0 ± 5.76 months) discontinuation of lithium ($\chi^2 = 49.7$, df = 1, $p < .0001$ [Figure 1, Table 2]). The small subgroup (N = 17) with uncertain duration of lithium discontinuation (presumably including gradual and rapid discontinuations) had an intermediate median recurrence interval (7.00 ± 7.68 months). In addition, the times to 50% risk of mania versus bipolar depression were similar at each lithium discontinuation rate (rapid: 2.50 ± 0.66 vs. 5.00 ± 1.03 months; gradual: 11.0 ± 1.49 vs. 17.0 ± 3.27 months, respectively), with similar corresponding reductions of risk for mania (4.40-fold) and depression (3.40-fold) after slower removal of lithium (Table 2).

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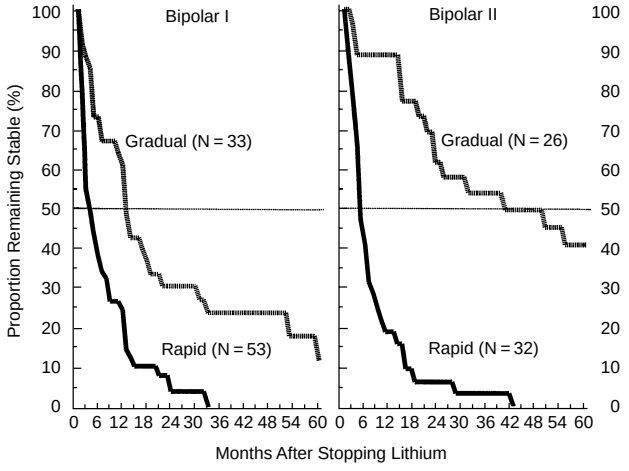
Table 2. Rate of Lithium Discontinuation and Median Latency (mo) to a First Recurrent Episode in Bipolar Disorders*

	All Discontinued[a]			Rapid			Gradual			
Group	Median	SE	N	Median	SE	N	Median	SE	N	Gradual/Rapid[b]
All cases	7.00	2.38	161	4.00	0.69	85	20.0	5.76	59	5.00
Bipolar type[c]										
I	6.00	1.63	96	3.00	1.21	53	12.0	0.96	33	4.00
II	13.0	4.03	65[d]	4.00	0.85	32	39.0	21.6	26[d]	9.75
Cycling type[e]										
Rapid/continuous/erratic	6.00	0.99	99	3.50	0.70	50	22.0	9.36	39	6.29
Regular polarity sequences	11.0	0.96	62	4.00	0.74	35	14.0	2.98	20	4.70
Mania	4.00	0.58	73	2.50	0.66	44	11.0	1.49	20	4.40
Depression	7.00	2.06	68	5.00	1.03	38	17.0	3.27	24	3.40

*Data are computed median latencies to a recurrence or time to 50% recurrence by Kaplan-Meier survival analysis.
[a]Median survival time in 17 additional cases of uncertain discontinuation time (7.00 ± 7.68 months) was intermediate between that with rapid vs. gradual discontinuation.
[b]From survival analyses for gradual vs. rapid: all Mantel-Cox $\chi^2 \geq 12$, df = 1, all $p \leq .0007$.
[c]In bipolar I cases, 62/86 recurrences (72.1%) off lithium were manic, and their median latencies differed significantly by the rate of lithium discontinuation ($\chi^2 = 6.82$, p = .009); in bipolar II cases, 44/55 recurrences (80.0%) were depressive (8 were hypomanic), and their median latencies also differed significantly by discontinuation rate ($\chi^2 = 11.6$, p = .0007).
[d]From survival analyses for bipolar Type I vs. II: both Mantel-Cox $\chi^2 = 6.6–6.7$, both $p < .01$; no other pair within each discontinuation rate differs significantly (i.e., all other $\chi^2 \leq 3.4$, N.S.).
[e]Cycling types are defined by prelithium course (regular = mania then depression or depression and then mania, with a euthymic interval of at least 1 month in regular cycles at < 4/year vs. those with rapid, continuous, or an erratic and inconsistent pattern are pooled since preliminary survival testing revealed no significant differences in recurrence intervals between members of each grouping).

Figure 2. Survival Analyses for Bipolar I (Total N = 86) and Bipolar II (Total N = 58) Subjects in Months After Stopping Lithium Rapidly (lower solid lines) or Gradually (upper shaded lines)*



*Horizontal dotted lines indicate 50% recurrence.

Median survival times after rapid discontinuation of lithium were similar in both major subtypes of bipolar disorder, suggesting similar risks (Type I vs. II: 3.00 ± 1.21 vs. 4.00 ± 0.85 months; Table 2, Figure 2). However, the relative benefit of gradual discontinuation of lithium in bipolar II subjects was significantly greater, with a 3.25-fold longer median survival time after gradual discontinuation of lithium (Type I vs. II: 12.0 ± 0.96 vs. 39.0 ± 21.6 months). Bipolar II patients also showed a 2.17-fold more prolonged overall median survival time after discontinuing lithium at all rates (Type I vs. II: 6.00 ± 1.63 vs. 13.0 ± 4.03 months; both $\chi^2 \geq 6.6$, df = 1, $p < .01$ [Table 2]). Moreover, as indicated by the ratio of median latencies to a first recurrence after gradual versus rapid removal of lithium, the apparent protection afforded by slow discontinuation was 2.44-fold greater in the Type II cases (Type I vs. II: 4.00-fold vs. 9.75-fold [Table 2]).

After stopping lithium gradually versus rapidly, the actuarially computed proportion of patients remaining stable for 12 months differed by 3.30-fold (72.9%/22.1%); by 2 years of follow-up, survival differed by 8.28-fold (43.9%/5.3%), and by 3 years, by 20.4-fold (36.8%/1.8%). These differences are highly significant on the basis of the overall $\chi^2 = 49.7$, df = 1, $p < .0001$ (see Figure 1). Indeed, all patients stopping lithium rapidly became ill again within 42 months of follow-up, while nearly a third remained stable off lithium treatment for up to 5 years after discontinuing lithium gradually.

Most of the difference in the consequences of rapid versus gradual discontinuation of lithium appeared to be accounted for by sharp differences in early relapse risk. The mean ± SE relapse rate was 6.49 ± 0.84%/month (99% CI = 3.82 to 9.16) versus 2.28 ± 0.31%/month (99% CI = 1.30 to 3.26) in the first year ($p < .01$) after rapid versus gradual discontinuation, respectively, but was much lower and more similar (with a somewhat *lower* late relapse rate after rapid discontinuation) at times after the first 12 months of follow-up (rapid vs. gradual: 0.426 ± 0.029%/month [99% CI = 0.345 to 0.508] versus 0.631 ± 0.037%/month [99% CI = 0.532 to 0.730]). The marked disparity in recurrence rate in the first 12 months (rapid vs. gradual: 6.5% vs. 2.3%/month) and nearly parallel risk-over-time after the first year after stopping lithium (mean = 0.53%/month) are illustrated in Figure 1.

The polarity of the first recurrent episode when the subject was off lithium treatment was highly concordant with that of the first lifetime episode and agreed in 70.2% of the

141 subjects who had a recurrence ($\chi^2 = 25.7$, df = 1, $p < .0001$), with a higher association for depression (57/68 = 83.8%) than for mania (42/73 = 57.5%) ($\chi^2 = 25.7$, df = 1, $p < .0001$). Even among subjects with Type I disorder expressing both mania and depression, there was 65.1% concordance (56/86; 41/62 manic and 15/24 depressed at both times). However, several factors that may be associated with greater morbidity before or during lithium maintenance treatment were not associated with the time to a recurrence or the number or duration of episodes of mania or depression after stopping lithium, overall, or within the first year off lithium treatment. These factors included family history, onset age, gender, marital status, polarity of first lifetime episode, mean cycling rate (episodes/year), course of illness (rapid cycling, continuous, or irregular vs. regular and discrete cycles at < 4 episodes/year), percentage of time ill before or during lithium maintenance, or the mean or final serum lithium concentration (ANOVA, regression, and contingency analyses not shown). However, there was a trend toward an association of a longer duration of lithium treatment and shorter time to a first recurrence when subjects were off lithium therapy ($r = –0.152$, df = 139, $p = .07$). Duration of treatment was not associated with possible indications of illness intensity before starting lithium (onset age, episodes/year, or percentage of time ill; all N.S. by linear regression, not shown).

Finally, we compared cycling intervals before lithium treatment with the latency to a first recurrence off lithium. Among subjects stopping lithium rapidly, the mean and median time to a first recurrence (6.27 ± 7.32 months; computed median = 4.00 months) was 2.33- to 3.65-times shorter than the mean cycling interval before maintenance treatment (onset-to-onset, 14.6 ± 16.5 months; paired $t = 4.16$, df = 81, $p < .0001$), and was significantly shorter than the mean euthymic interval between episodes of illness (10.4 ± 16.2 months; paired $t = 2.08$, df = 81, $p < .05$). In contrast, subjects stopping lithium gradually not only did not become ill more rapidly than predicted by their spontaneous cycling intervals before lithium, but tended to relapse somewhat more slowly off lithium treatment (intervals after vs. before lithium: 20.5 ± 24.4 vs. 12.1 ± 12.0 months; paired $t = 1.87$, df = 43, $p = .068$). However, the mean prelithium cycling times did not differ between those stopping lithium rapidly versus gradually (respectively, 14.6 ± 16.5 vs. 12.1 ± 12.0 months; unpaired $t = 1.05$, df = 142, N.S.) and had a mean of 13.8 ± 15.3 months overall.

DISCUSSION

The present findings with a pooled analysis of previously studied subjects[11,*] as well as new data strengthen the impression that early morbid risks are much lower after gradual than rapid discontinuation of lithium and permitted further assessments of subgroups. It is important to emphasize that the groups of subjects pooled and those stopping lithium rapidly versus gradually were well matched by demographic, past history, lithium treatment, and other clinical factors before being entered into the pooled analysis. Moreover, subjects with emerging illness that might have contributed to the decision to stop treatment or to a biased excess of early morbidity were specifically excluded. The close similarity of the rapid versus gradual lithium discontinuation groups indicates that systematic clinical biases between those stopping lithium at different rates are unlikely to account for the main finding of an overall fivefold reduction of risk by gradual removal of lithium (Figure 1, Table 2). The finding was further supported by the intermediate risks encountered among a small subgroup in which the time of stopping lithium was uncertain, but presumably included a mixture of rapid and gradual rates.

It is also important to emphasize that our studies of lithium discontinuation involve clinically encountered events, typically due to elective discontinuation in patients doing well for prolonged periods (78% of cases) and discontinuation in others due to medically adverse effects or pregnancy. As such, these studies are less than ideal methodologically since discontinuation was not determined prospectively by strict randomization with blinded assessments, although those stopping lithium rapidly versus gradually were closely matched on pertinent clinical variables. However, on the basis of the findings reported, it would be difficult to design ethical prospective studies, which may provoke potentially life-threatening clinical risks.[4–9] If suitable research strategies can be developed, some additional questions need to be resolved. For example, it remains unknown whether discontinuing lithium even more slowly than over 2–4 weeks or use of alternative mood-stabilizing agents, such as anticonvulsants, can further limit early recurrence risk after stopping lithium.[5–7]

The present results may or may not generalize to populations in other geographic areas or clinical settings. Most were relatively well functioning and quite responsive to moderate doses of lithium, suggesting incomparability to more severely ill and chronically disabled bipolar disorder patients or those requiring multiple maintenance medications. Bipolar disorder patients in two recent follow-up studies from university-based mood disorder clinics in the United States suffered recurrences at rates of 40% in 3 years[13] and 73% in 5 years,[14] or a mean of 14%/year, and our recent review of 20 available studies of long-term recurrence risk during lithium maintenance found an overall risk of 14%/year.[7] That rate is identical to the one observed in the present subjects, suggesting their comparability to broader international experience.

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An important new contribution of the present findings is the indication that the benefits of slowing removal of lithium may be relatively greater in Type II bipolar disorder patients, though clearly present in both Types I and II. None of the patients diagnosed as bipolar Type II, based on their course of illness prior to starting lithium, experienced a manic episode over the entire 16.5 years at risk, further supporting the validity of this diagnostic construct.[11,15] Differences between bipolar I and II subjects were apparent in survival functions after rapid versus gradual discontinuation of lithium (Figure 2) and in the 2.4-fold greater ratio indicating lengthening median times to recurrence after stopping lithium gradually/rapidly in Type II versus I patients (9.75- vs. 4.00-fold, respectively [Table 2]). Much of this difference is accounted for in the striking delay of recurrences of depressive morbidity in the bipolar II subjects stopping lithium gradually, in whom the computed median time to a first recurrence while off lithium treatment was 3.25 ± 1.80 years (Table 2). In contrast, while gradual discontinuation of lithium had a highly significant early beneficial effect on bipolar I subjects, delaying recurrences by fourfold (Table 2), nearly 80% of bipolar I subjects who discontinued lithium *gradually* suffered a recurrence within 3 years, while more than half of the bipolar II subjects discontinuing slowly remained stable (Figure 2).

Overall, the risk of depression tended to be insignificantly lower than mania among first recurrences after rapid discontinuation of lithium. Also, the lowering of risk after gradual discontinuation tended to be slightly more for depression than mania, although this difference was not significant (Table 2). Therefore, differences in risk of mania versus bipolar depression after stopping lithium are not likely to account for differences between bipolar I and II subjects. In addition, although more rapidly cycling or persistent affective illness before starting lithium might be expected to predict earlier or greater morbidity after stopping lithium, bipolar I patients were not more frequently or persistently ill than Type II cases before lithium treatment. Instead, Type II patients tended to have a somewhat greater number of episodes/year (2.80 ± 3.26 vs. 1.94 ± 2.27; F = 3.88, df = 1,159; p = .051) but a similar percentage of time ill as Type I subjects before lithium treatment (56.2 ± 33.2% vs. 51.8 ± 40.9%; F = 0.52, df = 1,159; N.S.); moreover, rapid cycling (≥ 4 episodes/year) was more common in Type II patients (55.4% vs. 27.1%; $\chi^2 = 32.9$, $p < .0001$). Nevertheless, it remains possible that bipolar I disorder is more virulent, with a greater risk of early recurrence after even gradual discontinuation of lithium. The possibility of greater severity in Type I disorders is suggested by several observations: Type I patients were ill longer due to an earlier onset age (25.5 ± 10.1 vs. 32.6 ± 14.0 years; F = 14.0, df = 1,159; $p < .0003$), and they were more likely to be unemployed (26.0% vs. 7.70%; $\chi^2 = 8.6$, p = .003) and single (56.3% vs. 35.4%; $\chi^2 = 6.8$, p = .009) compared with bipolar II patients.

Many bipolar disorder subjects remained stable for long periods of follow-up after gradual discontinuation of several years of effective lithium maintenance treatment (Figure 1). By 3 years of follow-up off lithium therapy, 36.5% of those stopping lithium gradually remained stable, compared with only 1.7% of those who discontinued lithium rapidly (Fisher's exact test, $p < .0001$ [Figure 1]). This observation suggests that slow removal of lithium not only can delay, but may actually *avoid* recurrence risk even during prolonged follow-up without lithium maintenance treatment, at least in a substantial minority of subjects.[11] Moreover, the risk of recurrences may be further limited by early intervention at the emergence of prodromal indications of an impending episode.[16]

Potentially important additional findings were a lack of correspondence of the timing of recurrences after stopping lithium with various measures of prelithium illness severity or frequency. Thus, patients with rapid (≥ 4 episodes/year) or continuously cycling illnesses or irregular courses before starting lithium maintenance treatment did not differ among themselves with respect to median recurrence times off lithium and did not suffer recurrences earlier than those with less frequent cycles or a more consistent sequence of affective episodes before lithium treatment (Table 2). Since rapid cycling before lithium may in part reflect use of antidepressants without a mood stabilizer, it may not be a reliable index of the course of untreated bipolar illness nor a valid predictor of the course of illness during or after lithium therapy. In addition, other potentially relevant clinical factors, including familial affective illness, onset age, and episode frequency or proportion of time ill before lithium treatment also failed to predict the time to a first recurrence after either rapid or gradual discontinuation of lithium, overall. This evident lack of correspondence of earlier illness intensity and recurrence risk off lithium seems to support the possibility that effects of lithium discontinuation *itself* may have been a dominant determinant of morbid risk and its timing after stopping lithium.

Most of the excess risk following removal of lithium rapidly occurred within several months, as reflected in the median (50%) risk of recurrence within 4 months after rapid removal of lithium (Figure 1; Table 2). Moreover, the monthly recurrence rate was significantly greater in the first year after stopping lithium rapidly versus gradually (6.5% vs. 2.3% of patients relapsed per month), whereas later rates were much lower and quite similar (0.4 vs. 0.6%/month, respectively), indicating nearly parallel late risk-by-time functions after the first year off lithium treatment. These observations are consistent with the proposal that early risk in the first 6 to 12 months off lithium treatment may reflect a stressful ef-

fect of drug removal itself, particularly rapid removal, and that later risk over Years 2 to 5 may largely reflect the course of untreated bipolar illness, perhaps modified by several years of effective maintenance therapy.[4–7,11,*]

The high early risk of recurrence after rapid removal of lithium extended well beyond the week or so required for lithium to be cleared from tissue.[6,17,18] Accordingly, mechanisms underlying early risk may reflect slower neurobehavioral readjustments to the complex pharmacodynamic effects of lithium. These include changes in neurotransmitter release, receptor sensitivity, and adaptive changes in receptor effectors and other postsynaptic molecular and cellular mechanisms whose physiologic, behavioral, and clinical significance remains largely unknown.[4–6,18–23] Additional suggestive evidence bearing on a pharmacodynamic contribution to the early effects of stopping lithium is the suggestive trend toward an *inverse* correlation of duration of lithium treatment and the latency to a first recurrence when off lithium therapy, though duration of treatment itself was unrelated to the past history, illness severity, or bipolar diagnostic subtype. Serum lithium concentration also was apparently not determined by past history, but the limited variance in lithium levels (coefficient of variation = 20.1% [Table 1]) precluded adequate testing of their possible predictive relationship to risk or timing of recurrences after stopping treatment.

The phenomenon of postdiscontinuation risk of relapses in recurring or chronic psychiatric illness may also occur in other disorders and with other treatments.[4,5,7] Early re-emergence of anxiety symptoms is well known after stopping benzodiazepines and other sedative-anxiolytic agents,[24–26] but may be less likely after discontinuing antidepressants in panic-agoraphobic disorders.[26,27] Seizures are likely to follow rapid interruption of long-term anticonvulsant treatment in epileptic patients,[28] although effects of discontinuing anticonvulsant maintenance therapy in bipolar disorder patients are unknown. Discontinuing maintenance treatment with antipsychotic agents in schizophrenic patients is also followed by a high risk of early relapses.[29,30] There is preliminary evidence that slowing the rate of discontinuing oral neuroleptics or stopping injected long-acting agents is associated with a lower risk (or delay) of early relapses of psychotic illness, and there is a relationship between higher *clinically determined* doses and risk of morbidity after stopping antipsychotic treatment (perhaps linked through illness severity).[29,30] Long-term benefits of maintenance treatment with antidepressants in unipolar major depression after the first few months following clinical remission of an acute episode have been suggested.[31,32] Stopping an antidepressant after 3 years of successful maintenance treatment is followed by a high risk of recurrences within several months,[33] although a potential relationship of risk to the rapidity of discontinuing antidepressant maintenance treatment remains to be demonstrated. Even a sharp reduction of antidepressant dose can lead to a high early risk of a recurrence of depression.[34] Following dose reduction or discontinuation of imipramine maintenance therapy, recurrence risks *after* the first year were similar with and without continued antidepressant treatment in small numbers of subjects.[33,34] This temporal pattern again suggests a treatment-withdrawal-related effect within the first months after removing an antidepressant. A significant impact of rapid reduction of lithium dose in bipolar disorders also has been suggested.[4,5,7,35,36]

The present findings relate to our initial hypotheses as follows. (1) Gradual removal of lithium evidently can delay and perhaps be followed by reduced morbid risk of both mania and bipolar depression after discontinuing lithium. (2) Though slow discontinuation of lithium was followed by less early morbidity in both types of bipolar disorders, Type II patients showed particularly great benefits. (3) Patients with rapid or continuous cycling or other indications of greater morbidity during the time before lithium, overall, did not have greater morbid risks in the months after stopping lithium, suggesting that the rate of lithium removal itself was a stronger predictor of postdiscontinuation morbid risk. (4) The time to relapse after stopping lithium abruptly was shorter than cycling intervals before lithium treatment, again supporting an effect of lithium removal that exceeds the risks associated with the untreated disorder. (5) The polarity of recurrences when subjects were off lithium therapy was predictable by that of the first lifetime episode, even in bipolar I patients.

In conclusion, the present findings add further support and greater detail to our earlier findings that recurrences in bipolar disorders after stopping lithium are predictable by timing and polarity, and that early recurrence risk can be markedly reduced by slow removal of lithium. This phenomenon has considerable clinical significance for the safe management of bipolar disorder patients, particularly when consideration is given to discontinuing lithium maintenance treatment electively. Furthermore, if the phenomenon of reducing early risk of relapses by slowing the rate of stopping long-term lithium therapy extends to other agents and disorders, this approach might be considered in the design of research protocols that require reducing or stopping active treatment.[5] Finally, the present findings should stimulate further investigations into the long-term adaptations to the molecular and physiologic pharmacodynamic actions of lithium and other agents, and particularly into the nature and timing of readjustments that follow their discontinuation.

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Drug name: imipramine (Tofranil and others).

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