

Reduced Morbidity After Gradual Discontinuation of Lithium Treatment for Bipolar I and II Disorders: A Replication Study

Ross J. Baldessarini, M.D., Leonardo Tondo, M.D., Gianfranco Floris, M.D.,
and Nereide Rudas, M.D.

***Objective:** The aim of this study was to verify reduction of early affective morbidity by gradual, rather than rapid, discontinuation of lithium treatment. **Method:** For 78 patients with bipolar disorders, lithium treatment was discontinued either rapidly (over 1–14 days) or gradually (over 15–30 days). The effects of the two schedules were compared by survival analysis of time to first recurrence. **Results:** Median time to recurrence was 5.6 times as long for gradual discontinuation (14.0 months) as for rapid discontinuation (2.5 months). The ratios of the median survival times for gradual and rapid discontinuation were similar in I and II subtypes and in depression and mania (4–6:1). The polarities of the episodes at onset and at first recurrence after lithium discontinuation were 83.6% concordant. **Conclusions:** These results independently confirm a reduction in morbid risk from slow discontinuation of lithium treatment for bipolar disorders.*

(Am J Psychiatry 1997; 154:551–553)

Gradual withdrawal of maintenance treatment with psychotropic medications may reduce early morbidity associated with treatment discontinuation (1–4). We found that the median time to recurrence of affective symptoms after lithium discontinuation in 64 patients with bipolar disorder was 4.7 times as great for gradual discontinuation (2–4 weeks) as for rapid discontinuation (less than 2 weeks) (4). We now report retesting this finding in a different group of 78 patients with bipolar I and II disorders in well-matched discontinuation groups.

METHOD

Our earlier methods were followed in this naturalistic replication study of clinically acquired data from a new group of patients, with single-blind analyses independent of knowledge of lithium discontinuation rates (4). Approval was obtained from the institutional review board, and the patients provided informed consent with assured

confidentiality. The patients were consecutively admitted adults (53 women, 25 men) with DSM-IV type I (N=47) or type II (N=31) bipolar disorder who had been receiving effective lithium maintenance treatment for more than 1 year with at least a 75% reduction in the time they were ill. Lithium treatment was clinically discontinued with or without medical advice over varying periods, subdivided into rapid discontinuation (1–14 days) and gradual discontinuation (15–30 days) for analysis; for 14 patients the speed of discontinuation could not be determined. Follow-up semistructured clinical assessments (averaging six per year) during and after lithium treatment were recorded on data forms and life charts by the same treating psychiatrists (4). Any patient who had been taking an antidepressant, antipsychotic, or anticonvulsant for 8 or more weeks, who was abusing drugs or alcohol, or who was experiencing an emerging affective episode when he or she stopped taking lithium was excluded. The matching of the groups with rapid and gradual discontinuation was tested with contingency tables (chi-square) or analysis of variance. Median time to 50% risk of recurrence of DSM-IV mania (five of 32 episodes were hypomania) or depression, and its variance, was computed by Kaplan-Meier survival analysis, and subgroups were compared by Mantel-Cox chi-square analysis. Nonsignificance was defined as $p > 0.05$ in two-tailed tests, at defined degrees of freedom.

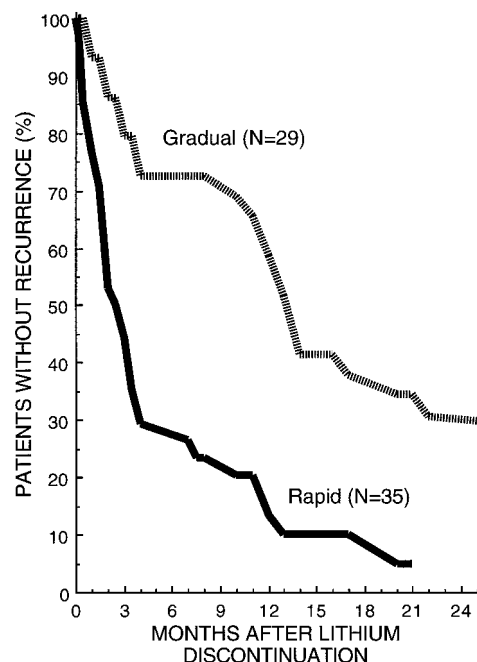
RESULTS

The subjects' mean age was 29.5 years (SD=12.7) at illness onset and 36.6 (SD=14.2) when they started lithium treatment, which lasted 4.25 years (SD=3.41) at an average serum concentration of 0.61 meq/liter (SD=0.12). The subjects discontinuing lithium treatment rapidly (N=35) and those stopping gradually (N=29) did not differ significantly in gender ratio, education, employment, marital status, family history, or I or II

Received March 28, 1996; revision received Oct. 2, 1996; accepted Nov. 14, 1996. From the International Consortium for Bipolar Disorder Research. Reprints are not available; address correspondence to Dr. Baldessarini, Mailman Research Center, McLean Hospital, 115 Mill St., Belmont, MA 02178; rjb@mc309.mclean.org (e-mail).

Supported in part by NIMH grants MH-31142 and MH-47370, a grant from the Consiglio Nazionale delle Ricerche (CNR), an Investigator Award from the National Alliance for Research on Schizophrenia and Depression, an award from the Stanley Foundation, a grant from the Bruce J. Anderson Foundation, and the McLean Private Donors Neuropharmacology Research Fund.

FIGURE 1. Proportion of Patients Without Recurrence of Affective Episodes Over 24 Months After Gradual or Rapid Discontinuation of Lithium Treatment (Survival Analysis)^a



^aGradual=15–30 days; rapid=1–14 days.

subtype ($\chi^2 \leq 3.5$, $df=1$, in all cases); nor did they differ in age at onset, time from onset to start of maintenance treatment, age when lithium started or stopped, duration of treatment, serum lithium level, frequency of follow-up, episodes or hospitalizations per year, or proportion of time ill before or during lithium maintenance ($F \leq 0.75$, $df=1$, 62, in all cases). Prolonged well-being was the reason for discontinuation given by 60 (76.9%) of the 78 patients, and side effects or pregnancy were

cited by 18 (23.1%); the reasons were similar in the groups with rapid and gradual discontinuation ($\chi^2 = 0.22$, $df=1$, n.s.).

Patients who gradually stopped taking lithium relapsed much later than did those who experienced rapid discontinuation of lithium treatment; at 2 years of follow-up, the proportions who had not experienced recurrences were 30.7% and 4.9%, respectively, a 6.3:1 ratio (figure 1). Median time to 50% risk of recurrence of mania/hypomania or depression according to survival analysis was 4.00 months overall, and this interval was 5.6 times as long for gradual discontinuation as for rapid discontinuation ($\chi^2 = 16.1$, $df=1$, $p < 0.0001$) (table 1). The subgroup of patients ($N=14$) with uncertain durations of lithium discontinuation had an intermediate computed 50% recurrence latency (5.00 months). The times to 50% risk of mania and depression were similar at each rate of discontinuation, and the reductions in risk with gradual discontinuation were similar for mania and depression (table 1). Moreover, the corresponding 50% survival times were similar in the subjects with bipolar I and bipolar II disorder at each discontinuation rate, and the length of stability in both diagnostic types was six times as long after slow discontinuation as after rapid discontinuation (table 1). Finally, the polarity of the first recurrence after lithium discontinuation was highly concordant with that of the first lifetime episode, agreeing for 83.6% of the 67 patients who had recurrences ($\chi^2 = 31.3$, $df=1$, $p < 0.0001$).

DISCUSSION

The present findings with a new group of patients replicate initial observations suggesting that rapid and gradual discontinuation of lithium are followed by clinically significant, and somewhat predictable, differences in morbidity (4). Predictability was found in the time to a first recurrence (figure 1) and in the polarity

TABLE 1. Time to 50% Risk of Recurrence of Affective Symptoms for Patients With Bipolar Disorders Whose Lithium Treatment Was Discontinued Rapidly or Gradually^a

Group	All Patients ^b			Rapid Discontinuation (Over 1–14 Days)			Gradual Discontinuation (Over 15–30 Days)			Ratio of Median Values for Gradual and Rapid Discontinuation
	N	Time to 50% Risk of Recurrence (months)		N	Time to 50% Risk of Recurrence (months)		N	Time to 50% Risk of Recurrence (months)		
		Latency	SE		Latency	SE		Latency	SE	
Total	78	4.00	0.83	35	2.50	0.99	29	14.0	2.65	5.60
Subtype										
Bipolar I	47	4.00	2.28	21	2.00	0.57	17	12.0	1.02	6.00
Bipolar II	31	6.00	2.78	14	3.50	0.70	12	20.0	6.93	5.71
Polarity ^c										
Mania	32	4.00	2.22	14	2.00	0.45	9	10.0	4.49	5.00
Depression	35	4.00	1.10	18	3.00	0.79	14	12.0	3.74	4.00

^aLatency to 50% risk of recurrence computed by Kaplan-Meier survival analysis. All rapid-versus-gradual pairs differed significantly ($\chi^2 \geq 3.8$, $df=1$, $p < 0.05$), but pairs within each discontinuation type (bipolar I versus bipolar II disorder and mania versus depression) did not ($\chi^2 < 0.2$, $df=1$, n.s.).

^bIncludes 14 patients with uncertain discontinuation times.

^cPolarity of first recurrence after discontinuation of lithium treatment.

of the recurrences, which closely accorded with the polarity of the patients' first lifetime episodes, for uncertain reasons (5). Slower discontinuation of lithium was followed by a latency to 50% risk of a recurrence that was four to six times as long as that for rapid discontinuation—overall, for both type I and II disorders, and for mania and depression (table 1). By 2 years of follow-up, almost all of the rapidly withdrawn patients had relapsed but nearly one-third of those discontinuing lithium gradually remained stable, suggesting that slow removal of lithium may *reduce*, and not only delay, recurrences (5). It is not known whether even slower discontinuation of lithium or use of an alternative mood-stabilizing agent, such as an anticonvulsant, would further reduce the risk of early recurrence after discontinuation of lithium (2, 3).

The risk of early recurrence may reflect the stress of drug removal, particularly abrupt discontinuation, and the risk of later recurrence may mainly reflect the spontaneous course of untreated bipolar illness, perhaps modified by previous long-term lithium treatment (2–5). One-half of the recurrence risk occurred within 2.5 months after rapid removal of lithium (table 1) but well beyond the week or so required for lithium to be cleared from tissue (6). Accordingly, mechanisms underlying early risk may reflect slower neurobehavioral readaptations to incompletely defined pharmacodynamic actions of lithium (6, 7).

These findings indicate that patients with bipolar disorder should be advised not to discontinue lithium treatment without psychiatric consultation; if elective discontinuation is considered, it should be done gradually under close clinical supervision.

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