Lithium Therapy and Suicide Risk

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Background: Studies from the early 90s have suggested that patients selected for and compliant with treatment at specialized lithium clinics have lower-than-expected suicide rates. The present study examines whether such findings can be replicated under less select treatment conditions. ***Method:*** All 362 patients in Göteborg, Sweden, with DSM-III-R mood or schizoaffective disorders, hospitalized at least once during an 8-year period and treated with lithium for a minimum of 1 year, were followed. The study included 3911 patient-years on lithium and, because of permanent or temporary discontinuation, 1274 patient-years off lithium. ***Results:*** The risk of suicide was significantly increased on (standard mortality ratio [SMR] = 6.1) as well as off lithium (SMR = 29.0), but the relative risk of suicide was 4.8 times higher during periods off lithium ($p < .02$; 95% confidence limits 1.1 to 12.6). Ongoing lithium treatment was associated with a 77% reduction in the risk of suicide, whereas alcohol or drug abuse was associated with a 284% increased risk. ***Conclusion:*** The findings suggest that ongoing lithium treatment is associated with a lower suicide risk. Whether this is due to lithium's mood-stabilizing properties, to lower suicide risk per se in the patients who remain in treatment, or to a specific antisuicidal effect of the lithium ion cannot be determined since patients were not randomized to discontinue treatment. This methodological shortcoming is shared with every study in the field. All results regarding the influence of lithium on suicide rates must therefore be interpreted with extreme caution.

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Whether lithium reduces the high suicide rates of mood disorders is very much a matter of controversy within the field of lithium research today. According to Goodwin and Jamison,[1] suicide rates in manic depressive illness vary from 5% to 50%. This extreme variability is most likely attributable to variations in the length of follow-up periods and in the age-distribution of the populations investigated. Guze and Robins[2] concluded in their classic compilation of studies that if we were to follow a cohort of affectively ill patients until they have all died, approximately 15% will have died from suicide. This figure, which is often quoted in the literature, has recently been challenged as being much too high,[3] and modern statistical methods applied to the same data set have indicated a figure of no more than 6%.[4] Since the vast majority of suicides take place during an acute, most often depressive or mixed episode of the illness,[5–7] it is indeed an appealing and natural assumption that a treatment like lithium, which reduces affective morbidity,[8,9] would also reduce suicide rates.

The idea that lithium might reduce suicide rates in affective disorders is not entirely new. It was briefly discussed already in the 70s,[10] but it was not until the early 90s that this important issue was brought back on the agenda. Coppen and coworkers[11] followed a group of elderly and predominately unipolar patients treated in a specialized lithium clinic. The standard mortality ratio (SMR) of this cohort was surprisingly low, 0.60, and no patient committed suicide. In an international collaboration project carried out by the International Study Group of Lithium-Treated Patients (IGSLI),[12] patients receiving lithium, mainly at specialized, research-oriented lithium clinics, were followed and found to have mortality rates no different from those of the general population. The suicide rate was 16% in the IGSLI sample, corresponding to an SMR of 5.2 for suicide,[13] i.e., significantly higher than in the general population, but the authors argue that this is still lower than one might reasonably expect in a high-risk mood disorder population. On the basis of these findings,[11–13] one may conclude that there is evidence that patients *selected for* and *compliant with* treatment at specialized lithium clinics have mortality rates that are similar to those of the general population. In addition, they seem to have lower-than-expected suicide rates. Some authors have therefore discussed the possibility that lithium may

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have specific antisuicidal properties.[13,14] It is not certain, though, that this is nothing but a lithium effect. Lower mortality and suicide rates could be due to a selection bias, to treatments other than lithium, or maybe to some unspecific benefit from the highly specialized care given at these clinics. Whether lithium would lower suicide rates under less select treatment conditions remains to be determined. The aim of the present study has therefore been to evaluate lithium treatment implemented under ordinary, everyday clinical conditions, i.e., to analyze the long-term impact of prophylactic lithium on mortality and suicide mortality of virtually all patients with mood disorder or schizoaffective disorder within a specific geographical area, the city of Göteborg, Sweden, with a population of 450,000 inhabitants. Some of the findings from this study will serve as a starting point for further discussion as to what conclusions can actually be made regarding the influence of the lithium ion on suicide rates.

METHOD

The screening procedure, inclusion criteria, and data collection have been presented in detail elsewhere.[15] In summary, all 120,000 admissions to the psychiatric hospital in Göteborg, Sweden, during 1970–1977 were screened for patients fulfilling the following inclusion criteria:

1. At least 1 admission to the study hospital during 1970–1977.
2. A diagnosis of mood disorder or schizoaffective disorder according to DSM-III-R.[16]
3. At least 1 year of prophylactic lithium, initiated and monitored at the study hospital.
4. Prophylaxis monitored with serum lithium levels (usually every third month) according to clinical praxis at the study hospital.

Each patient was followed through public record and medical files from the day all inclusion criteria were met until July 1, 1991, or date of death, whichever was first. No patient was lost to follow-up, including those who discontinued lithium or left the Göteborg area.

Statistics

Age- and sex-standardized mortality ratios were calculated with 95% confidence limits, i.e., the number of observed deaths in the study population was divided by number of deaths expected in the general Swedish population.[17] Poisson distribution was used to test whether the observed number differed from the expected.

All patients remained in the study regardless of whether or not they stayed on lithium throughout the observation period. Since each individual contributed to the mortality rate calculated for "period on lithium" for as long as he or she continued taking the drug and to the mortality rate for "period off lithium" if and when he or she discontinued lithium, it was possible for patients to change lithium treatment status more than once during the course of the study.

Intracohort relative risks comparing sex- and age-adjusted mortality during "periods off lithium" with "periods on lithium" were calculated by introducing "lithium treatment status" as a time-dependent covariate. Poisson distribution was used to test for the difference between observed and expected numbers, and 95% confidence limits for the risk ratios were formed by applying the duality between tests and confidence sets.[18]

Poisson models[19] were also used to calculate the risk of suicide within the cohort in relation to the variables gender, current age, lithium treatment status, and alcohol and drug abuse. The following formula was used: risk of suicide = $1000 \times \exp(\beta_0 + \beta_1 x_1 + \ldots + \beta_k x_k)$, i.e., the risk of suicide is presented as number of suicides per 1000 years of observation.

Table 1. Mortality Rates (SMR) in 362 Patients With Mood Disorders and Schizoaffective Disorder and Lithium Treatment for a Minimum of 1 Year

Variable	Observed Number of Deaths	Expected Number of Deaths	SMR	95% Confidence Limits
Total mortality[a]	129	60.7	2.1*	1.8 to 2.5
Mortality during periods on lithium[b]	78	44.2	1.8†	1.4 to 2.2
Mortality during periods off lithium[c]	51	16.5	3.1†	2.3 to 4.1

*$p < .0001$.
†$p < .001$.
[a]Observation period = 5185 patient-years.
[b]Observation period = 3911 patient-years.
[c]Observation period = 1274 patient-years.

RESULTS

The inclusion criteria were met by 362 patients, 140 men and 222 women. Mean age at inclusion was 48 ± 14 years, and duration of illness was 14 ± 11 years. The primary diagnosis was depressive disorder in 78 (21.5%), bipolar disorder in 240 (66.3%), and schizoaffective disorder in 44 (12.2%) patients. Alcohol or drug abuse were present in 35 patients (9.7%).

Total mortality. Table 1 presents total mortality in the cohort using the general population as a reference. The SMR was clearly elevated, with a mortality twice the expected. It was significantly increased during periods on lithium (SMR = 1.8) as well as during periods off lithium (SMR = 3.1), but the relative risk of death was 1.7 times higher during periods off than on lithium ($p < .01$; 95% confidence limits 1.2 to 2.6).

Cause-specific mortality. Table 2 presents cause-specific mortality in relation to lithium treatment status. Only the most common and significantly increased causes of death are included. The relative risk of suicide was 4.8

Table 2. Cause-Specific Mortality Rates (SMR) in 362 Patients With Mood Disorders and Schizoaffective Disorder Treated With Lithium for a Minimum of 1 Year

	Periods On Lithium[a]			Periods Off Lithium[b]		
Cause of Death	Observed Number of Deaths	Expected Number of Deaths	SMR	Observed Number of Deaths	Expected Number of Deaths	SMR
Suicide	6	0.98	6.1*	9	0.31	29.0†
Pulmonary embolism	8	0.39	20.5†	4	0.16	25.0†
Pneumonia	9	0.86	10.5†	7	0.36	19.4†
Pyelonephritis	1	0.00	...†	3	0.00	...†

*p < .01.
†p < .001.
[a]Observation period = 3911 patient-years.
[b]Observation period = 1274 patient-years.

Table 3. Factors Associated With Suicide in 362 Patients With Mood Disorders and Schizoaffective Disorder and Lithium for a Minimum of 1 Year*

Factor	β	SE	Risk Ratio	95% Confidence Limits	p Value
Constant	–5.55	1.03	–		
Gender (0 = male, 1 = female)	–0.87	0.65	0.42	0.12 to 1.50	.177
Lithium (0 = no, 1 = yes)	–1.48	0.54	0.23	0.08 to 0.66	.007
Alcohol and drug abuse	1.35	0.59	3.84	1.21 to 12.3	.022
Current age	–0.03	0.02	0.97	0.93 to 1.01	.150

*Total observation period = 5185 patient-years.

times higher during periods off than periods on lithium ($p < .02$; 95% confidence limits 1.1 to 12.6).

Factors associated with suicide. Table 3 presents the analysis of factors associated with suicide, i.e., an analysis within the cohort without using the general population as a reference. Ongoing lithium treatment resulted in a 77% reduction in the risk of suicide, whereas alcohol abuse and drug abuse were associated with a 284% increase in the risk of suicide.

DISCUSSION

Patients with mood disorders and schizoaffective disorder, hospitalized at least once during an 8-year period and treated with lithium for a minimum of 1 year, had a significantly increased risk of death, including risk of suicide, as compared with the general population, irrespective of whether lithium was continued throughout the observation period or not. This is the one unequivocal conclusion allowed by the design and results of this study.

Periods off lithium were associated with an almost 5 times higher risk of suicide than periods on lithium, using the general population as a reference, and lithium treatment was also shown to be associated with a 75% reduction in the risk of suicide within the cohort. *Does this mean that lithium reduces suicide risk or that lithium has an antisuicidal effect?* This is where the controversy still remains among researchers, and there is no simple and uncomplicated answer to this question, since, for obvious ethical reasons, discontinuation of lithium was not randomized. Any serious discussion must take the following factors and their implications into account:

1. As described in a previous paper,[15] patients who discontinued lithium remained in contact with their psychiatrist and were prescribed psychotropic drugs other than lithium with the same frequency as the patients who stayed on lithium. Therefore, the lower suicide rate on lithium could very well be consistent with a suicide-reducing effect of the lithium treatment.
2. On the other hand, discontinuation of drug therapy, including lithium, is by no means a chance event in a naturalistic setting, and patients who stay on lithium may be fundamentally different from those who do not. Maj and coworkers[20] have pointed out that patients who remain on lithium for several years constitute a self-selected population in which those at high risk of poor outcome are underrepresented. Further studies are desperately needed to explore to what extent lithium discontinuation and suicide risk covary and may be influenced by variables such as severity of illness, response to treatment, predisposition to side effects, and comorbidity. The latter is of particular significance since comorbidity has been shown to be associated with nonadherence[21] as well as with an increased risk of death.[22] In this study, comorbid alcohol abuse and drug abuse were extremely strong predictors of suicide.
3. What follows lithium discontinuation? It has been argued that discontinuation of lithium may result in a high risk for early recurrences,[23,24] and it has also been suggested that gradual rather than abrupt discontinuation is less likely to cause a new episode even in a long-term perspective.[25] These find-

ings still await replication but can, of course, turn out to have very important implications for the understanding of the results of this study, since every new episode, whether triggered by lithium discontinuation or not, is likely to be associated with an increased risk of suicide. Such a line of reasoning suggests that lower suicide rates during periods on lithium would be the effect of lithium's mood-stabilizing properties rather than a specific antisuicidal effect. The hazard of further episodes is also underlined by the fact that, as previously reported,[15] 4 of 6 patients on and 5 of 9 patients off lithium suffered from a current depressive episode or were recovering from a recent one the last month before suicide.

In conclusion, the findings of this study suggest that ongoing lithium treatment is associated with lower suicide risks in patients with mood and schizoaffective disorders. Whether this is due to lithium's mood stabilizing properties, to lower suicide risks per se in the patients who remain in treatment, or to a specific antisuicidal lithium effect cannot be determined, since patients were not randomized to discontinue treatment. This is an important methodological shortcoming, shared with every other study in the field. *Since correlation must not be confused with causation, findings have to be interpreted with great caution.*

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