

# Suicide Risk in Patients Treated With Lithium

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**Context:** Prior observational studies suggest that treatment with lithium may be associated with reduced risk of suicide in bipolar disorder. However, these studies are biased toward patients with the most severe disorders, and the relation to sex and age has seldom been investigated.

**Objective:** To investigate whether treatment with lithium reduces the risk of suicide in a nationwide study.

**Design:** An observational cohort study with linkage of registers of all prescribed lithium and recorded suicides in Denmark during a period from January 1, 1995, to December 31, 1999.

**Setting:** All patients treated with lithium in Denmark, ie, within community psychiatry, private specialist practice settings, and general practice.

**Participants:** A total of 13 186 patients who purchased at least 1 prescription of lithium and 1.2 million subjects from the general population.

**Main Outcome Measure:** All suicides identified on the basis of death certificates completed by doctors at the time of death.

**Results:** Patients who purchased lithium had a higher rate of suicide than persons who did not purchase lithium. Purchasing lithium at least twice was associated with a 0.44 reduced rate of suicide (95% confidence interval, 0.28-0.70) compared with the rate when purchasing lithium only once. Further, the rate of suicide decreased with the number of prescriptions of lithium. There was no significant interaction between continued lithium treatment and sex and age regarding the suicide rate.

**Conclusion:** In a nationwide study including all patients treated with lithium, it was found that continued lithium treatment was associated with reduced suicide risk regardless of sex and age.

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**D**EPRESSIVE AND BIPOLAR disorders are associated with a high risk of recurrence<sup>1,2</sup> and a 10- to 15-time increased rate of suicide compared with the suicide rate in the general population.<sup>3-5</sup> Nevertheless, there is a rarity of data pertaining to long-term treatment and suicide in affective disorders.<sup>6</sup> Although the mood-stabilizing effect of lithium is well established,<sup>7</sup> it is less established whether treatment with lithium may prevent suicide. A recent Cochrane review<sup>7</sup> identified only 2 randomized placebo-controlled lithium trials that included suicide as an outcome and concluded that the number of suicides was too small for reliable conclusions to be drawn. This paucity of data reflects that when suicide is an anticipated outcome, conducting randomized controlled trials is unethical. Moreover, as suicide is a rare event, it would require a very large number of patients and prolonged study periods.<sup>8</sup> Alternatively, the issue may be enlightened in observational studies. From a review and meta-analysis of 22 observational long-term studies including 5647 patients with

major affective disorders, it was concluded that the suicide risk is lower during periods with lithium treatment than during periods without<sup>6</sup>—a conclusion similar to that in a prior review.<sup>9</sup> More recent studies have also found that continued treatment with lithium is associated with reduced suicide rates,<sup>10</sup> although it was revealed in a long-term observational study that lithium alone did not have any effect on suicide risk but did have an effect in combination with antidepressant and/or antipsychotic medication.<sup>11</sup>

So far, studies have mainly been conducted in lithium clinics or specialist university clinics<sup>8,10-17</sup> to which patients with nonresponse to treatment or severe courses of illness, such as rapid cycling, are often referred. These studies presumably include mostly patients with severe disorders and, thus, prior studies may not be representative of patients with affective disorders in general. Thus, the rate of suicide and the effect of lithium on suicide may vary according to the severity of the illness and according to the treatment setting.<sup>4</sup> In support of this point of view, bipolar patients who received lithium did not have sig-

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nificantly lower rates of suicide than bipolar patients who did not receive lithium or other mood-stabilizing medication in a more representative study<sup>18</sup> using administrative databases from California and Washington, as was pointed out in a comment to the paper.<sup>19</sup> This large study included 11 544 patients who had at least 1 filled prescription for lithium or divalproex and a total of 34 suicides.<sup>18</sup> The main finding was that the rate of suicide was lower among patients treated with lithium than among patients treated with divalproex.

It is well known that the rate of suicide is substantially higher for men and elderly persons,<sup>20,21</sup> and it is possible that different biological mechanisms are involved in suicidality among men and women and among younger and older persons. Thus, the effect of lithium on the risk of suicide may vary with sex and age. However, as the absolute number of suicides is small in all studies (34 suicides in the largest study<sup>18</sup>), few studies on lithium have reported age- and sex-specific rates of suicide.<sup>12,15,22</sup>

The aim of the present study was to investigate whether treatment with lithium is associated with reduced risk of suicide by comparing the rate of suicide for patients who purchased lithium at least once with the rate of suicide for persons who did not purchase lithium, using linkage of large nationwide registers of all deaths and all prescribed medication in Denmark. Further, it was the aim to investigate whether sex and age interact with the association between lithium and suicide.

Patients with bipolar disorder and, to some degree, patients with recurrent depressive disorder are often treated with lithium and have a high risk of suicide as well. To try to separate the effect of the illness from the effect of lithium on the risk of suicide (ie, the phenomenon of confounding by indication), patients in the analyses were dynamically divided into a group of patients purchasing lithium only once and a group of patients purchasing lithium twice or more. Patients who purchased lithium only once had the illness but did not maintain lithium treatment, and patients who purchased lithium twice or more had the illness and continued treatment with lithium.

## METHODS

### REGISTERS

Data were obtained by linking Danish population-based registers using the unique personal identification numbers assigned to all 5.3 million persons living in Denmark, thus ensuring accurate linkage of information between registers irrespective of changes in name and so on.<sup>23</sup> In this way, the Medicinal Product Statistics register<sup>24</sup> was linked with the Danish Medical Register on Vital Statistics.<sup>25</sup>

In Denmark, all medication prescribed by doctors, such as lithium, is purchased only at pharmacies. The Medicinal Product Statistics register contains data on all prescribed medication purchased at pharmacies from January 1, 1995, onward.

The Danish Medical Register on Vital Statistics contains dates and causes of all deaths in Denmark recorded from the death certificates since 1976 and of suicides between April 1, 1970, and December 31, 1999. The death certificates are completed by doctors at the time of death. Suicide was identified when the cause of death was coded as intentional self-harm (*International Classification of Diseases, 10th Revision* codes X600 to X840).

The study period in the present study was from January 1, 1995, to December 31, 1999.

## SAMPLE

This study was part of a larger ongoing study. A random sample of 1.2 million persons was identified in the Danish Medical Register on Vital Statistics among the 4.1 million inhabitants in Denmark who were alive and who were aged 18 years or older on January 1, 1995. Additionally, all persons aged 18 years or older and who purchased lithium at least once in the study period from January 1, 1995, to December 31, 1999, were identified in the Medicinal Product Statistics register.

## STATISTICAL ANALYSIS

Poisson regression analyses were conducted with suicide as the outcome and censoring at death by reasons other than suicide, emigration, or end of the study period (December 31, 1999). At any given point in time, the sample was dynamically categorized into 3 groups: group 1 included persons who had not purchased lithium (the unexposed population), group 2 included patients who had purchased 1 prescription of lithium, and group 3 included patients who had purchased 2 or more prescriptions of lithium. Patients could shift from group 1 to group 2 and from group 2 to group 3 but could not shift the opposite way.

Sex, age group (18-25 years, 26-30 years, 31-35 years, 36-40 years, 41-45 years, 46-50 years, 51-55 years, 56-60 years, 61-65 years, 66-70 years, 71-75 years, 76-80 years,  $\geq 81$  years), and employment status (working, unemployed, disability or age pension, student, other) were included in the model as covariates. Additionally, purchasing antidepressant medication of any kind was dynamically included in the model.

Two supplementary analyses were made. First, the association between the number of prescriptions, subdivided into 0, 1, 2 to 5, 6 to 10, and 11 or more prescriptions, and the rate of suicide was further investigated. Second, purchasing antipsychotic, anxiolytic/sedative, or anticonvulsant medication of any kind was dynamically included in the model.

## RESULTS

A total of 13 186 persons aged 18 years or older and who purchased lithium at least once in the study period from January 1, 1995, to December 31, 1999, was identified in the Medicinal Product Statistics register. Thus, among the approximate 4.1 million people in Denmark aged 18 years or older, 13 186 (0.3%) purchased lithium at least once during the study period.

Among the 4.1 million Danish inhabitants who were alive and who were aged 18 years or older on January 1, 1995, 1.2 million persons were randomly identified and 937 persons from this group were excluded because they were older than 110 years, were not residing in Denmark on January 1, 1995, or died by this date, leaving 1 199 063 persons for analysis. The 1 199 063 persons had 5 704 734 person-years and 1141 suicides, resulting in an estimated crude suicide rate among the general population of 20.0 suicides per 100 000 person-years. For men and women separately, the rates were 790 suicides per 2 782 654 person-years (28.4 suicides per 100 000 person-years) and 351 suicides per 2 922 080 person-years (12.0 suicides per 100 000 person-years), respectively.

**Table 1. Characteristics of Persons Receiving and Not Receiving Lithium Treatment, According to Sex, Age, Employment, Number of Suicides, and Censoring**

Characteristic	Received 1 Lithium Prescription*	Received $\geq 2$ Lithium Prescriptions†	Received No Lithium Prescriptions‡
N at end of follow-up	1 348	11 838	1 195 191
Total person-years	5 134	40 794	5 691 048
Sex, person-years (%)			
Men	1 864 (36.3)	15 010 (36.8)	2 777 761 (48.8)
Women	3 270 (63.7)	25 784 (63.2)	2 913 287 (51.2)
Age at inclusion, median (quartiles), y	54.7 (44.1-67.9)	55.0 (44.5-67.9)	45.0 (31.3-60.1)
Employment, person-years (%)			
Working	1 692 (33.0)	11 533 (28.3)	3 463 558 (60.9)
Unemployed	216 (4.2)	1 576 (3.9)	294 712 (5.2)
Disability or age pension	2 733 (53.3)	24 705 (60.6)	1 421 866 (25.0)
Student	94 (1.8)	557 (1.3)	178 255 (3.1)
Other	398 (7.8)	2 423 (5.9)	332 657 (5.8)
Suicides, No.			
<b>Total</b>	<b>23</b>	<b>79</b>	<b>1 098</b>
Men	8	31	777
Women	15	48	321
Per 100 000 person-years, total	448.0	193.7	19.3
Per 100 000 person-years, men	429.2	206.5	28.0
Per 100 000 person-years, women	458.7	186.2	11.0
Censoring, No.			
Death for reasons other than suicide	175	1 160	84 614
Emigration	16	68	25 119
End of study	1 134	10 531	1 084 360

\*Crude rate ratio (relative risk) = 23.2; 95% confidence interval, 15.4 to 35.0.

†Crude rate ratio (relative risk) = 10.0; 95% confidence interval, 7.9 to 12.7.

‡Crude rate ratio (relative risk) = 2.3; 95% confidence interval, 1.4 to 3.7.

Characteristics of persons who purchased 1 prescription of lithium, persons who purchased 2 or more prescriptions of lithium, and persons who did not purchase lithium (the unexposed population) are presented in **Table 1**. The figures for sex and employment status represent person-years under risk in each of the 3 groups. Additionally, the number of suicides and the number censored in each group are given. In total, 1200 persons (816 men and 384 women) committed suicide during the study period. The crude rates of suicide per 100 000 person-years are presented in Table 1 for each group in total and for each sex. Among the unexposed population, men committed suicide 2.3 times more often than women (28.0 suicides/100 000 person-years vs 11.0 suicides/100 000 person-years, respectively). The crude suicide rate among patients who continued lithium treatment ( $\geq 2$  prescriptions) in the present study was 10 times higher than the suicide rate among the unexposed population (193.7 suicides/100 000 person-years vs 19.3 suicides/100 000 person-years, respectively). The crude rate ratio of suicide among persons with any lithium use compared with the unexposed population was 11.5 (95% confidence interval [CI], 9.4-14.1).

In Poisson regression analyses, significant main effects were found for lithium treatment (0, 1,  $\geq 2$  prescriptions), sex, age, and employment status on the rate of suicide (results not presented). No significant interaction was found with age ( $\chi^2=0.9$ ,  $P=.60$ ) on the association between lithium and suicide, and no interaction was found with sex and age on the rate of suicide ( $\chi^2=0.8$ ,  $P=.40$ ). In contrast, there was a significant interaction

between sex and lithium on the rate of suicide in this model ( $\chi^2=20.7$ ,  $P<.001$ ). The associations between lithium and suicide are presented in total and for each sex in **Table 2**. Patients who purchased lithium only once had a 4.86-fold increased rate (95% CI, 3.20-7.39) of suicide compared with persons who did not purchase lithium. Patients who purchased lithium twice or more had a 2.11-fold increased rate (95% CI, 1.66-2.68) of suicide compared with persons who did not purchase lithium. Thus, patients with 2 or more prescriptions of lithium had a 0.43-fold reduced rate (95% CI, 0.27-0.69) compared with patients with only 1 prescription of lithium. Women and men showed the same pattern in the rate ratios; however, the rate ratios were less pronounced for men and did not reach statistical significance in all of the comparisons. The difference between women and men in the rate of suicide for patients purchasing lithium twice or more vs the rate for patients purchasing lithium only once was not statistically significant ( $\chi^2=0.57$ ,  $P=.40$ ) and the common estimate for both sexes was 0.44 (95% CI, 0.28-0.70).

The relation in suicide rate between men and women is presented in **Table 3**. Among the unexposed population, men had a 3.57-fold higher rate (95% CI, 3.12-4.07) of suicide than women had. Among patients purchasing lithium, the rate of suicide did not differ significantly for men and women.

The association between the number of prescriptions, subdivided into 0, 1, 2 to 5, 6 to 10, and 11 or more prescriptions (with 1 prescription as the reference), and the rate of suicide was further investigated. As can be seen

**Table 2. Risk of Suicide Related to Number of Lithium Prescriptions and Sex, Adjusted for Age, Employment Status, and Purchasing Antidepressant Medication**

	Adjusted RR (95% CI)			
	No Lithium Prescription	1 Lithium Prescription	≥2 Lithium Prescriptions	≥2 Lithium Prescriptions Vs 1 Lithium Prescription
Total	1.00	4.86 (3.20-7.39)	2.11 (1.66-2.68)	0.43 (0.27-0.69)
Women	1.00	8.03 (4.77-13.52)	3.38 (2.48-4.61)	0.42 (0.24-0.75)
Men	1.00	2.81 (1.40-5.67)	1.33 (0.92-1.93)	0.47 (0.22-1.03)

Abbreviations: CI, confidence interval; RR, relative risk.

in **Table 4**, the results vary according to sex, with a different pattern for the 2 sexes ( $\chi^2=22.14$ ,  $P<.001$ ). For men, the rate of suicide was greatest for patients purchasing lithium 2 to 5 times whereas patients who purchased lithium 6 to 10 times or 11 or more times had reduced rates as compared with patients who purchased lithium only once. For women, the rate of suicide decreased more steadily with the number of prescriptions.

Patients who purchased antidepressant medication had a 6.07-fold increased rate (95% CI, 5.10-7.21) of suicide compared with persons who did not purchase antidepressant medication, regardless of whether lithium was purchased or not ( $\chi^2=0.64$ ,  $P=.70$ ). In the model where the suicide rate was further adjusted for the effects of antipsychotic, anxiolytic/sedative, and anticonvulsant medications, the rate of suicide was increased for patients who purchased antipsychotic medication (relative risk [RR]=1.78; 95% CI, 1.50-2.11) or anxiolytic/sedative medication (RR=1.73; 95% CI, 1.45-2.06) compared with the rate for persons who did not purchase these drugs. There was no significant effect of purchasing anticonvulsant medication ( $\chi^2=1.26$ ,  $P=.30$ ). Including variables for antipsychotic and anxiolytic/sedative medications in the model only marginally changed the rate ratios of suicide presented in Table 2, so purchasing lithium twice or more was still associated with a decreased rate of suicide compared with the rate for patients purchasing lithium only once (men: RR=0.47; 95% CI, 0.21-1.01; women: RR=0.41; 95% CI, 0.23-0.73).

## COMMENT

The results of the present study (primarily that continued lithium treatment is associated with reduced suicide risk) confirm the findings from the majority of prior observational studies and generalize these findings to all of the patients treated with lithium in a whole nation. Continued lithium treatment, ie, purchasing lithium twice or more, was associated with reduced suicide risk in both sexes. Patients who continued lithium treatment had a 0.44-time decreased rate (95% CI, 0.28-0.70) of suicide compared with patients who purchased lithium only once, and this relationship did not differ significantly with sex or change with age.

We used register data of all purchased lithium in Denmark, including prescriptions by specialists within hospitals, private practice settings, and general practitioners in

**Table 3. Risk of Suicide for Men Compared With Women, Related to the Number of Lithium Prescriptions and Adjusted for Age, Employment Status, and Purchasing Antidepressant Medication**

Sex	Adjusted RR (95% CI)		
	No Lithium Prescription	1 Lithium Prescription	≥2 Lithium Prescriptions
Women	1.00	1.00	1.00
Men	3.57 (3.12-4.07)	1.25 (0.53-2.95)	1.41 (0.90-2.21)

Abbreviations: CI, confidence interval; RR, relative risk.

**Table 4. Risk of Suicide Related to Number of Lithium Prescriptions and Adjusted for Age, Employment Status, and Purchasing Antidepressant Medication**

Lithium Prescriptions, No.	Adjusted RR (95% CI)		
	Men	Women	Total
0	0.36 (0.18-0.72)	0.12 (0.07-0.21)	0.21 (0.14-0.31)
1	1.00	1.00	1.00
2-5	1.17 (0.52-2.65)	0.50 (0.24-1.02)	0.73 (0.43-1.23)
6-10	0.35 (0.12-1.08)	0.66 (0.33-1.33)	0.53 (0.30-0.96)
≥11	0.15 (0.05-0.46)	0.29 (0.14-0.57)	0.23 (0.13-0.42)

Abbreviations: CI, confidence interval; RR, relative risk.

a period from January 1, 1995, to December 31, 1999. Thus, our results pertain to all of the patients treated with lithium nationwide. All suicides were identified on the basis of death certificates completed by doctors at the time of death.

The Danish population is ethnically and socially homogeneous and has a very low migration rate. Psychiatric care is well developed, so persons can easily come in contact with general practitioners or specialists in psychiatry. Psychiatric treatment is available free of charge in Denmark, and as lithium is cheap with 75% refunding from the state, the study is not biased by socioeconomic differences.

## SUICIDE RATES IN THE GENERAL POPULATION

The crude rate of suicide was found to be 20.0 suicides per 100 000 person-years in the general population aged 18 years or older, which is identical to the official Dan-

ish national average annual figure of 20.0 suicides per 100 000 person-years of the total population during the period.<sup>26</sup> Among the general population, men had a 2.4-time increased crude rate of suicide in accordance with the extensive literature consistently finding higher rates of suicide among men.<sup>20</sup>

### PREVALENCE OF LITHIUM TREATMENT

In total, 0.3% of the Danish population was treated with lithium during the study period. We do not know the diagnoses of patients treated with lithium.<sup>6</sup> However, this medication is primarily given to patients with bipolar disorders and more seldom to patients with recurrent depressive or other disorders. The lithium treatment frequency of 0.3% of the Danish population should be compared with the general estimated prevalence rates of bipolar disorder of 1.0%.<sup>3</sup> A proportion of patients with bipolar disorder does not contact a doctor, a proportion may have been treated with poor response to lithium prior to the study period, and a proportion may have been treated with mood stabilizers other than lithium. We are not aware of other national lithium prevalence rates besides that in Germany, where lithium has been estimated to be prescribed for 0.06% of the German population.<sup>10</sup> Compared with this figure, the frequency of lithium treatment is high in Denmark. Reasons for this relatively high use of lithium in Denmark may be that lithium was introduced early in Denmark owing to the pioneering work by Schou<sup>27,28</sup> and that, for decades, lithium has been regarded as the drug of choice within mood stabilizers.<sup>29</sup> Nevertheless, the frequency of lithium treatment does not reach the recommended level of 0.6% of the population as suggested by Müller-Oerlinghausen et al<sup>10</sup> as a rational treatment strategy.

### SUICIDE RATES AMONG PATIENTS RECEIVING LITHIUM TREATMENT

Patients who purchased lithium had higher rates of suicide than those in the unexposed population. This finding replicates prior results<sup>6</sup> and was anticipated, as having an affective disorder severely increases the risk of suicide. Patients who purchased lithium only once may have discontinued treatment owing to adverse effects, lack of effect, manic or depressive symptoms, lack of insight, or other psychological reasons associated with long-term treatment with a drug. In any case, a medical doctor has found indication for treatment with lithium but the patients have only taken the drug during a short period corresponding to 1 prescription at most.

In the present study, the unadjusted rate of suicide was 194 suicides per 100 000 person-years for patients who continued treatment with lithium (Table 1), which was somewhat higher than the aggregated rate of 159 suicides per 100 000 person-years in the meta-analysis of 22 studies by Tondo et al<sup>6</sup> and the rate of 70 suicides per 100 000 person-years in the administrative database study by Goodwin et al.<sup>18</sup> Conversely, the unadjusted suicide rate for patients who discontinued lithium in the present study (Table 1; 448 suicides per 100 000 person-years) was between the corresponding rates in the ar-

ticles by Tondo and colleagues and Goodwin and colleagues (875 suicides per 100 000 person-years and 120 suicides per 100 000 person-years, respectively). Different inclusions of populations and designs of analyses may account for these differences. We believe our populations to be the most representative as all patients treated with lithium and a random proportion of 1.2 million persons from the Danish population were included. In the study by Goodwin and colleagues, poor and elderly persons were somewhat underrepresented. In the meta-analysis by Tondo and colleagues, patients with less severe disorders may have been underrepresented as illustrated by the high suicide rate among patients who discontinued lithium treatment (875 suicides per 100 000 person-years).

Despite these dissimilarities between studies, the crude suicide rate among patients who continued lithium treatment ( $\geq 2$  prescriptions) in the present study was 10-fold higher than the suicide rate among the unexposed population—a figure exactly identical with the figures estimated in the meta-analysis by Tondo et al.<sup>6</sup> The average rate of suicide among patients during maintenance of lithium treatment was estimated to be increased 10-fold as compared with international general populations.<sup>6</sup>

We analyzed the association between the number of prescriptions and the rate of suicide and defined continued lithium treatment as prescription of lithium twice or more. Our finding of a 0.44-time reduced rate (95% CI, 0.28–0.70) of suicide among patients who purchased lithium at least twice compared with patients who purchased lithium only once reflects minimum figures of the effect of lithium; first, the analyses showed that the rate of suicide decreased further with the number of prescriptions, and second, some patients in the group of those receiving 2 or more prescriptions of lithium may not have had continued use of lithium, as they may have purchased lithium with irregular intervals or long pauses between the prescriptions. Similarly, the crude overall suicide rate was 2.3-fold higher for patients who discontinued lithium treatment than for patients who continued the treatment (448 suicides per 100 000 person-years vs 194 suicides per 100 000 person-years, respectively; Table 1), which also reflects minimum figures. In previous studies,<sup>6</sup> the risk of suicide has been estimated to be, on average, 8.85-fold higher for patients not receiving lithium treatment as compared with patients receiving lithium treatment.

The importance of taking treatment duration into consideration when analyzing the effect of lithium on suicide has also been emphasized by Wolf et al<sup>30</sup> and is reflected in the diverging mortalities in various studies. Studies<sup>14,15,31</sup> with an average lithium treatment duration of 2 to 5 years have found high mortalities whereas studies<sup>13,17,32</sup> with an average treatment of 5 to 10 years of continuous lithium treatment have found standard mortality ratios below 1.

### CONFOUNDING BY INDICATION

It has been found that receiving treatment is associated with worse outcome, eg, longer affective episode<sup>33</sup> and increased risk of recurrence.<sup>34</sup> These seeming paradoxes may be owing to the confounding of prognostic factors of the

illness and treatment effects (confounding by indication), as patients with more severe illness may be more prone to seek treatment and are treated for a longer time than patients who are less ill.<sup>35,36</sup> As expressed by Keller et al,<sup>37</sup> in naturalistic studies, "treatment itself becomes an outcome, because patient's state [is] likely to help determine the choice of treatment." Thus, one should presume that patients who take lithium for longer periods have more severe illness and an increased risk of suicide. It is surprising that, even with this background, continued lithium treatment was associated with a reduced suicide rate in the present study. On the other hand, the finding of a reduced suicide rate among patients who continued lithium treatment may be a result of selection bias. Undefined individual factors associated with acceptance and adherence to long-term treatment might tend to select for lower suicide risk during treatment,<sup>6,11</sup> and nonadherence may be associated, for example, with alcoholism, drug addiction, and personality disorders that, in themselves, are associated with an increased risk of suicide.<sup>28</sup> However, this does not seem to be a general phenomenon that can fully explain the association between lithium and suicide, as with a similar design and similar analyses, we have not found that patients who purchased older antidepressant medications (mainly tricyclic antidepressant medication) 2 or more times had a lower rate of suicide than patients who purchased these drugs only once (L.S., K.K., P.K.A., L.V.K., unpublished data, 2004). Angst et al<sup>11</sup> similarly found that subgroups of medicated patients did not have an equal reduction in suicide risk and argued that this opposes the possibility that the effect of medication is entirely a general effect of long-term contact with the doctor and the health care system. Furthermore, no evidence has been published concerning a connection between suicide and long-term treatment with other mood stabilizers,<sup>28</sup> and the risk of suicide has been found to be lower among patients treated with lithium than among those treated with divalproex in the comparative study by Goodwin et al.<sup>18</sup>

It may be argued that our results reflect that the suicide rate may increase following abrupt discontinuation of lithium, probably owing to rebound recurrences as suggested by some studies,<sup>38-40</sup> rather than decrease following continued lithium treatment. This does not, however, seem to be a likely explanation, as patients who discontinued lithium treatment purchased only 1 prescription corresponding to 3 months of treatment at most. Thus, it is not likely that a rebound phenomenon may be induced in patients following treatment for only weeks or a few months.

#### SEX AND AGE DIFFERENCES IN SUICIDE

We found the usual male predominance of suicide in the unexposed population, as men committed suicide 3.57 times (95% CI, 3.12-4.07) more often than women (Table 3). In contrast, there was no overall sex difference in the rate of suicide among patients treated with lithium. Thus, our results show, in accordance with prior findings,<sup>12,22</sup> that the great male preponderance in suicide that is found in the general population is eliminated among patients purchasing lithium. Two other studies<sup>12,22</sup> that have

compared rates of suicide in men and women treated with lithium found, in fact, higher rates for female patients. A third study<sup>15</sup> found higher rates of suicide among male compliers and female noncompliers with lithium. The diverging findings may relate to bias in relation to sex and duration/severity of the affective illness owing to a reduced number of patients and absolute suicides in the studies. In the present study, more detailed analyses of sex and the duration of treatment showed that the rate of suicide declined with the number of prescriptions of lithium with a different pattern for men and women (Table 4). Women who purchased lithium had 4- to 8-time higher rates of suicide than women in the unexposed population, although the rates declined with the number of prescriptions to approximately 2 times the rates among the unexposed female population. Men who purchased lithium had up to 3-time higher rates of suicide than men from the unexposed population, but men who purchased lithium many times (6 times or more) had rates that were equal or even reduced compared with the rates for the unexposed male population. It has been proposed by Ahrens et al<sup>12</sup> that this sex difference in the rate of suicide among patients treated with lithium may be owing to the antiaggressive effect of the serotonin agonist properties of lithium protecting men from committing violent suicide. Other possible explanations inherent to bipolar illness may be the increased prevalence of mixed episodes<sup>41-43</sup> and rapid cycling,<sup>44-47</sup> which are both associated with female sex and with suicide. Further, adherence to treatment may influence the risk of suicide. In fact, further analyses of the present data showed that men adhered substantially longer to lithium than women did (L.V.K., K.K., P.K.A., unpublished data, 2004).

We found no interaction of age on the association between lithium and suicide in accordance with Ahrens et al,<sup>12</sup> who found no difference in the suicide rate among patients younger and older than 45 years who were treated with lithium. To our knowledge, no other study has investigated the interaction of age, lithium, and suicide.

#### EFFECT OF ADDITIONAL PSYCHOTROPIC DRUGS

In the study by Angst et al,<sup>11</sup> lithium alone did not have any effect on suicide risk but lithium in combination with antidepressant and/or antipsychotic medication did have an effect. In the present study, continued lithium treatment was associated with a decreased suicide rate when adjusted for the effect of other psychotropic drugs. Purchasing antidepressant medication was associated with a substantially increased rate of suicide (RR=6.07; 95% CI, 5.10-7.21) regardless of whether lithium was purchased or not. This may presumably reflect that patients are at an especially high risk of committing suicide during depressive episodes rather than a suicidal-inducing effect of antidepressant medication (ie, it is a result of confounding by indication). Notably, the association between antidepressant medication and suicide was independent of whether patients received lithium.

Furthermore, purchasing antipsychotic and anxiolytic/sedative medications in addition to lithium was associated with a moderately (2-time) increased rate of suicide, presumably reflecting an increased risk of suicide during

psychotic, manic/mixed episodes and during unstable periods of agitation, anxiety, or sleep problems. Purchasing anticonvulsant medication was not associated with an effect on the suicide rate. This cannot be taken as evidence against a possible antisuicidal effect of anticonvulsant medication, as these drugs may have been given primarily for epilepsy rather than as a mood stabilizer.

## CONCLUSIONS

The present study adds to prior evidence that continued lithium treatment is associated with reduced suicide risk and further generalizes these findings to all of the patients treated with lithium in a whole nation without regard to sex, age, and severity of illness. Importantly, however, the rate of suicide is still considerably higher (10-fold) in patients treated continuously with lithium in the present study and in most other studies<sup>6,12,13,27,28</sup> than the rate for the general population. Thus, further research is needed to reveal how lithium treatment can be combined with other treatments to reduce suicide.

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