ORIGINAL ARTICLE

Lithium Treatment and Risk of Dementia

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Context: It has been suggested that lithium may have neuroprotective abilities, but it is not clear whether lithium reduces the risk of dementia.

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

Design: An observational cohort study with linkage of registers of all patients prescribed lithium and diagnosed as having dementia in Denmark from January 1, 1995, through December 31, 2005.

Setting: We identified all patients treated with lithium in Denmark within community psychiatry, private specialist, and general practices and a random sample of 30% of the general population.

Subjects: A total of 16 238 persons who purchased lithium at least once and 1 487 177 persons from the general population who did not purchase lithium.

Main Outcome Measure: Diagnosis of dementia or Alzheimer disease during inpatient or outpatient hospital care.

Results: Persons who purchased lithium at least once had an increased rate of dementia compared with persons not exposed to lithium (relative risk, 1.47; 95% confidence interval, 1.22-1.76). For persons who continued to take lithium, the rate of dementia decreased to the same level as the rate for the general population. The rate of dementia decreased early after the consumption of lithium tablets corresponding to 1 prescription (typically 100 tablets) and stayed at a low level, although with a slight increase according to the number of subsequent prescriptions. The association between the number of prescriptions for lithium and dementia was unique and different from the association between the number of prescriptions for anticonvulsants and dementia. All findings were replicated in subanalyses with Alzheimer disease as the outcome.

Conclusions: Continued lithium treatment was associated with reduction of the rate of dementia to the same level as that for the general population. Methodological reasons for this finding cannot be excluded, owing to the nonrandomized nature of data.

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Studies suggest that bipolar disorder is associated with increased risk of developing dementia[1,2] and that the risk increases with every new affective episode.[3] On the other hand, it has been suggested that lithium may have neuroprotective abilities and may reduce the risk of developing dementia because lithium inhibits glycogen synthase kinase 3, which is a key enzyme in the metabolism of amyloid precursor protein and in the phosphorylation of the tau protein involved in the pathogenesis of Alzheimer disease.[4-6] However, the association between lithium consumption and dementia has been investigated in only 2 human studies. One study suggested an increasing risk of dementia with increasing numbers of lithium prescriptions,[7] whereas the other study found that patients receiving long-term lithium therapy had decreased prevalence of Alzheimer disease compared with patients not receiving recent lithium therapy.[8] Findings from both studies were hampered by the inclusion of low numbers of patients taking lithium, including 87 and 114 patients, respectively.

The aim of the present study was to investigate whether continued treatment with lithium is associated with a reduced risk of dementia by linkage of Danish nationwide registers of all lithium prescriptions and all diagnoses of dementia given at hospital inpatient or outpatient settings in Denmark. We hypothesized that (1) continued treatment with lithium is associated with a decreased risk of developing dementia and (2) the risk of dementia decreases with the number of prescriptions for lithium.

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Table 1. Characteristics of Persons Exposed and Not Exposed to Lithium

	Exposed to Lithium	Not Exposed to Lithium
No. at end of follow-up	16 238	1 487 177
Total person-years	131 283	10 719 792
Sex, No. (%) of person-years		
Male	47 872 (36.5)	4 820 971 (45.0)
Female	83 411 (63.5)	5 898 822 (55.0)
Age at inclusion, median (25th-75th percentiles), y	52.5 (43.6-64.8)	52.7 (41.9-67.8)
No. of patients with dementia		
Total	820	47 663
Per 10 000 person-years	62.5	44.5
No. of patients with Alzheimer dementia		
Total	134	9862
Per 10 000 person-years	10.2	9.2
No. of patients with other dementia		
Total	686	37 801
Per 10 000 person-years	52.3	35.3
Censoring, No. of patients		
Death	3156	286 919
End of study	12 262	1 152 595

METHODS

THE REGISTERS

Data were obtained by linking Danish population-based registers using the unique personal identification number, which is assigned to all 5.3 million persons living in Denmark, thus ensuring accurate linkage of information between registers, irrespective of changes such as in names.[9] In this way, the Medicinal Product Statistics register[10] was linked with the Danish Medical Register on Vital Statistics,[11] the Danish National Hospital Register (DNHR),[12] and the Danish Psychiatric Central Register (DPCR).[13]

The Medicinal Product Statistics register contains data on all prescribed medication purchased at pharmacies from January 1, 1995, onward.[10] In Denmark, all medication such as lithium, which is prescribed by physicians, is purchased at pharmacies only. Information on the indication for the prescription is not available.

The Danish Medical Register on Vital Statistics[11] contains data on death.

The DNHR[12] contains data on all patients treated at all somatic hospitals as inpatients or outpatients in Denmark from January 1, 1977, onward as a part of the official Danish health survey.[14] Likewise, all psychiatric admissions have been registered in the nationwide DPCR,[13] from April 1, 1970, onward. Since January 1, 1994, the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*), has been in use in both registers.[14]

The study period was from January 1, 1995, through December 31, 2005, although the period before 1995 was used to exclude patients with a prior diagnosis of dementia.

STUDY SAMPLE

A random sample consisting of 30% of the Danish population was identified in the Danish Medical Register on Vital Statistics among all inhabitants of Denmark who were alive on January 1, 1995. In addition, all persons who purchased lithium, anticonvulsants, or antidepressants at least once during the 1995-2005 study period were identified in the Medicinal Product Statistics register.

Main and auxiliary diagnoses of dementia given after a hospitalization or outpatient contact were identified in the DNHR (*ICD-10* codes G30.0-G30.9) and the DPCR (*ICD-10* codes F.00-F00.9 and F0.1-F01.9) during the study period.

Patients who were recorded in the DNHR or the DPCR as having received a diagnosis of dementia before starting lithium therapy were excluded from analyses. The period in which we searched for dementia diagnoses included that before 1995, with diagnoses from the *International Classification of Diseases, Eighth Revision* (back to 1977 in the DNHR and back to 1970 in the DPCR).

STATISTICAL ANALYSIS

We conducted Poisson regression analyses with a diagnosis of dementia as the outcome and the number of prescriptions for lithium as the variable of interest, with censoring at death or at the end of the study period (December 31, 2005). Poisson regression models[15] are standard multiple regression models for incidence rates where numbers of dementia diagnoses and person-years at risk are computed and analyzed in subgroups given by covariates that may be time dependent. Confounding by indication may occur if the period with continued lithium consumption (≥2 prescriptions) was compared with the period with 0 prescriptions because the indication for lithium is affective disorder, which is associated with an increased rate of dementia development.[1,2] The number of lithium prescriptions was parameterized with the period with 1 prescription as the reference to reduce confounding by indication because patients who received only 1 prescription for lithium presumably may have an affective disorder (most frequently bipolar disorder) but did not continue treatment. In a previous study on the association between lithium and suicide, our group used the same kind of analyses to reduce confounding by indication.[16] Risk time was estimated from the age of 40 years. Sex, age, and calendar period in 1-year periods were included in the model as covariates. In addition, the purchase of antidepressants or anticonvulsants of any kind was included in the model as a time-dependent variable.

To further investigate whether the association between the number of prescriptions and a diagnosis of dementia was unique for lithium, we repeated the described analyses with the number of prescriptions for anticonvulsants as the variable of interest and adjusted for the same covariates, with dynamic inclusion of the purchase of lithium and antidepressants of any kind in the model. In this model, all persons treated with anticonvulsants during the study period in Denmark were included.

Finally, we repeated all analyses with a diagnosis of Alzheimer disease (*ICD-10* codes G30-G30.9, F00-F00.9) and other dementia (*ICD-10* codes F01-F0.39) as the outcomes.

RESULTS

During the study period, a total of 1 503 415 persons older than 40 years were included in the study. Among these, 16 238 purchased lithium at least once (exposed), and 1 487 177 did not purchase lithium (unexposed) according to data from the Medicinal Product Statistics register. Characteristics of persons exposed and unexposed to lithium are given in **Table 1**. **Table 2** presents the rate of dementia related to the number of lithium prescriptions (0, 1, 2, 3-9, 10-19, and ≥20) and adjusted for age, sex, calendar period, and the purchase of antidepressants and anticonvulsants. Purchase of lithium once

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Table 2. Rate of Dementia Related to Number of Lithium Prescriptions[a]

No. of Prescriptions	Person-years at Risk	RR (95% CI)		
		Total Dementia	Alzheimer Disease	Other Dementia[b]
0	10 747 361	0.68 (0.57-0.82)	0.76 (0.50-1.16)	0.66 (0.54-0.81)
1	11 156	1 [Reference]	1 [Reference]	1 [Reference]
2	6290	0.66 (0.46-0.94)	0.61 (0.26-1.43)	0.67 (0.45-0.99)
3-9	23 603	0.68 (0.54-0.87)	0.50 (0.27-0.90)	0.73 (0.56-0.95)
10-19	20 016	0.75 (0.59-0.95)	0.64 (0.36-1.15)	0.77 (0.59-1.00)
≥20	42 649	0.85 (0.69-1.05)	0.76 (0.46-1.23)	0.88 (0.69-1.11)

Abbreviations: CI, confidence interval; RR, risk ratio.
[a] Adjusted for age, sex, calendar period, and the purchase of antidepressants and anticonvulsants.
[b] Includes all except Alzheimer disease.

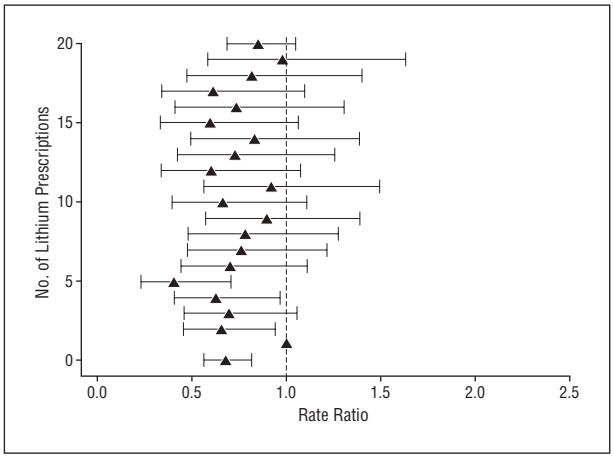

Figure 1. Rate ratios (bars represent 95% confidence intervals) of dementia according to the number of prescriptions for lithium (the period with 1 prescription is used as the reference). Findings are adjusted for the effect of age, sex, calendar period, and purchase of antidepressants or anticonvulsants.

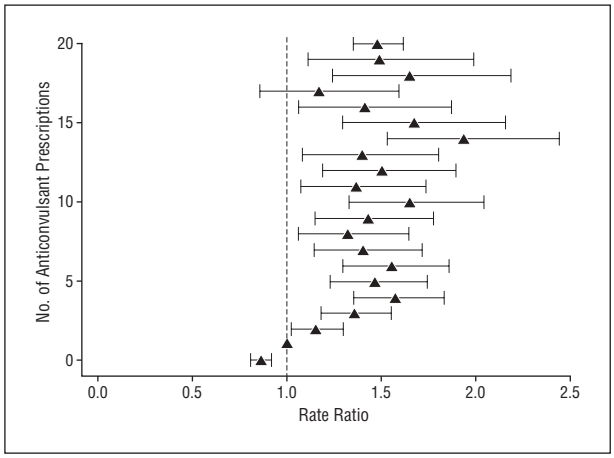

Figure 2. Rate ratios (bars represent 95% confidence intervals) of dementia according to the number of prescriptions for anticonvulsants (the period with 1 prescription is used as the reference). Findings are adjusted for the effect of age, sex, calendar period, and purchase of antidepressants or lithium.

(100 tablets) was chosen as the reference. Table 2 presents 3 major findings. First, persons not exposed to lithium had a decreased rate of dementia compared with persons who purchased lithium once (relative risk [RR], 0.68; 95% confidence interval [CI], 0.57-0.82) or, conversely, persons who purchased lithium once had an increased rate of dementia compared with persons not exposed to lithium (1.47; 1.22-1.76). Second, the rate of dementia was decreased during all periods when persons purchased more than 1 prescription for lithium. Third, the rate of dementia did not decrease incrementally with the number of prescriptions for lithium. In fact, there seemed to be a slight increase in the rate of dementia from the period with 2 prescriptions to the period with 20 or more prescriptions. **Figure 1** presents these findings graphically for every new purchase of lithium. Furthermore, we investigated whether persons who purchased only 1 prescription and persons who purchased 2 or more prescriptions differed by sex, age at first prescription, calendar time for first prescription, and exposure to antidepressants or anticonvulsants. The only difference was that more persons in the group with 2 or more prescriptions purchased their first prescription during 1995. For this reason, all analyses were repeated when the risk time started during 1996. The results did not differ from the results when 1995 was included.

A total of 102 644 persons were exposed to anticonvulsants during 674 082 person-years. The median age at inclusion was 55.8 years (25th and 75th percentiles, 44.3-69.4 years), and 3969 were diagnosed as having dementia. **Figure 2** presents the same type of analyses for anticonvulsants as for lithium, that is, the association between the number of prescriptions for anticonvulsants and the rate of dementia among all persons treated with anticonvulsants in Denmark. This pattern was quite different from the pattern illustrated in Figure 1.

Finally, all analyses were repeated with Alzheimer disease and other dementia as the outcomes. A total of 9996 persons were diagnosed as having Alzheimer disease for the first time ever during the study period, and 38 487 persons were diagnosed as having other dementia (Table 1). The findings were generally the same for these 2 outcome measures as those when a diagnosis of dementia was the outcome (Table 2).

COMMENT

We confirmed our first hypothesis that continued treatment with lithium was associated with a decreased risk of developing dementia but not our second hypothesis that the risk of dementia decreased with the number of prescriptions for lithium. More specifically, the study dis-

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closed the following 4 major findings: (1) persons who purchase lithium once (most frequently 100 tablets) have an increased rate of dementia compared with persons not exposed to lithium (RR, 1.47; 95% CI, 1.22-1.76); (2) for persons who continue to take lithium, the rate of dementia decreases to the same level as the rate for the general population; (3) the rate of dementia decreases early after the consumption of lithium tablets corresponding to 1 prescription and does not continue to decrease with an increase in the number of prescriptions for lithium; and (4) the association between the number of prescriptions for lithium and dementia was quite different from the association between the number of prescriptions for anticonvulsants and dementia. All findings were replicated in analyses with Alzheimer disease and dementia of other kinds as the outcomes.

We used register data of all purchased lithium in Denmark, including prescriptions from specialists within hospitals and private practice settings and prescriptions from general practitioners from 1995 to 2005. Thus, our results pertain to all patients treated with lithium nationwide. The register contains no data on indications for treatment, but in Denmark most lithium is prescribed for bipolar disorder.

The validity of the diagnosis of dementia in the DNHR and the DPCR has been found to be high, with a correct register diagnosis in 85.8% of the cases.[17] The prevalence of the *ICD-10* subtype diagnosis of dementia was rather low, but Alzheimer disease, although underregistered, also had a good validity once the diagnosis was registered. It is estimated that at least two-thirds of patients with dementia in Denmark will receive the diagnosis during a contact with secondary hospital health care (T. K. Phung, MD, B. D. Waltoft, MD, PhD, L.V.K., P. B. Mortensen, DMSc, and G. Waldemar, DMSc, unpublished data, 2008). Nevertheless, general practitioners or private practicing specialists in psychiatry or neurology might diagnose persons as having dementia without this being recorded in the registers.

The Danish population is ethnically and socially homogeneous and has a very low migration rate. Psychiatric and medical care is well developed, and persons can easily come in contact with general practitioners or specialists in psychiatry or neurology. Psychiatric and other medical treatment is available free of charge in Denmark and, because lithium is cheap (ie, 75% of the cost is refunded by the state), the study is not likely to be biased by socioeconomic differences.

The first finding in our study is in accordance with our previous finding of an increased risk of developing dementia among patients who received a diagnosis of bipolar disorder during psychiatric hospitalization[1,2] because lithium is prescribed mainly for bipolar disorder. We are further able to generalize our previous findings to the larger population of all patients treated with lithium in Denmark. The second finding suggests that consumption of lithium is associated with the decreased risk of developing dementia, although the early decrease after consumption of lithium tablets corresponding to a single purchase is somewhat spurious and deserves further discussion. The third finding that the rate of dementia did not decrease with the number of lithium prescriptions may at first glance argue against a dose-response relationship between lithium and dementia. Nevertheless, the rate of dementia was at the same low level among patients who continued taking lithium (although with a slight increase from the period with 2 prescriptions to the period with ≥20 prescriptions) as that among the general population, with little room for decreasing the rate. Furthermore, it should be recalled that data from previous studies by our group suggest that the rate of dementia increases with the number of affective episodes in patients with bipolar (and unipolar) disorder.[3] Thus, according to those findings, the present study should have found that the rate of dementia would increase with time and with the number of prescriptions. However, this was not the case; although the rate of dementia increased slightly during periods with 2 or more prescriptions, the rate of dementia remained at the same low level as that of the general population for persons who had been ill with bipolar disorder for many years, as reflected by their purchase of 20 or more prescriptions for lithium (Table 2).

There are 2 possible explanations for our findings. First, continued treatment with lithium suppresses the harmful effect on cognition associated with affective episodes and thus decreases the rate of developing dementia to the same rate as that among the general population. If this should be the case, a protective effect of lithium seems to begin already after intake of a few hundred tablets of lithium. In fact, increases in gray matter volume in the human brain[18,19] and in *N*-acetyl-aspartate levels,[20] a putative marker of neuronal viability and function, have been found after only 4 weeks of lithium treatment. In addition, no correlation has been found between the length of lithium treatment and gray matter brain volume.[19]

The second explanation is that the finding is a methodological artifact due to the following: (1) Lithium treatment is not continued for patients who the clinician believes will later develop dementia (eg, patients with mild cognitive impairment, because clinicians may believe that lithium may induce confusion in such patients). (2) Patients who continue taking lithium for long periods presumably adhere well to treatment, with less alcohol use and a healthier lifestyle associated with decreased risk of developing dementia. Explanation 1 relates to the rather sudden decrease in the rate of dementia as reflected in the rate during the period with 2 prescriptions compared with the rate during the period with 1 prescription (RR, 0.66; 95% CI, 0.46-0.94 [Table 2]). An argument against this explanation is that one should presume that clinical evaluation of cognitive function is undertaken before starting lithium treatment and not when the patient has consumed tablets from the first prescription for lithium. In addition, we excluded all patients with a diagnosis of dementia before starting lithium therapy. Furthermore, in relation to explanations 1 and 2, one should presume that the same relationships should occur with a prescription for anticonvulsants. Anticonvulsants are mainly prescribed for epilepsy (although there are other indications such as bipolar disorder), epilepsy may be associated with increased risk of dementia,[21] anticonvulsants may be associated with confusion among patients with mild cognitive impairment in much the same way as lithium,[22] and taking anticonvulsants for longer periods requires good adherence to treatment possibly related to a healthier life-

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style. Finally, anticonvulsants have been associated with neuroprotective abilities in much the same way as lithium, including inhibition of glycogen synthase kinase 3.[23,24] As can be seen from Figure 2, the rate of dementia was increased when patients received 1 prescription for anticonvulsants compared with 0 prescriptions and increased further to a rate ratio ranging from 1.5 to 2.0 when patients received more prescriptions. Thus, this pattern is quite different from the pattern seen with lithium in Figure 1. Although we do not find it likely that our results can be explained entirely by methodological drawbacks, we cannot exclude this possibility because of the nonrandomized nature of our data.

Our finding is in accordance with the finding by Nunes et al[8] of a decreased prevalence of Alzheimer disease among patients receiving long-term lithium therapy. However, in contrast, Dunn et al[7] previously found an increasing risk of dementia with increasing numbers of lithium prescriptions. Their earlier study compared the number of lithium prescriptions among individuals with and without dementia. As argued by Gattaz et al[25] and acknowledged by Dunn et al,[7] the finding may be due to "reverse causation" related to the sampling method because affective disorder may increase the risk of dementia[1,2] and the likelihood of receiving lithium after a diagnosis of dementia.[26] In the present study, patients who received a diagnosis of dementia before the start of lithium therapy were excluded.

It is not possible from the present study to decide whether lithium has a protective effect against dementia due to increased neurogenesis, due to mood stabilizing abilities that prevent recurrence of affective episodes, or due to other treatment-related factors. In naturalistic data, as were used in the present study, it is not possible to validly investigate the association between treatment, such as lithium therapy, and the course of illness, owing to confounding by indication because patients with many episodes tend to take lithium for a longer time. As expressed by Keller et al,[27(p693)] in naturalistic studies "treatment itself becomes an outcome, because [the] patient's state [is] likely to help determine the choice of treatment."

In conclusion, in a nationwide study that included all patients treated with lithium, it was found that continued lithium treatment was associated with a reduced rate of dementia to the same level as the rate for the general population, although this rate increased slightly with the number of prescriptions. Methodological reasons for this finding cannot be excluded, owing to the nonrandomized nature of data.

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