Does Lithium Therapy Protect Against the Onset of Dementia?

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Abstract: Lithium compounds might theoretically play a role in preventing dementia by inhibiting formation both of beta amyloid and hyper phosphorylated tau protein. We carried out a case-control study to assess any possible clinical effects of lithium therapy on the diagnosis of dementia, using data from the General Practice Research Database, which collects routine data from primary care patients in the UK. Patients who received lithium had a higher risk of a diagnosis of dementia compared with those who did not (adjusted odds ratio 1.8, 95% CI 1.1–2.8). There was a trend toward increasing risk with increasing numbers of lithium prescriptions. This evidence does not support the use of lithium for preventing dementia.

Key Words: dementia, diagnosis, lithium therapy

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Although the exact pathogenesis of Alzheimer disease, a primary degenerative disorder, is not fully understood, the most widely accepted hypothesis is that accumulation of beta amyloid peptide is the main trigger for formation of neurofibrillary tangles, which are associated with tau protein hyperphosphorylation. Degeneration and death of affected neurones then follows.[1] Lithium is a drug that could influence this basic pathologic mechanism. Lithium is normally used for the suppression of an affective disorder, be it unipolar depression or bipolar disorder. One of its modes of action is thought to be related to up-regulation of production of the neuroprotective protein bcl-2, and also to inhibition of the enzyme glycogen synthase kinase 3beta (GSK-3β).[2] Several workers have shown that inhibition of GSK-3β blocks the formation of beta amyloid peptides and the hyperphosphorylation of tau protein, at least in animal models.[3–5] Other work on rats has shown that there is a temporal association between lithium-induced up-regulation of the protein bcl-2 and attenuation of neuronal death caused by beta amyloid.[6] As yet, there have been no published clinical studies on the use of lithium for dementia. We present here the results of a retrospective study to examine the hypothesis that patients with a history of lithium therapy are less likely to be diagnosed with dementia than those without such a therapeutic history.

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METHODS

We carried out a nested case-control study using patient records from the General Practice Research Database (GPRD). This is a well validated database that is currently collecting data from about 3 million patients in about 300 separate general practices in the UK. The database has been collecting data since 1987. The study population was all patients on the GPRD over the age of 60 years, with data available between January 1, 1992 and January 1, 2002. We identified cases as all those patients with an incident diagnosis of dementia, who had at least 4 years of research standard data preceding the date of first diagnosis (median time from onset of symptoms to diagnosis has been estimated at 4 years).[7] We included cases with a definite diagnosis of Alzheimer disease, vascular dementia (with which there is diagnostic overlap), and those with uncertain cause of dementia. Other specified causes of dementia were excluded (eg, dementia in Parkinson's disease). Controls were randomly selected from patients without a diagnosis of dementia, having at least 4 years of data available before the matched case date of diagnosis. There was 1 control per case. We validated a random sample of the cases and controls by writing directly to their GP for confirmation of their medical history.

Exposure to lithium was measured by searching prescription records for any preparation of lithium. Each date of prescription was included in the data set.

We counted the number of prescriptions and analyzed by categories (in quarters of distribution), by a dichotomous variable of any prescription or none, and also by duration of lithium therapy in two categories ($\leq$5.5 years, $>$5.5 years, where 5.5 years was the median duration of therapy in cases and controls).

Statistical analysis used the technique of Mantel Haenszel for weighted odds ratios. Each potential confounder was added in univariate analysis, and in the final analysis only age was included. Calculations were performed on Stata 7.

RESULTS

Table 1 shows the characteristics of the case and controls with reference to demography, potential confounding factors, and exposure to lithium therapy. Cases were older than controls, more likely to be female, to smoke and to be diabetic.

TABLE 1. Baseline Characteristics of Case and Controls at Date of First Diagnosis

	Cases	Controls
Number	9954	9374
Type of dementia: Alzheimer	238 (2.4%)	
Vascular	688 (6.9%)	
Not recorded	9028 (90.7%)	
Sex: male	3266 (32.8%)	4021 (42.9%)
Age at diagnosis: mean (SD)	82.1 (6.9)	72.7 (8.0)
60–74	1609 (16.2%)	5975 (64.0%)
75–84	4734 (47.6%)	2574 (27.6%)
85+	3611 (36.3%)	791 (8.5%)
Diabetes mellitus present	772 (7.8%)	536 (5.7%)
Current smoker	710 (7.1%)	395 (4.2%)
Lithium therapy positive, n	47	40
Number of lithium prescriptions, n (%): 1–13	10 (21)	12 (30)
14–24	11 (23)	12 (30)
25–39	12 (26)	9 (22.5)
>/=40	14 (30)	7 (17.5)
Median (IQR) number of years on lithium, preceding diagnosis date	5.4 (4.0–9.1)	6.0 (3.7–8.5)

More cases (n = 47) than controls (n = 40) were exposed to lithium in the period preceding the date of the case diagnosis. The crude odds ratio for exposure to lithium was 1.2 (95% CI 0.8–1.8), which increased to 1.8 (95% CI 1.1–2.8) when adjusted for age (see Table 2). We found that age was the only confounding factor that made a significant difference to the crude odds ratio. When lithium exposure was categorized according to number of prescriptions issued per patient, there was a significant trend toward higher odds ratios in those with higher numbers (odds ratio 1.3, 95% CI 1.1 to 1.6 for each unit increase in quarter).

When we analyzed by duration of lithium exposure, in 2 categories, the age-adjusted odds ratios for exposure to lithium of "short" duration (up to 5.5 years) was 2.3 (95% CI 1.2–4.3), and of "long" duration (>5.5 years) was 1.4 (95% CI 0.8–2.8).

Our validation study on 150 cases and 50 controls did not reveal any patients with incorrect diagnoses (ie, there were no controls who should have been cases, and all the cases were subsequently confirmed as having dementia, which was irreversible).

TABLE 2. Odds Ratios for Association Between Dementia and Use of Lithium in Preceding Four Years

Exposure	Crude Odds Ratio (95% CI)	Odds Ratio (95% CI), Adjusted for Age
Lithium therapy (yes/no)	1.2 (0.8 to 1.8)	1.8 (1.1 to 2.8)
Number of prescriptions:		
1–13	0.8 (0.4 to 1.9)	1.4 (0.6 to 3.1)
14–24	0.9 (0.4 to 2.0)	1.5 (0.6 to 3.9)
25–39	1.3 (0.6 to 3.1)	1.8 (0.7 to 4.5)
>/=40	2.0 (0.8 to 4.9)	3.1 (1.1 to 8.9)

DISCUSSION

Our analysis of this data set has shown that lithium does not seem to confer any protective effect on the development of the common types of dementia. Although 90.7% of the cases were recorded in the data set as "dementia" (ie, the etiology is undefined), we may assume that about 70% of these will be cases of Alzheimer disease.[8] If anything, the odds ratios suggest that use of lithium may be a risk factor for the onset of dementia, and the fact that there is a positive trend with increasing 'dose' lends biologic credence to this association. There are a number of possible explanations for this association. First, there may be increased contact between health worker and patient, because of the use of chronic lithium therapy, and this might present more opportunity for dementia to be recognized, and recorded in the notes. This would lead to a bias of recorded cases toward those on lithium. However, we have tested frequency of consultation before the date of diagnosis of dementia as a potential confounder for a subset of this data set on whom we have full data of all consultations (4805 patients, 25 on lithium). In this subset, consultation frequency did not have any confounding effect on the association. Second, this might be explained by lithium therapy acting as a marker for depression as the true risk factor. Although depression is a known pre-disposing cause of reversible dementia, such cases of dementia are relatively rare compared with the irreversible, and the validation study suggests that they are not likely to constitute a large proportion of cases in this data set. Third, there is the possibility that this is the result of "reverse causation", in that dementia is known to be associated with depression (although not with bipolar disorder), and lithium is used to treat depression. In fact, the analysis by duration of lithium therapy lends some support to this hypothesis, since the odds ratios are higher in those with relatively short duration of therapy (>5.5 years) than for those with longer-term therapy (odds ratios 2.3 compared with 1.4, although the confidence intervals overlap). Nevertheless, there is still no suggestion of a protective effect of lithium, even in those with many years of therapy preceding the diagnosis of dementia.

There are clearly some limitations to this study, notably the relatively small numbers of patients being treated with lithium, and also the fact that we are unable to fully disentangle the effects of lithium itself and that of depression in terms of the association with dementia. However, it is clear that any protective effect of lithium is not strong, if it exists at all. Also, we are using data on prescriptions written by the doctor, and we have no measure of patient compliance with the recommended medication. Despite these caveats, this study is important in that it is the first to report the effects of lithium in patients developing dementia, and the results are not encouraging clinically.

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