

Lithium use and the risk of fractures

Ingeborg Wilting^{a,b}, Frank de Vries^a, Brahm M.K.S. Thio^a, Cyrus Cooper^c, Eibert R. Heerdink^a,
Hubert G.M. Leufkens^a, Willem A. Nolen^d, Antoine C.G. Egberts^{a,e}, Tjeerd P. van Staa^{a,f,*}

^a Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht, The Netherlands

^b Department of Clinical Pharmacy, TweeSteden hospital and St Elisabeth Hospital, Tilburg, The Netherlands

^c Medical Research Council Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, England, UK

^d Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands

^e Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

^f General Practice Research Database, Medicines and Healthcare products Regulatory Agency, London, England, UK

Received 18 October 2006; revised 6 December 2006; accepted 13 December 2006
Available online 21 December 2006

Abstract

A recent study reported a decreased risk of fractures among lithium users. We conducted a case–control study within the UK General Practice Research Database, comparing never, ever, current, recent and past lithium use in 231,778 fracture cases to matched controls. In addition, the risk of fractures was assessed in relation to cumulative duration of use and time since discontinuation. Current use of lithium was associated with a decreased risk of fractures (adjusted odds ratio [OR]=0.75, 95% confidence interval [CI]=0.64–0.88), which did not vary with cumulative duration of use. Among past users an increased risk of fractures was observed (adjusted OR=1.35, 95% CI=1.01–1.79), increasing with time since discontinuation. Our results support the role of the underlying mental disorders in the aetiology of fractures and do not support a pharmacological effect of lithium based on lack of an association with cumulative duration of use.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Fractures; Lithium; Mania; Depression

Introduction

Bipolar disorder is characterised by (hypo)manic and depressive episodes alternated with periods of euthymia. Mania is associated with uncontrolled behaviour that may lead to accidents [6], while depression is associated with an increased risk of suicide and suicide attempts [12,26], thereby possibly increasing the risk of fractures. Lithium salts are one of the first choice agents for the long-term treatment of bipolar disorder and have been demonstrated to be effective in the treatment of acute mania and depression and to attenuate further

manic and depressive episodes [1,11,25]. Moreover, lithium protects against suicide, which is possibly independent of its effects on mood [11,16]. Discontinuation of long-term lithium treatment has been shown to result in recurrence of both depression as well as mania [2,7,24], and this risk of recurrence is larger after abrupt discontinuation [7].

Lithium has been reported to affect bone density. Observational studies have shown a decrease in bone mineral content within 6 months of initiation of lithium treatment [18]. Reduced bone resorption in patients on long-term lithium treatment was suggested, based on a decrease in 24-h urinary calcium excretion [13]. However, two other studies reported no effect of chronic lithium treatment on bone mineral density [3,17]. The reasons for the different results are not clear. Recently, a large population-based case–control study reported a decreased risk of fractures in users of lithium further decreasing with cumulative dose [27]. However, this study did not take into

* Corresponding author. Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, PO Box 80.082, 3508 TB, Utrecht, The Netherlands. Fax: +31 30 2539166.

E-mail address: T.P.vanStaa@pharm.uu.nl (T.P. van Staa).

account the timing of lithium use. Any patient who ever received at least one lithium prescription in the 4 years prior to the date of fracture was considered to be exposed to lithium.

It is unclear whether the association between lithium use and risk of fractures is due to a direct effect of lithium, or can also be attributed to the therapeutic effects of lithium on the underlying mood disorder. In order to elucidate which of these two potential influencing factors predominates, investigating timing of lithium exposure is important. Therefore the objective of our study was to further explore the association between lithium and fractures, taking into account the timing of lithium use.

Materials and methods

Setting

General practitioners (GP) play a key role in the public health care system in the United Kingdom, being responsible for primary health care as well as being the gatekeepers for secondary care. The information in this study was obtained from the General Practice Research Database (GPRD), which contains the computerised medical records of about 650 general practitioner practices. Approximately 5 million of the total registered population of England and Wales are represented in this database. The GPRD includes demographic information about the patient, diagnoses, prescription details, preventive care provided, referrals to specialist care, hospital admissions and their major outcomes. Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OXMIS) and Read codes for diseases or causes of morbidity and mortality that are cross-referenced to the International Classification of Diseases (ICD-9). Several independent validation studies have shown that the GPRD database has a high level of completeness and validity [28]. A validation study by Van Staa et al. reported a high validity of the GPRD with respect to fractures [23]. In this study, data assembled in the GPRD from January 1987 to July 1999 were used. All patients aged 18 years or older registered in the GPRD were eligible for participation. Within this study base, a case–control study was conducted.

Study population

In this study, cases were patients aged 18 years or older with a first record of any fracture during GPRD follow-up. The first occurrence of a fracture during follow-up was identified through relevant OXMIS and Read codes, which were converted to ICD-9 codes. The index date was defined as the date of the first fracture. Each case was matched to one control patient (without a history of fractures) by year of birth (with a maximum difference of 10 years), gender and general practice. The index date of the control patient was the date of the first fracture of the matched case. We collected data on occurrence of any fracture, osteoporotic fracture (defined as one or more of all hip, femur, radius, ulna, vertebral, rib, humerus and clavicle fractures) and hip/femur fracture.

Exposure patterns

The primary exposure variable was ever use of lithium; ‘ever use’ was defined as having received at least one prescription for lithium (British National Formulary Chapter 4.2.3) prior to the index date. Information on use of lithium was extracted from the patients’ medication file. Next, all ever lithium users were classified as either ‘current’, ‘recent’ or ‘past’ users. Current users were those who received a lithium prescription within 2 months prior to the index date. Patients who had been prescribed their last lithium prescription more than 2 months but less than 12 months prior to the index date were considered recent users. Past users were those who received their last lithium prescription more than 12 months before the index date (Fig. 1).

For current lithium users the cumulative duration of use was determined for the period between the initiation of lithium therapy and the index date. For each lithium prescription, the expected duration of use was estimated using the data

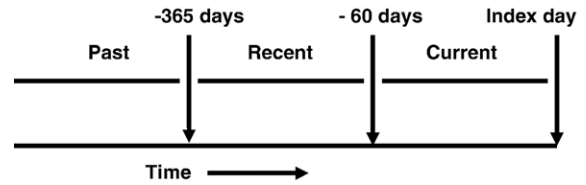


Fig. 1. Timing of lithium use.

on the prescribed quantity and the written dosage instruction. In case of missing data, the duration of use was taken as the median value of duration of use in patients from the same age category. The cumulative duration of use was calculated by adding all separately calculated expected durations of use before the index date. In recent and past lithium users, we determined the time since lithium discontinuation, defined as the time period between the last lithium prescription and the index date. An analysis of cumulative lithium dose was also conducted, expressing cumulative dose in Defined Daily Doses (DDD), with one DDD corresponding to 24 mmol lithium. This analysis was conducted for ever-users and also separately for current, recent and past lithium users.

Potential confounders

Potential confounders in this study were prior medical conditions and concomitant use of medications known to be associated with falls, fractures or known to be associated with either bone anabolic or catabolic effects. Medical conditions included diabetes mellitus, psychotic disorders, cerebrovascular accidents, anaemia, congestive heart failure, hypothyroidism, hyperparathyroidism, history of falls and renal impairment, evaluated within 1 year prior to the index date. Concomitantly used medications were evaluated within a 6-month period prior to the index date. Concomitantly used medication assessed included non steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), hormone replacement therapy (HRT), thyroid hormones, thiazide diuretics, anxiolytics/hypnotics, antipsychotics, antidepressants, anticonvulsants, anti-parkinsonian drugs, calcitonin, oral and inhaled glucocorticoids, and bronchodilators. In addition, we also included body mass index (BMI) (<20, 20–25, >25 kg/m², or unknown) and smoking status (history, no history of smoking, or unknown). Lastly, we also considered severity of the mood disorder as potential confounder, as patients with more severe forms might be more prone to fracture risk-increasing behaviour. As a measure for severity of disease we considered whether patients had been admitted to a psychiatric hospital or ward during the year prior to the index date.

Data analyses

Patients who had ever been on lithium treatment were compared to never users. In addition, ever use was stratified to current, recent and past use. The strengths of the associations between lithium exposure and fractures were evaluated using conditional logistic regression and were expressed as odds ratios (OR) and 95% confidence intervals (CI). Final regression models were determined by backward elimination of potential confounders using a significance level of $p < 0.05$. In order to differentiate between the effect of lithium itself and the underlying mood disorder two separate analysis were performed, on cumulative duration of use in current users and on time since discontinuation of lithium treatment in ever users. Cumulative duration of lithium use in current users was investigated as the onset of an effect of lithium on bone may only be several months after start of treatment. Time since discontinuation of lithium was investigated to evaluate the offset of any lithium effect. Smoothing spline regression analysis was used in these analyses. The group of current lithium users was subdivided into 10 subgroups based on deciles of the cumulative duration of use (or time since discontinuation). An OR was calculated for each of the subgroups. Spline regression was then used to smooth these estimates and to visualise any trends. This method has been advocated as an alternative to categorical analysis [8]. In addition, a linear trend analysis (r^2) was performed on these ORs.

In order to determine any effects of disease severity, we determined whether current lithium users had been on concurrent psychotropic medication

(antipsychotics, antidepressants, valproic acid or carbamazepine – agents that are frequently used as mood stabilising agents) within 6 months prior to the index date or had been admitted to a hospital because of a mental disorder within 1 year prior to the index date. Current users were subsequently stratified according to concurrent use of antipsychotics, antidepressants or valproic acid/carbamazepine or recent hospitalisation for a mental disorder.

All analyses were performed using SAS 9.1.3.

Results

The study population included 231,778 adult patients who sustained a fracture and 231,778 age-, gender- and practice-matched control patients. The median time of enrolment before the index date was 2.8 years. The characteristics of the study population are listed in Table 1. Average daily lithium dose did not differ between cases and controls within the group of current lithium users. Psychotic disorder, depression and bipolar disorders were all more frequent in the fracture cases, as was hospitalisation for a mental disorder and the use of anticonvulsants, anxiolytics/hypnotics and antipsychotics.

Ever use of lithium was associated with a decreased risk of fractures (adjusted OR=0.85, 95% CI=0.74–0.96) (Table 2). The timing of prior use of lithium was found to be important: current lithium users had a decreased risk of fractures (adjusted OR=0.75, 95% CI=0.64–0.88), whereas an increased risk was observed in patients who discontinued lithium at least 1 year ago (adjusted OR=1.35, 95% CI=1.01–1.79). The risk of fractures increased with time since discontinuation in patients who had discontinued their lithium treatment (linear regression coefficient; $r^2=0.66$) (Fig. 2). A similar trend was observed when separately performing the analysis for those who did not use an antipsychotic, an antidepressant, valproic acid or carbamazepine in the 6 months prior to the index date and those who did receive at least one prescription for any of these drugs. However, the overall risk in those not having been prescribed one of these drugs in the 6 months prior to the index date was smaller (results not shown).

A similar trend was observed for osteoporotic fractures (results not shown). The risk of hip/femur fracture was increased in ever users of lithium (adjusted OR=1.97 95% CI=1.24–3.12). This effect persisted when taking into account timing of lithium use resulting in an adjusted OR of 1.39 [95% CI 0.80–2.43] for current lithium users that further increased after lithium discontinuation (adjusted OR of 3.14 [95% CI=0.84–11.8] for recent users and an adjusted OR of 4.29 [95% CI=1.39–13.2]) for past users. No differences were found in the risk estimates of lithium use and fractures across age and gender.

Fig. 3 shows the risk of any fracture with cumulative duration of lithium use among current lithium users. There was no change in risk of fractures with increasing cumulative duration of lithium use (linear regression coefficient, $r^2=0.035$).

In order to investigate the influence of the severity of the underlying mental disorder we stratified the current lithium users according to concurrent use of antipsychotics, antidepressants or valproic acid/carbamazepine or recent hospitalisation

Table 1
Baseline characteristics

	Cases (n=231,778)		Controls (n=231,778)	
Age (years), mean (S.D.)	51	(22)	51	(22)
Gender (female), n (%)	121,615	(52.5)	121,615	(52.5)
Ever use of lithium, n (%)	538	(0.23)	489	(0.21)
Average daily use of lithium (mmol), mean (S.D.)	16.4	(14.1)	16.6	(9.6)
Cumulative duration of lithium use (years), median	1.3		1.3	
Medical history before the index date, n (%)				
Bipolar disorder (ever prior)	850	(0.4)	665	(0.3)
Depression (1 year prior)	11,791	(5.1)	8121	(3.5)
Psychotic disorders (1 year prior)	946	(0.4)	763	(0.3)
Hospitalisations for psychiatric disorder (1 year prior) ≥ 1	1775	(0.8)	1083	(0.5)
Renal impairment (ever prior)	2339	(1.0)	1730	(0.7)
Hyperparathyroidia (ever prior)	116	(0.1)	95	(0.0)
Anaemia (1 year prior)	4117	(1.8)	3004	(1.3)
Cerebrovascular disease (1 year prior)	10,846	(4.7)	8291	(3.6)
Heart failure (1 year prior)	9636	(4.2)	8239	(3.6)
Epilepsy (1 year prior)	5186	(2.2)	2707	(1.2)
Diabetes (1 year prior)	7101	(3.1)	6331	(2.7)
Hypothyroidism	4144	(1.8)	3466	(1.5)
BMI				
0–19.99 kg/m ²	13,439	(5.8)	11,316	(4.9)
20–24.99 kg/m ²	65,457	(28.2)	60,283	(26.0)
≥ 25 kg/m ²	87,161	(37.6)	97,228	(41.9)
Not recorded	65,721	(28.4)	62,951	(27.2)
Smoking				
Yes	49,059	(21.2)	40,419	(17.4)
No	106,014	(45.7)	101,892	(44.0)
Missing	76,705	(33.1)	89,467	(38.6)
Co-medication 6 months prior, n (%)				
Anticonvulsants	5282	(2.3)	2682	(1.2)
Hormone replacement therapy	5685	(2.5)	6164	(2.7)
Anxiolytics/hypnotics	22,328	(9.6)	16,577	(7.2)
Antipsychotics	6157	(2.7)	4564	(2.0)
Antidepressants	16,449	(7.1)	11,545	(5.0)
Levothyroxin/liothyronin	5941	(2.6)	5166	(2.2)
Calcitonin	30	(0.0)	12	(0.0)
Thiazide diuretics	13,373	(5.8)	13,532	(5.8)
DMARDs	1660	(0.7)	1225	(0.5)
NSAIDs	32,209	(13.9)	23,617	(10.2)
Anti-parkinsonian drugs	2808	(1.2)	1846	(0.8)
Oral corticosteroids	7704	(3.3)	4692	(2.0)
Inhaled bronchodilators/corticosteroids	19,579	(8.4)	14,554	(6.3)

for psychiatric disorder (Table 3). Current lithium users who also used antidepressants had a similar fracture risk compared to non-users, while the current lithium users who did not use antidepressants had a statistically significant reduced risk of fracture (test for interaction P -value <0.05).

We observed a decreased risk of fractures in ever users of lithium, with the largest reductions at the highest cumulative doses (cumulative dose <250 DDD: adjusted OR=0.84 [95% CI=0.50–1.39]; cumulative dose 250–849 DDD: adjusted OR=0.85 [95% CI=0.72–0.99]; cumulative dose 850 DDD or more: adjusted OR=0.59 [95% CI=0.45–

Table 2
Exposure patterns to lithium in cases and controls

	Fracture (any type)		Crude OR (95% CI)	Adjusted OR ^a (95% CI)
	Cases (n=231,778)	Controls (n=231,778)		
Never used lithium	231,240	231,289	Reference	Reference
Ever user of lithium	538	489	1.10 (0.97–1.24)	0.85 (0.74–0.96)
Current users	313	312	1.00 (0.86–1.17)	0.75 (0.64–0.88)
Recent users	91	93	0.98 (0.73–1.31)	0.75 (0.55–1.01)
Past users	134	84	1.60 (1.21–2.10)	1.35 (1.01–1.79)
	Osteoporotic fractures		Crude OR (95% CI)	Adjusted OR ^b (95% CI)
	Cases (n=108,754)	Controls (n=108,754)		
Never used lithium	108,451	108,496	Reference	Reference
Ever user of lithium	303	258	1.17 (0.99–1.39)	0.83 (0.69–0.99)
Current users	184	170	1.08 (0.88–1.33)	0.74 (0.59–0.92)
Recent users	48	46	1.04 (0.70–1.56)	0.72 (0.47–1.11)
Past users	71	42	1.69 (1.15–2.48)	1.35 (0.90–2.02)
	Hip/femur fractures		Crude OR (95% CI)	Adjusted OR ^c (95% CI)
	Cases (n=22,250)	Controls (n=22,250)		
Never used lithium	22,165	22,222	Reference	Reference
Ever user of lithium	85	28	3.03 (1.98–4.64)	1.97 (1.24–3.12)
Current users	50	21	2.38 (1.43–3.96)	1.39 (0.80–2.43)
Recent users	15	3	5.00 (1.45–17.3)	3.14 (0.84–11.8)
Past users	20	4	5.00 (1.71–14.6)	4.29 (1.39–13.2)

^a Adjusted for: 1 year prior: heart failure, anaemia, cerebrovascular disease, diabetes, and renal impairment. 6 months prior: thiazide diuretics, history of falls, HRT, NSAIDs, anxiolytics/hypnotics, antidepressants, anticonvulsants, anti-parkinsonian drugs, inhaled bronchodilators/corticosteroids, oral corticosteroids, antipsychotics, thyroid drugs, smoking and quetelet index.

^b Adjusted for: 1 year prior heart failure, anaemia, cerebrovascular disease, renal impairment, and psychotic disorders. 6 months prior, history of falls, thiazide diuretics, HRT, DMARDs, NSAIDs, anxiolytics/hypnotics, antidepressants, anticonvulsants, anti-parkinsonian drugs, inhaled bronchodilators/corticosteroids, oral corticosteroids, antipsychotics, thyroid drugs, smoking and quetelet index.

^c Adjusted for: 1 year prior heart failure, anaemia, cerebrovascular disease, diabetes, renal impairment, and psychotic disorders. 6 months prior, history of falls, thiazide diuretics, HRT, DMARDs, NSAIDs, anxiolytics/hypnotics, antidepressants, anticonvulsants, anti-parkinsonian drugs, inhaled bronchodilators/corticosteroids, oral corticosteroids, antipsychotics, smoking and quetelet index.

0.77]). These results changed, however, when taking into account the timing of lithium use. No association was found between cumulative dose and the risk of fractures in recent

and past lithium users. In our study, 75% of the lithium users with the highest cumulative dose (≥ 850 DDD) could be classified as current users, whereas those with the lowest

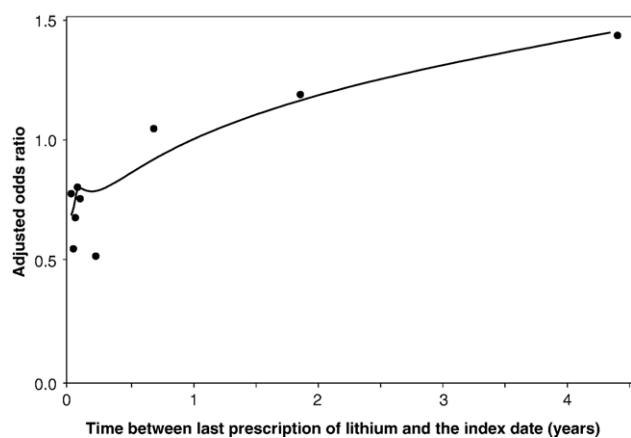


Fig. 2. Risk of fracture (any type) and time since lithium discontinuation. Time since discontinuation of lithium was investigated to evaluate the offset of any lithium effect. Smoothing spline regression analysis was used. The group of ever lithium users was subdivided into 10 subgroups, based on deciles of time since discontinuation. An OR was calculated for each of the subgroups. Spline regression was used to smooth these estimates and to visualise any trends.

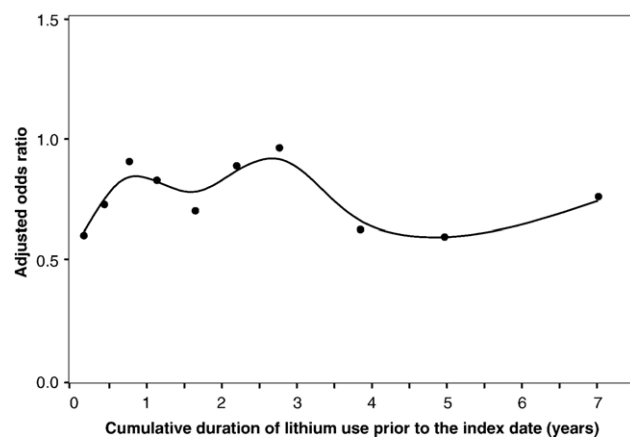


Fig. 3. Risk of fracture (any type) and cumulative duration of lithium use. Cumulative duration of lithium use in current users was investigated as the onset of an effect of lithium on bone may only be several months after start of treatment. Smoothing spline regression analysis was used. The group of current lithium users was subdivided into 10 subgroups, based on deciles of the cumulative duration of use. An OR was calculated for each of the subgroups. Spline regression was used to smooth these estimates and to visualise any trends.

Table 3
The risk of fractures (any type) and concurrent use of psychotropic medication or a history of psychiatric hospitalisation in current lithium users

	Current lithium users		Adjusted OR ^a (CI 95%)
	No. cases	No. controls	
Antipsychotics			
Yes	134	109	0.86 (0.66–1.12)
No	179	203	0.72 (0.58–0.88)
Antidepressants			
Yes	185	141	1.02 (0.82–1.28)
No	128	171	0.61 (0.48–0.77)
Valproic acid/carbamazepine			
Yes	24	21	0.90 (0.50–1.65)
No	289	291	0.75 (0.64–0.89)
Hospitalisations			
Yes	44	40	0.80 (0.51–1.24)
No	269	272	0.75 (0.63–0.89)

^a Adjusted for: 1 year prior: heart failure, anaemia, cerebrovascular diseases, diabetes, renal impairment, psychotic disorders, and hyperparathyroidism. 6 months prior: calcitonin, thiazide diuretics, HRT, DMARDs, NSAIDs, anxiolytics/hypnotics, anti-parkinsonian drugs, inhaled corticosteroids and bronchodilators, oral corticosteroids, thyroid drugs, smoking status and quetelet index.

cumulative dose (<250 DDD) were recent or past lithium users (73%).

Discussion

Our results show a decreased risk of fractures in current lithium users (adjusted OR=0.75, 95% CI=0.64–0.88). Duration of use did not substantially change this risk. On the other hand, an increasing risk of fractures with time since lithium discontinuation was observed. The increasing risk for fractures after discontinuation of lithium was present in patients both with and without use of an antipsychotic, an antidepressant, valproic acid or carbamazepine in the 6 months prior to the index date. However, the risk in those only using lithium was smaller. These results indicate that discontinuation of lithium results in an increasing risk of fractures with time since discontinuation, while the finding that the risk was higher in patients who had used concurrent medication indicates that the risk is higher in those being more severely ill. The importance of the severity of mental illness in the evaluation of the association between lithium exposure and fractures is further substantiated by the observed trend towards an increase in the risk in current lithium users concurrently using other psychotropic medication or previously having been hospitalised for a mental disorder compared to those currently only using lithium.

In line with the results from the previous case–control study conducted by Vestergaard et al. [27], we observed in ever lithium users an association between risk of fracture and cumulative dose. However, this study did not consider the timing of lithium exposure and only considered ever use before of lithium. When taking into account the timing of lithium use in our study, the results of the cumulative dose based stratified analysis changed substantively, resulting in a disappearance of the association between cumulative lithium dose and the risk of

fractures. Thus, it is likely that the finding of cumulative dose response on fractures in lithium users in the study performed by Vestergaard et al. can be explained by confounding by timing of lithium exposure. Epidemiological studies should therefore take into account the timing of exposure.

Several physiological mechanisms have been proposed for bone catabolic or anabolic effects of lithium. Long-term lithium treatment has been associated with the risk of secondary hyperparathyroidism that occurs in about 12–25% of long-term users [3,13,17,18]. Hyperparathyroidism may cause hypercalcaemia, thus stimulating bone resorption. Levels of ionised calcium were found to increase from baseline after 3 months of lithium treatment [14,15]. Another study found that administration of lithium to healthy volunteers resulted in an acute increase in ionised parathyroid hormone, without concurrent alterations in ionised calcium levels [20]. On the other hand, lithium treatment may have bone anabolic effects through stimulating Wnt signalling. Wnts are glycoproteins that can initiate a signal transduction cascade, ultimately resulting in initiation of Wnt-responsive gene transcription. Through this mechanism Wnt is involved in the proliferation of bone marrow-derived mesenchymal stem cells, thereby controlling proliferation of osteoprogenitor cells which are the precursors to the bone mineralising osteoblasts. Lithium is a known Wnt mimic and has, in vitro, at low concentration been shown to stimulate the proliferation of bone marrow-derived mesenchymal stem cells [4,5].

In our study, the duration of lithium use in current users did not change the risk of fractures, even when only focusing on osteoporotic fractures alone. With regard to hip/femur fractures, a trend toward an increased risk of fractures was observed in ever users; this effect persisted when taking into account the timing of lithium use. These findings, therefore, do not support the hypothesis that long-term use of lithium causes clinically meaningful permanent alterations in bone quality by known mechanisms.

Besides the possible effects of lithium on bone, the disorders for which lithium was prescribed may also affect the risk of fractures. Lithium is predominantly prescribed for long-term treatment of bipolar disorders and depression. During manic episodes, patients may show a more dangerous life style with more accidents and thus an increased risk of fractures, while depressive episodes are associated with a higher risk of suicide and suicide attempts [12,26]. In this study, we observed an increased risk of fractures in patients who had discontinued lithium treatment, increasing with time since discontinuation. This finding supports a role of the underlying mental disorder in the aetiology of fractures in past lithium users. Following discontinuation of lithium treatment, its mood-stabilising effects may have disappeared.

We found that current lithium users who also used other psychotropic medications had smaller reductions in the risk of fractures, than the current lithium users who did not use those drugs. This could reflect a role of the severity of the underlying disease. Alternatively, use of antidepressants, antipsychotics, valproic acid and carbamazepine have all been associated with an increased risk of fractures [9,10,19,21,22,29] and it may be

possible that any beneficial effects of lithium on fractures is counteracted by these drugs.

There are several limitations to our study. First, we did not have information on lithium serum levels. Data on lithium serum level could have been interesting in order to determine any “serum level” response relation. Lithium shows large inter- and intra-individual differences in pharmacokinetics resulting in the need to individually adjust lithium dosage to obtain therapeutic target serum level. Because of the poor relation between lithium dose and serum level we decided not to incorporate dosage instead of serum level into our analysis. The fact that the lithium serum level is kept within a narrow therapeutic window might, however, render this limitation less important. Second, a psychiatrist often initiates lithium treatment in the UK and, therefore, the general practitioner, who plays a key role in the health care system in the United Kingdom, may not record the first prescription of lithium. Furthermore, periods of hospitalisation or treatment by community mental health teams may also have resulted in some under recording of lithium use. The likely result of this under recording is an underestimation of the effects of lithium. In determining the time since discontinuation of lithium we determined the time between the last prescription and the index date. It is most likely that patients discontinued using lithium somewhere between the start and the end of their last prescription thus resulting in a maximum overestimation of about 1 month for time since discontinuation. Another limitation of this study concerns lack of clinical details on the type and severity of the mental disorders. Therefore, we were unable to determine the association between specific aspects of the disorders and the risk of fractures. Lastly, some data were missing or incomplete. For example, BMI was not recorded for all patients and BMI is known to be associated with risk of fractures. However, adjustment for BMI did not modify results substantially.

In conclusion, it remains to be elucidated why current users of lithium display a decreased risk of fractures independent of duration of use. Based on the increasing risk of fractures with time since discontinuation of lithium treatment and the increased risk of fractures in those that used concomitant psychotropic medication or having been hospitalised for a mental disorder, our findings support a role of the underlying mental disorders in the aetiology of fractures in past lithium users. However, in order to fully unravel the association between the drug, the underlying mental disorder and the risk of fractures, a prospective cohort study in which patients suffering from bipolar disorder are followed in time would be desirable. Patients with bipolar disorder treated with lithium could then be compared, with respect to bone quality parameters, fractures and disease severity/patterns, to patients with bipolar disorder not using lithium. A complicating factor, however, is that the main pharmacological alternatives for lithium in bipolar disorder, e.g. carbamazepine, (also) have influence in bone quality and fracture risk [30].

References

- [1] Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. *Cochrane Database Syst Rev* 2001 [CD003013].

- [2] Cavanagh J, Smyth R, Goodwin GM. Relapse into mania or depression following lithium discontinuation: a 7-year follow-up. *Acta Psychiatr Scand* 2004;109:91–5.
- [3] Cohen O, Rais T, Lepkifker E, Vered I. Lithium carbonate therapy is not a risk factor for osteoporosis. *Horm Metab Res* 1998;30:594–7.
- [4] de Boer J, Siddappa R, Gaspar C, van Apeldoorn A, Fodde R, van Blitterswijk C. Wnt signaling inhibits osteogenic differentiation of human mesenchymal stem cells. *Bone* 2004;34:818–26.
- [5] De Boer J, Wang HJ, Van Blitterswijk C. Effects of Wnt signaling on proliferation and differentiation of human mesenchymal stem cells. *Tissue Eng* 2004;10:393–401.
- [6] Denning TR. Lithium and motor vehicle crashes: perhaps bipolar disorder is the risk, not its treatment. *BMJ* 2004;328:895–6 [author reply 896].
- [7] Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M. Outcome after rapid vs. gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry* 1993;50:448–55.
- [8] Greenland S. Dose–response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology* 1995;6:356–65.
- [9] Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. *Am J Epidemiol* 2003;158:77–84.
- [10] Hugenholtz GW, Heerdink ER, van Staa TP, Nolen WA, Egberts AC. Risk of hip/femur fractures in patients using antipsychotics. *Bone* 2005;37:864–70.
- [11] Kessing LV, Sondergaard L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. *Arch Gen Psychiatry* 2005;62:860–6.
- [12] Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 1999;56:617–26.
- [13] Mak TW, Shek CC, Chow CC, Wing YK, Lee S. Effects of lithium therapy on bone mineral metabolism: a two-year prospective longitudinal study. *J Clin Endocrinol Metab* 1998;83:3857–9.
- [14] Mallette LE, Eichhorn E. Effects of lithium carbonate on human calcium metabolism. *Arch Intern Med* 1986;146:770–6.
- [15] Mallette LE, Khouri K, Zengotita H, Hollis BW, Malini S. Lithium treatment increases intact and midregion parathyroid hormone and parathyroid volume. *J Clin Endocrinol Metab* 1989;68:654–60.
- [16] Muller-Oerlinghausen B. Arguments for the specificity of the antisuicidal effect of lithium. *Eur Arch Psychiatry Clin Neurosci* 2001;251(Suppl 2):II72–5.
- [17] Nordenstrom J, Elvius M, Bagedahl-Strindlund M, Zhao B, Topping O. Biochemical hyperparathyroidism and bone mineral status in patients treated long-term with lithium. *Metabolism* 1994;43:1563–7.
- [18] Plenge P, Rafaelsen OJ. Lithium effects on calcium, magnesium and phosphate in man: effects on balance, bone mineral content, faecal and urinary excretion. *Acta Psychiatr Scand* 1982;66:361–73.
- [19] Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ. Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987;316:363–9.
- [20] Seely EW, Moore TJ, LeBoff MS, Brown EM. A single dose of lithium carbonate acutely elevates intact parathyroid hormone levels in humans. *Acta Endocrinol (Copenh)* 1989;121:174–6.
- [21] Souverein PC, Webb DJ, Petri H, Weil J, van Staa TP, Egberts T. Incidence of fractures among epilepsy patients: a population-based retrospective cohort study in the General Practice Research Database. *Epilepsia* 2005;46:304–10.
- [22] Souverein PC, Webb DJ, Weil JG, Van Staa TP, Egberts AC. Use of antiepileptic drugs and risk of fractures: case–control study among patients with epilepsy. *Neurology* 2006;66:1318–24.
- [23] van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HGM. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. *Pharmacoepidemiol Drug Saf* 2000;9:359–66.
- [24] Suppes T, Baldessarini RJ, Faedda GL, Tohen M. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Arch Gen Psychiatry* 1991;48:1082–8.
- [25] Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. *Acta Psychiatr Scand* 2001;104:163–72.
- [26] Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P,

- Isometsa ET. Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry* 2005;66:1456–62.
- [27] Vestergaard P, Rejnmark L, Mosekilde L. Reduced relative risk of fractures among users of lithium. *Calcif Tissue Int* 2005;77:1–8.
- [28] Walley T, Mantgani A. The UK general practice research database. *Lancet* 1997;350:1097–9.
- [29] Yazici KM, Akinci A, Sutcu A, Ozcakar L. Bone mineral density in premenopausal women with major depressive disorder. *Psychiatry Res* 2003;117:271–5.
- [30] Souverein PC, Webb DJ, Weil JG, VanStaa TP, Egberts AC. Use of antiepileptic drugs and risk of fractures: case–control study among patients with epilepsy. *Neurology* 2006;66:1318–24.