Lithium in older patients: treatment patterns and somatic adverse effects

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Lithium in older patients: treatment patterns and somatic adverse effects

Lithium in oudere patiënten: behandel patronen en somatische bijwerkingen

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 17 april 2014 des ochtends te 10.30 uur

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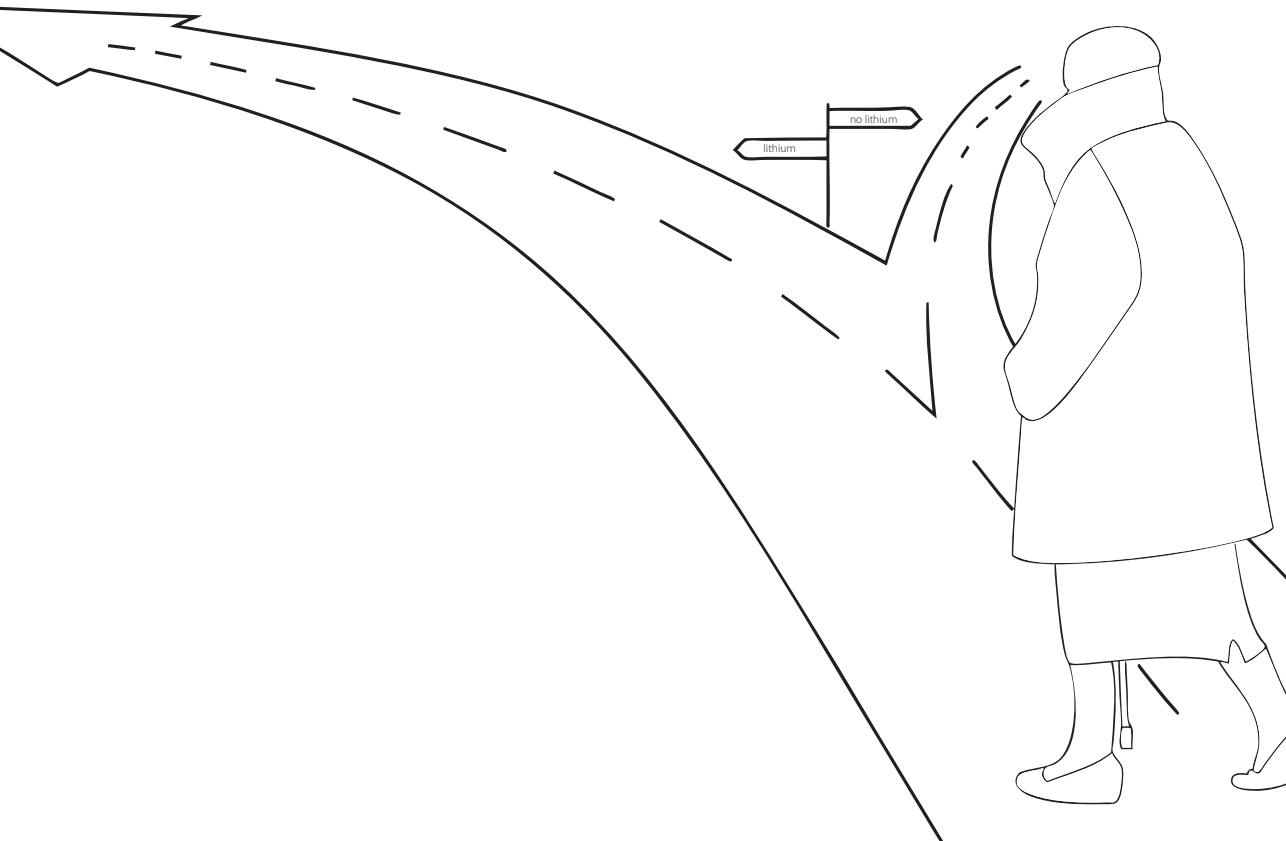
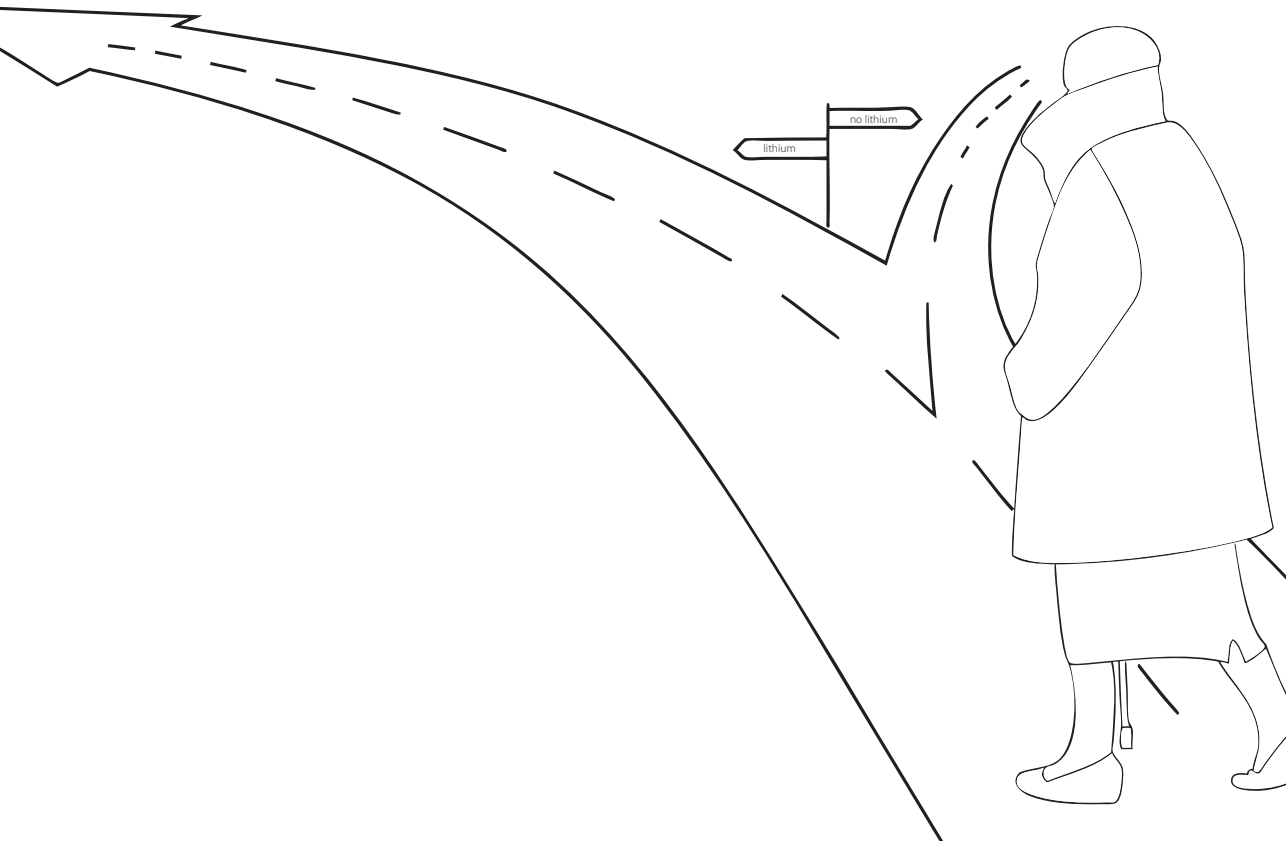


Contents

1

Introduction



Introduction

Background

Lithium has been used in psychiatry since the publication of Cade in 1949.[1] He observed a sedative effect of lithium when given to guinea-pigs. This discovery was a classic example of serendipity as he was investigating the toxicity of urea and lithium was in his experiments merely added to increase the solubility of urea. Cade followed up his observation by treating ten manic patients with lithium citrate resulting in a positive effect in eight patients. Mogens Schou continued this line of research and confirmed the efficacy of lithium as anti-manic treatment.[2] Baastrup et al. demonstrated the prophylactic effect of lithium in bipolar disorder, despite great scepsis, especially from British psychiatrists.[3] During the decennia after this publication lithium has become one of the first-line treatments of acute mania and prophylaxis of bipolar disorder. In addition, lithium is used as augmentation to antidepressants in the treatment of depression and lithium is the only mood stabilizer of which anti-suicidal effects in patients with mood disorders have been established.[4,5]

Pharmacology

Lithium is a naturally occurring alkali metal, a monovalent cation, associated with various salts.[6] In the Netherlands lithium is available as lithiumcarbonate in a standard-release preparation (lithiumcarbonate) and in a sustained-release preparation (Priadel®, Camcolit®). Their T_{max} is respectively 1½-2 hours and 2-3 hours.[6] In the Netherlands, as in many other European countries, lithium is given once a day in the evening. The serum lithium concentration (SLC) is a trough level determined 12 hours after the last dose. Lithium salts are water soluble and the bioavailability is 80-100%. Lithium passes the blood-brain barrier and the concentration in the brain reaches about 50% of the SLC, sometimes rising to 75-80%. Moore et al. found a positive association between age and the ratio brain/SLC in younger patients, but this was not confirmed in an older study group.[7,8] Lithium is not metabolized and is almost exclusively excreted by the kidneys. It passes the glomerular membrane and is for 80% reabsorbed in the proximal tubules. There is a substantial inter-individual variation in $T_{½}$, even between individuals with normal renal function. Intra-individual variation in $T_{½}$ is caused by circumstances that influence water and sodium handling in the kidney like the addition of diuretics, angiotensin-converting-enzym inhibitors or non-steroidal anti-inflammatory drugs, changes in sodium content of diet, changes in hydration by exertion or higher temperature in the environment and co-morbidity like decompensatio cordis or dehydration during diarrhea and vomiting.

Lithium is a drug with a small therapeutic window. The Dutch Guideline on Bipolar Disorder advises a SLC of 0.8-1.2 mmol/L in acute mania and 0.6-0.8 mmol/L during

maintenance treatment.[9] In case of bothersome adverse effects it is advised to try if a lower SLC between 0.4 and 0.6 mmol/L is effective. In a meta-analysis of lithium augmentation in patients with depression the SLC was between 0.5 and 1.1 mmol/L.[4] As the SLC can be influenced by many individual and external factors, extensive monitoring is essential during initiation and long-term treatment.[10] A subtherapeutic SLC can increase the risk of relapse, whereas a SLC above the upper limit of the therapeutic range can increase the risk of adverse effects and even cause (ir)reversible toxicity. In addition, monitoring of adverse effects is essential as they can become manifest even when the SLC is within the therapeutic window because of differences in individual susceptibility. This is especially important in older patients, because they often have multimorbidity and polypharmacy, which both can increase the risk of pharmacodynamic and pharmacokinetic interactions with lithium. The discussion on the most optimal SLC in the elderly is still unresolved.[11] Shulman states that in his personal experience a SLC > 0.8 mmol/L in patients over 75 years of age substantially increases the risk of adverse effects and intoxication. When patients grow older they generally need a lower lithium dose to maintain the same SLC because of changes in body composition with lower V_d and because of declining renal function.[6] Additionally, an older patient can develop adverse effects on a SLC that he could well tolerate before. Reevaluating the optimal SLC for patients while age is increasing is therefore important.

Although lithium has been used in psychiatry for over sixty years, the mechanism of its therapeutic action has not been fully elucidated. At first the effect of lithium was ascribed to its direct effect on neurotransmitter systems. Nowadays it is thought that these changes in neurotransmitters are downstream effects resulting from the influence of lithium on signaling pathways in the central nervous system. This would explain why the therapeutic effect of lithium takes some time to become manifest. Animal studies support the hypothesis that the inhibition of glycogeen synthetase kinase-3 (GSK-3) is one of the mechanisms of lithium that contribute to its efficacy in the treatment of bipolar disorder.[12] Besides the use of lithium in patients with psychiatric diseases, there is a growing field of research focusing on disorders in which the signaling pathways, influenced by lithium, are important such as stroke, Alzheimer dementia and Parkinson's disease.[12] GSK-3 plays a role in signaling pathways throughout the body which could be an explanation why lithium has, next to the desired therapeutic effects, adverse effects on many organ systems.

Indications of lithium in gerontopsychiatry

The incidences and prevalences of late life depression indicate that there are many older patients who are potential candidates for lithium treatment. Beekman er al. found a prevalence of major depression in late life in the general population in the

Netherlands of 2.0%.[13] In their review of the literature on late life depression worldwide they found an average prevalence of major depression of 1.8%, with a prevalence of clinical significant depressive disorder of 13.3%. The incidence rate of major depression in a cohort of the general population in the Netherlands was 7.0/1000 person years in people 55 years and older with a recurrence rate of 27.5/1000 person years.[14] Another study reported on a group of 105 patients, mean age 70.6 years, who were hospitalized for major depression.[15] After 6-8 years 40% had died; of the remaining patients 33% were in remission, 24 % had a relapse with recovery, 22% had residual symptoms, 11% remained ill and 9% probably had dementia. According to the authors these results are in line with results from other studies. In a study on the incidence of bipolar disorder in the Netherlands an incidence rate of 0.7/10.000 person years was found with a peak in early adulthood (15-24 years) of 0.68/10.000 person years and in later life (45-54 years) of 1.2/10.000 person years.[16] A review on the prevalence of late-life mania in inpatients aged 60-96 years reported an estimated prevalence of 6.0% and the patients often had somatic comorbidity.[17] The indications for which lithium is used make long-term treatment often necessary and besides the patients who start lithium treatment in older age, there is a growing group of patients who have grown old with lithium. One has to bear in mind that many of the older patients who are on long-term lithium treatment probably started on an SLC that was much higher than the SLC which is now thought of as optimal.

Adverse effects of lithium in the elderly

In older patients lithium has not specifically been studied in blind, randomized, placebo-controlled trials, but it is assumed that lithium is as effective in the elderly as in the younger population.[18] Lithium was the preferred mood stabilizer for treatment resistant unipolar depression and for prophylaxis of affective disorders according to a recent survey amongst old age psychiatrist in the UK, but it was also the mood stabilizer which generated the highest level of concern regarding its safety.[19] During its long history as therapeutic drug, many studies have been conducted on the adverse effects of lithium. Lithium has many effects on different organ systems and the distinction between adverse effects and (ir)reversible toxicity is not always clear. Generally, adverse effects can become manifest during treatment with SLC that is considered normal and intoxication symptoms become manifest when the SLC is above the therapeutic window. After initiation of lithium treatment a patient can develop a tremor of the hands. This has been ascribed to a too steep incline in SLC and it can disappear after a while, but sometimes it persists.[20] When the SLC increases during maintenance treatment the tremor can return or worsen and become the first sign of intoxication. Gastro-intestinal symptoms, like nausea, vomiting and diarrhea, can also develop shortly after the start of treatment and disappear after a while, but just

Table 1. Adverse effects of lithium treatment[21,22]

	Adverse effects of lithium treatment
Kidney	-decreased urine concentrating capacity -nephrogenic diabetes insipidus -decline in glomerular filtration rate (?)
Thyroid	-hypothyroidism -goiter -hyperthyroidism (?)
Parathyroid	-mild hypercalcemia -lithium associated hyperparathyroidism
Central nervous system	-postural and action tremor
Gastrointestinal	-nausea, diarrhea
Haematologic	-leucocytosis
Metabolic	-weight gain -insuline like effect
Cardiovascular	-T-wave flattening or inversion -sinoatrial node dysfunction (?)
Dermatologic	-exacerbation psoriasis (?) -acneiform reactions (?)
Teratogenic	-cardiovascular malformations (?)

(?) no definite association with lithium treatment

like a worsening tremor these symptoms may also be the first signs of intoxication during maintenance treatment. Many adverse effects, described in Table 1, become manifest during long-term treatment (Table 1).

McKnight et al. conducted a systematic review on lithium associated major adverse effects.[22] They concluded that lithium is associated with an increased risk of reduced renal concentrating capacity, hypothyroidism, hyperparathyroidism and weight gain. There was no significant increased risk of congenital malformations, alopecia or skin disorders and "little evidence for clinically significant reduction in renal function in most patients".

The factors that determine the individual susceptibility for adverse effects are mostly unknown and it is not clear if age itself can influence this susceptibility. Studies on the adverse effects of lithium in older patients are sparse. One of the first studies in older patients was conducted by Roose et al. in 1979.[23] This publication was short and not many details were given. The study group consisted of 31 outpatients treated with lithium with a mean age of 67 years. During a period of 18 months there were four episodes of intoxication in the 31 elderly patients, while during the same period there were only two intoxications in 164 patients younger than 60 years. They tried to keep the SLC for maintenance treatment between 0.6-0.7 mmol/L. Shulman et al. studied a group of 43 outpatients, mean age 74 years.[24] They used lithium for 3-44 months, 30% for bipolar disorder and 70% for refractory or recurrent depression. The

mean 12 hour SLC was 0.5 mmol/L. The side effects reported were hand tremor (33%), polyuria (25%) and polydipsia (50%). Information on polyuria and polydipsia was based on symptoms and was not substantiated with further diagnostic tests. Subjective memory impairment was present in one-third of the patients but this was not substantiated with objective cognitive tests. In a 2-year study of outpatients with bipolar and unipolar disorders treated with lithium, Murray et al. found hand tremor in 29% and polydipsia/polyuria in 44% of the patients.[25] The prevalence and the severity of the tremor tended to increase with age, but not the polydipsia/polyuria. The study group consisted of 166 patients, 37 were older than 60 years and 67.5% used lithium for more than one year. The diagnosis of hand tremor and polydipsia/polyuria were subjectively made. In a retrospective study Holroyd et al. reported on the adverse effects of 114 patients with a mean age of 74.1 years, treated with lithium for an average of 7.5±2.1 years.[26] The average SLC was 0.5 mmol/L (0.3-1.5 mmol/L). During their visits to the outpatient clinic 38.6% of the patients had no adverse effects recorded. The patients who suffered from adverse effects, had been treated for a total of 388 patient years and had a calculated adverse effect rate of 0.23 per year. The most frequent adverse effects were respectively delirium, tremor, hypothyroidism, nausea/diarrhea and polyuria/polydipsia. The adverse effects were extracted from the medical files and no details were given of how the diagnosis were made. In two patients lithium treatment was discontinued because of the severity of the adverse effect, four required hospitalization and 48 adjustment of the lithium dose. In a cross sectional study of 12 octogenarians Fahy et al. found one patient with nephrogenic diabetes insipidus and one patient with hypothyroidism.[27] The mean age of the patients was 83.7 years, the mean duration of lithium use was 53.7 months and the mean SLC was 0.42 mmol/L.
The studies mentioned here used subjective tools, often questionnaires, to evaluate the adverse effects of lithium treatment in the elderly. Up to the start of this thesis no studies in the elderly have been conducted using more objective diagnostic strategies. Homeostatic functions decline in older age, with decreasing renal concentrating capacity and declining glomerular filtration rate. Older patients have more cardiovascular diseases and endocrinological disorders like hypothyroidism and hyperparathyroidism. It is important to know if lithium use can make older patients more vulnerable for these disorders and if there are other determinants which can influence this possible association in the elderly.

Objectives of this thesis

The main objectives of this thesis are to investigate the treatment patterns of lithium in older patients and to study the occurrence of somatic adverse effects of lithium and their possible determinants in older patients.

Outline of this thesis

This thesis consists of two parts of which one is focused on pharmacoepidemiological and clinical pharmacological aspects of lithium use and one is focused on the adverse effects during lithium use in the elderly. In chapter 2.1 a database study is presented in which differences in lithium use patterns are compared between middle-aged and elderly patients during a follow up period from 1996 to 2008. In chapter 2.2 a case report is presented to alert treating physicians on the signs of intoxication, especially in older patients, and to reemphasize the importance of monitoring especially in case of off-label prescription by physicians not familiar with the effects of lithium. In a retrospective study in chapter 2.3 data from laboratories of three hospitals in The Netherlands are studied to investigate if age is a determinant of instability of serum lithium concentration.

In chapter 3.1 a cross-sectional study is presented on the effects of long-term lithium use on the maximum renal concentrating capacity and glomerular filtration rate in a group of older psychiatric patients. Also possible risk factors are studied and in case of a reduced renal concentrating capacity the clinical impact is studied. The cross-sectional study in chapter 3.2 is focused on the prevalence of known cardiovascular risk factors (CVR) and the prevalence of cardiovascular disease (CVD) in older patients treated with lithium and to compare the prevalence to data from studies in the general population and to study the association with the duration of lithium use. In chapter 3.3 a cross-sectional study is presented on the prevalence and determinants of thyroid disorders in older patients with affective disorders who use lithium and in those who do not use lithium. In chapter 3.4 the possible association between duration of lithium use and parameters of calcium homeostasis is studied, corrected for renal function and vitamin D level in older patients. Also in this cross-sectional study the point prevalence of hypercalcemia and raised parathormone are ascertained.

In the final chapter the results of the studies will be discussed together with their implications for daily practice and future perspectives for research.

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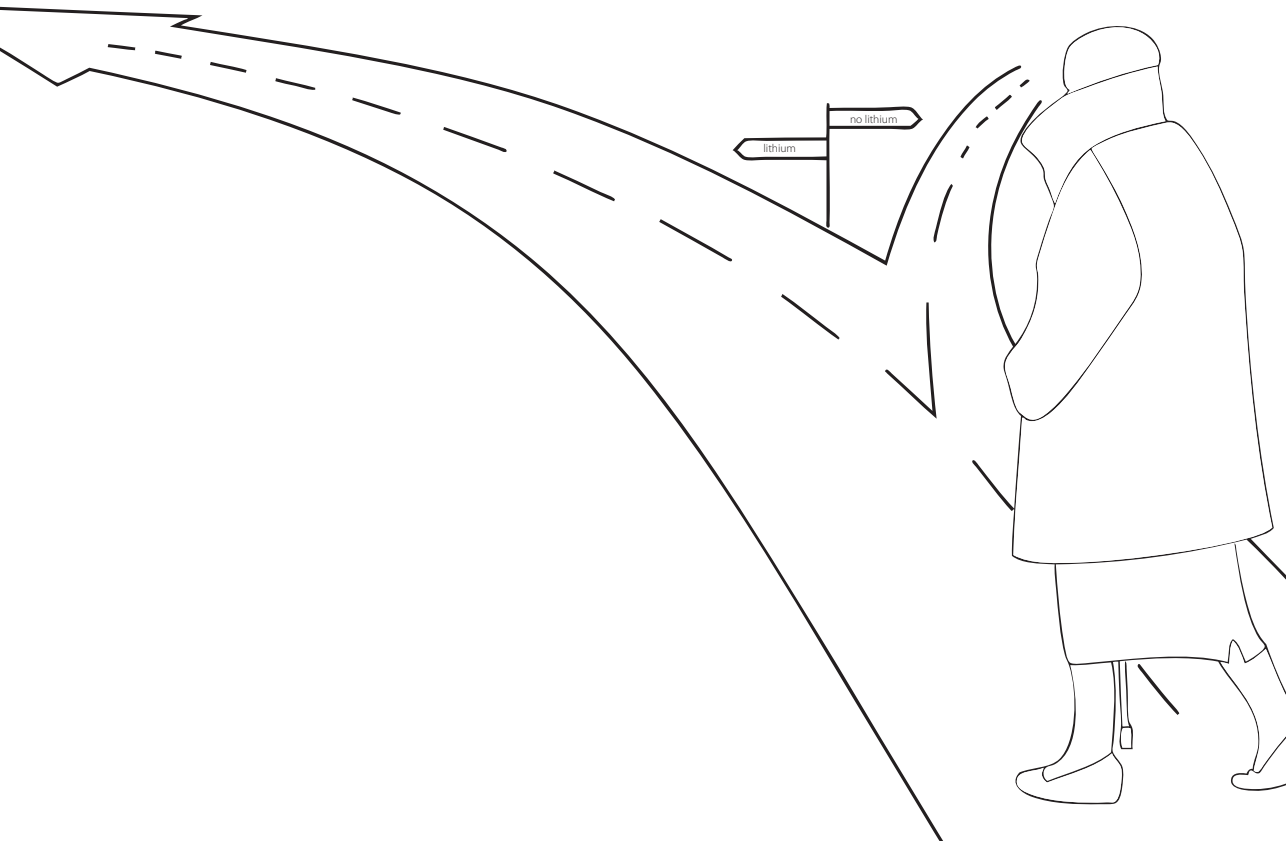
2

Pharmacoepidemiological and clinical pharmacological aspects of lithium use



2.1

Differences in lithium use patterns in the Netherlands: comparing middle-aged and older patients in a database study.

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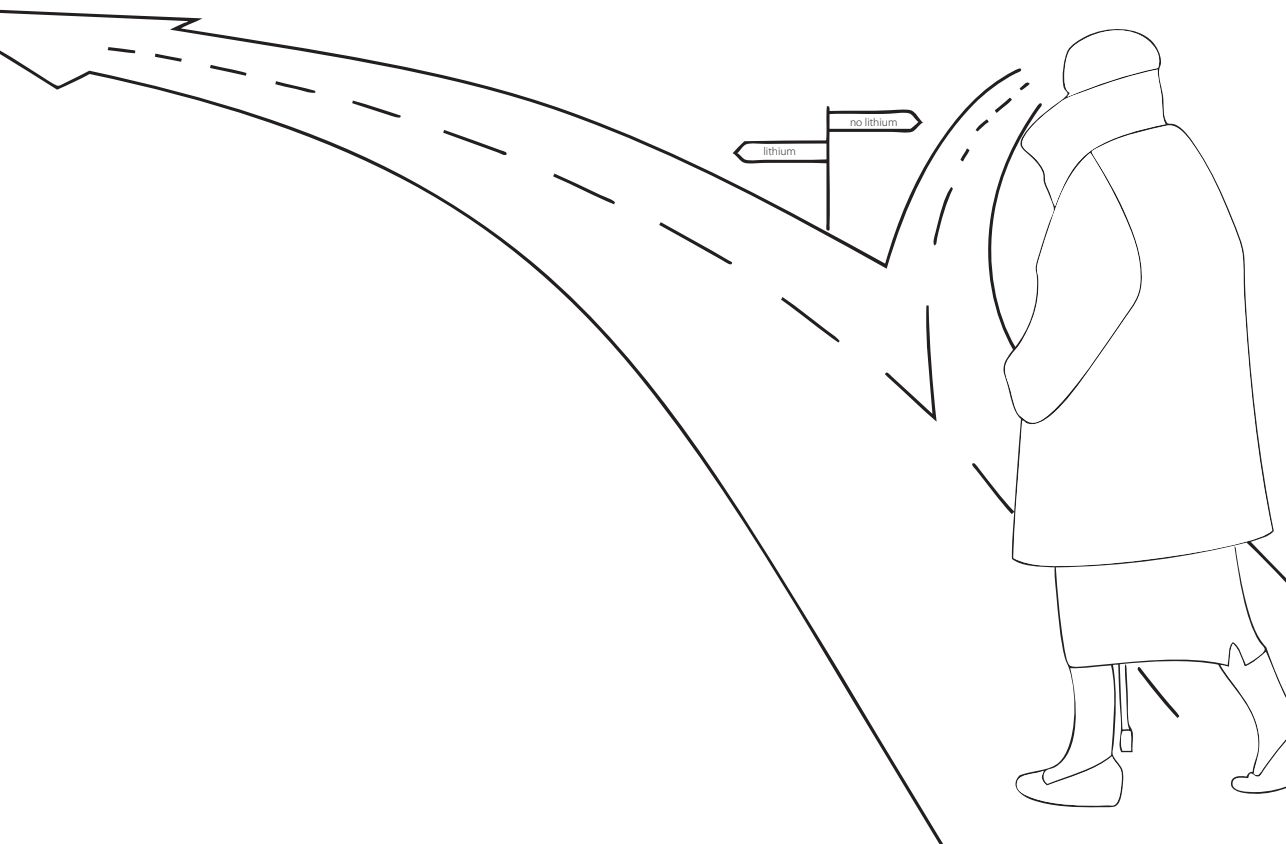

Abstract

Background: Age-dependent changes in lithium pharmacokinetics and pharmacodynamics can influence lithium use in an ageing population, especially as newer treatment options are available.

Objective: We compared lithium use patterns between middle-aged and elderly outpatients in the Netherlands.

Methods: Data for this study were obtained from the Dutch PHARMO Record Linkage System. Incident lithium users, 40 years or older, were identified in the period 1996-2008. Four lithium use patterns were defined: continuation, add-on, switch and discontinuation. Differences were assessed for four age groups: 40-49, 50-59 ,60-69 and 70 years or older. The youngest group was the reference group. Patient baseline characteristics and potential determinants of changes in lithium use patterns were asessed.

Results: We identified 2081 incident lithium users. Use of antidepressants was not different at baseline between age groups but elderly starting lithium treatment less frequently used baseline antipsychotics ($P<0.05$). Older patients were less likely to receive add-on of psychotropics to ongoing lithium therapy ($P<0.05$). The frequency of discontinuation and switch events did not differ between the age groups. In the whole studygroup age was associated with any change in lithium use patterns.

Conclusion: Older patients were less likely to receive add-on of psychotropic drugs to ongoing lithium therapy compared to middle-aged patients. There was no significant difference between older and younger age groups with respect to discontinuation and switch events.

Introduction

Since the early fifties of the twentieth century lithium has been used in the treatment of mood disorders.[1] Lithium is currently part of the first-line treatment in bipolar disorder in guidelines worldwide.[2-5] In addition, it is the first choice medication used as augmentation to antidepressants in treatment-resistant major depression.[6]
In the last decades, anticonvulsants (eg, valproic acid, lamotrigine) and atypical antipsychotics (eg, olanzapine, risperidone, quetiapine) have been introduced for the treatment of bipolar disorders. For the treatment of unipolar depression new antidepressants have become available. Wilting et al.[7] found an increase in switching from lithium to another drug along with a decrease in discontinuation of lithium in the Dutch population aged 18 years or older for the time-period between 1998 and 2003.
The chronic character of mood disorders often requires long-term lithium treatment. Lithium pharmacokinetics change with increasing age due to a decrease in body water and a decrease in renal clearance.[8] Furthermore, elderly people are more susceptible to the adverse effects of lithium even with serum levels within the normal range, which is why lower serum levels are advised by some.[8,9] When people grow older they are at increased risk for developing comorbid disease, which can lead to polypharmacy and an increased risk of drug-drug interactions with lithium.[10] All these age-dependent changes can make physicians more reluctant to initiate or continue lithium therapy, especially with the newer pharmacotherapeutic treatment options that are currently available. Age may therefore influence lithium use patterns.
The objective of this study is to investigate differences in lithium use patterns in middle-aged and older patients. The hypothesis was that older patients less often continue lithium and more often switch to other psychotropic medication.

Methods

Setting

Data for this study were obtained from the PHARMO Record Linkage System (PHARMO RLS). (www.pharmo.nl) The PHARMO RLS includes the demographic details and complete medication history of more than two million community-dwelling residents of more than fifty regions scattered over the Netherlands. Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records can be considered complete with regard to prescription drugs.
The computerized drug-dispensing histories contain information concerning the dispensed drugs, dispensing date, the prescriber, amount dispensed and prescribed

dosage regimen. The duration of use for each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. Patient information per prescribed drug includes gender and date of birth. Each patient is identified with an anonymous unique patient-identification code that allows for the observation of patient drug use in time.
The database does not provide information on indications or reasons for changes in drug use and does not include information on drug dispensing to patients during admission in psychiatric and general hospitals.

Definition of the study cohort

All incident users of lithium were identified in the time-period between January 1996 and August 2008. Incident users were defined as patients with a first prescription for lithium who did not have a prescription for lithium in the previous two years. The

Table 1 Characteristics of incident lithium users at the start of follow-up

Characteristic	40-49 yrs (n=790)		50-59 yrs (n=677)		60-69 yrs (n=344)		70+ yrs (n=270)		All (n=2081)	
Demographics										
Women	456	(57.7)	367	(54.2)	228	(66.3)**	183	(67.8)**	1,234	(59.3)
Age (mean)	44.4		54		64.4		76.2		55	
Prescriber										
Psychiatrist	551	(69.7)	459	(67.7)	232	(67.5)	168	(62.2)	1410	(67.7)
Geriatrician	0		0		0		1	(0.4)	1	(0.05)
General practitioner	80	(10.1)	78	(11.5)	32	(9.3)	46	(17.0)	236	(11.3)
Other prescriber	119	(15.1)	111	(16.4)	59	(17.2)	41	(15.2)	330	(15.9)
Unknown prescriber	40	(5.1)	29	(4.3)	21	(6.1)	14	(5.2)	104	(5.0)
Concomitant use of psychotropic drugs at baseline*										
Antipsychotic drugs	174	(22.0)	124	(18.2)	74	(21.5)	41	(15.1)**	413	(19.8)
Typical	87	(11.0)	53	(7.8)**	31	(9.0)	16	(5.9)**	187	(9,0)
Atypical	93	(11.8)	75	(11.1)	45	(13.1)	25	(9.2)	238	(11.4)
Antidepressants	309	(39.1)	282	(41.6)	133	(38.7)	98	(36.2)	822	(39.5)
TCA	125	(15.8)	130	(19.2)	93	(27.0)**	59	(21.8)**	407	(19.5)
SSRI	108	(13.7)	88	(13.0)	20	(5.8)**	23	(8.5)**	239	(11.5)
other	90	(11.4)	80	(11.8)	20	(5.8)**	24	(8.9)	214	(10.3)
Mood stabilisers	38	(4.8)	31	(4.6)	15	(4.4)	7	(2.6)	91	(4.4)
Valproic acid	2	(0.3)	1	(0.2)	1	(0.3)	0		4	(0.2)
Carbamazepine	15	(1.9)	8	(1.2)	6	(1.8)	3	(1.1)	32	(1.5)
Lamotrigine	22	(2.8)	23	(3.4)	10	(2.9)	4	(1.5)	59	(2.8)

* concomitant use: index date (t=0) is between start and end of prescription of concomitant drug
**Pearson Chi-Square < 0.05 (age group 40-49 years is reference group)

incident users could already be using other psychotropic medication and these were registered as baseline medication (Table 1). The date of the first lithium prescription was defined as the index date and marked the start of follow-up. Patients were eligible for inclusion if they were aged 40 years or older on the index date and had at least one year follow-up available after study entry. Patients could be included in the study only once. If, during follow up, lithium was discontinued and subsequently restarted after more than two years, only the first episode was included in the study.

Lithium use patterns

For each incident user, the lithium use pattern after treatment initiation was classified as either continuation, discontinuation, add-on or switching (Figure 1). Continued use of lithium was defined as not having a gap of six months or more after the theoretical end date of the last and the subsequent lithium prescription, meaning that a patient could have a "lithium free" period of less than 6 months if he used lithium according to his prescription and still be classified as continued user.[11] Psychotropic drug add-on was defined as continued lithium use next to the baseline psychopharmacologic drugs while starting another psychotropic drug. To fulfil add-on criteria this psychotropic drug could not have been prescribed in the six months prior to the add-on date. Psychotropic drugs were defined as antipsychotics, antidepressants and the following moodstabilisers: valproic acid, carbamazepine and lamotrigine. Benzodiazepines were not included.

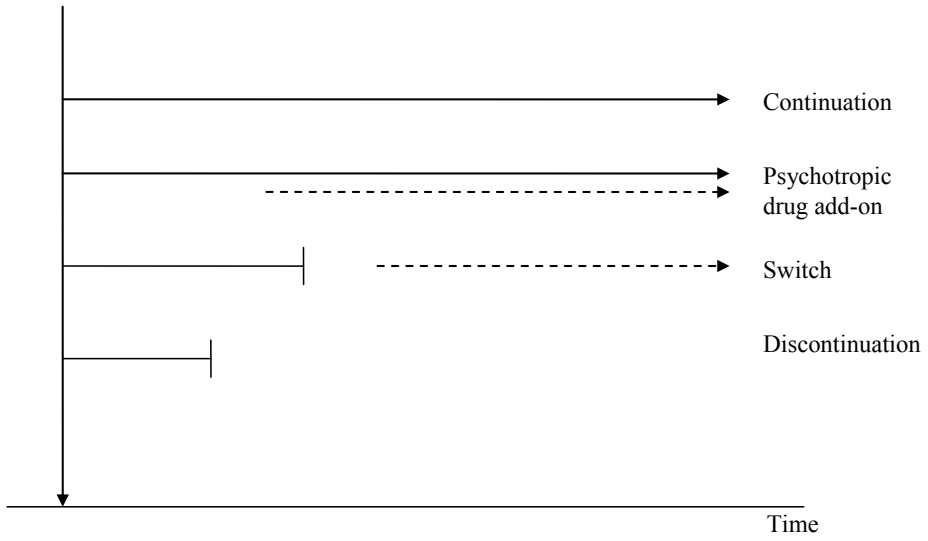

Figure 1. Lithium use patterns

Switching from lithium to another psychotropic drug was defined as discontinuation of lithium followed by the start of a new psychotropic drug within six months after the theoretical end date of the last lithium prescription. To fulfill switch criteria this psychotropic drug could not have been prescribed in the previous six months. Discontinuation without switching was defined as not having refilled a lithium prescription for at least six months after the theoretical end date of the last lithium prescription, indicating that a patient had a "lithium free" period of 6 months or more while not having been prescribed another psychotropic drug in these six months. During this period of six months the patients had to refill at least one prescription for any other drug to exclude that the period of not refilling a lithium prescription was due to hospitalisation in, for example, a psychiatric hospital or nursing home.
During follow up, changes in baseline use of psychotropic medication were not studied.

Data analysis

Lithium use patterns were assessed separately for the following age groups of incident lithium users: 40 to 49 years, 50 to 59 years, 60 to 69 years and 70 years and older, based on patients age on the index date. The age group 40-49 years was the reference group.
Differences between the four age groups with respect to baseline patient characteristics and baseline psychotropic drug use were assessed using Pearson Chi square tests for categorical variables and t-test for continuous variables. Differences in lithium use patterns and differences in drugs used in add-on and switch between the four age groups were assessed using Pearson Chi square tests.
Patient characteristics age (both as continuous and categorical variable), gender and baseline use of psychotropic drugs were investigated as potential determinants of any change in lithium use patterns using Cox regression analysis. All variables associated with lithium use patterns ($P < 0.05$) were included in the multivariate model. Subsequently, baseline use of antidepressants and antipsychotics were investigated as potential determinants in the four separate age groups for add-on, switch or discontinuation.

Results

A total of 2081 incident lithium users were included in the study. Baseline characteristics are presented in Table 1. There were statistically significantly more women in the two older age groups ($P < 0.05$). General practitioners (GP's) prescribed lithium in the 70+ age group more frequently than in younger age groups, although the difference

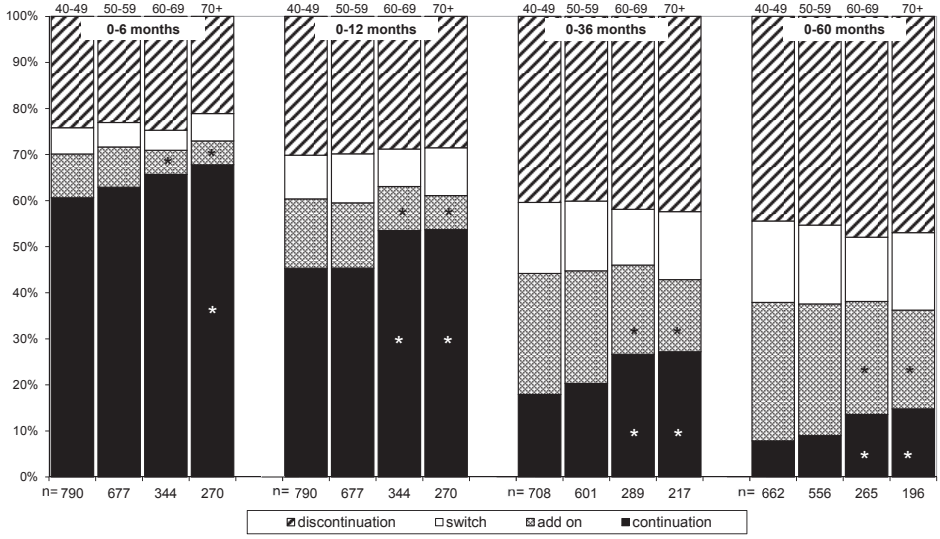

Figure 2. lithium use patterns in four age groups during different cumulative time-episodes
* Significant difference (<0.05) with reference group (40-49years)

was not statistically significant. Use of antipsychotics at baseline was lower in the oldest age group, mainly due to less prevalent use of typical antipsychotics ($P < 0.05$). The use of antidepressants at baseline did not differ between the age groups, but as a subgroup tricyclic antidepressants were used more frequently in the older age groups ($P < 0.05$).

Figure 2 shows the lithium use patterns for every age group for different time periods of follow-up. At six months 62% of the patients in the youngest age group continued lithium compared to 70% in the 70+ age group ($P < 0.05$). After five years this was decreased to 7% in the youngest age group and 14% in the 70+ group ($P < 0.05$). The percentage of patients who were prescribed add-on medication next to lithium increased over time from 10% after six months to 32% after five years in the youngest group. In the 70+ group the corresponding percentages were 6% and 22% respectively. This difference between the reference group and the 70+ group was statistically significant at both six months and five years after initiation of lithium ($P < 0.05$). During every time period the frequency of lithium discontinuation was not different between the age groups. In the youngest age group, 24% of the patients discontinued lithium within six months after initiation of lithium treatment compared to 22% in the 70+ age category. After five years this was 46% and 49% respectively. The proportion of patients switching from lithium to other medication was similar in each age group and time period.

Figure 3 shows the add-on and switch medication in the different age groups for the total study period. There were no significant differences between the youngest age

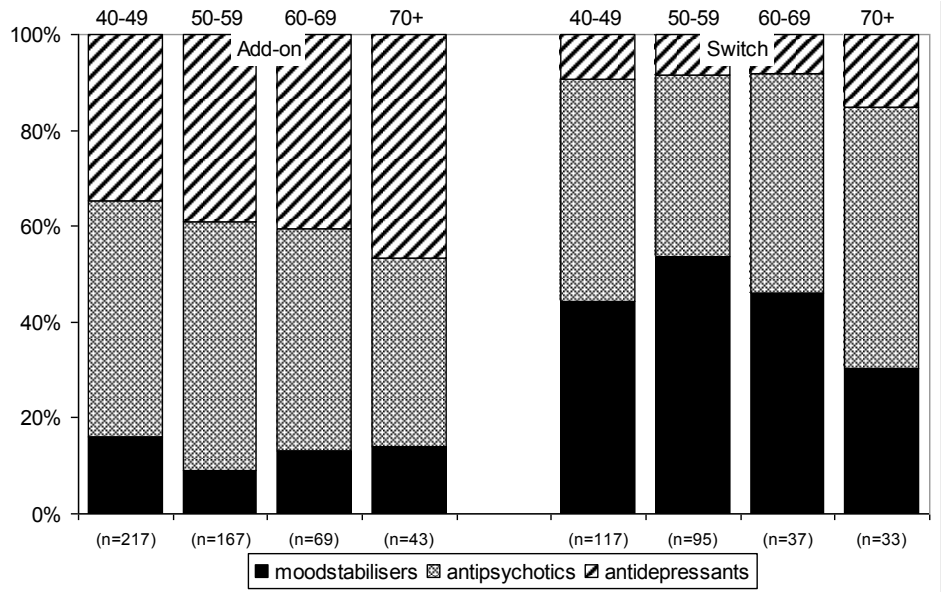

Figure 3. Add-on and switch medication in four age groups

group and the other age groups in add-on and switch medication except a decreased add-on of moodstabilisers in age group 50 to 59 years compared to patients aged 40 to 49 years ($P < 0.05$). Overall antipsychotics and antidepressants were used as add-on medication and antipsychotics and moodstabilizers as switch medication.

Table 2 shows the determinants that were significant related to any change in lithium use pattern or with a specific lithium use pattern in an age group. Age, both as a continuous and as a categorical variable, was the most important determinant in the whole study group for having any change in lithium use pattern (HR 0.988; 95%CI 0.984-0.993, respectively HR 0.888; 95%CI 0.845-0.934), but there was no association with gender, use of antidepressant or use of antipsychotics. In the age group 40-49 years patients with antidepressants at baseline were less likely to be prescribed add-on medication next to lithium then the patients from the same age group but without

Table 2. Determinants which were significantly associated with any change in lithium use pattern or with a specific lithium use pattern.

	Event	Determinant	HR	95% CI	P
All patients	Any event	Age continuous	0.988	0.984-0.993	< 0.001
All patients	Any event	Age categorical	0.888	0.845-0.934	< 0.001
40-49 years	Add-on	Antidepressant use at baseline	0.739	0.552-0.990	0.042
40-49 years	Switch	Antipsychotic use at baseline	0.588	0.351-0.983	0.043
70+	Add-on	Antidepressant use at baseline	0.279	0.110-0.709	0.007

antidepressants at baseline (HR 0.739; 95% CI 0.552-0.990). Patients with antipsychotic drug use at baseline were less likely to switch from lithium to other medication (HR 0.588; 95% CI 0.351-0.983). In the age group 70+ antidepressant use at baseline was also associated with a decreased probability of being prescribed add-on medication after starting with lithium (HR 0.279; 95% CI 0.110-0.709).

Discussion

In this database study we investigated differences in lithium use patterns in three older age groups compared to a middle-aged group. Patients aged 70 years and older were most likely to continue on lithium therapy, predominantly due to less frequent prescription of add-on medication to their baseline medication and after starting with lithium.

The finding that the proportion of patients with add-on was higher in the younger age group could be explained by more severe underlying bipolar disease. This hypothesis is supported by a higher prevalence of antipsychotic use at baseline in younger patients. Oostervink et al.[12] found more manic and psychotic symptoms in younger bipolar patients than in an older age group. On the other hand, Sajatovic et al.[13] found almost similar rates of hospitalisation in elderly and middle-aged bipolar patients.

There is no information in the literature on differences in severity of treatment-resistant major depression in various age groups.

Less add-on in the older group can also be related to underprescription. There is a lot of attention paid to polypharmacy in older patients, but this can cause an inappropriate reticence in prescribing drugs for the elderly, especially if there are co-morbidities.[14,15] Changes in the pharmacokinetic and pharmacodynamics properties of lithium in older age make patients more susceptible to adverse effects. The prevalence of cardiovascular disease increases with age, making treatment with diuretics, angiotensin-converting enzyme inhibitors or calcium antagonists necessary. These medications can cause drug-drug interactions with lithium. The potential risk of intoxication could prompt physicians to discontinue lithium or switch to other psychotropic drugs.[10,16] Umapathy et al. analyzed the psychotropic medications in 2000 community-based bipolar patients; two-thirds of the patients older than 65 years used lithium and less than one third used anticonvulsants.[17] Shulman et al. concluded that from 1993 to 2001 the number of patients 65 years and older starting on lithium declined, while the number of patients starting on valproic acid increased.[18] We found no difference with respect to switching or discontinuation of lithium in older patients compared to the reference group.

Kessing et al.[19] found that adherence to lithium was significantly poorer in younger (18-39 years) and older (≥60 years) patients compared to middle-aged patients. In their

database study, they used different definitions for discontinuation than were used in our study. They did not have information about the daily prescribed dosage. To calculate the lithium treatment time, they used the daily defined dose (DDD). If there was no new prescription within the calculated treatment time, lithium was regarded as discontinued. Because the lithium dosage used by older people is almost always much lower than the DDD, the calculated treatment time was probably often incorrect, and patients could unjust be classified as patients who discontinued lithium.

Patients aged 50 years and older used less typical antipsychotics at baseline than the younger patients. This finding might be explained by cautiousness due to fear of adverse effects in the elderly. Older people are more prone for extrapyramidal symptoms and tardive dyskinesias during treatment with typical antipsychotics.[20,21] Although some studies have suggested an excess mortality with atypical antipsychotic use in the elderly,[22] other studies found no difference in mortality risk between atypical and typical antipsychotics.[23,24]

Higher use of tricyclic antidepressants (TCA) in the older age groups at baseline is not easy to explain. There is no reported difference in efficacy in the literature of selective serotonin reuptake inhibitors (SSRI's) and TCA in the treatment of bipolar disorder and major depression in younger and older adults.[18,25] Overall, TCAs have different adverse effects than SSRIs and especially anticholinergic adverse effects of TCAs can have more impact in a geriatric patient with comorbidity.[20,26,27] On the other hand, in the Netherlands, severe depression with psychotic symptoms is often treated with a TCA. The high prevalence of TCA use in the elderly could indicate that there are more older patients included with treatment-resistant depression. Supporting this hypothesis is the finding of Paton et al.[28] that in a large group of lithium treated patients with affective disorders there were more patients with bipolar disorders in the group younger than 65 years and more patients with other affective disorders in the group older than 65 years. Another possibility is that in the older age group, more patients are misdiagnosed with unipolar depression and, after treatment with a TCA, develop a manic episode for which lithium is started.[12]

Psychiatrists are the physicians who treat patients with bipolar disorder and treatment-resistant major depression also at older ages. Therefore, they are the most frequent prescribers of lithium in all age groups. Geriatricians do not play an important role in gerontopsychiatry in the Netherlands at this time. The number of GPs who prescribe lithium in the elderly is unexpectedly high. This study only included incident lithium users, suggesting that a GP was the initiator of this treatment. Lithium is not a pharmacotherapeutic agent that is part of the depression guideline for GPs. An explanation could be that prescriptions of patients admitted to a hospital are not included in the PHARMO RLS and lithium treatment was actually initiated during a hospital stay and the first prescription after discharge was issued by the GP.

This study has several limitations. The interpretation of our findings is hampered because we had no information on indication of the lithium prescription or on severity of the psychiatric disorder. Most patients probably had a psychiatric diagnosis, as this is the primary indication for lithium use. Patients without antidepressant use at baseline probably had bipolar disorder and patients with baseline antidepressant use could have either bipolar disorder or treatment-resistant major depression. In addition, we had no information about the reason of change in lithium use patterns. As we had no clinical data or serum lithium levels, this could be due to treatment inefficacy, adverse effects or non-compliance. Also we had no information on patients who started their treatment during hospital admission and perhaps had more severe disease.

The strength of our study is our high quality exposure information. The data are from defined regions in the Netherlands. In the Netherlands, patients usually visit one pharmacy only, and therefore any change in medication use is likely to be registered, except when this is due to hospital admission.

Conclusions

In this database study, older patients were less likely to receive add-on psychotropic drugs to ongoing lithium treatment compared to younger patients, while these younger patients already used more antipsychotic drugs at baseline. This could be in accordance with previous findings of more severe disease in younger patients. Despite changes in pharmacokinetic and pharmacodynamic properties in the elderly, there was no significant difference between older and younger age groups with respect to discontinuation and switch events.

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2.2

Lithium intoxication in an older patient with cluster headache: the importance of monitoring and recognizing symptoms of intoxication.

Case report, submitted

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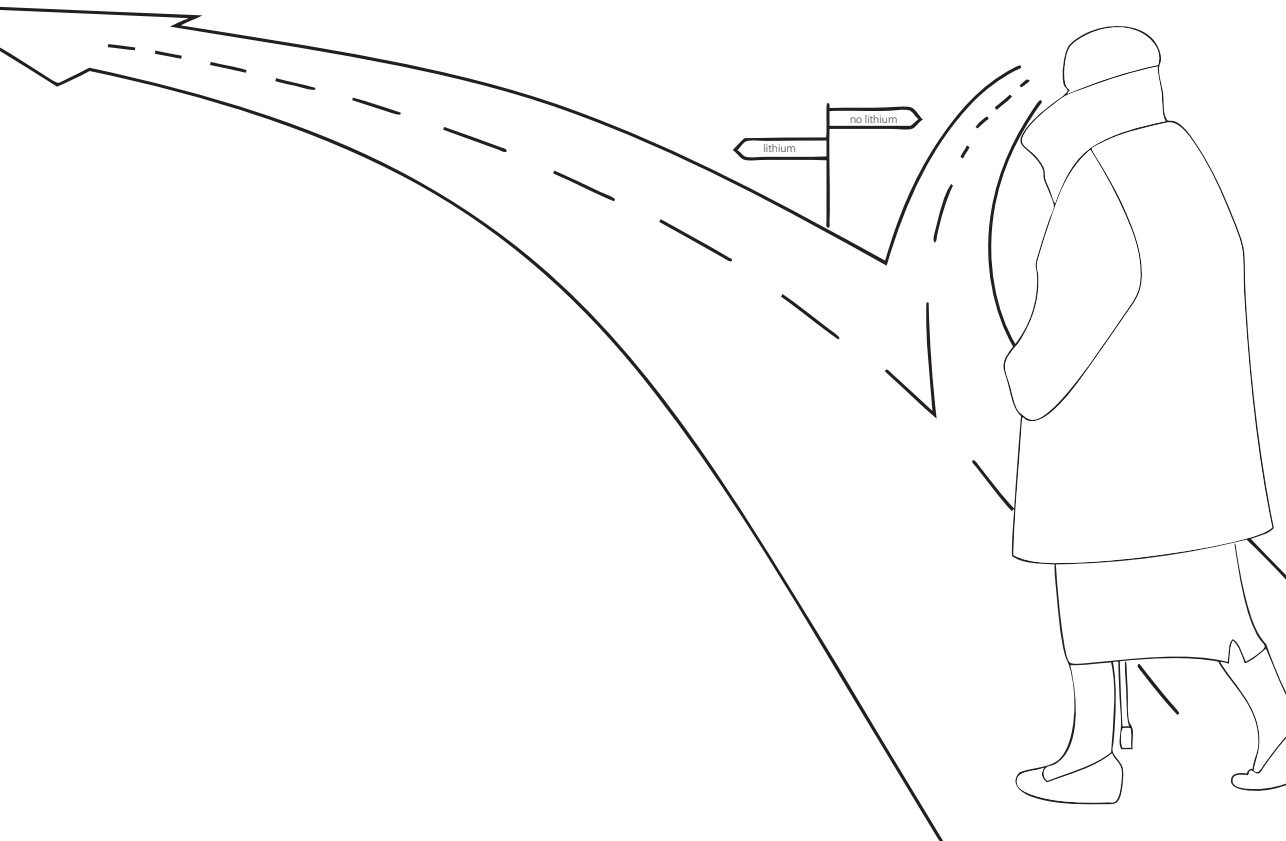

Abstract

Introduction: Lithium is prescribed by psychiatrists as first-line treatment in bipolar disorder and as add-on in therapy-resistant unipolar depression; sporadically lithium is prescribed by neurologists for the prevention of cluster headache. They are not always aware of the therapeutic risks.

Case report: We present a case of an elderly man with cluster headache who was treated for many years with lithium and who developed a chronic lithium intoxication. The clinical symptoms of lithium intoxication with delirium are presented and the possibility of headache as complicating symptom of intoxication is described. The occurrence of irreversible neurologic sequelae and the possible interaction between lithium and verapamil are discussed.

Conclusions: Lithium intoxication is a serious and potentially life threatening condition and to minimise the risk, regular and correct monitoring is important. Knowledge of signs of intoxication, in the elderly often presenting as delirium, is necessary to allow instant treatment and to prevent long-term sequelae. Especially in patients with cluster headache, it is important to realise that headache can also be a symptom of lithium intoxication.

Introduction

Lithium is used as first line treatment in bipolar disorder and as add-on in treatment-resistant unipolar depression.[1,2] Consequently it is almost exclusively prescribed by psychiatrists. Sporadically lithium is prescribed off-label by neurologists for the prevention of cluster headache.[3,4]
The narrow therapeutic window (0.6-1.2 mmol/L), the large interindividual variability in lithium pharmacokinetics and the many within-person factors that can influence lithium clearance, necessitate frequent monitoring of the serum lithium concentration (SLC).[5]
Lithium is highly water soluble and when patients grow older their volume of distribution declines. In addition lithium is eliminated by the kidneys and renal function often declines with increasing age. These alterations in pharmacokinetics generally make dose reduction in older patients necessary to maintain lithium on the target serum level.[6]
But even with the same SLC the vulnerability for lithium can change in older patients. They can develop adverse effects on a SLC which was well tolerated before. These pharmacodynamic changes have led to an advised lower therapeutic window in older patients (0.4-0.7 mmol/L).[7]
International guidelines on the treatment of bipolar disorder worldwide advise to monitor SLC and possible adverse effects every 3-6 months when a steady state has been reached and more often in case of declining renal function, changed lithium dose or initiation/discontinuation of interacting drugs.[5] In addition, renal and thyroid function should be monitored every 6-12 months. In the guidelines on the treatment of cluster headache, there is only a brief summary concerning the monitoring of lithium.[3,4]
Inadequate monitoring may predispose patients to the risk of SLC outside the therapeutic window. This can cause inadequate treatment in case of subtherapeutic levels or increasing adverse effects and eventually lithium intoxication in case of high levels. The neurologic adverse effects of lithium are diverse and are often the first clinical signs of a serious intoxication.

Case report

A 76-year-old Caucasian man, with a history of severe cluster headache, visited our neurologic outpatient clinic at regular intervals since 1974. He lived alone without any help. His medical history included an hernia nucleus pulposi operation in 1952, nicotine abuse and hypercholesterolemia for which he was treated with gemfibrozil

600mg td. He also used temazepam 20mg for many years. In the first years he visited our outpatient clinic, he was treated with pizotifeen, methysergide and oxygen. Since his cluster headache was difficult to control, he started with lithium carbonate treatment in December 1995. His serum lithium concentration (SLC) and lithium dose are shown in Figure 1.

After lithium was started, the patient had at first a slight tremor of the hands, but this disappeared after several months and there was a complete remission of his cluster headache. Therefore the lithium dose was in 1997 gradually tapered off and stopped. The cluster headache returned immediately and verapamil was started. This was without any effect and lithium was restarted. From 1998 until 2001 he was without complaints, but at the end of 2001 his cluster headache returned. The attacks persisted despite an increase of the lithium dose and verapamil was added. After this addition he was free from headache, but in 2005 a course tremor was described and the verapamil was stopped. As the cluster headache returned, the verapamil was again added with good result on the attacks. The tremor persisted but the character and seriousness of the tremor were not recorded. Other symptoms that were recorded were an atactic gait in 2006 resulting in lithium dose reduction (Fig 1) and rigidity without cogwheel phenomenon in 2007. In the second half of 2008 the patient was tapered off verapamil because he was free from attacks

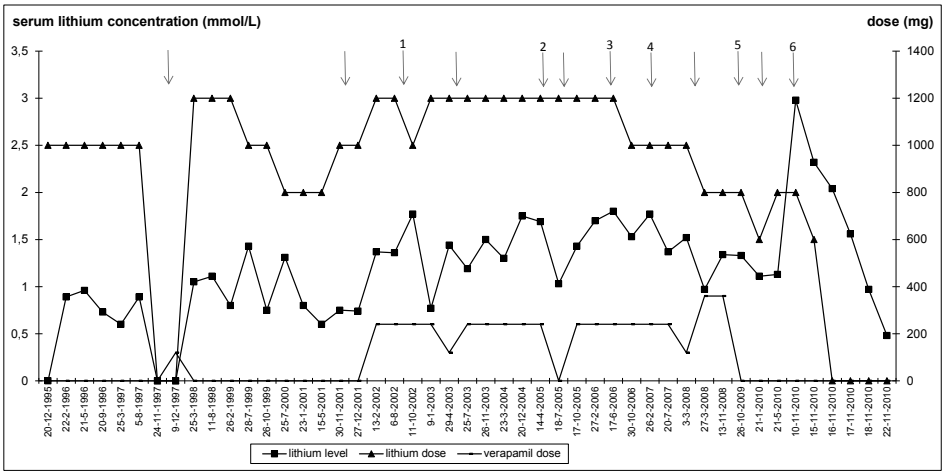

Figure 1. Lithium dose, verapamil dose and serum lithium concentration.
Arrow without number: return or worsening cluster headache
Arrow 1: tremor of the hands
Arrow 2: coarse tremor of the hands
Arrow 3: coarse tremor and mild ataxia
Arrow 4: coarse tremor and rigidity without cogwheel phenomenon
Arrow 6: lithium intoxication

At the beginning of 2010 the lithium dose was lowered to 600mg daily divided in two gifts because the tremor of the hands became increasingly invalidating. The cluster headache returned almost immediately and the dose was again raised to 800mg daily as the patient stated that the headaches were far worse than the tremor. In June 2010 the SLC was 1.11 mmol/L; the tremor was the same as before, but he could still function adequately in daily life.

On November 1st 2010 the patient visited the outpatient clinic with again worsening of the tremor in his hands. It was now almost impossible for him to hold a cup and in addition he had fallen a few times. No SLC was determined at this visit; based on the clinical symptoms the neurologist decided to lower the lithium dose again to 600mg daily divided in two gifts. On November 9th 2010 he was admitted to the neurologic ward because his condition had deteriorated; he complained of progressive headache, although the character of the headache was different from cluster headache. Prior to admission he was treated elsewhere with antibiotics because of a urinary tract infection and with haloperidol 1mg because of confusion.

On admission he was disoriented, suffered from dysarthric speech, an atactic gait, dysdiadochokinesis and tremor of the hands. One day later a CT-scan of the brain did not show pathology, but the trough SLC was 2.94 mmol/L. The patient's condition had further deteriorated, he was disoriented and unable to focus his attention. He was alternating somnolent and hyperactive and during the night he kept coming out of his bed. He persisted in complaining about his headache. The patient was diagnosed with a lithium intoxication and the treating neurologist decided to lower the lithium dose, because of fear of return of the cluster headache in case of discontinuation.

On November 15th the geriatrician was consulted and it was concluded that the patient was delirious because of lithium intoxication. He was slightly dehydrated (creatinin 128 µM/L, ureum 11.7 mM/L, Na 140 mM/L, MDRD of 47 ml/min). TSH and calcium were normal and the trough SLC was 2.34 mmol/L. Lithium was discontinued and a 4 liter infusion/24h with NaCl 0,9% was started. The 24h urine output was determined to make certain that there was no polyuria as patients long-term using lithium can develop a nephrogenic diabetes insipidus. The patient was transferred to the geriatric ward.

The SLC declined, but the patient remained in a hyperactive delirious state. After two days the haloperidol was discontinued because of concern for additional neurotoxicity in combination with lithium and lorazepam 0.5mg td was started. As this was not effective he was started on a rivastigmine patch 4.6mg. After November 20th he improved day by day. He could focus his attention but was still disoriented in time and showed memory deficits. He still had an atactic gait and a slight tremor of the hands. Ten days after lithium discontinuation he could walk without aid and the tremor had ceased. He scored 21/30 on the MMSE and was discharged on November 29th to a nurs-

ing home for revalidation. At discharge there was no tremor, normal coordination tests, normal speech, no extrapyramidal symptoms and normal walking pattern. His cognition was still not as it was prior to the intoxication. During his recovery period he did not complain of headache. In January 2011 his MMSE score was 27/30 and polyneuropathy was diagnosed, confirmed by EMG. In November 2011 his MMSE was 29/30, he was living on his own again, cooked every day and did his own shopping. His cluster headache had returned but was bearable with pizotifeen, although this had not been effective in the past.

Discussion

This case report is presented because every clinician who prescribes lithium should be aware of the importance of monitoring SLC and assessment of clinical signs of adverse effects and intoxication. (Table 1)[6-16] Lithium intoxication often starts with worsening of an existing tremor and problems with concentration.[5,8] This was the case in this patient at the beginning of November.

There are several possible reasons for the development of a lithium intoxication in this case. During the years this patient was treated his SLC was almost always supratherapeutic with evident adverse effects, which some would already call mild intoxication. However, at lower doses he invariably complained of new cluster headaches. Perhaps his tolerability decreased in the last years because of pharmacodynamic changes in older age and only a small rise in SLC would have been necessary to cause a delirium.[16] Furthermore our patient was treated for a urinary tract infection prior to admission. This could have contributed to the development of a delirium and to taking the wrong lithium dose in his confusion. It also is possible that he took more lithium because of his headache thinking that the cluster headaches were starting or that he confused his lithium tablets with paracetamol. His family told afterwards that lithium tablets were lying between the paracetamol. As far as we know he did not take any NSAID nor any other drug that may have been of influence.

When the patient was admitted to the hospital he presented an almost classic picture of lithium intoxication but the severity of the situation was not recognised at first and inadequate measures taken to treat the lithium intoxication. (Table 1) Despite the SLC of 2.94 mmol/L it was decided not to discontinue lithium. Perhaps the patient's frequent complaints about headache influenced this decision. As the current headache had a different character than the cluster headache and disappeared when the SLC decreased, this headache could have been a symptom of lithium intoxication.[17]

In case of a serious intoxication with high SLC during maintenance treatment and clinical symptoms of intoxication, consistent with chronic intoxication, discontinua-

Table 1. Characteristics of lithium and lithiumintoxication[6-16]

Pharmacokinetic properties lithium carbonate	T_{max}: 1-4 hours; steady state: 6-10 days; therapeutic window: 0.6-1.2 mmol/L , in older patients 0.4-0.7 mmol/L; serum lithium concentration (SLC) is a trough level determined in blood sampled 12±0.5 hours after last intake. Highly water-soluble; renally cleared; large interindividual variablility in lithium half-life.
Classification lithium intoxication	Acute: acute ingestion in a patient not currently taking lithium; sometimes very high SLC but no or low tissue levels. Acute on chronic: acute ingestion in excess of prescribed dose in a patient currently taking lithium. Chronic: intoxication in the context of chronic therapeutic administration (for example caused by deteriorating renal function). The most serious because of already high tissue levels.
Serum lithium concentration (SLC) causing intoxication	Intoxication possible when levels lie within the therapeutic window. Risk for intoxication increases when trough levels are above 1.2 mmol/L.
Pharmacodynamic risk factors	Older age Neurodegenerative disorders
Pharmacokinetic risk factors (often cause of chronic intoxication)	Smaller volume of distribution: age, dehydration Decreased renal clearance: renal disease, dehydration, low salt diet, decompensatio cordis, concomitant medication recently added (ACE-inhibitors, NSAID, thiazide diuretics, loopdiuretics)
Symptoms	Mild: (worsening of) postural tremor of the hands, nausea, vomiting, diarrhea, (especially in older patients) concentration disturbance, confusion Moderate: coarse tremor, dysarthria, (mild) ataxia, hypertonia, somnolence, nausea, vomiting, delirium, deterioration renal function Severe: stupor, rigidity, fasciculations, coma, seizures, nausea, vomiting, arrhythmia, death
Therapy	Discontinuation lithium (temporary) Rehydration Renal replacement therapy: SLC > 3.5 mmol/L; SLC > 2.5 mmol/l with symptoms and depressed GFR; in case of moderate intoxication with expectation of rising SLC
Recovery after intoxication	Symptoms disappear but sometimes neurologic sequelae persist: syndrome of irreversible lithium-effectuated neurotoxicity (SILENT), often consisting of cerebellar symptoms. Risk of SILENT probably higher in patients who use antipsychotics besides lithium, especially haloperidol.

tion of lithium is always the first step. After lithium was discontinued in our patient and although the SLC declined, the symptoms of neurotoxicity persisted. This is often seen and is attributed to the fact that SLC in the brain lags behind.[9]

Apart from the lithium intoxication our case shows that in the years following the addition of verapamil in 2002 the SLC was higher than before (Figure 1). There is one case report of neurotoxicity after starting verapamil in a patient already using lithium but without an increase in SLC.[18] Thomsen et al. state that verapamil can decrease lithium clearance by reducing renal perfusion pressure and this could result in increased SLC.[10] In line with this, our patient showed a decrease in SLC upon discontinuation of verapamil (Figure 1) As verapamil and lithium are often concomitantly used in the treatment of cluster headache, more frequent monitoring of lithium as well as monitoring for neurotoxic effects is necessary if verapamil is added. If lithium is added to verapamil a lower starting dose might be indicated.

Despite of the serious lithium intoxication the patient recovered completely, but it took several months before his cognition had again returned to the same level as it was before. The polyneuropathy could be a sequel of the lithium intoxication.[14]

Conclusion

Lithium is one of the first-line treatments of affective disorders also in the elderly. In addition, it has a role in the treatment of cluster headache. Lithium has a narrow therapeutic window with small changes resulting in either subtherapeutic or toxic levels. Lithium intoxication is a serious and potentially life threatening condition and to minimise the risk, regular and correct monitoring of SLC is important. Knowledge of signs of intoxication is necessary for both physician and patient in order to prevent long-term sequelae.

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2.3

Age as a determinant of instability of serum lithium concentrations

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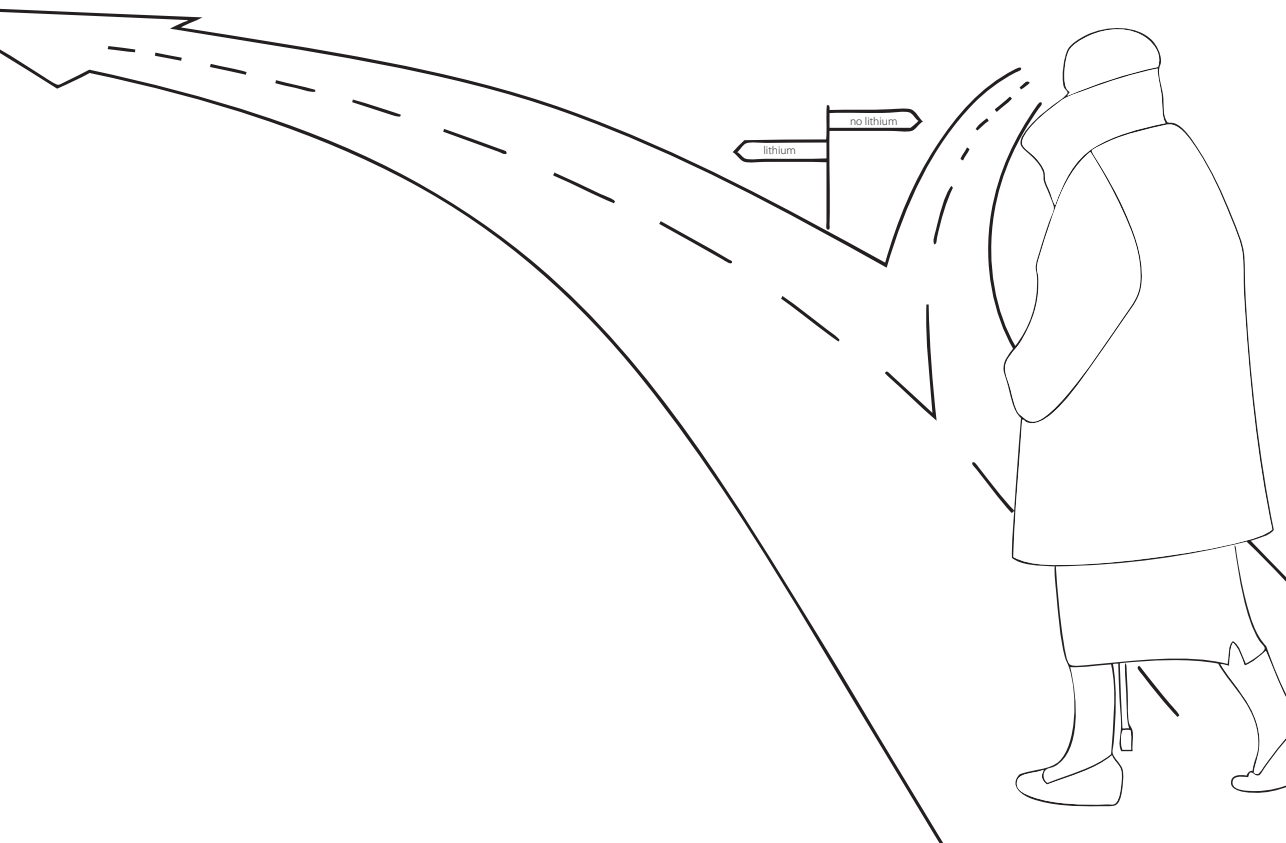

Abstract

Background: Lithium is used both in bipolar disorder and as augmentation in treatment resistant unipolar depression. Long-term treatment is often indicated. Pharmacokinetic and pharmacodynamic changes in older age, as well as increasing co-morbidities and polypharmacy, could result in instability of serum lithium concentratins. In this study several parameters, considered proxy for instability, were compared between age groups. These parameters were derived from studies involving oral anticoagulants.

Methods: A retrospective study (1995-2004) was conducted using serum lithium concentrations from the laboratories of three hospitals in the Netherlands; 759 patients treated with lithium, 40 years or older, with at least two years' follow-up were identified. They were divided into four age groups: 40-49 years, 50-59 years, 60-69 years and 70+; the youngest group was used as a reference group. The variance growth rate and percentage of time below, in and above treatment range are all proxies for instability. They were analysed between the age categories.

Results: There was no significant difference for these variables between the reference group and the older age groups. In a subgroup of 454 patients the parameters considered as proxy for instability during titration; number of days and number of serum lithium concentration measurements during titration, were evaluated; no significant difference was found between the age groups. In a small group of 117 patients titration and maintenance treatment for at least two years could be analyzed separately. Also in this group, there was no difference between the age groups.

Conclusions: Age is not a determinant of serum lithium concentration instability. Therefore, age is not a reason to not initiate or to discontinue lithium therapy.

Introduction

Lithium salts have been used in the treatment of bipolar disorders for more than 50 years and are also used frequently as augmentation therapy with antidepressants in treatment-resistant unipolar depression.[1,2] Because of the many serious consequences of affective disorders, long-term treatment with lithium is often indicated.[3]

Lithium has a narrow therapeutic range, meaning that subtherapeutic, therapeutic and toxic serum concentrations are not far apart.[4] Lithium intoxication, especially chronic intoxication, can be very harmful, potentially resulting in permanent neurological sequelae or even death.[5] In addition, there are major inter- and intraindividual differences in lithium pharmacokinetics rendering serum lithium concentration monitoring essential.[4]

The Dutch guideline recommends that serum lithium concentrations should be kept within the range 0.6-0.8 mmol/L in prophylaxis of bipolar disorder and between 0.8 and 1.2 mmol/L during the treatment of acute mania.[6] In the case of a good clinical response, but with bothersome or serious adverse effects, a lower range of 0.4-0.6 mmol/L is advised. The British National Formulary recommends a serum concentration of 0.4-1.0 mmol/L and advises keeping the concentration towards the lower end of the therapeutic range in the elderly.[7] Severus et al.[8] conclude that lithium concentrations between 0.4 and 1.2 mmol/L are effective in the long-term treatment of bipolar disorder and that the optimal balance between efficacy and adverse effects can be achieved with serum concentrations between 0.6 and 0.75 mmol/L. Crossley et al.[2] performed a meta-analysis of studies on lithium augmentation in patients using antidepressants. In the studies they analyzed, the lithium concentrations were kept between 0.5 and 1.1 mmol/L.

According to the Dutch guideline, measurements are recommended every third or fourth day during the titration phase of lithium treatment until at least two subsequent lithium serum concentrations are within the therapeutic range. During the maintenance phase, measurement of serum lithium concentrations at least two to four times a year, and more frequently in case of suspicion of subtherapeutic or toxic serum concentrations, initiation or discontinuation of potentially interacting drugs or alteration of renal function is recommended.[9] According to the guidelines, laboratories should structure a 12-hour time interval between the last lithium intake and blood sampling for serum concentration measurement.[6,7,9]

Because of the chronic nature of affective disorders, the elderly represent an increasingly important group of patients treated with lithium. However, increased age is associated with multiple factors with the potential to influence lithium pharmacokinetics, such as a decline in renal function and polypharmacy.[10-12] In addition, age has been associated with an increased risk of adverse effects, possibly resulting in

non compliance.[13] These age-related factors may put the elderly at increased risk of serum lithium concentration instability during long-term use and, more frequently, subtherapeutic or elevated serum lithium concentrations. Apart from the British National Formulary, none of the current guidelines specifically advises either on the therapeutic window or on the frequency of serum concentration monitoring in the elderly. On the other hand, lithium is a very effective treatment in the elderly, and not instituting a valuable treatment option because of fear of intoxication might result in suboptimal treatment.

The objective of our study was to investigate age as a determinant of serum lithium concentration instability during both the titration and maintenance phase of lithium treatment.

Methods

Setting and study population

A retrospective study (January 1995 – July 2004) was conducted using all available serum lithium concentration measurements from in- and outpatients in the laboratories of three large teaching hospitals in different parts of the Netherlands: TweeSteden Hospital, Tilburg; Altrecht Institute for Mental Health Care, Utrecht; and Reinier De Graaf Hospital, Delft. Patient data on gender, year of birth, serum lithium concentrations and corresponding dates of blood sampling were gathered, along with a unique patient identification number. Because of limitations of the analysis of serum lithium concentrations, lithium concentrations below 0.2 mmol/L cannot be measured reliably and therefore were interpreted as 0.2 mmol/L. Approval to use anonymous patient data for this study was obtained from the scientific boards of the three participating institutions.

Patients were eligible for inclusion in the study if they were aged 40 years and older at the time of the first serum lithium concentration measurement and had at least one treatment episode with a duration of ≥ 2 years to allow for determination of instability of serum lithium concentrations with sufficient follow-up.

Episodes of lithium use were defined as the time-period between a first measurement with no measurement in the seven months before and a last measurement not followed by a new measurement within seven months. The seven month time period is based on the Dutch guideline, advising two to four measurements a year (every three to six months) after stable serum lithium concentrations have been reached.[6] Patients could only be included once; patients who had multiple episodes only had the first episode included in the analysis.

This treatment episode could consist of both a titration phase and maintenance phase, but as patients could have been monitored in other laboratories, the first measurement in our study could already be a measurement during maintenance phase.
The titration phase was defined as the time period after initiation of lithium treatment until stable serum lithium concentrations had been reached. The guideline advises measurements every three to four days until at least two successive measurements are within the therapeutic range[6]. Therefore, the titration phase was defined as the time between the first encountered measurement, followed by a second lithium measurement within ten days and the occurrence of stable serum lithium concentrations. Stable serum lithium concentrations were defined as two subsequent measurements within the therapeutic range of 0.4-1.2 mmol/L, with an absolute difference of no more than 0.2 mmol/L.

Outcome

Parameters considered as a proxy for instability were variance growth rate (VGR), the percentage of treatment time that serum lithiumconcentrations were in, below or above the therapeutic range and annual number of measurements.[14,15] Furthermore, two parameters were considered as a proxy for instability during the titration phase: the number of days and the number of measurements until stability was reached.

Variance growth rate

The VGR of Cannegieter is a measurement of variability and therefore an increasing VGR can be considered a proxy for instability.[14] The VGR was determined using the formula below:

$$\sigma^2 = \frac{1}{n} \sum_{i=1}^{n} \frac{(Li_{i+1} - Li_i)^2}{\tau_{i,i+1}}$$

This formula reflects how much serum lithium concentrations overall differ within the same patient in time. The outcome σ is high in a patient with a high variability across the different serum lithium concentration measurements and low in patients with rather constant serum lithium concentration measurements. In this formula, Li is the serum lithium concentration, n is the number of measurements and τ the time between two subsequent measurements.[14] The VGR does not provide information on the absolute accuracy of the serum lithium concentrations, so does not indicate if the serum lithiumconcentration is within the desired range. With a low σ a patient can have a fairly constant serum lithium concentration, but the absolute value can still be either too low or too high.

Percent treatment time with serum lithium concentrations in, below or above therapeutic range

To avoid ineffective treatment and adverse effects the serum lithium concentration should be kept within the therapeutic range. In this study 0.4-1.2 mmol/L was used, in accordance with the Dutch guideline on bipolar disorders.[6]. The time spent in, below and above the therapeutic range was calculated by the linear interpolation method,[14,15] whereby it is assumed that the change in serum lithium concentration between two subsequent measurements is linear. When for example one measurement is in the therapeutic range and the next above, the time at which the connecting line crosses the 1.2 mmol/L line can be calculated. When a measurement is again in the therapeutic range, the time interval this patient was above the therapeutic range can be determined. (Figure 1) By adding the different time intervals spent above the therapeutic range, the total time above the therapeutic range can be determined and is expressed as a percentage of the total follow up time: percent time above therapeutic range (T_aTR). The same method is used for calculating the percent time below the therapeutic range (T_bTR). Subtracting these periods from the total time a patient was in the study results in the percent time within therapeutic range (T_iTR).

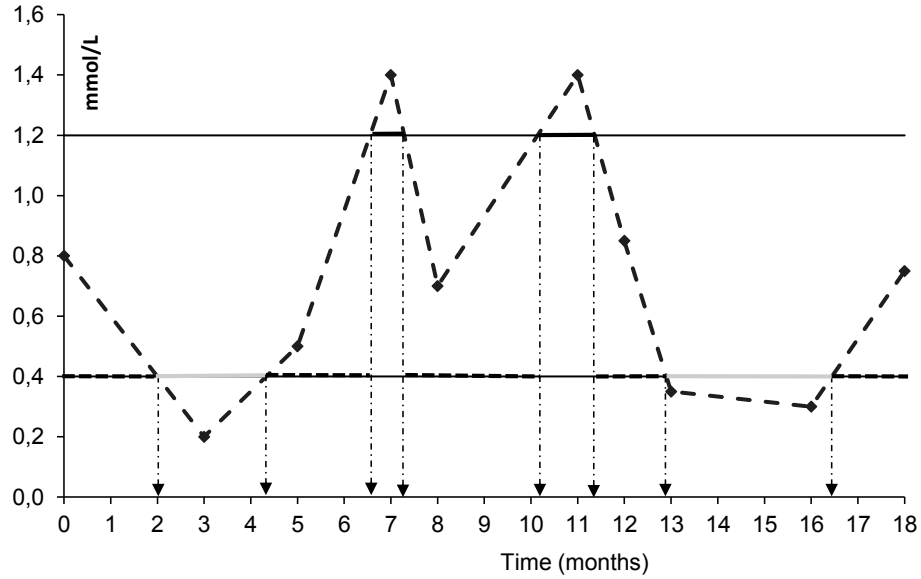

Figure 1. Treatment time with serum lithium concentrations in (horizontal black dotted line), below (horizontal gray line),and above (horizontal fat black line) therapeutic range (0.4–1.2 mmol/L).

Annual number of measurements

The median annual number of lithium serum concentration measurements per patient was determined. More measurements than the recommended number of 2-4 measurements a year by the Dutch guideline can be regarded as a proxy for instability, although it can also be caused by careful monitoring.

Data analysis

The different parameters regarded as a proxy for instability of lithium serum concentrations during titration and maintenance treatment were compared across the different age groups. The patients were distributed into four age categories based upon age at first lithium serum concentration measurement. These age groups were 40-49, 50-59, 60-69 and ≥70 years old. The group with patients aged 40-49 years was termed the reference group. Sex, as wel as low (≤6) and high (>6) annual number of lithium serum measurements were investigated as potential confounders. All continuous parameters were analysed with the T-test, whereas in case of non-normal distribution the Mann-Whitney U test was used. Categorical variables were analysed using the Chi-square test.

All analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 759 patients were included. The majority of patients were women (63%) with the highest percentage in the older age groups (Table 1). The duration of follow-up was significantly shorter in the ≥70 age group. Significantly lower lithium serum concentrations were observed in patients of 60 years and older compared to the reference group.

Table 1: Patient characteristics (n=759)

Age category (years) (n=number of patients, N=number of measurements)	**Age 40-49** (n=250, N=6565)	**Age 50-59** (n=221, N=5492)	**Age 60-69** (n=165, N=4243)	**Age ≥70** (n=123, N=3092)
Female gender (%)	141 (56.4)	134 (60.6)	110 (66.7)*	92 (74.8))*
Duration of follow-up in months per patient , median (5%, 95%)**	54.3 (28.9, 82.2)	55.4 (28.3, 81.2)	52.9 (26.8, 80.4)	40.0* (25.6, 80.0)
Lithium serum concentration per patient mmol/L, median (5%, 95%)	0.76 (0.51, 0.96)	0.76 (0.49, 0.98)	0.70* (0.47, 0.93)	0.67* (0.44, 0.88)

* Significantly different from reference group; $P < 0.05$

** Because of skewness of the data, median results are presented with 5% and 95% value

Table 2: Parameters investigated as proxy for instability per patient across age groups during titration and maintenance treatment (n=759)

	Age 40-49 (n=250)	**Age 50-59** (n=221)	**Age 60-69** (n=165)	**Age ≥70** (n=123)
Annual number of measurements Median** (5%, 95%)	4.9 (2.1, 14.1)	4.5 (1.8, 13.1)	4.9 (1.9, 14.3)	5.4* (3.0, 14.7)
Variance growth rate (10^{-3}) Median (5%, 95%)	1.0 (0.1, 17.2)	0.6* (0.1, 14.5)	0.7 (0.1, 9.6)	0.8 (0.1, 18.9)
Percentage time in range 0.4-1.2mmol/L (T_iTR) Median (5%, 95%)	98.6 (60.6, 100.0)	98.6 (60.9, 100.0)	98.1 (70.0,100.0)	97.7 (68.8, 100.0)
Percentage time below 0.4mmol/L (T_bTR) Median (5%, 95%)	0.0 (0.0, 37.8)	0.0 (0.0, 39.1)	0.3 (0.0, 29.9)	1.1 (0.0, 31.1)
Percentage time above 1.2mmol/L (T_aTR) Median (5%, 95%)	0.0 (0.0, 6.5)	0.0 (0.0, 6.9)	0.0 (0.0, 5.3)	0.0 (0.0, 3.7)

* Significantly different from reference group; $P < 0.05$

** Because of skewness of the data, median results are presented with 5% and 95% value

The VGR and the T_iTR, T_aTR and T_bTR did not differ significantly between the reference group and the two oldest age groups (Table 2). The annual number of lithium serum concentration measurements was higher in the oldest age groups and this difference was significant ($P < 0.05$).

For 454 patients a titration phase could be determined according to the defined criteria (Table 3). Within this group there was no difference in the number of days until stable lithium serum concentrations were reached when comparing the older

Table 3: Parameters investigated as proxy for instability during titration per patient across age groups (n=454)

	40-49 years n=163	**50-59 years** n=104	**60-69 years** n=93	**≥70 years** n=94
Days until stability, median** (5%, 95%)	21.0 (7.0, 164.2)	23.0 (7.0, 175.3)	24.0 (11.7, 113.9)	28.5 (7.0, 184.0)
Measurements until stability, median (5%, 95%)	4.0 (3.0, 7.0)	3.0 (3.0, 6.8)	4.0 (3.0, 7.0)	4.0 (3.0, 7.0)

* Significantly different from reference group; $P < 0.05$

** Because of skewness of the data, median results are presented with 5% and 95% value

age groups to the reference group. Compared to the reference group, the age group 50-59 years had a lower median number of serum concentration measurements until the end of the titration phase, but the difference was not significant. The duration of the titration phase was longest in the ≥70 age group, but this difference was also not significant.
For a small subgroup (n=117) within the total study population, a titration phase with an additional maintenance phase of at least two years was available. For these patients the maintenance phase was analysed separately. Results from this analysis did not differ from the results as presented for the total study population (Table 1 and 2), except that there was also no significant difference in the annual number of lithium serum concentration measurements.
Gender and low or high annual number of measurements did not influence the outcome.

Discussion

In this study on the association between age and instability of lithium serum concentrations we found no difference in parameters of instability comparing the middle-aged reference group aged 40-49 years and the older age groups, except for a significantly higher annual number of lithium serum concentration measurements in the oldest age group. As all the other parameters for instability did not differ, this is probably caused by more careful monitoring in the elderly. Also, when analysing titration and maintenance phase of lithium treatment separately, we did not find a difference in terms of stability between older and middle-aged patients. Our results indicate that age is not a determinant of lithium serum concentration instability.
Bipolar disorder and unipolar depression can manifest itself at any age, but the highest incidence of bipolar disorder is between 15 and 24 years. Therefore, one would expect the reference group aged 40-49 years to be well initiated on lithium treatment with little instability. Regarding the older age groups one may expect an increase in instability of lithium serum concentrations due to changing pharmacokinetics and pharmcodynamics in older age. However, our data did not confirm this.
As far as we know there are no studies on lithium serum concentration instability using parameters based on variation between serum concentrations with time. The parameters taken as a proxy for instability in our study are based on studies with oral anticoagulants.[14,15] There are many similarities between laboratory monitoring of coumarine and lithium, although for coumarine the outcome International Normalized Ratio (INR) is monitored, whereas for lithium serum concentrations are monitored. Both drugs have a narrow therapeutic window, with the risk of nonresponse if the

concentration is below the therapeutic window and the risk of adverse effects if the concentration is above the therapeutic window. In several studies on INR monitoring of coumarine, VGR and the T_iTR were taken as a proxy for instability and were found to be associated with haemorrhagic and thrombotic complications.[14,16]

Rose et al. studied characteristics associated with oral anticoagulation stability during the first 6 months of treatment and during maintenance.[16] They found a lower T_iTR in patients younger than 55 years for both treatment phases. In addition females had a lower T_iTR during maintenance treatment. In another study on chronic anticoagulation therapy, age of 70+ was an independent predictor of stable INR control.[17]

We did not find a significant difference in T_iTR and VGR between the older age groups and the reference group in our study. In addition, the T_aTR did not differ significantly between the age groups. At any age the risk for adverse effects increases with higher lithium concentrations and patients with concentrations > 1.2 mmol/L may suffer from toxicity, especially older patients.[13]

The median number of days until stability in the maintenance phase was highest in the oldest group, but there was no significant difference. There was a wide range in the number of days for duration of the titration phase for all the groups, indicating an overall large interindividual difference regardless of age.

The median annual number of measurements was slightly higher across all age groups in comparison with the advice of the Dutch Guideline on bipolar disorder of 2-4 measurements a year. Head et al. found a mean of 3,25 (SD 1,95) measurements during one year in 142 patients of 65 years and older.[18] Stratifying the results in our study into a low (≤ 6) or high (> 6) number of measurements a year did not result in significant differences in other parameters of instability between the age groups.

The Dutch Guideline advises a therapeutic window of 0.4-1.2 mmol/L and does not make a distinction for the elderly. But apparently Dutch clinicians aim at lower lithium serum concentrations in the elderly as the median lithium serum concentrations were significantly lower in the older age groups, with a serum concentration of 0.67 mmol/L (SD 0,11) in the oldest age group (Table 1). Head et al. found during a year a mean concentration of 0.64 mmol/L (SD 0,20) and Fahy et al. found a mean concentration of 0.42 mmol/L in 12 octogenarians.[18,19] In their study Paton et al. found a mean lithium concentration of 0.63 mmol/L in patients with bipolar disorder, mean age 53.5 years, and 0.60 mmol/L in patients with other affective disorders, mean age 61.9.[20]

Although we observed no differences with respect to lithium serum concentration instability between age groups, we observed several differences between hospitals, such as the average serum lithium concentration and the number of lithium serum concentration measurements per year. This variability probably reflects differences in therapeutic drug monitoring policy despite the existence of a national guideline.

This observation and the causes and consequences thereof are interesting subjects for further study

This study has several limitations. There was no information about the indication for lithium and, thus, no information about the desired therapeutic window. Because of this, we choose to use a very wide therapeutic window, resulting in the risk of not finding differences in instability in an individual (smaller) therapeutic window. Our definition of the titration phase was applied retrospectively and the deduced days and measurements until stability could be incorrect.

Co-morbidities of the patients were unknown as was use of other medication. The time between blood sampling and the last lithium intake was unspecified in most cases (93%). Blood taken soon after the last intake of lithium can result in falsely elevated concentrations and blood taken too late in falsely lowered concentrations.[21]

The indications for lithium serum concentration measurement were unknown. These could be regular measurements for monitoring long-term lithium treatment or measurements because of adverse effects or suspicion of noncompliance. Other reasons for serum measurements could be the anticipation of potential drug-drug interactions or decreasing kidney function.

We did not have information regarding compliance of patients to lithium use. From the study of Rose et al. it was concluded that alcohol abuse, bipolar disorder and major depression predicted a significantly lower T_i^1TR.[16] It is known that psychiatric patients are often noncompliant. Therefore it is possible that in this study the indication for lithium treatment can cause instability and this can impede other determinants reaching significance. The mean lithium serum concentrations were about 7% of the time under 0.4 mmol/L for all age groups; this could be due to either careful titration or to non-compliance. In a recent study on chronic lithium treatment Paton et al. found that 9.2% of 1734 bipolar patients had a lithium serum concentration < 0.4 mmol/L and 12.5% of 717 patients with other affective disorders had a lithium serum concentration < 0.4 mmol/L.[20]

Patients could only be included in this study if there was at least a follow-up of two years. Patients who were either noncompliant or for other reasons unstable on lithium treatment discontinued lithium probably early in the treatment potentially resulting in a depletion of susceptible patients. In a previous study, we found no difference in discontinuation between older and younger patients, which suggests that depletion of susceptible patients probably did not influence stability between the different age groups.[22]

The strengths of this study are the large sample size and the long-term follow-up and inclusion of patients in multiple centers.

In this study we explored whether older age is a risk factor for instability of lithium serum concentrations. Several parameters, considered a proxy for instability, were

used. These parameters were derived from studies with oral anticoagulants. Just as for lithium, anticoagulants have a narrow therapeutic window with risk of undertreatment and adverse effects.

During the titration phase and during maintenance treatment the parameters of instability did not differ between the reference group of 40-49 years and the older age groups.

In conclusion, age does not appear to be a determinant of lithium instability in this retrospective study and for that reason older age itself should not be a criterion to either not initiate lithium treatment or discontinue lithium treatment.

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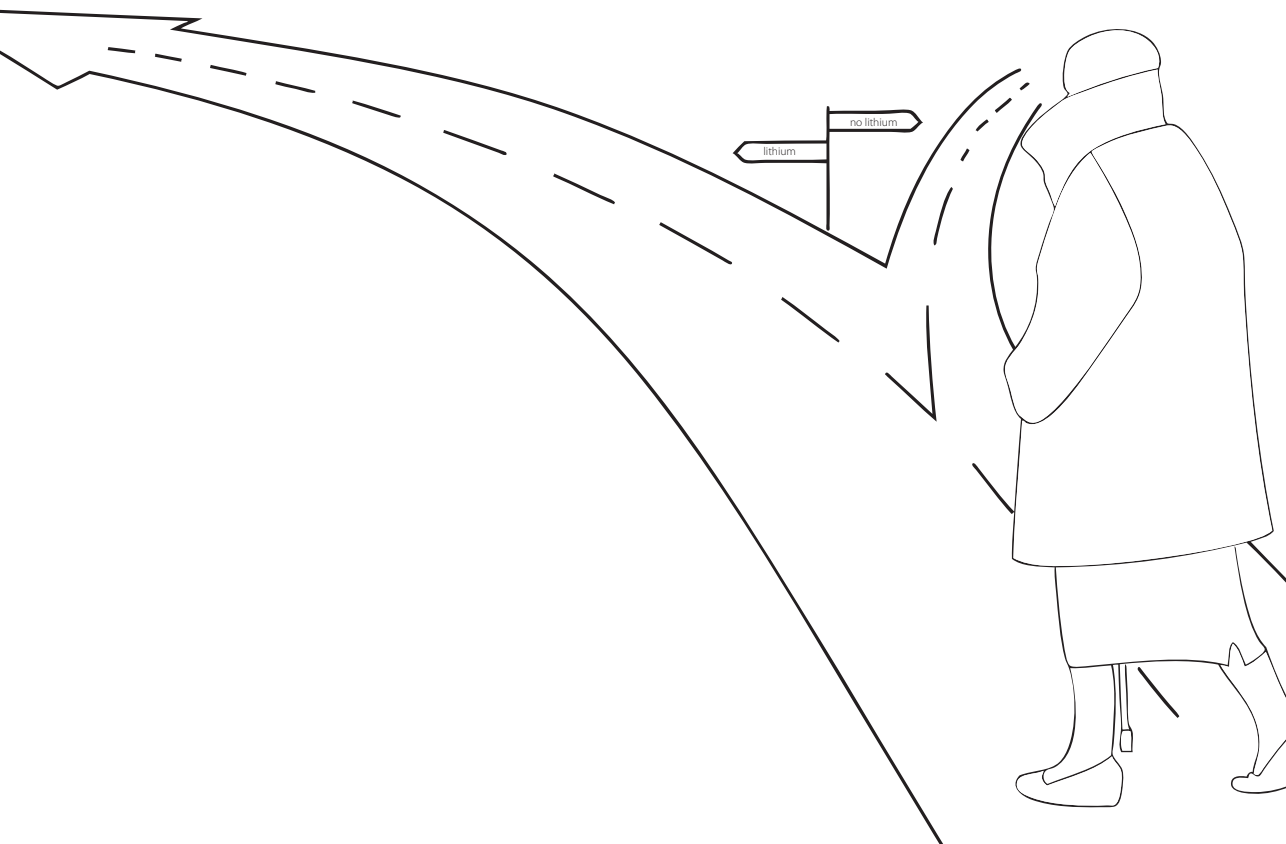
3

Somatic adverse effects of lithium use in older patients



3.1

Renal effects of long-term lithium therapy in the elderly: a cross-sectional study

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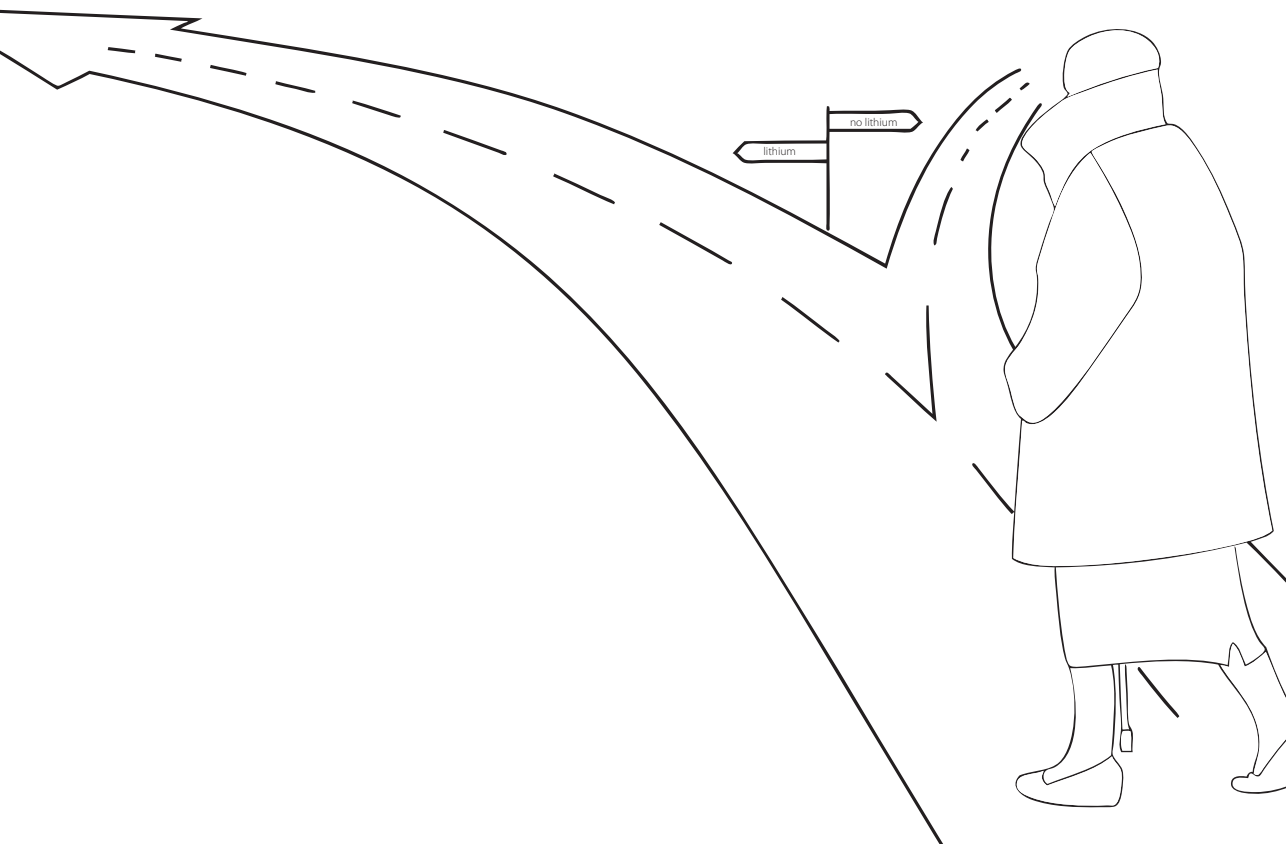

Abstract

Objectives: To determine the effect of long-term lithium therapy on glomerular filtration rate (GFR) and maximum renal concentrating capacity (Umax) in the elderly, to identify possible risk factors, to determine the clinical impact of a reduced Umax in this population and in case of polyuria to establish a diagnosis .

Methods: This is a cross-sectional study with 48 outpatients of 65 years or over (mean 74.8 years), who were treated with lithium for more than six months (mean 9.2 years). The GFR was determined with the Cockcroft-Gault formula (GFR-CG) and the Umax was measured in a urine sample collected between 3 and 5 h after the patients received 40µg desmopressin (DDAVP) intranasally.

Results: No relation was found between duration of lithium treatment and GFR-CG, but there was a significant negative relation between duration of lithium treatment and Umax (B -0.73; CI: -1.249/-0.212); 73% of the patients had a moderate to severe concentrating defect. No other risk factors than duration of lithium therapy were identified. A reduced Umax caused polyuria (> 2500mL/24h) in 33% but did not cause significant more thirst, incontinence or disturbed sleep.

Conclusions: In this geriatric population a negative relation was found between duration of lithium treatment and Umax. A reduced Umax did not result in significant more clinical symptoms. In case of polyuria other mechanisms besides nephrogenic diabetes insipidus were found to play a role in this age group.

Introduction

More than 57 years after the discovery of the therapeutic effects of lithium, it is still an important drug that is also used for people of 65 years and over.[1] In a cross-sectional study Head et al. found a prevalence of lithium use in older adults of 0.27%.[2] This is more than the prevalence of lithium use in people of all ages and probably due to the necessity of long-term treatment. The most important indications for lithium treatment in the elderly are bipolar disorder and unipolar depression.[3] It is well known that lithium can cause a decline in maximum renal concentrating capacity (Umax) especially after long-term use.[4,5,6] Risk factors for a more serious reduced Umax are concomitant use of other pyschotropics or somatic medication.[7]

The effect of lithium on glomerular filtration rate (GFR) is less clear. In most older studies there is evidence for a mild decline at the most, though Benz et al.[7] found in their study an age-adjusted reduction in GFR of 21%. From recent work there is evidence that lithium can also cause end-stage renal disease but the incidence is probably very low.[8,9]

Many studies have investigated the renal effects of lithium in groups of patients of all ages but, to our knowledge, this has never been studied specifically in an older population. The aim of this study was primarily to investigate the relationship between the duration of lithium use and Umax and GFR in people of 65 years or more and to identify possible risk factors. Secondly, to evaluate if a reduced Umax causes clinical symptoms or impact on daily activities in elderly lithium users. Finally, to investigate the most likely diagnosis in these elderly patients in case of polyuria.

Methods

Setting and study population

The study had a cross-sectional design and was conducted in the spring of 2005. The study protocol was approved by the medical-ethical committee of Dutch psychiatric institutions. The study population consisted of patients treated in Parnassia, a psychiatric institution with hospital and ambulatory facilities located in The Hague, the Netherlands, serving approximately 40 000 patients a year.

All ambulatory patients of 65 years and over who were treated with lithium for more than six months received an explanatory letter about the study. Exclusion criteria were severe urinary incontinenc (the patient can not control his/her voiding in any way and therefore can not collect even a small sample of urine), inability to understand Dutch and cognitive impairment. Of the 186 patients listed as user of lithium, 48 participated in the study (Figure 1).

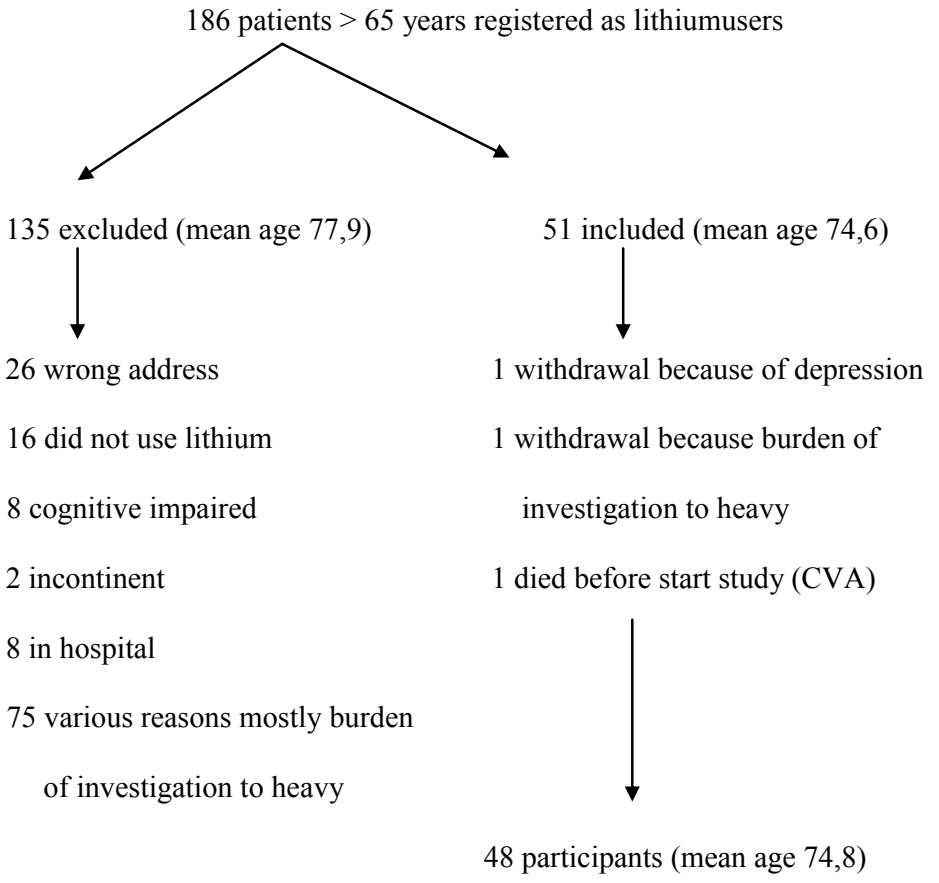

Figure 1. Patient selection

Measurements

The 48 patients who participated in the study were visited on study day one by a research nurse or a medical doctor. A questionnaire about polyuria-related problems was filled out: questions about how many times a patient had to void during the day and during the night and if the voiding frequency interfered with their social functioning and/or sleep and questions about thirst and incontinence. A separate questionnaire about lithium use, use of other medication and current and past illnesses was also filled out. These questionnaires were checked and if necessary completed with information from the medical record. All patients collected 24 hours urine (V24) on day two from 8.00h am until day three 8.00h am. In the morning of day three the patients came to the hospital, where they were weighted and blood samples were collected for the measurement of serum lithium concentration 12h post dosing, urea

nitrogen, creatinine, sodium, potassium, magnesium, calcium, phosphate, albumine, glucose, TSH, fT4, T3 and arginine vasopressin (AVP). Next 40 microgram desmopressin (DDAVP), a synthetic arginine vasopressin derivate, was administered intranasally.[10,11]
The 24-hours creatinine excretion was used to determine the completeness of the urine collection.[12] A sample of the 24h urine was taken for creatinine, sodium, protein, glucose and culture. Another urine sample was collected for the determination of the urine osmolality (Umax) at least three hours but no longer than 5 hours after DDAVP was administered. There was no fluid restriction during the study period.[10,13]
Plasma AVP was determined using a radio-immunoassay (Jodium 125) after plasma extraction over a C_{18} column. The AVP measurements had an intra-assay CV between 5,4 and 11,2% with concentrations resp 4,15 and 0,49 ng/L and the inter-assay CV was between 2,8 and 4,4% with concentrations resp 0,5 and 4,0 ng/L.
Urine osmolality was determined using an osmometer based on the principle of freezing point depression. The urine osmolality measurements had an intra- and interassay CV of 1%.
Plasma osmolality (Posmol) was calculated according to the following formula: 2[Na^+] (mmol/L) + urea(mmol/L)+ glucose(mmol/L).
The GFR was estimated by using the Cockcroft-Gault formula (GFR-CG).[14,15] As Umax declines with age the reference values according to Tryding et al.[13] were used. He stated that at the age of 80 the lowest maximum urine osmolality (mean – 2SD) is 600 mosmol/kg. No reference values are, to our knowledge, available for patients > 80 years.
The possible risk factors for a reduced Umax we studied were: vascular disease, vascular risk factors, the concomitant use of antispsychotics, use of different antidepressants, antihypertensive drugs and the total number of drugs currently used.[7,16]
To determine the clinical impact of a reduced Umax we looked for problems that could be related to polyuria. This was studied with the above mentioned questionnaire. As a reduced Umax with polyuria can increase the risk for dehydration and thereby for lithium intoxication this was also registered for every patient.[17]
To establish a diagnosis in patients with polyuria (> 2500mL/24 hours) the Posmol, Umax, plasma AVP and V24 were combined for diagnosing the individual patient. If the patient did not collect a complete V24 according to the creatinine excretion we made a correction (cV24). Expected creatinine excretion for a man [(28-(age/6)=…mg/kg/dag x bodyweight x 8,840 x 10^{-3} = …mmol/day] / measured creatinine excretion/L = cV24.[12] For a women the formula starts with 22-(age/9).
The patients were not subjected to a thirst test. Those with a normal Posmol and decreased Umax, could still have a significant clinical problem. We assumed that these patients should have a V24 or cV24 of at least > 2500mL. There are no absolute criteria in the literature available for the diagnosis of nephrogenic diabetes insipidus (NDI),

Table 1. Diagnostic criteria in case of polyuria[18]

Diagnosis	V24 ór cV24¶ (mL)	Umax □ (mosmol/kg)	Posmol ** (mosmol/kg)	AVP †† (ng/L)
NDI *	≥ 3000	≤ 300	> 290	> 1.5
pNDI †	> 2500	≤ 600	> 285	> 1.5
CDI ‡	≥ 3000	< 400	> 290	≤ 0.5
pCDI §	> 2500	< 700	> 285	≤ 0.5
PP //	> 2500	≤ 600	< 285	< 0.5

* NDI Nephrogenic Diabetes Insipidus, † pNDI partial Nephrogenic Diabetes Insipidus, ‡ CDI Central Diabetes Insipidus, § pCDI partial Central Diabetes Insipidus, // PP Primary Polydipsia, ¶ V24 or cV24 24-hours urine production measured or corrected according to creatinin excretion, □ Umax maximum renal concentrating capacity after DDAVP, ** Posmol Plasma-osmolality, †† AVP Arginine Vasopressin

central diabetes insipidus (CDI) and primary polydipsia (PP).The criteria we applied are given in table 1 and are partially derived from Rose BD.[18]

Data analysis

To examine the relation between duration of lithium use, GFR-CG and Umax, two hierarchical multiple linear regression analyses were used. In the first regression GFR-CG was used as dependent variable and in the second regression Umax, each with duration of lithium use as predictor. In both analyses, age was also included as predictor in the first block and vascular diseases and vascular risk factors were included in the second block using the method 'ENTER'. Use of Calcium-antagonists, use of ACE-inhibitors and use of thiazide and loop diuretics were included as predictors in the third block, but were dropped due to non-significance, except for use of Calcium-antagonists.

To examine the relation between duration of lithium use and AVP concentration a hierarchical multiple linear regression analyses was used with AVP as dependent variable and duration of lithium use and age as predictors.

To determine the clinical impact of a reduced Umax we studied the problems related to polyuria for three groups: severe reduction (≤ 300mosmol/kg), mild to moderate reduction (300 msomol/kg < Umax ≤ 600 msomol/kg) and no reduction of Umax.(> 600 mosmol/kg). A chi-square test was used to examine the distribution within the categories of Umax. An exact correction for small expected values was used when needed.[19] A logitmodel was not used due to small sample sizes. All calculations were carried out using SPSS version 13.0.

Results

In this study 48 patients participated with a mean age of 74.8 years (Table 2). Depression was the most frequent reason for lithiumuse (62.5%), followed by bipolar disorder (35%). This can be explained by the fact that lithium augmentation for treatment of resistant unipolar depression was a long-standing practice in Parnassia long before this was adviced in a national guideline.[20]

All patients were on lithium for more than six months with a mean of 9.2 years. They took their lithium medication once a day in the evening. The adviced lithium level for the elderly was 0.4-0.6 mmol/L for stable patients and up to 0.8 mmol/L in acute patients. Polypharmacy was a frequent finding with 52% of patients using five or more medications a day. This is higher than in the same age group in the general population.[21]

We found no significant relation between the duration of lithium treatment and the GFR-CG but there was a significant negative relation between duration of lithium use and Umax (Table 3). The Umax was reduced in 73% of the patients; 19% had a severe concentrating defect (≤ 300 mosmol/kg) and 54% had a moderate concentrating defect (> 300 and ≤ 600 mosmol/kg). None of the patients had abnormal plasma concentrations of Ca^{2+} or K^{+} and none had glucosuria. One patient had proteinuria of 0.3 gr/L, the others had lower or no proteinuria at all.

In this patient group we found no significant influence of vascular disease, vascular risk factors, concomitant use of SSRIs, TCAs, antipsychotics or antihypertensive drugs or of the total number of medications on the Umax in relation to duration of lithium use. Concomitant use of calcium-antagonists (amlodipine) was associated with less reduced GFR-CG and more reduced Umax. As only four patients used amlodipine the significance of this finding is not clear.

The clinical impact of a reduced Umax is given in Table 4. Patients with a severe concentrating defect had more frequently problems with incontinence, impact on social functioning and more thirst, but this was not statistically significant.

Although there was a significant rise in plasma AVP concentration with longer duration of lithium use B = 0.825 (CI: 0.369-1.281; P< 0.001), the AVP concentration was within the normal range (0.2-4.7 ng/L) as given by the manufacturer for all 48 patients. All patients with AVP > 1.5 ng/L had a reduced Umax (≤ 600 mosmol/kg), but not all patients with a reduced Umax had AVP > 1.5 ng/L.

In combining the results of Posmol, Umax, AVP and V24 or cV24 we tried to diagnose those patients with polyuria (Table 5). Of all 48 patients only two did not collect V24, but the results of the other parameters were enough to warrant a diagnosis. One patient could not be diagnosed, but was suspected of drug-induced SIADH due to concomitant SSRI use and polydipsia.

Table 2. Demographic and medical characteristics of the study population

Characteristics	Characteristics subdivison	Mean (range)	Standard deviation	Absolute number	Percentage
Gender	men			7	15
	women			41	85
Age (years)		74,8 (65-89)	5.65		
Bodyweight (kg)		76.6 (41-121)	14.37		
Duration lithium use (years)		9.2 (0.5-31)	8.58		
Serum lithium concentration 12h post dosing (mmol/L)		0.61 (0.13-0.86)	0.138		
Daily lithium dose (mg lithiumsalt)		470.65 (150-800)	149.66		
Indication lithium use	Bipolar disorder			17	35
	Depression			30	63
	Other			1	2
Vascular disease and vascular risk factors				30	63
	Cardiovascular disease			6	13
	Cerebrovascular disease			5	10
	Diabetes Mellitus			7	15
	Hypertension			21	44
	Hyperlipidaemia			5	10
Known renal disease				2	4
Hypothyroïdism*				17	35
Total number medication		4.8 (1-9)	2.27		
Antidepressants				29	60
	TCA†			19	40
	SSRI‡			7	15
	Other			4	8
Antipsychotics				6	13
	Atypical			5	10
	Classic			1	2
Loopdiuretics				3	6
Thiazide type diuretics	One with amiloride			5	10
NSAIDs§				0	0
ACE-inhibitors //				7	15
Calcium-antagonists				4	8

* Hypothyroidism defined as patients who were treated with thyroxine, all other patients had normal fT4 and TSH, except two who had subclinical hypothyroidism with normal fT4 and TSH > 4.0 and < 10.0 mU/L, † TCA: Tricyclic Antidepressant, ‡ SSRI Selective Serotonin Reuptake Inhibitor, § NSAID Non-Steroidal Anti-Inflammatory Drug, // ACE-inhibitor Angiotensin Converting Enzym-inhibitor

Table 3. Results of hierachic multiple linear regression analysis describing the relation between duration of lithium use and GFR-CG and Umax adjusted for age, vascular disease and vascular risk factors and the use of Calcium-antagonists

Predictors	GFR-CG * B (95% CI)	Umax† B (95% CI)
Lithium use (month)	-0.023 (-0.068/0.022)	-0.730 (-1.249/-0.212)
Age (years)	-1.052 (-1.831/-0.273)	-0.033 (-9.008/8.942)
Vascular disease and Vascular risk factors	-3.705 (-13.39/5.984)	-27.546 (-139.14/84.05)
Ca-antagonist	17.34 (1.108/33.58)	-188.47 (-375.45/-1.483)

*GFR-CG: Glomerular filtration rate calculated with Cockcroft-Gault formula
†Umax: maximum renal concentrating capacity after DDAVP

Table 4. Clinical impact of reduced Umax*

Symptoms	Umax ≤ 300 mosmol/kg n = 9	Umax > 300 and ≤ 600mosmol/kg n = 26	Umax > 600 mosmol/kg n = 13
Polyuria †	4 (44%)	9 (35%)	2 (15%)
Incontinence	3 (33%)	7 (27%)	3 (23%)
Disturbed sleep	1 (11%)	4 (15%)	1 (8%)
Impact on Social functioning	2 (22%)	1 (4%)	0 (0%)
Thirst	5 (55%)	13 (50%)	6 (46%)
Lithiumintoxication needing hospitalisation	0 (0%)	2 (8%)	1 (8%)
Any of the symptoms above	6 (67%)	16 (61%)	8 (62%)

* Umax: maximum renal concentrating capacity after DDAVP, † Polyuria: measured or corrected 24-hours urine production > 2500mL

Discussion

In this cross-sectional study of elderly patients we found no relation between duration of lithium treatment and GFR-CG after correction for age and vascular risk factors, but there was a significant negative relation between duration of lithium treatmen and Umax: 73% of the patients had a moderate to severe concentrating defect. We found no other risk factors other than duration of lithium therapy which contributed to the reduced Umax. The clinical impact of a reduced Umax was mild in this age group. Surprisingly there were not only patients with NDI or partial NDI (pNDI), but also with a partial CDI (pCDI) and PP.

Head et al.[2] found in their cross-sectional study of 148 people of 65 years and older no significant association between duration of lithium treatment and abnormal renal function. But they only used serum urea and creatinine as measure of renal function.

Table 5. Diagnostic characteristics of patients with V24 or cV24 > 2500mL

Patientnumber	Umax* mosmol/kg	Posmol† mosmol/kg	AVP‡ ng/L	V24§ mL	cV24 // mL	diagnosis
1‡‡	236	292	2.5	5600	7000	NDI¶
2	174	299	2.8	missing	missing	NDI
3	81	291	1.7	2100	3400	NDI
4	204	293	3.0	6000	6000	NDI
5	356	293	2.1	2000	2600	pNDI□
6	444	287	2.6	1400	2700	pNDI
7	573	285	1.5	2700	2900	pNDI
8	387	289	4.6	missing	missing	pNDI
9‡‡	480	291	0.5	2700	4600	pCDI**
10	400	287	0.2	2400	4000	pCDI
11	472	287	0.2	2800	2800	pCDI
12	416	288	0.6	2000	3200	pCDI?
13	396	283	0.2	3400	3700	PP††
14	185	283	0.27	2900	3100	PP
15‡‡	460	278	2.5	1800	3000	?
16	624	297	0.23	2600	2300	pCDI
17	653	291	0.22	4100	3000	pCDI

* Umax: Maximum renal concentrating capacity after DDAVP, †Posmol: Plasmaosmolality, ‡AVP: Arginine Vasopressin, § V24: measured 24 hours urine production, // cV24: calculated 24 hours urine production according to creatinin excretion, ¶ NDI: Nephrogenic Diabetes Insipidus, □ pNDI: partial Nephrogenic Diabetes Insipidus, ** pCDI partial Central Diabetes Insipidus, †† PP Primary Polydipsia, ‡‡ use of frusemide

Gitlin[22] found in his review no evidence for an important impact of lithium treatment on GFR. But recent studies indicate that there is probably a small group of patients who can develop end stage renal disease.[8,9]

We used the Cockcroft-Gault formula[14] which gives a better estimation of GFR in the elderly than serum creatinine.[15] Although we found no significant relation between duration of lithium treatment and GFR-CG, we found a significant negative relation with age (B = -1.052 (CI: -1.831/-0.273; P= 0.009).

There were 24 patients with a GFR-CG < 60 mL/min (stage 3 CKD) of which nine patients had a GFR-CG < 40 mL/min. Two patients had a GFR-CG < 30 mL/min (stage 4 CKD).[23] The mean age of these 11 patients was higher (79 years) than in the total group of patients as was the prevalence of vascular disease and vascular risk factors (72%) but the mean duration of lithiumuse (9.5years) was not different. Lamb et al.[24] state that the GFR declines with age but the mechanism is not clear. They refer to studies which show that aging itself does not cause the decline but an interplay of different

pathological processes, especially hypertension and heart failure. This could play a role in this subgroup of our patients. But the design of this study does not make it possible to exclude that lithium played a role in the decline in GFR in some of these patients.

There are many studies which have tried to determine the effect of lithium on renal concentrating capacity. Most but not all studies show that the Umax decreases with longer lithium treatment.[5,22] As far as we know no studies in the elderly have been undertaken. In our 48 patients with a mean age of 75 years we found a significant reduced Umax: 73% of patients had a concentrating defect defined as Umax ≤ 600mosmol/kg. Benz et al.[7] found in 138 patients with a mean age of 61 years an age corrected reduction in Umax in 44%. They found in 12% an Umax < 300mosmol/kg, in our study this was 18.7%. This could indicate that older people are more susceptible to a reduction of Umax during lithium treatment. Our patients had more vascular risk factors than in the study of Benz et al.[7] (62% versus 30%), but the mean duration of lithium use was shorter, respectively 9 and 19 years.

The clinical impact of a reduced Umax was low. We found no significant relation between Umax and incontinence, impact on social functioning, disturbed sleep and thirst. The fact that not all patients with a reduced Umax have polyuria could be an explanation.

Reduction of Umax during lithium treatment is almost always ascribed to an acquired NDI. By entering the distal tubular cells lithium interferes with the AVP effect of expression of aquaporine-2. This water channel is necessary for the absorption of water from the distal tubule. Lithium also reduces the AVP stimulated urea reabsorption and thereby the medullary concentration gradient which is necessary for maximum concentrating capacity.[25,26]

The significant increase of AVP with longer lithium use found in our study seems to confirm that a reduced Umax is related to AVP resistance. But although there were four patients with NDI and four with partial NDI, there were also three patients with partial CDI, three with probable pCDI and two with PP. Baylis et al.[27] found in their study one patient of 48 with probably CDI and Turan et al.[28] two out of 20. Based on animal studies there is a suggestion that lithium can interfere with the synthesis and release of ADH.[29] However it is not settled what happens to AVP production in older people. Some state that AVP decreases,[30,31] others say it increases,[32,33] and there are those who claim it doesn't change at all.[34]

Polyuria and subsequently thirst and polydipsia are the expected clinical consequences of reduced renal concentrating capacity irrespective of the cause, NDI or CDI. Nine patients (18,8%) collected V24 > 2500 mL; after correction according to the creatinine excretion in the urine 15 had cV24 > 2500mL. As 2 didn't collect , this is 33% of 46 patients,. If we apply the criteria for polyuria that are mostly used in the literature (≥

3000mL/24 h) the percentage patients with polyuria is 21%. Movig et al.[16] found in a group with a mean age of 52 years 37% polyuria.

This study suffers from several limitations due to the cross-sectional nature of the study. The measurements were done at one moment in time and the GFR and Umax from before the start of lithium were unknown. An important bias is that we can not correct for the possibility that in patients with a significant decline in their renal function lithium was stopped: depletion of susceptibles. A complicating factor is that there is almost no information about what happens to the Umax in healthy older people. Tryding[13] only gives values up to 80 years, but states that the Umax declines with age. We used the lowest Umax (-2D) on the age of 80 years as cut off point for a concentrating defect.

Of the total group of lithium treated older patients who were asked to participate only one third gave consent. The bias this introduced can work both ways. People who are already worried because they have doubts about their health will be more eager to give permission. On the other hand, not feeling well can also be a reason to decline participation. The number of patients who participated in the study was small and they came from one area in the Netherlands. Therefore generalisablity of the results may be limited. The risk factors we looked at were chosen on clinical grounds and after studying the literature. There may be factors we overlooked.

Considering the limitations we still think this study gives an indication of what happens to the renal function of older people during lithium treatment. In these patients we found no relation between duration of lithium treatment and GFR-CG and a significant negative relation with Umax. The prevalence of a reduced Umax was higher than in younger age groups studied[7] but this did not result in more polyuria in our older patients.[16]

A reduced Umax did not cause significant more clinical symptoms. For the clinician this is important because asking the patients for complaints related to polyuria will not always identify them.

The frequency of CDI as a cause of reduced Umax in this population needs confirmation. The question is wether this is a true lithium effect or an age-related problem of AVP production. As CDI has to be treated differently it is important to differentiate this from NDI in lithium treated patients.

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3.2

Prevalence of cardiovascular risk factors and cardiovascular disease in older lithium users

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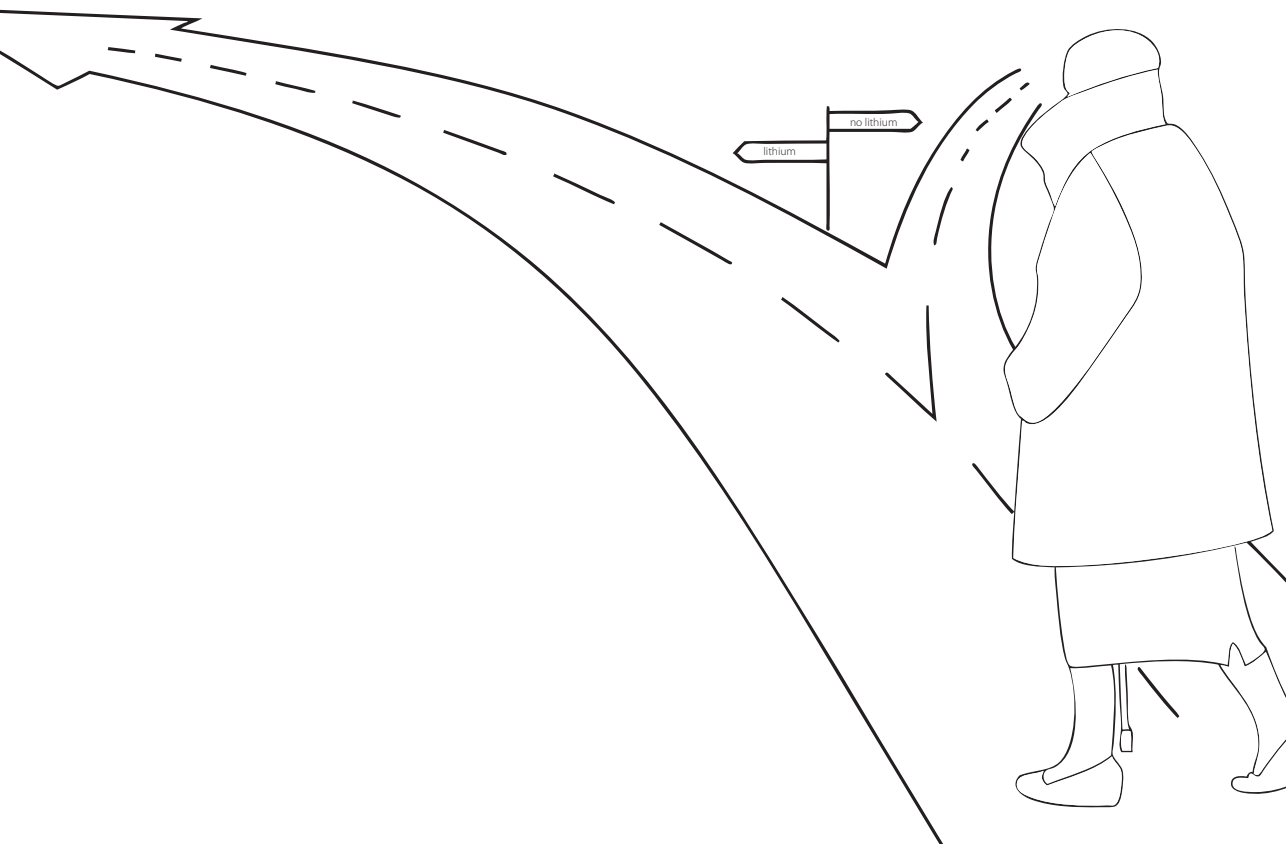

Abstract

Background: patients with an affective disorder are at increased risk for cardiovascular morbidity and mortality compared to the general population. The effect of lithium use is only sporadically studied.

Objective: to ascertain the prevalence of known cardiovascular risk factors (CVR) and the prevalence of cardiovascular disease (CVD) in older patients treated with lithium, to compare the prevalence to data from the general population and to study the association with the duration of lithium use.

Methods: A cross-sectional study of psychiatric patients visiting a specialized lithium ambulatory clinic for older patients was performed. Patients underwent a comprehensive assessment and potential confounders of CVR and CVD were recorded. Based on duration of lithium treatment, patients were divided into four groups.

Results: The prevalence of diabetes in women and the prevalence of overweight and hypertension in both sexes was higher in our study population compared to an older population study of the same age group. The prevalence of diabetes was lower in our study compared with a more recent population study. There was a striking lower prevalence of hyperlipidemia in our study compared with the general population. The prevalence of ischaemic heart disease was lower and the prevalence of cerebrovascular accident (CVA) was higher in our study than in the general population. There was no relation with duration of lithium use and CVR and CVD except for an increase in BMI in the first years of lithium use.

Conclusions: Apart from the effect on CVA prevalence, lithium seems to have a relatively mild cardiovascular risk profile in this group of elderly lithium users, but further studies are warranted.

Introduction

Cardiovascular morbidity is highly prevalent in the general population, with diabetes, overweight, hypertension, smoking and age as the most important risk factors.[1] In patients with uni- and bipolar disorder the incidence of cardiovascular mortality is higher than in the general population.[2] Ösby et al.[2] found compared to the general population a Standardized Mortality Ratio (SMR) for cardiovascular disease of 1.5 in men with unipolar disorder and of 1.9 in men with bipolar disorder; in women this was even stronger (SMR respectively 1.7 and 2.6). A meta-analysis on depression and cardiovascular disease concluded that major depression equals the risk of smoking and diabetes as a risk factor for cardiovascular disease (CVD) , with a pooled effect size of 2.54.[3] The reason why patients with an affective disorder are at increased risk for cardiovascular morbidity and mortality compared to the general population, is probably multifactorial.[4,5] Genetic predisposition and disease related factors (e.g. activation of stress hormones) could play a role, in addition to a more hazardous lifestyle with smoking, low physical activity, high alcohol and high caloric intake resulting in overweight and insulin resistance. Also the use of psychotropic medication may have a direct effect, for example on the cardiac conduction system[6,7] and on the thrombotic state, but may also have an indirect effect by causing weight gain and unfavorable lipid profile changes.[8] Antipsychotics, in particular second generation antipsychotics (SGA) have been extensively studied as a determinant for cardiovascular risk factors (CVR) and CVD, but much less is known on the effects of mood stabilizers.[5]

Lithium is a mood stabilizer used in the treatment of acute mania, maintenance treatment of bipolar disorder and as augmentation in treatment resistant unipolar disorder. Most indications make long-term treatment necessary, also in old age. As age itself is a risk factor of cardiovascular disease, it is important to know if lithium further contributes to this risk, because the treating physician can use this knowledge in his treatment decisions and, if necessary, take preventive measures according to the prevailing guidelines.[5]

The primary objective of this study was to ascertain the prevalence of known CVR as overweight, diabetes, hypertension and hyperlipidemia and the prevalence of CVD in older patients treated with lithium and to compare these prevalences to published data from the general population of the same age. The second objective was to study the association between the duration of lithium use and the prevalence of CVR and CVD in these older patients.

Methods

Setting, design and population

This was a cross-sectional study in elderly psychiatric patients. Eligible patients for this study were outpatients from Parnassia, aged 60 years or older who were treated with lithium. Parnassia is a psychiatric center with in- and outpatient facilities in The Hague, the Netherlands.

In 2005 a pilot of more extensive somatic screening of older patients treated with lithium was started in Parnassia, which was in 2008 implemented as routine care for the elderly seen in the specialized lithium ambulatory clinic (SLAC). All new referrals to the SLAC between January 2005 and March 2009 were included in this study. Patients visited the SLAC in the morning after a light breakfast. Blood was drawn between 9.30 and 10.00 am. Thereafter weight, height and blood pressure were measured and a comprehensive physical examination was conducted. Weight was measured with light clothing without shoes and blood pressure was measured in sitting position. As part of the screening, medical history and medication use as reported in the medical file were registered. In case medication use was not clear, a medication dispensing overview was obtained from the community pharmacy the patient visited.

The somatic screening of the lithium patients was in line with the Dutch national guideline on bipolar patients involving standard blood sampling in the morning.[9] As only a few extra tests were done in blood already sampled, the scientific board of Parnassia concluded that no additional approval from a medical-ethical committee was necessary to conduct this study.

Cardiovascular risk factors and diseases

Information on CVD and CVR was gathered from the medical files. BMI was calculated using the formula weight(kg)/height(m)^2. BMI was categorized according to the WHO criteria with underweight BMI < 18.5 kg/m^2; normal weight BMI 18.5–24.99 kg/m^2; overweight 25-29.99 kg/m^2 and obesity ≥ 30 kg/m^2. All patients with a BMI ≥ 25 kg/m^2 (overweight and obesity) were classified in this study as overweight. Diabetes was defined as having this diagnosis according to the medical file and/or being pharmacologically treated for diabetes. In addition, having a non-fasting glucose > 11.1 mmol/L after a light breakfast was defined as having diabetes.[10] Hypertension was defined as having this diagnosis according to the medical file and/or being pharmacologically treated for hypertension. In addition, having a systolic blood pressure ≥ 160 mmHg and/or a diastolic blood pressure of ≥ 95 mmHg during the screening was defined as hypertension.[11] Hyperlipidemia was defined as having this diagnosis according to the medical file and/or using lipid lowering medication without recorded use as secondary prevention. In addition, having a total cholesterol ≥ 6.5 mmol/L was defined

as hyperlipidemia.[10] High-density lipoprotein (HDL) was determined in each patient and low HDL ≤ 0.9 mmol/L was also considered a risk factor.[11] Triglycerides were not determined in this study. Data on CVR in the general population were derived from publications of the Rotterdam study, a population based study of people 55 years or older conducted in the early nineties[11,12] and from another population study in the Netherlands in 2009-2010.[10]
CVD was defined as ischaemic heart disease (IHD) (angina pectoris, myocardial infarction and/or treatment for coronary heart disease) and cerebrovascular accident (CVA). Data on CVD in the general population were derived from registration data from general practitioners for people 65 years and older in the Netherlands in 2007.[13,14]

Potential confounders

The following parameters were gathered as potential confounders for the association between duration of lithium use and CVD and CVR: age, gender, race, renal function calculated with the Modified Diet in Renal Disease (MDRD) formula, fT4 and TSH, psychiatric diagnosis for which lithium was used, current use of antidepressants, first and second generation antipsychotics (FGA and SGA) and mood stabilizers other than lithium. Each patient was asked about his smoking habits at the time he visited the SLAC. If the patients had smoked in the recent past this was not registered.

Data analysis

The point prevalence of overweight, diabetes, hypertension, hyperlipidemia and CVD were determined in our study group. This point prevalence was compared to the prevalence documented in the studies as described above. To determine the association between duration of lithium use and the CVR and CVD, the patients were categorized into four groups according to the duration of lithium use: ≤ 2 years, 2-5 years, 5-10 years and > 10 years. The demographic characteristics, possible confounders, CVR and CVD were ascertained for each treatment group. Within the four treatment groups the categorical variables were compared using the χ^2test and the continuous variables using one-way ANOVA, taking the group who used lithium ≤ 2 years as reference group. Stratification was performed in case potential confounders significantly differed ($p<0.05$) between the four groups.

Results

The study group consisted of 84 patients, 81 were Caucasian and the mean age of the study group was nearly 75 years (Table 1). All patients had an fT4 within the normal

Table 1. Patient and psychotropic medication characteristics.

Duration lithium use Number of patients Patient characteristics	N=84	≤ 2 years N=17	2-5 years N=14	5-10 years N=21	>10 years N=32
Age, mean(sd)	74.9 (6.6)	75.0 (6.8)	71.4 (5.1)	76.2 (7.0)	75.6 (6.6)
Women %(n)	78.6 (66)	88.2 (15)	78.6 (11)	81.0 (17)	71.9 (23)
Smoking %(n)	28.6 (24)	35.3 (6)	7.1 (1)	28.6 (6)	34.4 (11)
Race, Caucasian %(n)	96.4 (81)	100 (17)	92.9 (13)	100 (21)	93.8 (30)
Renal function MDRD mean(sd)	58.5 (14.1)	65.8(10.2)	60.7(11.5)	56.6(11.9)*	55.0(16.8)*
Lithium charactericstics					
Lithium dose mg/d mean(sd)	453 (168)	406 (100)*	532 (194)	426 (153)	458 (187)
Lithium serum level mmol/L mean(sd)	0.59 (0.20)	0.52(0.13)	0.55(0.11)	0.61(0.25)	0.63(0.21)
Lithium treatment in years mean(sd)	10.1 (9.1)				
Lithium indication %(n)					
Bipolar disorder	34.5 (29)	17.6 (3)	21.4 (3)	38.4 (8)	46.9 (15)*
Depression	58.3 (49)	82.4 (14)	78.6 (11)	52.4 (11)	40.6 (13)*
Other	7.1 (6)	0	0	9.6 (2)	12.5 (4)*
Other psychotropic medication characteristics					
Antipsychotics %(n)					
First generation	7.1 (6)	13.3 (2)	0	9.5 (2)	6.3 (2)
Second generation	16.7 (14)	13.3 (2)	14.3 (2)	23.8 (5)	15.6 (5)
Antidepressants %(n)					
Tricyclic	44.0 (37)	73.3 (11)	64.3 (9)	38.1 (8)	28.1 (9)*
SSRI	6.0 (5)	0	7.1 (1)	4.8 (1)	9.4 (3)*
Other	8.4 (7)	13.3 (2)	7.1 (1)	14.3 (3)	3.1 (1)*
Moodstabilisers %(n)					
Valproic acid	3.6 (3)	0	7.1 (1)	0	6.3 (2)
Carbamazepine	3.6 (3)	0	0	4.8 (1)	6.3 (2)
Lamotrigin	2.4 (2)	0	7.1 (1)	4.8 (1)	0

*$P < 0.05$ in the four treatment groups; the group ≤ 2 years is the reference group.

range (data not shown in the table). Patients who used lithium for more than 10 years had significantly more often a bipolar disorder and used less antidepressants compared to the patients who used lithium 2 years or less. The MDRD was significantly lower in the patients who used lithium for more than 5 years compared to the patients in the reference group. Use of antipsychotics and mood stabilizers other than lithium was low in the whole study group.

Table 2a Prevalence of cardiovascular risk factors in women 60-70 years using lithium and in the general population.

Cardiovascular risk factors	Women 60-70 years Lithium patients n=18	Women 60-70 years General population#
BMI ≥ 25 %(n)	56 (10)	56
Diabetes %(n)	6 (1)	11
Hypertension %(n)	44 (8)	55
Hyperlipidemia %(n)	6 (1)	48

Population study in the Netherlands in 2009-2010[10]

Table 2b Prevalence of cardiovascular risk factors in patients 60 years and older using lithium and in the general population 55 years and older.

Cardiovascular risk factors	Women Lithium patients n=66	Women general population[1]	Men Lithium patients n=18	Men general population#
BMI ≥ 25, %(n)¶	58.2 (32)	50.0	69.2 (9)	50.0
Diabetes %(n)	21.2 (14)	10.9	0	10.4
Hypertension %(n)	47.0 (31)	28.0	44.4 (8)	23.3
Hyperlipidemia %(n)	19.7 (13)	49.5	5.6 (1)	35.1
HDL ≤ 0.9mmol/L %(n)	1.5 (1)	2.8	5.6 (1)	7.9
Smoking %(n)	27.3 (18)	16.7	33.3 (6)	29.7

¶available in 55 women and 13 men
The Rotterdam Study[11,12]

The prevalence of the CVR is reported in Tables 2a and 2b. Table 2a shows the prevalence of a subgroup within our study of 18 women between 60 and 70 years old and the prevalence of CVR in women of the same age from a recent population study.[10] Table 2b shows the prevalence of CVR for all the women and men in our study and the prevalence in a group of a comparable age from another population based study.[11,12] The most striking difference is the low prevalence of hyperlipidemia in our study compared with the prevalence in the general population studies, with also a low prevalence of low HDL. The prevalence of diabetes in women and the prevalence of overweight and hypertension in both sexes was higher in our study population compared to the Rotterdam study. When comparing the prevalence of the CVR between the subgroup of women of our study with the women of the same age from the more recent population study,[10] the prevalence of diabetes and hypertension was lower in our study. The prevalence of IHD was lower and the prevalence of CVA was higher in our study population than in the general population (Table 3).

In our study there was a significant increase in BMI between the reference group and the group who used lithium between 2 and 5 years and also between the reference group and the group who used lithium for more than 10 years ($P < 0.05$). There was

Table 3. Prevalence of cardiovascular disease in patients 65 years and older using lithium and in the general population 65 years and older in the Netherlands.

Cardiovascular disease	Women Lithium patients n=63¶	Women general population#	Men Lithium patients n=18	Men general population#
Ischaemic heart disease %(n)	11.1 (7)	13.8	5.6 (1)	25.0
Cerebrovascular accident %(n)	7.9 (5)	5.3	11.1 (2)	6.3

¶ 3 women were younger than 65 years
# Registration data from general practitioners for people 65 years and older[13,14]

Table 4. Prevalence of cardiovascular risk factors and cardiovascular disease in four groups of patients according to duration of lithium use

Duration of lithium use Number of patients	Group I ≤2 years n=17	Group II 2-5 years n=14	Group III 5-10 years n=21	Group IV >10 years n=32
Cardiovascular risk factors				
BMI¶, mean (sd)	23.6 (3.5)	27.7 (5.9)*	26.5 (4.5)	26.8 (3.5)*
DM %(n)	17.6 (3)	7.1 (1)	23.8 (5)	15.6 (5)
Hypertension %(n)	41.2 (7)	35.7 (5)	57.1 (12)	46.9 (15)
Hyperlipidemia %(n)	11.8 (2)	28.6 (4)	9.5 (2)	18.8 (6)
Smoking %(n)	35.3 (6)	7.1 (1)	28.6 (6)	34.4 (11)
Cardiovascular disease				
Ischemic heart disease %(n)	6.3 (1)	7.1 (1)	19.0 (4)	6.3 (2)
Cerebrovascular accident %(n)	0	0	14.3 (3)	12.5 (4)

¶Available in 14,13,15 and 26 patients in respectively group I, II, III and IV
*$P < 0.05$ with group I as reference

not a significant difference between the four treatment groups and the other CVR and CVD (Table 4).

Discussion

In this study of older patients using lithium, CVR as overweight, hypertension and diabetes were more prevalent than in the general population. However compared with a more recent population study, the prevalence of hypertension and diabetes was lower in a subgroup of older women using lithium. The prevalence of hyperlipidemia was much lower in women and men using lithium compared with the older and recent population studies. Concerning CVD, the prevalence of IHD was also lower in our study group compared to the general population and the prevalence of CVA was

somewhat higher. We found no association between duration of lithium use and CVR or CVD, except an increased BMI in patients using lithium more than 2 years.
As far as we know this is the first study on the prevalence of CVR and CVD in elderly patients treated with lithium. Prevalence of CVR and CVD differ between geographic areas worldwide and between urban and rural areas, in addition the definition of CVR may differ between studies. Therefore we compared our Dutch study group to data reported for the general population in the Netherlands, all living in an urban area and using the same definition for CVR.[11,12] The data from the Rotterdam study also included the age group of 55-60 years and their data are from 15 years earlier than our data. The prevalence of CVR increases with age and the prevalence of diabetes and overweight have increased in the Netherlands in the past two decades. Therefore we also compared our study data to population data from a more recent study.[10] In this study age was between 35 and 70 years and in our study 22 patients, 4 men and 18 women, were between 60 and 70 years. The definitions for overweight, diabetes and hyperlipidemia used by Blokstra et al.[10] were similar to those used in our study, but the definition for hypertension was different. Blokstra et al.[10] used a systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 as a cut off for hypertension. We used higher values for defining hypertension and this might explain the lower prevalence of hypertension in our study.
In our study the prevalence of overweight was higher in men and women treated with lithium compared to the data from the Rotterdam study but did not differ from the population study of more recent date.[10,11] Most studies on lithium use report an increase in body weight during treatment, more frequent than in those treated with placebo.[15] The increase in body weight is much less than during treatment with olanzapine and clozapine and also less than during treatment with risperidon and quetiapine.[15,16] We found an association between duration of lithium use and BMI. The patients who used lithium more than 2 years had a higher BMI than those who used lithium ≤ 2 years. Although there was not a significant difference between the reference group and the group who used lithium 5-10 years, the mean BMI was almost the same as in patients who used lithium more than 10 years. The difference with this group and the reference group was significant but the group consisted of more patients. What is evident from the mean BMI in the 4 groups is that the BMI stabilises after 2-5 years of lithium use. Vestergaard et al.[17] found in a prospective study a maximum increase in bodyweight during the first two years of lithium treatment. Apart from recovery of weight after remission of the affective disorder, many mechanisms have been suggested as cause of too much weight gain during lithium treatment. Increased thirst with intake of high caloric beverages, increased insulin sensitivity and direct stimulation of the hypothalamic appetite centre have all been implicated.[15]

A relation with hypothyroidism seems less likely as weight would decrease when patients are adequately treated.

The prevalence of hypertension was higher in our study than in the Rotterdam study, but the inclusion of younger patients in the Rotterdam study in addition to the difference in timing of the study data could have reduced the prevalence.[11] On the other hand, use of lithium or the psychiatric disorder for which it is used may cause hypertension. De Hert et al.[5] concluded that the literature does not show a consistent association between psychiatric illness and hypertension, but psychotropic drugs may cause hypertension by inducing weight gain. A more recent study on bipolar I and unipolar patients reported a significant higher prevalence of hypertension as compared to controls adjusted for age, sex and race.[18] Wu et al.[19] also found a higher prevalence of hypertension in patients with major depressive disorder. The prevalence of hypertension in the study of Wu et al.[19] was 51.13% in patients who were 60 years and older. This was a database study conducted in Taiwan and patients with hypertension were defined as patients who were diagnosed with hypertension and/or used antihypertensive drugs. They did not find a significant association between prevalence of hypertension and the use of mood stabilizers.

The prevalence of diabetes in women was higher in our study than in the Rotterdam study,[12] but we found no diabetes in the (small) group of men in our study population. Compared to the data from the more recent population study, the prevalence of diabetes in women was lower in our study.[10] Bipolar and unipolar depression are associated with a higher prevalence of diabetes, and vice versa.[20,21,22] The mechanism behind this association is not fully understood, although it seems plausible that low self-care and unhealthy lifestyle resulting in weight gain are contributing factors, just like the use of psychotropic medication. Lithium treatment has not been associated with higher prevalence of diabetes. Vestergaard et al.[23] did not find an association between long-term lithium use and diabetes. In a study with rats lithium was found to significantly increase insulin sensitivity and insulin responsiveness.[24] Lithium has even been used to improve glycaemic control of patients with diabetes.[25]

We found a surprisingly low prevalence of hyperlipidemia and HDL ≤ 0.9mmol/L in our study group. There are two case reports of severe hyperlipidemia possible associated with lithium use.[26,27] This is contrary to what we have found and is probably a coincidence rather than a real association because in the long history of lithium treatment serious hyperlipidemia has not been noted more often. There is one study on the metabolic effects of aripiprazole and lithium and there were no significant differences in total cholesterol and HDL after one year of treatment as opposed to baseline with both treatments.[28] There are many studies on the metabolic syndrome in bipolar patients and Vancamfort et al.[29] published a meta-analysis on this subject. They stated that patients with bipolar disorder had a greater risk of developing a meta-

bolic syndrome compared to the general population and the prevalence was higher in the older population. Because they had limited data on individual medication they were not able to draw conclusions about the contribution of specific drugs. Mean age was 42.8 years and the meta-analysis was comprised of studies from all over the world. Overall they found a prevalence of low HDL of 42.1% as opposed to 1.5% in women and 5.6% in men in our study. In this study low HDL was defined as < 1.3 mmol/L in women and < 1.08 mmol/L in men. Using this definition the prevalence in our study would have been 22.7% in women and 22.2% in men. Taking into account that in older age the prevalence of lipid abnormalities increases and is lower in Europe than in the US, the prevalence in our study is still very low. This raises the question if lithium may protect against hyperlipidemia.

Concerning CVD, the prevalence of IHD is lower, but the prevalence of CVA is higher in our study than in the general population.[13,14] In most studies the prevalence of IHD and CVA is higher in patients with affective disorders than in the general population.[18,30,31] Ösby et al.[2] found almost the same SMR for cardiovascular and cerebrovascular diseases in bipolar and unipolar disorder, but both were higher compared to the general population. IHD and CVA have many risk factors in common, but there is evidence that treatment with antipsychotics can increase the risk of CVA, especially in older people.[32] Angst et al.[32] found higher SMR for cerebrovascular disease in patients with uni- and bipolar disorder treated with antipsychotics. In our study the prevalence of CVA was 13.3% in women who used antipsychotics and 6.5% in those without antipsychotics. The lower prevalence of IHD compared to the general population in our study is consistent with the findings of Coppen et al.[33] and Ahrens et al.,[34] who found that cardiovascular mortality in patients who were treated with lithium was not much different from the general population.

This is the first study examining the prevalence of CVR and CVD in elderly lithium users and comparing this to the prevalence in the general population. The patients underwent a thorough assessment and the CVR and CVD were defined according to the criteria used in the prevalence studies in the general population of similar age and from the same geographic area that were used for comparison.

This study has several limitations. Because of its cross-sectional design there could be depletion of susceptibles. But most important, because of its cross-sectional design causal relationships could not be determined as it was not known, if the CVR and/or CVD preceded the affective disorder or the treatment with lithium. CVR and CVD can cause damage in the brain and it is suggested that this may result in depression and possible also bipolar disorder.[35,36] This could contribute to a higher association between CVR, CVD and affective disorders. This has to be taken into account when studying the impact of psychotropic medication in older patients. The number of patients studied was limited and within the study group the number of men was es-

pecially small. There was no information about the treatment history on use of other psychotropic medication besides lithium. At the time of this study many patients used other psychotropics, which could also influence the CVR and CVD. In our study 19 patients used lithium as monotherapy; 39 in addition used an antidepressant, 7 used an antipsychotic next to lithium and 4 used another mood stabilizer in addition to lithium. The other 15 patients used more than one psychotropic medication next to lithium. The size of the comparison study group in the general population was not known and therefore we could not calculate if the differences in prevalence were statistically significant.

Despite its limitations, this study gives an indication on the prevalence of CVR and CVD in elderly psychiatric patients using lithium compared to the general population. There is an increase in BMI in the first years of treatment and a higher prevalence of hypertension compared to data from the Rotterdam study[11] which used the same criteria, but the effect on the prevalence of diabetes, if any, is small. The prevalence of hyperlipidemia is lower compared to the general population and this could in part explain the fact that the prevalence of IHD is lower than in the general population. The higher prevalence of CVA compared to the general population is consisted with other studies in patients with affective disorder, but it is not clear from this study what the association is with lithium.

The effect of lithium use on CVR and CVD warrants further study as confirmation of the relatively mild cardiovascular risk profile of lithium could have important implications in treatment decisions especially in older patients who already have CVR and/or CVD.

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3.3

Prevalence and determinants of thyroid disorders in elderly patients with affective disorders: lithium and nonlithium patients

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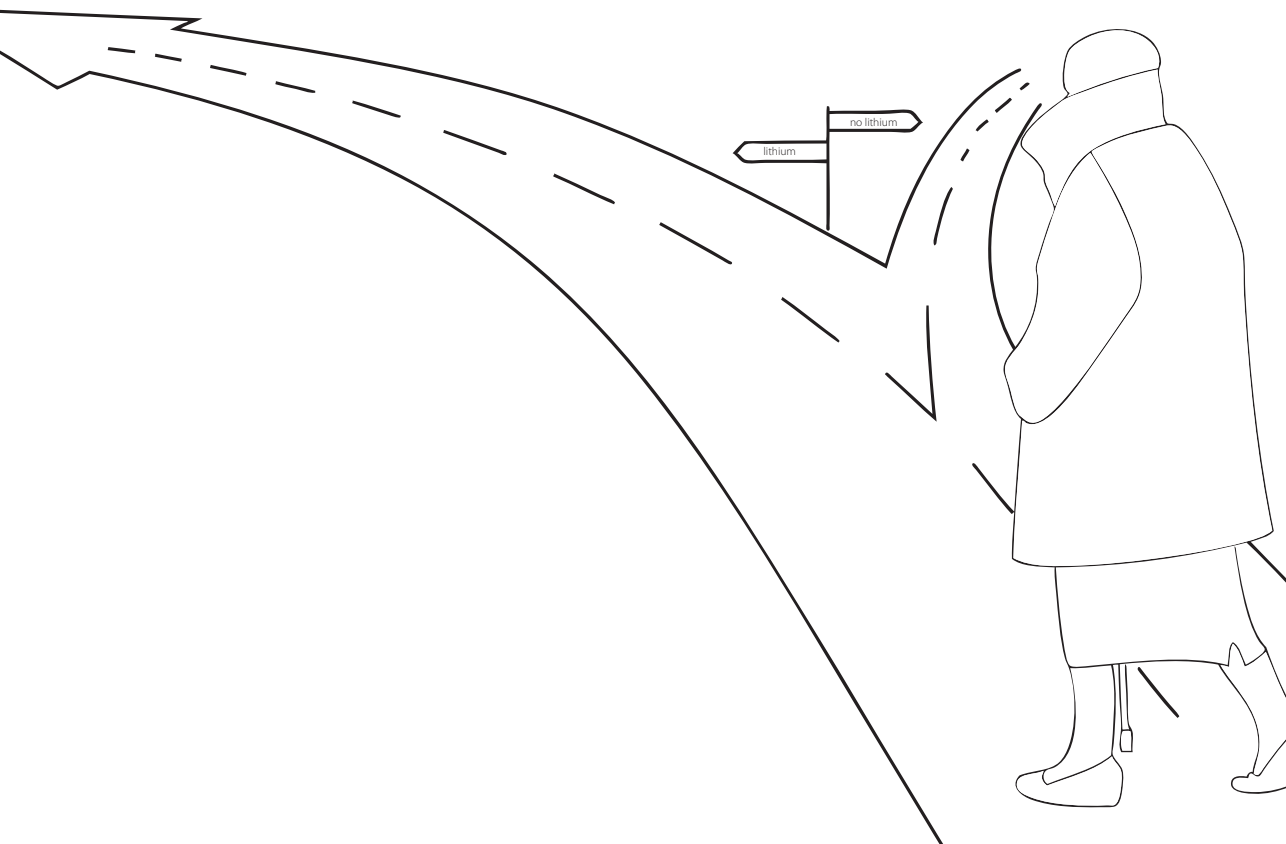

Abstract

Objectives: To determine the prevalence and determinants of thyroid dysfunction in older patients with affective disorders divided in lithium and nonlithium patients.

Methods: This study was conducted as a retrospective cross-sectional study in patients of 65 years and older with affective disorders according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria. The presence of thyroid disorders was determined on the index date defined as the date of the first available thyroid-stimulating hormone in 2005. The presence of thyroid disorder was diagnosed according to defined criteria and in case of a previous diagnosis, confirmed by researching the medical files.
In a subgroup of 45 lithium patients thyreoperoxidase- and thyreoglobulin antibodies were determined.

Results: A total of 79 lithium patients and 85 nonlithium patients were included. The prevalence of hypothyroidism (subclinical and clinical) was 35.4% among the lithium patients, with women having a prevalence as high as 41.3% and men 12.6%. In the nonlithium patients the prevalence was 7.1%; very close to that in the general population. No other determinant than female gender was identified. Seventeen of the 26 lithium patients were diagnosed with hypothyroidism in the first three and a half year after the start of lithium.
The prevalence of thyroid antibodies was 27% in 45 lithium patients which was no different than the prevalence in the same age group in the general population.

Conclusions: The prevalence of hypothyroidism during lithium treatment was very high in the elderly, especially in women. Autoimmunity did not seem to play a major part in lithium-associated hypothyroidism in this age group. The timeframe between start of lithium and diagnosis of hypothyroidism suggests an individual susceptibility. The prevalence of hypothyroidism in nonlithium patients with affective disorders was not very different from the general population.

Introduction

There is much although conflicting evidence about the association between affective disorders and dysfunction of the hypothalamic-pituitary-thyroid (HPT) axis. Some find hyperfunction but most studies find hypofunction.[1] It has not been resolved whether this association is causal and whether it applies to affective disorders in general or only to a subclass of affective disorders. In some studies, a higher prevalence of hypothyroidism was found in patients with rapid cycling bipolar disorder compared to patients with nonrapid cycling bipolar disorder.[2] In other studies this observation could not be confirmed.[3,4] Some studies have also reported an association between refractory depression and hypofunction of the HPT axis.[1]

The role of thyroid antibodies as a manifestation of autoimmune thyroid disease in affective disorder is also not resolved. Haggerty et al.[5] did not find differences in the prevalence of thyroid antibodies between patients with affective en nonaffective disorders and Baethge et al.[6] did not find a difference between patients with affective disorders and patients without an Axis I diagnosis. Kupka et al.[4] found a higher prevalence of thyreoperoxidase antibodies (TPO-ab) in patients with bipolar disorders compared to the general population and psychiatric inpatients.

Lithium, given as treatment for bipolar disorder and as an add-on to antidepressants in refractory depression, can further complicate the association between affective disorders and the HPT axis as lithium itself can induce changes in this axis. Already in 1968 Schou et al.[7] noticed an increased prevalence of goiter in patients treated with lithium and many prevalence studies on hypothyroidism during lithium treatment have been published since.[8,9]

Hyperthyroidism is seldom seen during lithium treatment and it is not clear whether lithium is the causal factor. Barclay et al.[10] found an increased risk of thyreotoxicosis during lithium treatment in a New Zealand population, but this was not confirmed in other studies.[11]

No studies specifically studying elderly patients have been undertaken. Johnston et al.[12] investigated the prevalence of clinical hypothyroidism in lithium treated patients in general and additionally stratified their study population into different age groups. Within the group of 60-79 years they found a prevalence of hypothyroidism of 16% in women and 7.5% in men on long-term lithium treatment compared to respectively 8.8% and 1.9% in the same age group in the general population.[12] Kirov et al. even found a prevalence of 29% for women over 60.[13]

The primary aim of our study is to ascertain the prevalence and determinants of thyroid dysfunction in older patients with affective disorders. In view of the influence of lithium on the HPT-axis we selected a lithium and nonlithium group.

Methods

Setting and study design

This study was conducted at Parnassia Psycho Medical Center, a psychiatric hospital with in- and outpatient facilities in the western part of the Netherlands serving approximate 40.000 patients a year. The psychiatric care for the elderly in this region is provided by four outpatient facilities and one clinical center for the Elderly.
The study has a cross-sectional design and was conducted retrospectively in 2005. As we used data that were gathered as part of the usual patient care, the scientific board of Parnassia Psycho Medical Center concluded that no additional approval from the medical-ethical committee was necessary to conduct our study.

Study sample

The study sample consists of patients 65 years and older with an affective disorder, according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM IV) criteria.
Inclusion criteria for the lithium group were lithium use for at least 6 months before inclusion. Inclusion criteria for the nonlithium group were having an affective disorder, for which hospitalisation was necessary and not having used lithium within the six months before admission. Exclusion criteria for both groups were current use of thyroid hormone as an add-on treatment for affective disorder and the presence of a comorbid Axis I disorder according to DSM IV criteria. The exclusion criterion for the lithium group was a diagnosis of thyroid disorder before the start of lithium.
The lithium patients were all outpatients: 48 had participated previously in a study on renal function in the spring of 2005.[14] The other 37 lithium patients were randomly selected from two out clinics in the same area. Six of these 85 patients were subsequently excluded since the diagnosis of thyroid disease predated the lithium treatment, three patients with clinical hypothyroidism and three patients with hyperthyroidism. This resulted in inclusion of 79 patients in the lithium group.
The nonlithium group consisted of 85 patients. These were all the patients who were admitted to the Parnassia Clinical Center for the Elderly between January and November 2005, fulfilling the inclusion criteria.

Outcome

Thyroid disease was defined according to the criteria in Table 1.[15,16] In the subsequent text, hypothyroidism stands for subclinical hypothyroidism and clinical hypothyroidism taken together. The index date (ID) was defined as the date of the first thyroid-stimulating hormone (TSH) measurement in 2005.

Table 1. Definition of thyroid disease

Clinical hypothyroidism	- Diagnosis of hypothyroidism in the past and thyroxine suppletion on ID*, or - TSH>4.0mU/L and fT4<10pmol/L on ID
Subclinical hypothyroidism	- Diagnosis of subclinical hypothyroidism in the past and thyroxine suppletion on ID, or - TSH>4.0mU/L and fT4≥10pmol/L on ID
Clinical hyperthyroidism	- Diagnosis and treatment of hyperthyroidism in the past - Diagnosis of hyperthyroidism in the past and treatment on ID with thyreostatica alone or in combination with thyroxine, or - TSH<0.1mU/L and fT4>25pmol/L on ID or - TSH<0,1 mU/L and T3>3.2nmol/L on ID
Subclinical hyperthyroidism	- Diagnosis of subclinical hyperthyroidism in the past and treatment with thyreostatica alone or in combination with thyroxine on ID, or - TSH<0.1mU/L and fT4≤25pmol/L and T3≤3.2 on ID (NTI† excluded)

*ID = Index Date: date TSH, used in this study, is determined
†NTI = Non Thyroidal Illness

In the Netherlands, outpatients using lithium are regularly monitored according to a national guideline.[17] Their lithium serum level is determined every 3 months and TSH and creatinine every six months. Because in the Netherlands lithium levels are determined 12 hours (±1 hour) after ingestion, lithium is usually taken once a day in the evening around 10:00 PM and all bloodtests for the lithium outpatients are done in the morning between 09:00 en 10:00 AM

The 85 nonlithium patients had their TSH checked as part of the routine bloodtest on admission in our psychiatric ward for the elderly. If the TSH was abnormal, fT4 was subsequently determined from the same bloodsample. Bloodsamples at our hospital are taken in the morning between 09:00 en 10:00 AM.

The blood of almost all patients (in- and outpatients) was tested at the same laboratory. For the determination of the fT4 the AxSYMFreefT4, a microparticle enzyme immunoassay (MEIA), was used; intra-assay coefficient of variation (CV) 2.5-6% and inter-assay CV 0-7.7%. For the determination of the TSH the AxSYM3rdgenerationTSH (MEIA) was used: inter-assay CV ≤ 20% at < 0.02 mU/L.

If thyroid disease was present before the ID we searched the medical file for confirmation of the diagnosis and the moment the thyroid disease was first discovered. If on the ID the TSH < 0.1mU/L, without a previous diagnosis of thyroid disease, we tried to exclude nonthyroidal illness (NTI).

Potential determinants

Data on medical history, lithium treatment and concomitant drug use were extracted from the medical file. Amiodaron, prednisone, carbamazepine and propranolol are

known to interfere with the HPT-axis and/or the metabolism of thyroid hormones and of the psychoactive drugs possible tricyclic antidepressants.[18,19]
Forty-five lithium patients were tested for TPO- and thyreoglobulin antibodies (TG-ab). A chemiluminescence immunometric essay Immulite 2000 (Siemens) was used for TPO-ab and TG-ab; (TPO-ab intra-assay CV 4.4-7.4%, inter-assay CV 3.2-7.2%, TG-ab intra-assay CV 3.2-4.9%, inter-assay CV 4.6-5.8%, for both tests < 35 IU/L indicating a normal result).
The classification of the affective disorder stated in the medical file was used. The patients diagnosed with depression were divided into patients with a first episode of depression in older age and patients with recurrent depressions. It is suggested in the literature that the late-onset depression is caused by different pathophysiologic mechanisms than the early onset depression.[20,21]

Data analysis

The prevalence of thyroid disorders was determined on the ID in the group of lithium patients and in the group of non-ithium patients. Within both the groups of patients the potential determinants age, gender, medication and diagnosis of bipolar disorder or depression were assessed for the presence of a statistically significant association with thyroid disorder by performing a univariate logistic regression analysis. Determinants that were univariate significantly associated with thyroid disorder ($P < 0.05$, Waldtest, $df=1$) were incorporated into our multivariate model.
The prevalences of TPO- and TG-antibodies were assessed in a subgroup of lithium patients and these were ascertained as potential determinant for the presence of thyroid disorders.
All analyses were performed using SPSS 14.0.

Results

The characteristics of our study sample are reported in Table 2. Consistent with the indication for lithium treatment there were more patients with bipolar disorder and almost none of the patients with a first episode of depression in the lithium group.
The majority of the thyroid disorders concerned hypothyroidism. The prevalence of subclinical hypothyroidism and clinical hypothyroidism in these elderly patients with affective disorders is shown in Table 3. The lithium patients showed a much higher prevalence of hypothyroidism (35.4%) than the nonlithium patients (7.1%). In the lithium patients the prevalence was higher in women (41.3%) than in men (12.6%) and although this difference was also found in the nonlithium patients, this was less marked, respectively 8,5% and 3,8%.

Table 2. Characteristics of the study population

	Lithium (n=79)	Nonlithium (n=85)
Female gender	63 (80%)	59 (69%)
Age, mean SD (range)	75.6 SD 5.9 (65-94)	76.3 SD 7.5 (65-94)
Psychiatric diagnosis		
- bipolar disorder	32 (40.5%)	5 (5.9%)
- first episode of depression	1 (1.3%)	25 (29.4%)
- recurrent depression	41 (51.9%)	52 (61.2%)
- schizoaffective disorder	5 (6.3%)	3 (3.5%)
Lithium use before ID*		
- current	79 (100%)	
- never		68 (80%)
- past; but not in the last 6 months		8 (9.4%)
- unknown, but not in the last 6 months		9 (10.6%)
Lithium use in years, mean SD (range)	10.0 SD 7.8 (0.5-31.0)	
Lithium serum level on ID 12h post dosing mM, mean SD (range)	0.64 SD 0.18 (0.13-1.18)	
Daily lithium dose in mg, mean SD (range)	470 SD 150 (150-1000)	
Carbamazepine	1 (1.2%)	1 (1.2%)
Amiodaron	0	1 (1.2%)
Propranolol	2 (2.4%)	0
Prednison oral/nasal	1 (1.2%)/ 3 (3.5%)	3 (3.5%)/ 5 (5.9%)
Antidepressants	38 (48%)	42 (49%)
Tricyclic antidepressants	25 (32%)	10 (12%)
Number of drugs used on ID, mean SD (range)	5 SD 2.5 (1-11)	5 SD 3 (0-12)

*ID: Index Date: date of TSH measurement

The thyroid disorders in these patients were mostly diagnosed before this study. All patients, except one, with a known thyroid disorder on the ID used medication to treat this disorder. Of the five newly diagnosed patients on the ID four patients had

Table 3. Prevalence of subclinical hypothyroidism and clinical hypothyroidism in patients with an affective disorder: lithium and non-lithium patients

	Lithium n (%)			Nonlithium n (%)		
Gender	Men n=16	Women n=63	Total n=79	Men n=26	Women n=59	Total n=85
Subclinical hypothyroidism	1 (6.3)	8 (12.7)	9 (11.4)	1 (3.8)	2 (3.4)	3 (3.5)
Clinical hypothyroidism	1 (6.3)	18 (28.6)	19 (24.0)	0 (0.0)	3 (5.1)	3 (3.5)
Total hypothyroidism	2 (12.6)	26 (41.3)	28 (35.4)	1 (3.8)	5 (8.5)	6 (7.1)

a TSH > 4.0 mU/L and were diagnosed with subclinical hypothyroidism, two in the lithium group and two in the nonlithium group. One patient with a TSH < 0.1 mU/L was diagnosed with nonthyroidal illness. Only four other patients had a TSH < 0.1 mU/L on the ID; they were all treated with thyroid hormone.

Twenty-eight patients developed subclinical or clinical hypothyroidism while on lithium treatment and we could determine the time of diagnosis in twenty-six. Seventeen patients were diagnosed in the first three and a half year of treatment (Figure 1). One patient developed hyperthyroidism during lithium use, she had a multinodular goiter. In the nonlithium group none of the patients had hyperthyroidism.

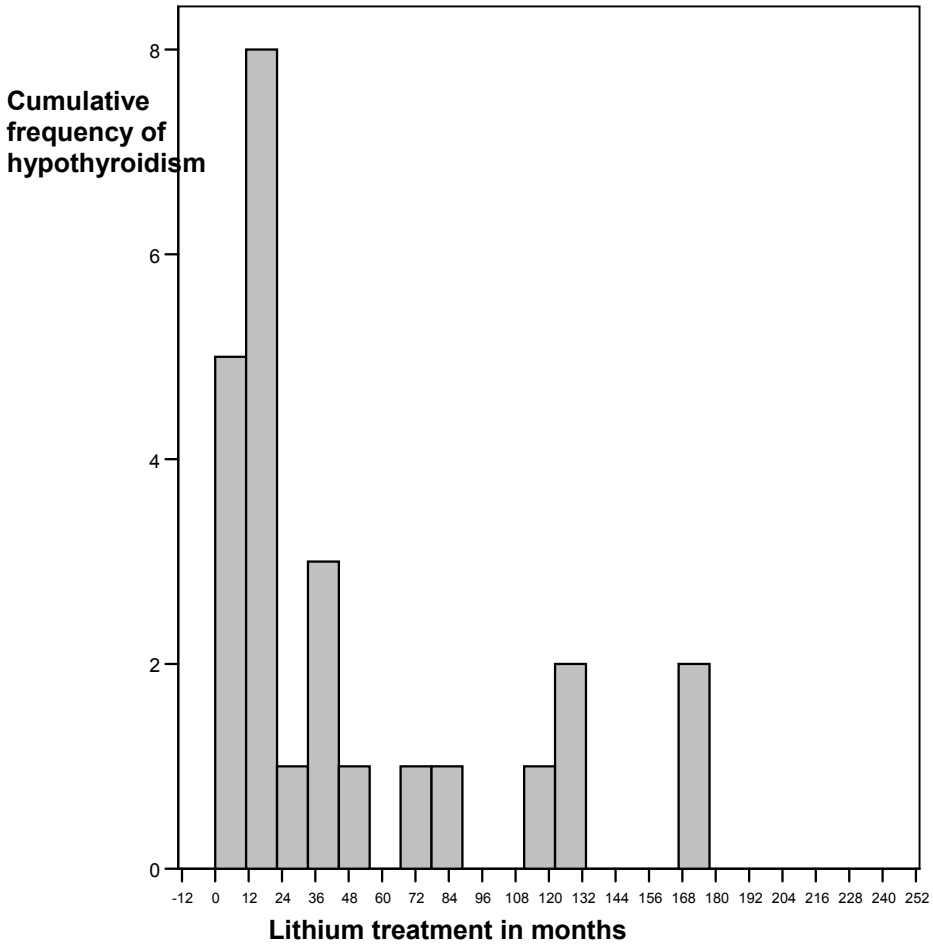

Figure 1. Time of diagnosis of hypothyroidism in 25 patients after start of lithium treatment(t=0 on x-axis); one patient who was diagnosed with hypothyroidism after 30 years of lithium treatment is not included in the histogram

The results of our univariate analysis on potential determinants of hypothyroidism are reported in Table 4. Female gender was significantly associated with hypothyroidism only in the lithium group. Bipolar disorder and recurrent depression were not found to be significantly associated with hypothyroidism in the lithium group. In the nonlithium group not enough patients with a bipolar disorder were present to establish an association. But, patients with a recurrent depression showed a higher risk for hypothyroidism than patients with a first episode of depression, although this was not significant. Age was not found to be univariately associated with hypothyroidism in both groups, neither as a continuous variable, and not when stratified in different age groups.

Tabel 4 Univariate analysis of potential determinants of hypothyroidism*

Determinant	Lithium patients (n=79) OR(95%CI)§	Nonlithium patients (n=85) OR (95%CI)§
Women	4.9 (1.0-23.5)‡	2.3 (0.3-20.9)
Age	1.0 (0.9-1.1)	1.1 (0.9-1.2)
Bipolar disorder	1.5 (0.8-3.7)	
Recurrent depression	0.7 (0.3-1.8)	3.4 (0.4-30.5)
Tricyclic antidepressants	1.3 (0.5-3.5)	0.7 (0.1-6.4)
	Lithium patients (n=45)	
TPO-ab	3.2 (0.7-14.1)	
TG-ab	2.3 (0.5-10.9)	

* subclinical hypothyroidism ánd clinical hypothyroidism together
§ Waldtest, *df* = 1
‡ significant

Within the group of 45 lithium patients, tested for the presence of TPO- and TG-ab, the prevalence of TPO-ab was 16% and the prevalence of TG-ab was 11%. All patients with positive antibodies were women. TPO-ab were not found in 17 bipolar patients, 3 bipolar patients were TG-ab positive. Seven (out of 27) patients with recurrent depression were TPO-ab positive, two were also TG-ab positive. In these lithium patients TPO-ab and Tg-ab were not found to be significantly associated with hypothyroidism.
Patients in this study who used drugs known to interfere with the HPT-axis and/or thyroid hormone metabolism like prednisone, amiodarone, propranolol or carbamazepine did not have a thyroid disorder. And, we found no association between hypothyroidism and the use of tricyclic antidepressants.
As female gender in the lithium group was the only significant determinant of hypothyroidism, a multivariate analysis was not performed

Discussion

In our group of older patients with an affective disorder, we found a high prevalence of thyroid disorders in the lithium patients. The thyroid disorders consisted almost exclusively of hypothyroidism. In the lithium group, female gender was the only determinant found to be significantly associated with hypothyroidism.

In the nonlithium patients, the prevalence of hypothyroidism was close to that reported for the general population. Gussekloo et al.[22] found in a population of 85-year-old people in the same region in the Netherlands as our study was conducted a prevalence of hypothyroidism of 12%. In our slightly younger nonlithium patients, we found a prevalence of 7.1%.

Lithium can alter thyroid function but the underlying mechanism is not completely understood. It is proposed that lithium blocks the TSH-induced release of thyroxine (T4) possibly by interfering with the formation or the intracellular effects of cAMP.[23] Another mechanism by which lithium potentially interacts with the thyroid is by stimulating DNA synthesis under basal conditions which could explain, together with the inhibition of the T4 release, the goitrogenic action of lithium.[24]

After initiation of lithium, TSH levels rise in most patients but usually not above the normal range. After 2-3 months a new equilibrium is found and TSH decreases to (almost) the pre-lithium value with normal fT4.[25]

However, some patients subsequently develop subclinical hypothyroidism or even clinical hypothyroidism. What makes them more vulnerable? In our group female gender was significantly associated with hypothyroidism in the lithium group (Table 4) the same as in the general population. Unexpectedly we did not find a significant association with female gender and hypothyroidism in the nonlithium group. An explanation could be a power problem because the prevalence of hypothyroidism is low and the sample size is relative small. Therefore, the one man with subclinical hypothyroidism in the nonlithium group had a large impact.

Age is a determinant of hypothyroidism in the general population but we did not find a significant association with age in both groups. This can most likely be explained by the fact that we are looking at an elderly subgroup of the population.

Because of the cross-sectional design of our study, it was not possible to investigate the association between both duration of lithium treatment and cumulative lithium dose and hypothyroidism. Similar to the study by Johnston et al.[12] we found that most patients were diagnosed with hypothyroidism in the first years of lithium treatment. The fact that the majority of patients are diagnosed with hypothyroidism after a relative short time of lithium treatment suggests that there must be an individual susceptibility like genetic predisposition and/or the amount of iodine intake.[26] Countries were iodine intake is sufficient have a much higher prevalence of lithium-induced

hypothyroidism than countries where the iodine intake is relatively low. Johnston et al.[12] and Kirov et al.[13] reported a much higher prevalence in the U.K. were Iodine intake is sufficient, in line with results of Cowdry et al.[2] in the US. Brochetta et al.[27] did not find such an association in Italy and neither did Lee et al.[28] in Hong Kong, both are area's with mild to moderate Iodine deficiency. The high rates of goiter in the last two studies is also concurrent with a relation with iodine deficiency.

In the Netherlands baker's salt may be fortified by iodine since 1968 and therefore the intake in general is sufficient.[29,30] We find a prevalence rate of clinical hypothyroidism very near the rate reported in the U.K. studies.

The important question remains whether there ís an association between iodine intake and the prevalence of hypothyroidism during lithium use, and whether changes in iodine intake before the start of lithium might prevent the development of lithium induced hypothyroidism?

Lithium also has a direct influence on cellular and humoral immunity. Many studies have measured thyroid antibodies in lithium patients. It is not clear if lithium is the direct cause of the formation of thyroid antibodies. Some cross-sectional studies show a higher prevalence of antibodies in lithium patients, but in more recent studies, this is not confirmed and in some studies lithium only induced a rise in antibody titer.[9,11] Some studies found a high antibody titer in patients with affective disorders irrespective of lithium use. In the general population there is an increased prevalence of thyroid antibodies in older age especially in women; 9.9% versus 26.2% in respectively people of 20-40 years and people 80 years or older.[31]

The presence of antibodies in our study was tested for in a subgroup of 45 lithium patients. We found only positive antibodies in women, but the participation of men was relatively low (15%). The prevalence of thyroid antibodies (TPO- and TG-ab together) in this group was 27%. This is not different from the prevalence in the same age group in the general population. Based on this finding, it is less probable that the high prevalence of subclinical and clinical hypothyroidism during lithium treatment is induced by an autoimmune mechanism. This is substantiated by the fact that thyroid antibodies are not significantly associated with hypothyroidism in these elderly lithium patients. This could be because lithium itself has such a big impact on thyroid function in this age group.

Contrary to Kupka et al.[4] we only found TPO-ab in patients with recurrent depression and none in patients with a bipolar disorder. Although they used an enzyme-linked immunosorbent assay for antibodies, they found in their study a positive correlation with the Lumitest, which is a luminescence test just like ours. Haggerty et al.[5] did not find a difference in the prevalence of antibodies between patients with affective disorder and patients with nonaffective disorder and between patients with lithium and without lithium use. He found a higher prevalence in women and in patients

with bipolar disorder mixed or bipolar disorder depressed (DSM-III). It is possible that part of the patients with recurrent depression in our study were actually patients with bipolar II disorder (DSM IV text revision). Although Kupka et al.[4] state that part of their patients have bipolar II disorder, they give the prevalence of antibodies for the whole group of bipolar patients. The patients in the nonlithium group were not tested for the presence of antibodies, but the patients with recurrent depression had a higher risk for hypothyroidism than the patients with first depression. Valle et al.[32] found in a lithium naïve bipolar group, a higher prevalence of high TSH response to thyrotropin-releasing hormone (TRH) in the bipolar II patients. Taken together, this could indicate that there is an association between (subtle) dysfunction of the HPT-axis and/or thyroid autoimmunity and recurrent depression or type II bipolar disorder, but this needs further investigation.

Our study has several limitations. The lithium patients were all outpatients in a relatively stable psychiatric condition. The nonlithium group comprised of in-patients whose blood was drawn soon after admittance and in a time of psychiatric stress. The TSH could be expected to be suppressed in this situation, but we did not find this other than could be explained by thyroxine suppletion and one NTI. So we do not think that this introduced a bias.

The lithium and nonlithium group consisted of patients who were diagnosed with affective disorders, but as shown in Table 2, the distribution of the different affective disorders was not the same.

The study was conducted in a specific region of the Netherlands, so the question of generalizability arises. However the prevalence of hypothyroidism in this older group did not differ much from those in other regions with the same iodine intake.

We conclude that the prevalence of hypothyroidism in older patients with an affective disorder is not different from the general population, but the prevalence is high in older patients with an affective disorder on lithium treatment, especially in women. Although hypothyroidism is easy to treat, it is certainly worth to explore mechanisms that might cause this and to find methods to prevent this. We postulate that it might be worthwhile to explore the role of iodine intake as a potential way to influence this. Autoimmunity does not seem to play a major role in lithium-related hypothyroidism in the elderly.

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The influence of lithium on calcium homeostasis in older patients in daily clinical practice.

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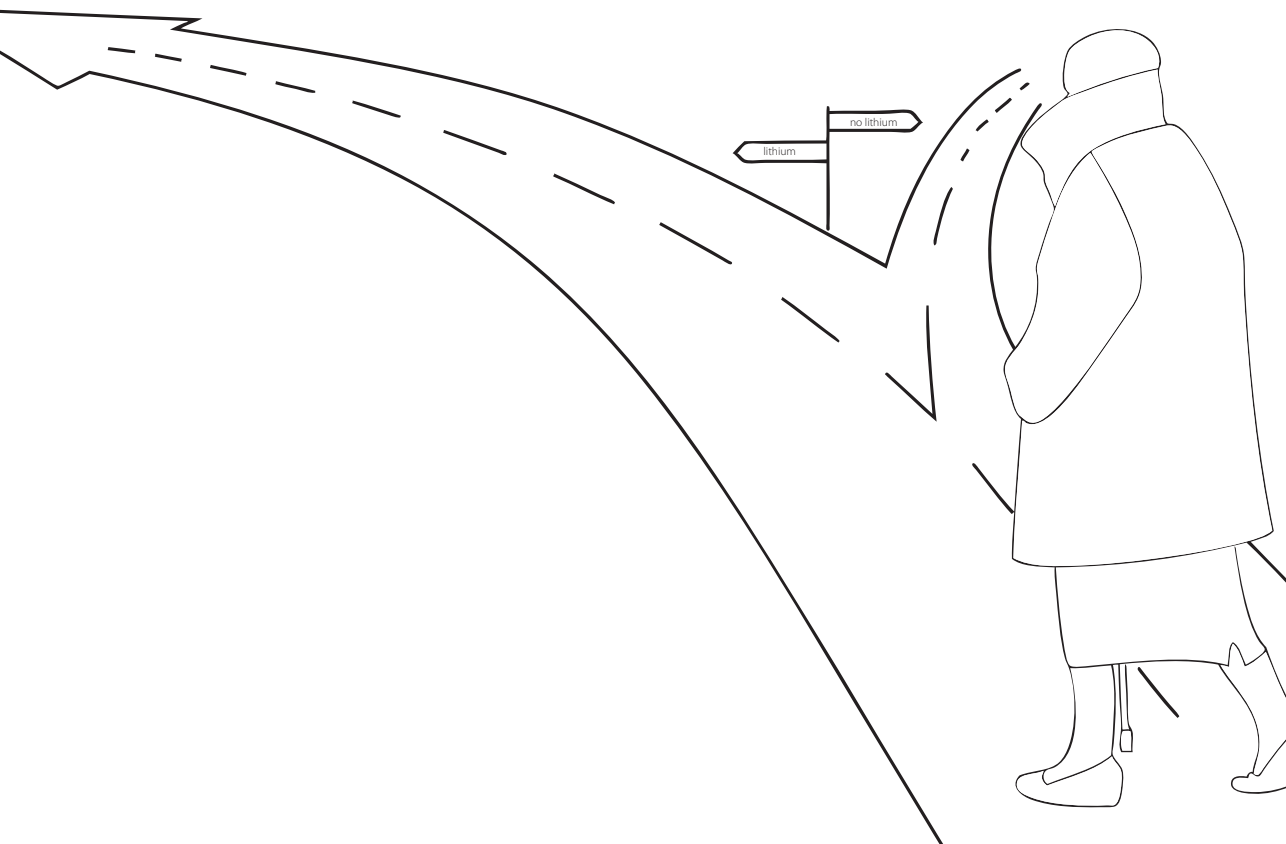

Abstract

Background: Lithium can influence calcium homeostasis resulting in changes in parathormone set point and renal calcium handling. The clinical significance of these changes in older patients is unknown. The objective of this study was to investigate the possible association between duration of lithium treatment and corrected calcium, parathormone and 24-h urinary calcium excretion in older psychiatric patients corrected for renal function and vitamin 25OH D and also to estimate the point prevalence of hypercalcemia and raised parathormone.

Methods: A cross-sectional study of psychiatric outpatients visiting a specialized facility for elderly patients treated with lithium was performed. Patients underwent a comprehensive assessment and blood and urine testing. Potential confounders of calcium homeostasis were recorded. Based on duration of lithium treatment, patients were divided into four groups.

Results: One hundred eleven patients were included, mean age 75.2 years. There was no significant association between the duration of lithium treatment and corrected calcium, parathormone and 24-h urinary calcium excretion. The point prevalence of hypercalcemia was 2.7% and 47.8% for raised parathormone. There was an unexpected but significant negative association between duration of lithium treatment and vitamin 25OH D, with 76.9% vitamin 25OH D deficiency (<50nmol/L) in the group using lithium for more than 10 years.

Conclusions: No association was found between duration of lithium treatment and calcium parameters in older psychiatric outpatients, but there was a high prevalence of raised parathormone and an unexpected negative association between duration of lithium treatment and 25OH D.

Introduction

Since the first publication by Garfinkel et al.[1] many articles on the association between lithium, hypercalcemia and hyperparathyroidism have been published. However, the clinical impact of this association is still not fully resolved. Calcium (Ca^{2+}) is important in multiple intra- and extracellular reactions. The extracellular calcium concentration is kept within a strict range by homeostatic mechanisms regulated by the parathyroid glands and the kidneys in the presence of vitamin D.[2]

Lithium can interfere with these homeostatic mechanisms. There is evidence that lithium shifts the parathormone (PTH) set point (calcium concentration at which PTH levels are half maximally inhibited) to the right, resulting in a higher calcium threshold level for the inhibition of PTH production.[3,4] Lithium induces a decrease in calcium excretion in the kidneys, probably in part by interacting with the calcium-sensing receptor in the tubuli, which normally results in an increase of calcium excretion. The net result is a rise in serum calcium, which can still be within the normal range, with a normal or slightly elevated PTH and low or normal urinary calcium excretion.[4,5] The prevalence of hypercalcemia during lithium treatment varies enormously between studies (0-42%) just like the prevalence of raised PTH (0-34%).[5-9] In most studies there is no correction for vitamin D level or renal function. There is evidence from nonrandomised studies that there is an association between lithium treatment and hyperparathyroidism, although there is still discussion about the underlying pathophysiologic mechanism.[10]

In a recent review, Lehmann et al.[11] concluded that there are no specific studies about the effect of lithium on calcium homeostasis in older patients. Because older patients have a higher prevalence of kidney disorders, vitamin D deficiency and primary hyperparathyroidism, lithium treatment could have a greater impact on calcium homeostasis in older patients.[11,12]

The primary objective of this study is to determine the association between the duration of lithium treatment and calcium, calcium excretion in 24-h urine (24-h Ca excretion) and PTH in older psychiatric patients corrected for renal function and vitamin 25OH D level. The secondary objective is to determine the point prevalence of hypercalcemia and raised PTH in this group of older lithium users.

Methods

Setting, design and population

This was a cross-sectional study in older psychiatric patients. Eligible patients for this study were outpatients from Parnassia, aged 60 years or older and treated with

lithium. Parnassia is a psychiatric center with in- and outpatient facilities in The Hague, the Netherlands.
In 2005 a more extensive somatic screening of older patients treated with lithium, was started as a pilot and in 2008 this was introduced on a regular basis in a specialized lithium ambulatory facility. As part of this screening the medical history and medication use was registered, internal and neurologic examination was conducted and comprehensive blood and urine testing was done. Patients seen for the first time between January 2005 and March 2009 were included.
The somatic screening of the lithium patients was in line with the Dutch national guideline on bipolar patients involving standard blood sampling in the morning.[13] As only the PTH was performed as extra test in blood already sampled, the scientific board of Parnassia concluded that no additional approval from a medical-ethical committee was necessary to conduct our study. The date of the blood test was termed the index date (ID).

Endpoints

The outcome measures were albumin-corrected calcium (cCa), calculated with the formula: measured calcium + [(40-albumine)* 0.02], PTH, measured with a second generation assay of "intact"PTH (Siemens Immulite 2000; intra-assay coefficient of variation (CV) 4.2-5.7%; inter-assay CV 6.3-8.8%), reference range 1.3-6.8 pmol/L (12-65 pg/mL) and 24-h Ca excretion, reference range 2.50-7.50 mmol/24 h. Hypercalcemia was defined as cCa above 2.55 mmol/L and raised PTH was defined as PTH above 6.8 pmol/L.

Potential confounders and effect modifiers

Apart from demographic characteristics, other possible confounders or effect modifiers were registered. Laboratory data that were obtained were urea, creatinine, sodium, potassium, phosphate, thyroid stimulating hormone (TSH), free thyroxine (fT4), glucose and 25OH D (DiaSorin; intra-assay CV 7.7-12.7%; inter-assay CV 11.6-25.0%)). With this 25OH D assay 25OH D_2 and 25OH D_3 are determined.
The patients were asked if they had a medical history of thyroid disorder, hyperparathyroidism, osteoporosis, kidney disorders and malignancy; these data were completed from the medical files. Medication use that could influence calcium handling in the kidney like thiazide diuretics was registered. Also registered were the use of vitamin D and calcium supplements and medication which induces or inhibits the hepatic P450 enzyme system and thus could interfere with the production of 25OH D, like phenytoin, carbamazepine and cimetidine. For determining the renal function the glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease formula (MDRD).[14] As volume depletion may increase the calcium reab-

sorption in the proximal tubule, dehydration was defined as urea (mmol/L)/creatinine (µmol/L)> 100.[15] Because the season and bodyweight could influence the 25OH D level, these were also recorded.[16]

Data analysis

The patients were divided into four groups according to the duration of lithium treatment: group I ≤ 2 years, group II 2-5 years, group III 5-10 years, group IV > 10 years. The demographic characteristics, other possible confounders and effect modifiers were ascertained for each treatment group. Within the four treatment groups, the categorical variables were compared using the χ^2test and the continuous variables using one-way ANOVA. Corrected Ca, PTH and 24-h Ca excretion were also compared using one-way analysis of variance in these four groups corrected for variables that differed significantly between the four groups using multivariate analysis of variance. A multiple linear regression analysis was conducted in the total study group with cCa as dependent variable and duration of lithium treatment, age, gender, MDRD and 25OH D as independent variables. Confounders that were significantly different between the four groups were incorporated into the multiple linear regression analysis. Comparable multiple linear regression analysis was conducted with respectively PTH and 24-h Ca excretion as dependent variables.

Results

A total of 111 patients were included; the demographic characteristics did not significantly differ between the four lithium treatment groups (Table 1). The study population was Caucasian, except for three patients. The patients using lithium for less than 10 years were mainly treated for unipolar depression, and the patients who used lithium for 10 years or more were mainly treated for bipolar disorder. Medication potentially influencing calcium homeostasis or 25OH D metabolism was infrequently used in all the groups. As expected the prevalence of thyroid disorders was high, but most patients were already diagnosed and treated. All patients had a fT4 within the normal range, except for three patients who had a fT4 of 10 pmol/L (normal 11-24 pmol/L) with normal TSH, one patient in group I, II and IV each. Only one patient had a TSH < 0.1 mU/L with a fT4 of 20 pmol/L and 12 patients had a TSH > 5.0mU/L, all with normal fT4.

Corrected Ca, PTH and 24-h Ca excretion together with MDRD and 25OH D are given in Table 2. Corrected Ca, PTH and 24-h Ca excretion were not significantly associated with the duration of lithium treatment according to the four groups , although the 24h Ca-excretion was lower in the patients who used lithium more than five years.

Table 1. Characteristics of four groups of patients treated with lithium; * P < 0.05

Group (duration lithium treatment)	I (≤ 2 years) N=19	II (2-5 years) N=27	III (5-10years) N=25	IV (>10 years) N=40
Demographic criteria				
Age in years, mean (sd)	74.8 (6.5)	74.0 (6.3)	76.8 (6.4)	75.3 (6.4)
Women, % (n)	73.7 (14)	88.9 (24)	84.0 (21)	75.0 (30)
Caucasian race, % (n)	100 (19)	96.3 (26)	100 (25)	95.0 (38)
Smoking, % (n)	42.2 (8)	25.4 (7)	24.0 (6)	32.5 (13)
Weight in kg, mean (sd)	68.1 (13.6)	75.7 (13.8)	72.3 (15.2)	74.0 (15.0)
Lithium indication* , % (n)				
Bipolar disorder I	15.8 (3)	18.5 (5)	24.0 (6)	55.0 (22)
Bipolar disorder II	0	0	8.0 (2)	2.5 (1)
Depression	84.2 (16)	81.5 (22)	60.0 (15)	32.5 (13)
Other	0	0	8.0 (2)	10.0 (4)
Season % (n)				
Spring	36.8 (7)	48.1 (13)	44.0 (11)	27.5 (11)
Summer	10.5 (2)	7.4 (2)	8.0 (2)	15.0 (6)
Autumn	15.8 (3)	11.1 (3)	16.0 (4)	12.5 (5)
Winter	36.8 (7)	33.3 (9)	32.0 (8)	45.0 (18)
Somatic comorbidities % (n)				
Thyroid disorder	21.2 (4)	37.0 (10)	40.0 (10)	48.8 (19)
Hyperparathyroid	0	0	0	2.5 (1)
Osteoporosis	5.3 (1)	3.7 (1)	0	0
Dehydration	10.5 (2)	3.7 (1)	12.0 (3)	10.0 (4)
Medication % (n)				
Antidepressants*				
Tricyclic	70.6 (12)	59.3 (16)	36.0 (9)	27.5 (11)
SSRI	0	3.7 (1)	12.0 (3)	10.0 (4)
other	17.6 (3)	11.1 (3)	16.0 (4)	2.5 (1)
Antipsychotics				
Classic	11.8 (2)	0	8.0 (2)	5.0 (2)
Atypical	11.8 (2)	18.5 (5)	20.0 (5)	15.0 (6)
Thiazide diuretics	5.9 (1)	11.1 (3)	4.0 (1)	5.0 (2)
Loop diuretics	0	0	8.0 (2)	10.0 (4)
Carbamazapine	0	0	4.0 (1)	5.0 (2)
Phenytoin	0	0	0	0
Cimetidine	0	0	4.0 (1)	0
Vitamin D supplement	5.9 (1)	7.4 (2)	8.0 (2)	17.5 (7)
Calcium supplement	5.9 (1)	7.4 (2)	16.0 (4)	10.0 (4)
Bisphosphonates	5.9 (1)	3.7 (1)	0	2.5 (1)
Medication currently used, mean (sd)	4.9 (2.0)	5.1 (2.6)	5.7 (2.6)	5.4 (2.8)

Table 2. Distribution of effect modifiers and dependent variables in 4 lithium treatment groups

Group (duration lithium treatment)	I (≤ 2 years) N=19	II (2-5 years) N=27	III (5-10years) N=25	IV (>10 years) N=40
Renal clearance¶ ml/min, mean (sd)	64.7 (11.8)	56.8 (15.3)	56.8 (13.7)	52.9 (17.0)
>90, % (n)	0	0	4.0 (1)	2.5 (1)
60-90	63.2 (12)	59.3 (16)	40.0 (10)	30.0 (12)
30-60	36.8 (7)	40.7 (11)	56.0 (14)	57.5 (23)
15-30	0	0	0	10.0 (4)
≤15				
Vitamin 25OH D, nmol/L,* mean (sd)	54.7 (36.0)	40.5 (18.4)	37.7 (21.1)	35.5 (14.7)
>75, % (n)	26.3 (5)	3.7 (1)	4.0 (1)	0
50-75	31.6 (6)	37.0 (10)	24.0 (6)	23.1 (9)
30-50	10.5 (2)	22.2 (6)	28.0 (7)	41.0 (16)
15-30	21.1 (4)	33.3 (9)	32.0 (8)	33.3 (13)
≤15	10.5 (2)	3.7 (1)	12.0 (3)	2.6 (1)
Corrected calcium, mmol/ L,mean (sd)	2.33 (0.09)	2.35 (0.10)	2.37 (0.09)	2.36 (0.10)
≤2.15	0	3.7 (1)	8.0 (2)	0
2.15-2.55	100 (19)	92.6 (25)	92.0 (23)	95.0 (38)
>2.55	0	3.7 (1)	0	5 (2)
Parathormone, pmol/L, mean (sd)	6.7 (3.8)	7.2 (3.5)	6.4 (3.2)	8.4 (3.8)
≤1.3	0	0	0	0
1.3-6.8	55.6 (10)	48.1 (13)	64.0 (16)	41.0 (16)
>6.8	44.4 (8)	51.9 (14)	36.0 (9)	59.0 (23)
Calcium excretion, mmol/24h urine, mean (sd)	N = 13 2.34 (1.58)	N = 10 3.14 (2.34)	N = 18 1.82 (1.17)	N = 25 1.83 (1.36)
≤2.50	69.2 (9)	50.0 (5)	72.2 (13)	72.0 (18)
2.50-7.50	30.8 (4)	40.0 (4)	27.8 (5)	28.0 (7)
>7.50	0	10.0 (1)	0	0

*P < 0.05

¶ Renal clearance calculated with MDRD

Although there was no association between PTH and duration of lithium treatment, 54 patients (49%) had a PTH above the upper limit. Of these, 42 had a 25OH D level < 50 nmol/L (one missing) and 28 of these had a MDRD < 60ml/min. Of the 11 patients with high PTH and normal 25OH D, the highest level of cCa was 2.49 mmol/L, well within the normal range (2.15-2.55 mmol/L). In the total study group only three patients (2.7%) had a cCa above 2.55 mmol/L, two of which had chronic kidney disease

(CKD). The other patient had a relatively high, but normal PTH and she used a thiazide diuretic. (Table 3) Of the 66 patients whose 24-h Ca excretion was determined, 68.2% had an excretion below the reference range. The MDRD was lower if patients used lithium for a longer time period, but the difference between the treatment groups was not statistically significant. The 25OH D levels declined in the four treatment groups and were significantly associated with the time lithium was used (P = 0.02). There was no significant relation between the duration of lithium treatment as continuous variable and cCa, PTH or 24-h Ca excretion in multiple linear regression.

Table 3. Patients with corrected calcium above upper limit 2.55 mmol/L; ¶ use of thiazide diuretic

Age in years	Duration lithium treatment in years	PTH pmol/L	Corrected Calcium mmol/L	Phosphate mmol/L	Estimated renal clearance ml/min	25OH D nmol/L	24-h Calcium excretion mmol/24 h
68	20.5	6.5	2.63	1.40	30	37	unknown
86	26.0	11.0	2.58	1.18	25	37	0.80
70¶	3.7	6.1	2.57	1.0	80	25	unknown

Because there was an unexpected but significant decline in 25OH D level between the four treatment groups, a multiple linear regression analysis was done with 25OH D as dependent variable and duration of lithium treatment as continuous variable and MDRD, age and gender as independent variables. With this analysis there was also a significant association between 25OH D and duration of lithium treatment (B -0.712; 95% CI -1.270 -0.155; P = 0.013).Of 110 patients (one 25OH D missing) 103 (93.6%) had a 25OH D level < 75 nmol/L and 56.4% had a level < 50 nmol/L.

Discussion

In this cross-sectional study of 111 elderly patients treated with lithium no association between duration of lithium treatment and cCa, PTH and 24-h Ca excretion was found, neither when corrected for renal function and 25OH D. Only 3 patients had mild hypercalcemia and almost half of the patients had a PTH above the upper limit. More than half of the patients had a 24-h Ca excretion below the reference range. Interestingly, there was a significant negative association between duration of lithium treatment and 25OH D.

In the cross-sectional studies of McIntosh et al.[7] and Komatsu et al.,[17] ionized calcium was determined and they did not find an association between duration of lithium treatment and ionized calcium. The mean age of the patients in these studies was

respectively 48 and 36 years. Bendz et al.[18] determined total calcium in patients on long-term lithium treatment with a mean age of 61 years. They also did not find an association between duration of lithium treatment and uncorrected calcium level. Probably, the lithium associated changes in calcium homeostasis occur early after treatment is initiated, and after the PTH set point is shifted to the right, a new equilibrium is reinstated. Christiansen et al.[19] found a significant increase in calcium and PTH within 3 month after lithium was started. Mak et al.[5] followed 53 patients from baseline up to two years during lithium treatment. They found no significant change in cCa, but after one month of lithium treatment PTH was higher than at baseline and increased to a significant higher level after 6 months. Thereafter PTH stabilised more or less on the same level. In our study there were only 6 patients in group I who used lithium for less than 6 months, a number too small to detect a possible difference early after the start of lithium.

Mak et al.[5] also measured the 24-h Ca excretion corrected for creatinine clearance (24-h Ca excretion/creat). After one month treatment, they found a significant decline in 24-h Ca excretion/creat. After 6 months, one year and two years the difference with baseline was not significant. In our study, we did not find an association between the duration of lithium treatment and 24-h Ca excretion. A decline in excretion in the first months of treatment could have been missed because we did not have baseline measurements and because of the small number of patients who used lithium less than 6 months.

Several studies found a significant higher ionized calcium level in patients using lithium than in controls,[7,17,20] but Davis et al.[6] did not find a significant difference in total calcium. In the study of McIntosh et al.[7] five out of 61 patients (6%) treated with lithium had hypercalcemia, Mallette et al.[20] found two out of 24 patients (8.3%) with an ionized calcium value slightly above the reference value. Komatsu et al.[17] did not state the number of patients with hypercalcemia and Davis et al[6] found no hypercalcemia in their study. Nordenström et al.[8] found an ionized calcium above the reference range in 11 (42%) of 26 patients who used lithium for more than 10 years, but total calcium was normal in all patients. In our study we did not determine the ionized calcium but cCa; 2.7% of the patients had hypercalcemia with only slightly elevated values.

In our study 49% of the patients had a PTH above the upper limit. Kallner et al.[9] concluded that 34% of patients older than 60 years who were treated with lithium had raised PTH, and in studies with mixed age groups, this varied between 0 and 23%.[5,8,17] It is not possible to determine how many patients in our study had lithium associated hyperparathyroidism (LAH) camouflaged by 25OH D deficiency and/or CKD. From the three patients with hypercalcemia, only one had a raised PTH, but also 25OH D deficiency and CKD and all other patients with raised PTH had normal cCa. Only one

patient was diagnosed prior to the study with primary hyperparathyroidism, which could have been LAH.

The prevalence of LAH is still not definitely established as stated in the review of Lehmann et al.[11] Bendz et al.[18] found a point prevalence of surgical proven hyperparathyroidism of 2.7%, McIntosh at al.[7] of 3.3%, and 15 (4.3%) of 348 patients were diagnosed with hyperparathyroidism by Awad et al.[21] There are also studies were no hyperparathyroidism was diagnosed.[5,17]

Diagnosing hyperparathyroidism is not difficult if there are high calcium levels, high PTH, low phosphate, normal 25OH D and normal renal function. But if a patient has hyperparathyroidism, calcium levels can be within the normal range in case of a 25OH D deficiency. Vice versa 25OH D deficiency and/or CKD can cause raised PTH. Nakamura et al.[22] found raised PTH levels in frail elderly people when 25OH D was below 50-60 nmol/L. In more ambulatory elderly women the 25OH D threshold for raised PTH was 40 nmol/L. Raised PTH levels can also be found when the MDRD is 60 ml/min or lower.[23]

In our study we found 56.4% 25OH D deficiency and in the patients who used lithium more than 10 years the prevalence was 76.9%. In the literature the prevalence of 25OH D deficiency varies from 40-100% dependent on the population studied and on the 25OH D level that is defined as deficient.[16] In a population-based cohort study in the Netherlands, the prevalence of 25OH D deficiency (<50 nmol/L) was 48.9% in a group with a mean age of 76.5 years.[24] Rosenblatt et al.[25] determined in 10 psychiatric patients 25OH D_3, 1,25OH D_3, calcium and PTH at baseline and after 4 weeks of lithium treatment. He found an increase in PTH, a decline in 1,25OH D_3 and no change in 25OH D_3 and calcium. The decline in 1,25OH D_3 was unexpected, but as the baseline level of 25OH D_3 was not stated neither as the renal function, this finding is difficult to interpret. Mallette et al.[20] compared patients who used lithium less than 6 months or more than 3 years and found a slightly higher 1,25OH D in the long-term group; 25OH D was not determined. PTH can induce 25OH D deficiency by stimulating 1α hydroxylase, thereby increasing the conversion from 25OH D to 1,25OH D. Postulating that the PTH level is slightly raised in patients treated with lithium, even without LAH, this could induce 25OH D deficiency during long-term lithium treatment.

The high prevalence of 25OH D deficiency and raised PTH levels in our older psychiatric patients indicate that a more active attitude to the problem of calcium homeostasis during lithium treatment is warranted. This is particularly urgent in face of the increasing evidence that low 25OH D and high PTH levels are associated with depressed mood and possible impaired cognitive function.[26,27] Hoogendijk et al.[24] found significant lower 25OH D and higher PTH in people with minor and major depression as compared to those without a mood disorder. Only 10.8% of the studygroup used a vitamin D supplement, which is low in this age group. Because of the growing aware-

ness of the importance of 25OH D, the Health Council of the Netherlands advised in 2012 daily vitamin D supplement of 800IE (20 µgr) for people of 70 years and older.[28] In older age the prevalence of osteoporosis increases with higher risk of bone fractures. 25OH D deficiency and raised PTH levels could decrease bone mineral density (BMD). Both risk factors have a high prevalence in the patients in our study. In a study of 75 patients treated with lithium, mean age 37 years, BMD was significantly higher in women treated with lithium than in women in the control group.[29] There was not a difference between patients who used lithium less than 5 years or longer. In middle-aged patients (mean age in women 53 years and in men 48 years) treated with lithium for more than 10 years, Nordenström et al.[8] found a higher BMD in the patients than in the controls, although this did not reach statistical significance. Other studies already suggested that low 24-h Ca excretion could be an indication for low bone turnover and that contrary to what one would expect, lithium protects against osteoporosis and can reduce fracture risk.[4,5] BMD and fracture risk were not objectives in our study, but this is an interesting subject for further research in older patients treated with lithium.

This study had several limitations. Because of the cross-sectional design there is the possibility of depletion of susceptibles. In patients with serious hypercalcemia lithium could have been discontinued. As stated before we have only few patients who used lithium for less than 6 months, and thereby, we could not detect an early increase in cCa and PTH or a decrease in 24-h Ca excretion. Ionized calcium was not determined and this could have caused misdiagnosing hypercalcemia.[8,20] On the other hand cCa is a reasonable estimation of ionized calcium in ambulatory patients and is also recommended in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline.[30] Although there is a reference range for 24-h Ca excretion, this excretion is partly dependent on daily calcium intake and we did not gather this information from the patients. The strength of our study is, that we did not use any exclusion criteria. The study results give a good reflection of calcium homeostasis in older psychiatric outpatients who are treated with lithium in daily practice over different time periods.

Conclusions

In this cross-sectional study on older patients treated with lithium, we did not find an association between duration of lithium treatment and cCa, PTH and 24-h Ca excretion. There was a negative association between duration of lithium treatment and 25OH D and the prevalence of 25OH D deficiency was high. This may have contributed to the high prevalence of raised PTH and can have camouflaged hypercalcemia.

Both 25OH D deficiency and high PTH are associated with mood disorders and cognitive decline in older patients. Therefore, it is advisable to actively screen for 25OH D deficiency and raised PTH in patients treated with lithium, also if cCa is normal. It is important to realise that, if 25OH D deficiency is corrected, hypercalcemia and LAH can become manifest; so continued monitoring of cCa is necessary. It is also important to realise that after correction of 25OH D deficiency, continued suppletion is necessary in older patients.

The negative association between duration of lithium treatment and 25OH D level needs confirmation in longitudinal studies with elucidation of the possible mechanism.

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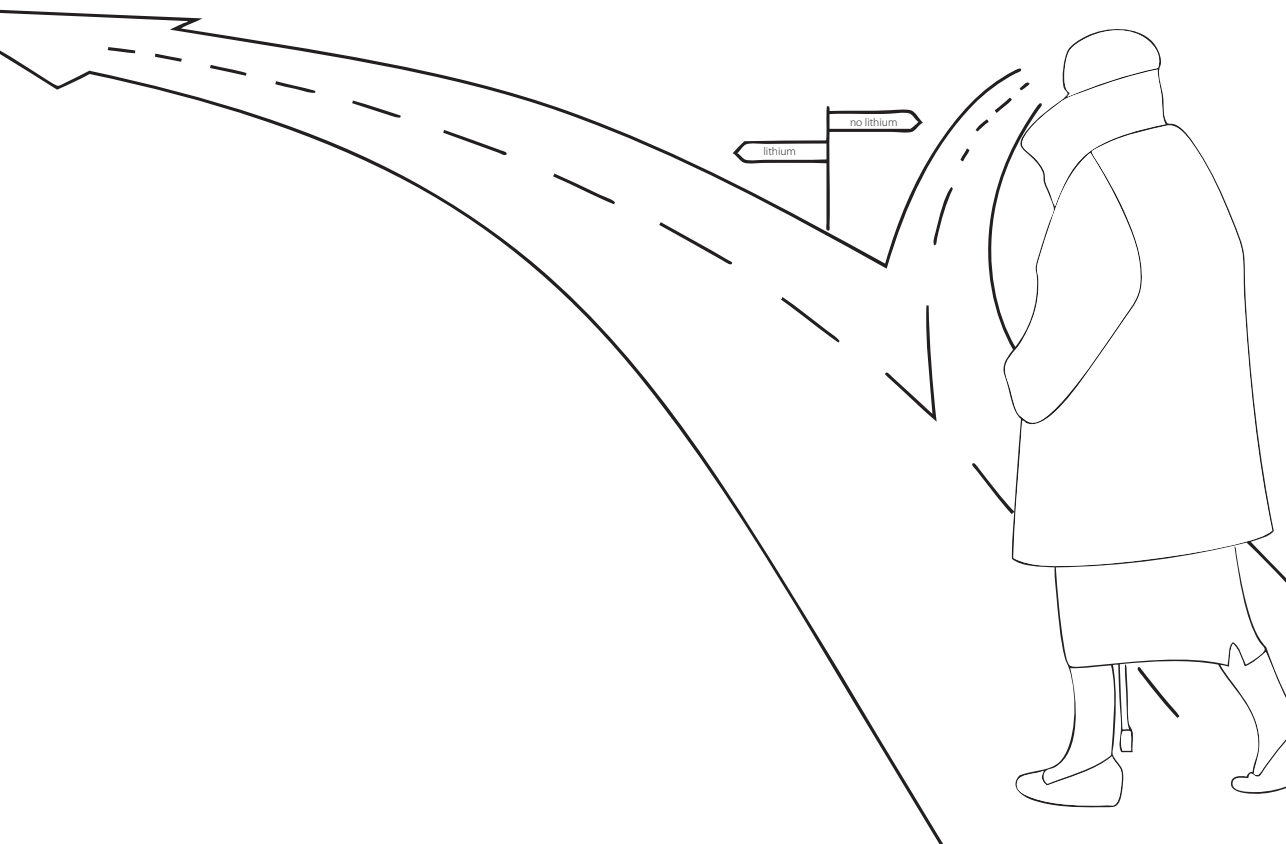
4

General discussion



Introduction

Lithium has been used in psychiatry for more than sixty years and is one of the first-line treatments in acute mania and prophylaxis of bipolar disorder.[1,2] In addition, it is used as augmentation to antidepressants in the treatment of depression.[3] The mechanism of the therapeutic action of lithium is still not fully resolved, but the inhibition of glycogeen synthetase kinase-3 (GSK-3) is probably one of the key mechanisms for its efficacy in bipolar disorder.[4]

Lithium is a drug with a small therapeutic window with an increased risk of relapse if the serum lithium concentration (SLC) is too low and an increased risk of intoxication if the SLC is too high. Many individual and external factors can influence the pharmacodynamics and pharmacokinetics of lithium. Regular monitoring of the SLC and adverse effects is therefore essential during initiation and maintenance treatment. The advised therapeutic window in the Netherlands is 0.4-1.2 mmol/L and it has been suggested that with increasing age the SLC should be < 0.8 mmol/L.[5] The optimal therapeutic window of lithium in the elderly is, however, not known.

Lithium has not been studied in double blind randomized trials in the elderly, but from mixed age studies in bipolar disorder it is extrapolated that lithium is as effective in older as in younger patients.[5,6] In a meta-analysis on treatment of refractory depression in the elderly, lithium was the best studied augmentation treatment and the overall response rate in five nonrandomized studies was 42%.[7] In the meta-analysis of Crossley et al.[3] on augmentation treatment in mixed age groups comparable efficacy of lithium was demonstrated. Lithium was the preferred mood stabilizer for treatment resistant unipolar depression and for prophylaxis of affective disorders according to a survey amongst old age psychiatrists in the U.K., but it was also the mood stabilizer that generated the highest level of concern regarding safety.[8] Lithium has many effects on different organ systems and the distinction between adverse effects and toxicity is not always clear. The factors that determine the individual susceptibility for adverse effects are mostly unknown and it is not clear whether age itself can influence this susceptibility. Studies on the adverse effects of lithium in older patients are sparse and they often used subjective tools to evaluate the adverse effects. Adverse effects that were frequently registered were tremor, polydipsia and polyuria.[9-11]

Homeostatic functions decline in older age and older people are already at higher risk of those disorders that are also adverse effects of lithium treatment. It is important to know if long-term lithium use can make older patients more vulnerable for these disorders and if there are other determinants which can influence this possible association in older patients. The prevalence of major adverse effects like reduction in renal function, reduced renal concentrating capacity, hypothyroidism, hyperparathyroidism and weight gain have not been objectively studied in the elderly. In a recent

review McKnight et al.[12] concluded that lithium is associated with an increased risk of reduced renal concentrating capacity, hypothyroidism, hyperparathyroidism and weight gain in mixed age groups. They found little evidence for clinically significant reduction in renal function.

The main objectives of this thesis were to investigate the treatment patterns of lithium in older patients and to study the occurrence of somatic adverse effects of lithium and their possible determinants in older patients.

In the study on lithium use patterns, older patients discontinued or switched lithium treatment not more frequently and they had less add-on of other psychotropic medication than middle-aged patients. In addition, we found that age was not a determinant of instability of SLC. The case report on lithium intoxication illustrates the pharmacokinetic and pharmacodynamic changes that may occur, especially in the elderly. It also illustrates the importance of correct monitoring of SLC and monitoring of adverse effects. In the studies on adverse effects in the elderly, we found an association between duration of lithium treatment and decrease of maximal renal concentrating capacity (Umax). During lithium treatment weight increased during the first five years, but there was no association between duration of lithium treatment and other cardiovascular risk factors and cardiovascular disease. There was a very low prevalence of hyperlipidemia in patients who used lithium compared with prevalence studies in the general population. The prevalence of hypothyroidism was very high, especially in women, with indication that hypothyroidism becomes manifest in the first three years of treatment in the majority of patients. In the study on calcium homeostasis there was neither association between duration of lithium treatment and for albumin corrected calcium (cCa), 24-h urinary calcium excretion (24-h Ca excretion) nor parathormone (PTH), but there was a significant association with vitamin D (25 OH D) deficiency. The prevalence of hypercalcemia was low and the prevalence of raised PTH was high.

In this final chapter the results of the studies will be discussed together with their implications for daily practice and future perspectives for research. The following topics will subsequently be discussed.

- Lithium use patterns and (in)stability of SLC in the elderly
- Somatic adverse effects of lithium use
- A specialized lithium ambulatory clinic for the elderly
- Future perspectives

Lithium use patterns and (in)stability of SLC in the elderly

Lithium has been used for many years in psychiatry and overall its adverse effects are known. It is also known that lithium has a small therapeutic window with the potential risk of intoxication if the SLC is too high and of relapse when the SLC is too low. When people grow older the pharmacokinetics of lithium change because of decreasing volume of distribution and declining renal function. Also, the prevalence of polypharmacy and multimorbidity is higher in the elderly which increases the risk of pharmacokinetic and pharmacodynamic interactions with lithium. In the last twenty years other drugs have become available to treat bipolar disorder and depression and together with the pharmacological changes in the elderly one could expect that this would cause more discontinuation of lithium and more switching to other psychotropic medication in older patients. In our database study from 1996 to 2008 (Chapter 2.1) we studied the changes in lithium use patterns and found significantly more continuation after five years or more of lithium use in the 70+ age group than in the group aged 40-49 years. This was caused by more add-on in the group aged 40-49 years. There was no difference in switch or discontinuation between the age groups. We did not investigate changes in incidence or prevalence of lithium use during the study period and therefore it is not possible to say if lithium was less often prescribed to older than to younger patients. Wilting et al.[13] studied the prevalence and incidence of lithium use in the Netherlands between 1998 and 2005 for patients of 18 years and older. The incidence was 0.2 patients per 1000 persons per year and constant over this period. The prevalence increased in this period from 0.95 to 1.2 patients per 1000 persons. Shulman et al.[14] found a decrease in new lithium users and an increase in new valproate users aged 65 years and older in Canada from 1993 to 2001. In Norway, Sweden and Denmark Bramness et al.[15] found an almost linear age-trend in lithium use prevalence in 2006 from 0.1-0.4/1000 in patients 18 years old up to 3-5/1000 in 70-80 year olds. The sales figures of lithium were on a high stable level in Sweden from 1981 to 2006 and in Norway they started low in 1981, followed by a steep increase to the same level as in Sweden in 2006. In Denmark they were stable but on a lower level. It seems that the geographical location, much more than age, determines if a patient is prescribed and continued lithium or not. This can be caused by differences in national guidelines, intensive lobby of pharmaceutical industries for other drugs, health care budgets and probably most important, by national key figures in psychiatry who teach and advise about lithium so that young doctors become confident with its use and learn how to monitor and recognize adverse effects.

In the study on instability of SLC (Chapter 2.3) we observed no significant difference between parameters of instability in the different age groups, except for a higher number of annual measurements in the group of ≥ 70 years. The therapeutic window

that was used to define stability of SLC was 0.4-1.2 mmol/L. This is the most important limitation of our study as instability by SLC outside a personal more narrow therapeutic window could have been missed. Especially in the older patient a smaller therapeutic range is advised, although, what the optimal range is in terms of optimal efficacy and minimal adverse effect, is not clear. In a review on the optimal SLC in long-term treatment of bipolar disorder it was concluded that lithium exerts its efficacy between 0.4 and 1.2 mmol/L and that SLC between 0.6 and 0.75/0.8 mmol/L combines efficacy with acceptable adverse effects.[16] In their review of lithium augmentation in patients treated for unipolar depression Crossley et al.[3] found the SLC between 0.5 and 1.1 mmol/L. The Dutch guideline[2] on bipolar disorder advises to keep the SLC between 0.4 and 1.2 mmol/L and does not give separate advise for the older patients, neither does the NICE guideline.[1] The British National Formulary (BNF) recommends a SLC of 0.4-1.0 mmol/L and advises to keep the concentration towards the lower end of the range in the elderly.[17] Shulman[5] states that SLC > 0.8 mmol/L in older patients increases the risk of serious adverse effects. In our study the median SLC in the group ≥ 70 years was 0.67 mmol/L and in the patients aged 40-49 years the median SLC was 0.76. We concluded that seemingly Dutch psychiatrists already treat older patients with lower SLC, but this could also mean that younger patients have more serious psychiatric disease and need higher SLC. Despite this, aiming at lower SLC in older patients is advisable although not proven. As patients grow older and especially if the patient has a cerebrovascular or neurodegenerative disease, like Alzheimer or Parkinson, they are more susceptible to intoxication.[18] Apart from a worsening tremor, delirium can be the presenting symptom of SLC which is too high, although the SLC can still be in the therapeutic window.[19] In our case report (Chapter 2.2) the patient presented with a delirium, but his SLC was far outside the therapeutic window. The delirium was severe and persisted for a long time. This case report illustrates what the risks are if the treating physician does not know how to monitor lithium and how to recognize symptoms of intoxication.

Clinical implications: In daily practice most laboratories in the Netherlands use for SLC the range of 4-1.2 mmol/L. Most psychiatrist however, already use lower SLC for the elderly and it would be better to maintain the range of 0.4-0.8 mmol/L in patients 70 years or older in the laboratory. Then the treating physician can be alerted in time while in case of the broader window the increased SLC could go unnoticed. To help treating physicians to interpret and prescribe lithium correctly, it is also advisable to add the comment in the laboratory list that the SLC has to be a trough level and to issue a warning in the electronic prescription system if lithium is not prescribed in the evening. If a physician wants to determine a SLC, he should state if the patient is in the titration phase or maintenance phase. If during maintenance treatment a SLC change

of 0.2mmol/L or more is found, a warning signal should be given. This is important because apart from psychiatrists, neurologists and general practitioners, also prescribe lithium and they are often not well informed about the correct monitoring of lithium.

Somatic adverse effects of lithium use

In our studies on adverse effects of long-term lithium use in older patients one has to bear in mind that the disorders studied are also known to be associated with ageing next to their association with lithium use. A small increase in relative risk in this age group can have a clinical relevant effect. Bipolar disorder itself is associated with some of these disorders like cardiovascular disease and the use of other psychotropic medication, often used for a long time, could also have an impact on the studied adverse effects. As we did not have the possibility to compare the elderly lithium users with a control group, except in the study on thyroid disorders, this limits the drawing of definite conclusions. Nevertheless there are results which can be used in daily practice.

Effect of lithium on the kidney

Renal function declines with age possibly caused in part by underlying cardiovascular disorders and the renal concentrating capacity decreases with age.[20,21] Lithium can reduce the maximum concentrating capacity (Umax) of the kidney by blocking the effect of arginine vasopressin (AVP) in the distal tubules and thereby inhibiting the reabsorption of water from the tubules. Many studies have been undertaken to evaluate the association between lithium treatment and Umax, although not specifically in the elderly. In the past decennia three reviews have been published on the effect of lithium on the kidney. Boton et al.[22] concluded in 1987 that the Umax, in most studies defined as 800mosmol/kg, was reduced in 54% of patients treated with lithium and 19% had polyuria, > 3 L/24 h. But there was also a reduced Umax in 32-53% of the control patients. Gitlin[23] stated in his review in 1999, that in most, but not all studies, lithium treatment is associated with a decrease in Umax. In most cross-sectional studies there is an association with duration of lithium use, but this is not confirmed in some longitudinal studies. In the most recent review of McKnight et al.[12] in 2012 they concluded that the Umax was reduced in 15% of the patients who used lithium compared with controls. We found a negative association between duration of lithium use and Umax with a decreased Umax in 72.7% of the patients (Chapter 3.1). The Umax was severely reduced (≤ 300 mosmol/kg) in 18.7% and moderately (> 300 and ≤ 600 mosmol/kg) in 54% of the patients. Benz et al.[24] used the same test as we did and found in 11.9% a decrease of < 300 mosmol/kg in a younger population (mean age 61 years)

who used lithium for a longer period. It is not conclusive from the literature what happens with the Umax in a normal ageing population, but these results indicate that lithium has a greater impact on the Umax in older than in younger patients. We found more incontinence and more impact on social functioning in patients with a severely reduced Umax (≤ 300 mosmol/kg), but this was not significantly different from the group with moderately reduced or normal Umax. Complaints of thirst were present in about 50% of the patients, independent of Umax. This is not only the case in elderly patients, who often have an impaired thirst signal. Vestergaard et al.[25], already noted in 1979 that patients, mean age 42 years, without complaints of thirst or frequent micturition, could still have serious polyuria. Therefore it is difficult to determine if a patient has polyuria and/or a reduced Umax solely on the basis of an interview.

The discussion on the effect of lithium use on the glomerular filtration rate (GFR) is not really resolved. McKnight et al.[12] concluded from their review of the literature that there is a reduction in GFR of 0-5ml/min/year. Meta-analysis of case-control studies showed that the GFR was lower in lithium patients than in the matched controls. They found the information on end-stage renal failure scarce and concluded that the risk seems to be low. But if a patient uses lithium for 20 years and the reduction in GFR is 5 ml/min/year than the GFR decreases over this period from 120 to 20 ml/min, in which case the patient has serious chronic kidney disease. But if the reduction is 1ml/min/year, than the GFR declines from 120 to 100 ml/min and the clinical effect would be minimal.

It is believed that there is a small group of patients who can develop end stage renal disease after 15 years or more of lithium use.[26,27] Proteinuria and vascular disease could be additional risk factors, but this is also true for patients with chronic kidney disease who do not use lithium. In our study on renal function in the elderly we did not find a significant association between the GFR, estimated with the Cockcroft-Gault formula, and duration of lithium treatment, but there was an evident association with age and vascular disease. In the larger study on calcium homeostasis (Chapter 3.4) there was no significant difference in GFR, estimated with the Modified Diet in Renal Disease (MDRD) formula, within the four groups classified according to the duration of lithium use (P = 0.074). In the study on vascular risk factors and vascular disease (Chapter 3.2) the patients were also classified in four groups according to the duration of lithium use. In this study the group that used lithium up to two years was used as the reference group and there was a significant decrease in the MDRD between the reference group and the group of patients that used lithium for 5- 10 years and the group that used lithium for 10 years or more. In a post hoc analysis of the data from the study on calcium homeostasis a linear regression analysis was conducted with MDRD as dependent factor and age and duration of lithium use as predictors. A significant association was found: B -0.45 (CI -0.79 /-0.11), P 0.01. When the patients

were divided in patients with vascular disease and without vascular disease the results were respectively, with vascular disease (n=53, one missing) B -0.88 (CI -1.42/-0.34) P 0.002 and without vascular disease (n=57) B -0.13 (CI -0.53/0.27) P 0.51. Although these data concern unpublished material, it indicates that older patients who do not have vascular disease are not at increased risk to develop renal disease during lithium treatment. The question if vascular disease alone is the cause of renal disease in the elderly during lithium treatment or that they are more vulnerable because of their vascular disease and have a more rapid decline in renal function, is unresolved, but this last option seems the most plausible.

Clinical implications: Measurement of urine osmolality has to be part of the lithium screening protocol once a year and in case of a low value and/or complaints about polyuria or thirst, 24 hour urine volume measurement is indicated. Creatinine measurement in the 24 hour urine can be used to calculate the creatinine clearance and to calculate if the collection was complete. If the urine volume is consistent with polyuria, this has to be followed up by a DDAVP test and vasopressin determination. This is important because polyuria during lithium treatment is not only caused by nephrogenic diabetes insipidus (NDI). It can also be caused by primary polydipsia (PP) or central diabetes insipidus (CDI). If it is clear what the underlying mechanism is, the polyuria can be treated; in case of NDI with amiloride and/or a thiazide diuretic, in case of CDI with DDAVP intranasal and in case of PP with verbal instructions. Apart from treatment, it is important to know if a patient has NDI or CDI, because these patients are susceptible to serious dehydration in case they are not capable of drinking enough during illness or during immobilization for other reasons.
Concerning the glomerular filtration rate (GFR) it is important to follow the guideline of bipolar disorder on lithium screening. But if an older patient has any cardiovascular risk factor (CVR) or cardiovascular disease (CVD) closer monitoring is necessary with estimation of the GFR (eGFR) every six months and active treatment of CVR and CVD according to the guideline cardiovascular risk management, also in patients older than 70 years. In older patients who already have a reduced eGFR (MDRD < 60ml/min) at the start of lithium treatment without CVR or CVD, adherence to the guideline is sufficient with every six months evaluation of the eGFR.

Effect of lithium on cardiovascular risk factors and cardiovascular disease

Studies on CVR and CVD in relation to lithium use are limited.[28] The study of these topics is difficult because there is a strong indication from the literature that bipolar disorder and unipolar depression are associated with CVR and CVD, but it is not certain if this is caused by genetic predisposition, unhealthy lifestyle, disease related hor-

monal changes, psychotropic mediation or most probable a combination of these.[28,29] The only item that has been studied more thoroughly is the association between lithium and weight gain. Lithium causes significant weight gain (>7%) more frequent than placebo but less than during treatment with second generation antipsychotics (SGA) like olanzapine.[12] In our study (Chapter 3.2) we found a significant increase in BMI between patients who used lithium for two years and patients who used lithium for 2-5 years. The mean BMI stayed around the same level after this period and did not continue to increase. Apart from weight gain there was no other association between CVR and CVD and duration of lithium use. Because of the cross-sectional design it is not known if many patients died of CVD during lithium treatment.

Age is one of the major risk factors for CVR and CVD and we set out to investigate if lithium use contributes to this risk. We studied the prevalence of CVR and CVD in patients with affective disorders treated with lithium and aged 60 years or older (Chapter 3.2). We compared them to the results from studies in the general population of similar age in the Netherlands. Thus, we did not compare them with other patients with affective disorder. The age in one general population study ascertaining CVR was 55 years or older and this study was conducted 15 years before our study. One would expect that these differences would all result in lower prevalences in the general population than in our older group. And indeed, in our study we found higher prevalence of high BMI, of diabetes in women and hypertension, but there was a very low prevalence of hyperlipidemia. When comparing our results, although in a small subgroup of women, to more recent data, the prevalence of high BMI was comparable, the prevalence of diabetes was lower and again the prevalence of hyperlipidemia was very low in our study group. The prevalence of hypertension was also lower in our group, but the criteria used were different. The prevalence of ischemic heart disease (IHD) and cerebrovascular accident (CVA) were respectively lower and higher in our study, with higher use of antipsychotics in the patients with CVA. The method of our study makes it not possible to draw definite conclusions on the association between lithium use and CVR and CVD in the elderly, but the results indicate that lithium has a possible benign cardiovascular profile regarding its effects on lipids and diabetes. This is more plausible because there are biological mechanisms that may explain this. Tabata et al.[30] found an increase in insulin sensitivity by lithium and Singer et al.[31] stated that lithium decreases hepatic cholesterol and fatty acid synthesis. The negative association with CVA has to be followed up and has to be ascertained if this is a lithium effect or related to antipsychotic use of which already an association with CVA is reported.[32]

Clinical implications: The possible favorable effect of lithium on lipids and glucose metabolism needs confirmation in other studies. If this is confirmed, it could play a

role in treatment decisions in the elderly with CVR and CVD. For now it is advisable to determine glucose after the titration phase of lithium in a patient with diabetes.

Effect of lithium on the thyroid

The existence of an association between thyroid (dys)function and psychiatric disorders, nobody will dispute, but the association is very complex. This is substantiated with the opposing viewpoints of Joffe et al.[33] and Bauer et al.[34] Joffe et al. state that affective illness is associated with relative hypofunction and Bauer et al. state that it is associated with relative hyperfunction of the thyroid. There is also a supposed relation between autoimmunity, especially between thyroid antibodies and affective disorder, although the conclusions in different studies are not consistent.[35,36] Lithium interferes with thyroid function in several ways, it interferes with the production of thyroxine (T4) and inhibits the release of T4 from the thyroid gland. This causes a rise in thyroid stimulating hormone (TSH) and this can, together with stimulation of DNA synthesis, result in goiter and/or hypothyroidism.[31,37] In older age the prevalence of hypothyroidism increases in the general population, especially in women.

In our study in elderly patients with affective disorders (Chapter 3.3), we found a prevalence of hypothyroidism of 35.4% in patients treated with lithium, mean age 75.6 years (range 65-94 years) mean duration of lithium use of 10.0 years. The prevalence in women and men was respectively 41.3 and 12.6%. The prevalence was 7.1% in nonlithium patients, mean age 76.3 (range 65-94 years). The prevalence of hypothyroidism in the general population aged 85 years and over in the same region in the Netherlands was 12%.[38] In a somewhat younger age group (60-79 years) in the U.K. the prevalence of lithium treated patients was for women 16% and men 7.5% and in the general population resp 8.8 and 1.9%.[39] Hypothyroidism is not more prevalent in elderly patients with affective disorders not treated with lithium, compared to the general population, but it is much more prevalent in patients treated with lithium. Female gender was the only determinant in this study that was associated with hypothyroidism.

Thyroid antibodies were determined in a subgroup of lithium users in our study. The prevalence of antibodies was comparable with the prevalence in the general population of the same age. There was neither association between the presence of antibodies and thyroid disorder nor bipolar disorder in this study.

Lithium treatment in older patients can cause hypothyroidism in many patients, especially women, and the diagnosis is made most frequently in the first three years after the start of lithium. Because differences in prevalence of lithium induced hypothyroidism over the world, there must be causes that are related to the geographical location. Apart from genetic causes, it is possible that the Iodine intake can play a role as regions with sufficient Iodine intake have more hypothyroidism and regions with

deficient Iodine intake have more goiter during lithium treatment. In our study we did not evaluate if patients had goiter, but that would certainly be interesting to study.

Clinical implications: Up till now there are no precautions that can be taken to prevent hypothyroidism during lithium treatment, but it is advisable to determine TSH more often in older women after the initiation of lithium treatment than is currently advised in the guidelines. In the first three years TSH should be determined every 3 months. Determination of TPO-antibodies before the start of lithium is not necessary in the elderly.

Effect of lithium on calcium homeostasis

Lithium can cause a rise in serum calcium by inhibiting the signal from the calcium sensing receptor in the parathyroid, which normally causes a decrease in PTH. Lithium also inhibits the signal from the calcium sensing receptor in the kidneys which normally causes a decrease in calcium reabsorption. This results in higher PTH and more calcium reabsorption in the kidneys, with higher, but often still normal, serum calcium and lower calcium in the urine.[40,41] In some patients lithium associated hyperparathyroidism (LAH) can develop, but the prevalence of this disorder is unknown.[42] In physiologic circumstances homeostatic mechanisms keep the serum calcium level within a certain range and PTH, renal function and vitamin D are important mediators. In older age the efficacy of the homeostatic mechanisms declines and real function decreases. The prevalence of vitamin D deficiency increases in the elderly and post or propter, the prevalence of hyperparathyroidism increases.[43] In view of these changes, we studied the calcium homeostasis in older patients treated with lithium.
Two longitudinal studies found a significant increase in PTH in the first months of lithium treatment.[44,45] Thereafter the PTH level stayed more or less the same. In one of these studies there was a rise in cCa,[44] but not in the other.[45] It seems logical to assume that lithium causes a rise in PTH early after the start of treatment, and that with a possible transient raise in cCa a new equilibrium is reinstated. In our study (Chapter 3.4) we did not find an association between duration of lithium treatment and most parameters of calcium homeostasis. This could be ascribed to the fact that there were only a few patients who used lithium less than 6 months. Studies on hypercalcemia in patients treated with lithium are mostly cross-sectional and the prevalence in these studies varies from 0-42%.[46-49] This variation is almost certainly caused by differences in methodology, differences in study population like age, renal function and vitamin D level and differences in determination of calcium. The same can be said about studies on raised PTH in which the prevalence varies between 0-34%.[45,49-51] In our study the prevalence of hypercalcemia was 2.7%, which is low, and a prevalence of raised PTH of 47.8%, which is high. Because of a very high prevalence of vitamin D (25 OH

D) deficiency in our study, it was not possible to determine the prevalence of LAH as 25 OH D deficiency can raise PTH and on the other hand can camouflage true hyperparathyroidism by keeping the calcium level low. In 53.2% of the patients the MDRD was < 60ml/min and this could also raise PTH. Additional imaging studies of the parathyroid were not part of the study protocol.

Clinical implications: In our study the prevalence of 25 OH D deficiency was very high, 93.6% < 75 nmol/L and 56.4% < 50 nmol/L. There was an unexpected significant association between duration of lithium treatment and 25 OH D deficiency. As there are indications that 25 OH D deficiency and raised PTH are associated with depression and cognitive impairment in the elderly, it is important to determine cCA, 25 OH D and PTH before the start of lithium.[52,53] If a patient has 25 OH D deficiency this has to be treated and subsequently suppletion is indicated. It seems warranted to determine cCa, 25 OH D and PTH also after six months of lithium treatment and thereafter cCa once a year.

A specialized lithium ambulatory clinic for the elderly

In the Netherlands older patients who use lithium are treated by ambulatory teams of mental health care. The teams consist of a psychiatrist, who is responsible for the treatment and psychiatric nurses who visit the patient at home. The SLC is checked every 3 months and the renal and thyroid function less frequently according to the guideline for bipolar disorder. The psychiatrist checks the results of the laboratory tests and depending on the psychiatric problem has face to face contact with the patient at least once a year or more often. Most workers in mental health care are aware of the risks of lithium treatment, but are not always familiar with the possible interactions with other diseases and medication in the elderly. Sometimes, when people become more frail with multimorbidity, the general practitioner is asked to take over the psychiatric care. It seems logical that in case of multiple chronic diseases one physician has the overview, but general practitioners do not have many patients who use lithium and therefore do not have the knowledge to give optimal care to these complex patients.
There are many similarities between treatment with lithium and the treatment with coumarines. Just like lithium the coumarines have to be kept within a small therapeutic window, which in case of the coumarines is determined by the outcome international normalized ratio (INR). The risks of inefficacy increases if the INR is too low and the risk of adverse effects increases if the INR is too high. Just like treatment with lithium, the treatment with coumarines can be compromised by pharmacodynamic and pharmacokinetic changes in a patient when new diseases develop and new

medication is added. Because of the importance of correct treatment a nationwide system has been developed for monitoring of patients treated with coumarines in the Netherlands. Although there are much more patients treated with coumarines than with lithium, a more coordinated approach for monitoring of lithium treatment is warranted especially in the elderly.

A specialized lithium ambulatory clinic for the elderly (SLAC-e) should be a place where knowledge of geriatric care, psychiatric care and pharmacology is centered. And specialists with nephrologic, cardiologic and neurologic expertise should be easy to consult. The SLAC-e can best be stationed in a general hospital in close association with a mental health care institution but the opposite is also possible. It is important that there is easy access to somatic care facilities; laboratory, ECG and radiologic facilities. The objective of the SLAC-e is prevention of adverse effects if possible, treatment of adverse effects, optimizing the somatic condition of the patients, coordination of medical care by other medical specialists and psycho-education for the patient and his caregiver about their psychiatric disorder and especially about lithium. As there are indications that psychiatric disorders are in itself associated with cardiovascular disease, just like the use of antipsychotics, the screening that is now advised according to the guidelines,[28] should be included in the comprehensive assessment in the SLAC-e.

The patients who visit the SLAC-e consist of different groups but they all have the same geriatric assessment (Table 1). The first group consists of older patients who have to start with lithium. Their co-morbidities and co-medication can be evaluated and optimized and preventive measures can be taken. If there are no complex problems needing specialized medical care, they are referred back to their treating psychiatrist

Table 1. Comprehensive assessment SLAC-e

Gathering information about medical history
Gathering information about lithium history
Gathering information about the medication that is used
Case history taken from patient and caregiver
Smoking/alcohol/drugs
Comprehensive physical assessement (internal and neurological)
Psychiatric examination
Renal function: MDRD, albumin/creat ratio in urine
Renal concentrating capacity: short DDAVP test
Endocrinology: glucose, TSH, Ca, P, albumin, PTH, 25 OH D
Cardiovascular: chol, HDL, LDL, triglyc, ECG
Central nervous system: MMSE, clock
Pharmacology: SLC, STRIP (Systematic Tool to Reduce Inappropriate Prescribing)
ADL and IADL functions

and if necessary treatment advise is given to their GP. It is not certain what would be the optimal follow-up time, but a new assessment at the SLAC-e after two years seems reasonable, but needs further study.
The second group consists of patients who already use lithium for a longer time and who have grown older during their lithium treatment. This group is also referred back to the treating psychiatrist and GP, unless there are reasons to continue the care in the SLAC-e. If there is multimorbidity and polypharmacy and patients are in care of other medical specialists, coordination and if possible centralization of the care in the SLAC-e is proposed. In this way patients don't have to visit four or more doctors who often only focus on their own domain.
The SLAC-e has also a function as expertise center, to be consulted by other professionals treating patients with lithium and where research can be conducted. The concept of a specialized lithium center is not new,[10,54] but in the Netherlands this has not been implemented on a regular basis and certainly not for the elderly. The costs of medical care always have to be compared with the benefits. At this moment there is no proof that the SLAC-e, besides improving the quality of care for the older psychiatric patient, also reduces or at least does not increase the costs; but it seems feasible. Twenty SLAC-e spread out over the Netherlands could guarantee accessibility to such care for most older patients.
This thesis is focused on lithium, but there is increasing interest in adverse effects of other drugs commonly used in psychiatry, especially the association between psychotropic drugs and cardiovascular disease. As there are indications that psychiatric disorders in itself are also associated with cardiovascular disease, the cardiovascular risk management that is now advised according to the guidelines, could be coordinated in these centers.[28]

Future perspectives

As more light is shed on the mechanism behind the effects of lithium in psychiatry, this may lead to the development of other drugs with less adverse effects. The proposed effects of lithium in neurodegenerative diseases like Alzheimer and Parkinson and the prevention of ischemic damage by lithium after CVA may lead to whole new treatment indications perhaps with much lower SLC, but also stimulate the research in new drugs with the same effect and less disadvantages.[4]
The clarification of the effects of lithium on many signaling pathways could contribute to solving the puzzle of why some patients develop adverse effects and others do not, even after many years of treatment. The fact that there are patients who have more than one major adverse effect, nephrogenic diabetes insipidus, hypothyroidism and

hyperparathyroidism together, suggests that there is an individual, possible genetically determined, sensitivity.[55] If this could be determined before starting treatment, the treatment decisions could be better balanced.

For now and in the near future lithium is a drug that continues to have an important place in the treatment of bipolar disorder and unipolar depression also in the elderly. When lithium is prescribed the physician has to determine the balance between benefits and risks in an individual patient. Prospective, controlled studies with lithium in older patients are needed to better determine the benefits. If the SLAC-e is implemented studies are needed to evaluate if it indeed contributes to better and safer care for the older lithium patient without more costs.

This thesis concentrates on the possible risks of lithium treatment in the elderly. Not to discredit lithium; quite the reverse. To see an elderly patient struggling with his depression and after lithium addition resuming his/her former life is very impressive. Withholding such an effective treatment for the wrong reasons should be prevented. From the studies presented here it can be concluded that lithium treatment in the elderly can be save, if the patient is monitored correctly.

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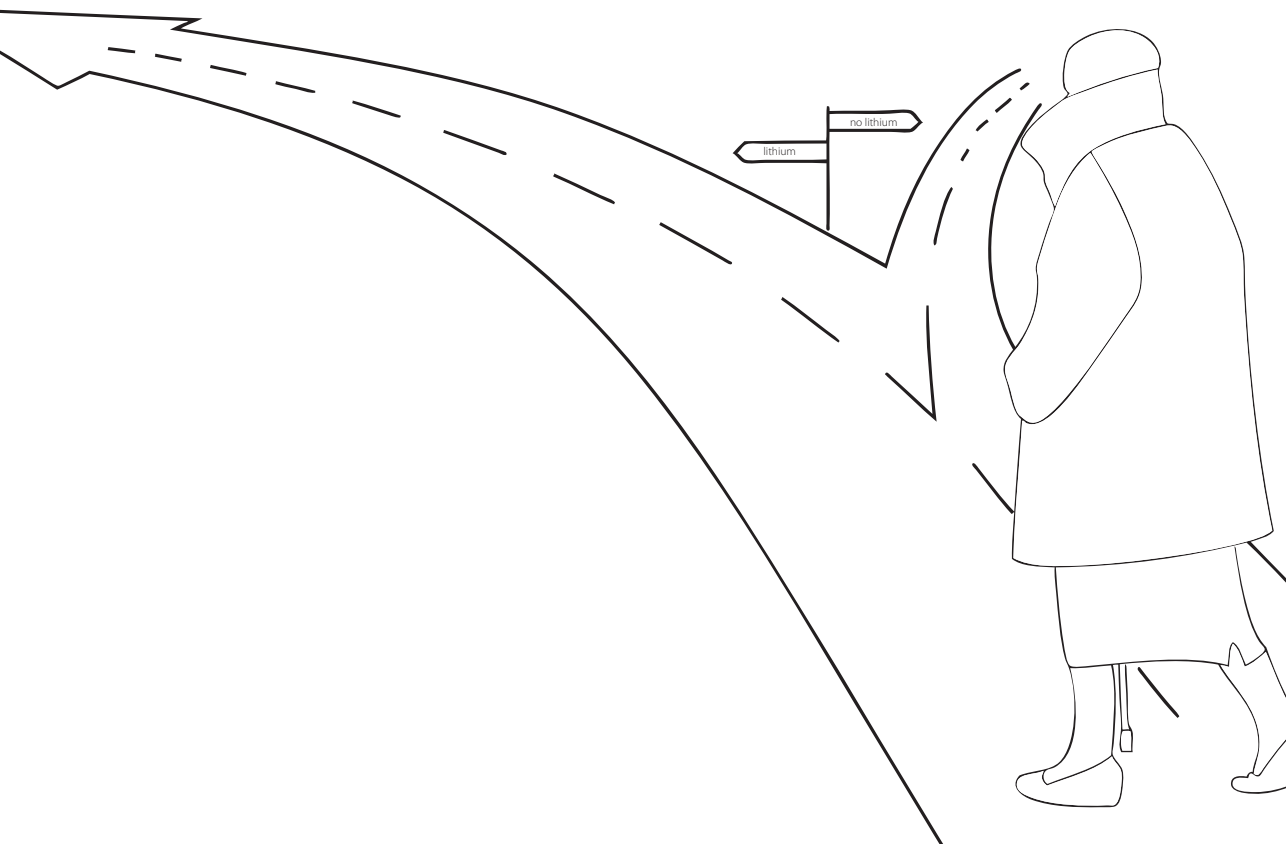
Summary



Lithium has been used in psychiatry for over 60 years and is still one of the first-line treatments in bipolar disorder. It is also used as augmentation to antidepressants in treatment resistant depression. In older patients lithium has not been specifically studied in randomized placebo-controlled trials, but it is assumed from mixed age studies that lithium is as effective in the elderly as it is in the younger population. Lithium has a narrow therapeutic window with toxic and ineffective serum levels not far apart. Age-dependent changes in lithium pharmacokinetics and pharmacodynamics may influence lithium use patterns in an ageing population, especially as newer treatment options have become available. In addition to age-dependent changes in the pharmacology of lithium, increasing multimorbidity and polypharmacy could make it more difficult to keep the serum lithium concentration (SLC) in the elderly within the therapeutic window.
Important adverse effects of lithium are reduction in renal function, decrease in renal concentration capacity, hypothyroidism, hyperparathyroidism and weight gain. The homeostatic functions decline with older age and amongst the elderly cardiovascular disease and endocrinological disorders are more prevalent. Therefore older age could make patients more vulnerable to the adverse effects of lithium use.
The main objectives of this thesis were to investigate the treatment patterns of lithium in older patients and to study the occurrence of somatic adverse effects of lithium and their possible determinants in older patients.

Pharmacoepidemiological and clinical pharmacological aspects of lithium use

In chapter 2 pharmacoepidemiological and clinical pharmacological aspects of lithium use were studied. In chapter 2.1 we compared lithium use patterns between middle-aged and older outpatients in the Netherlands. Data for this study were obtained from the Dutch PHARMO Record Linkage System. Incident lithium users of 40 years or older, were identified in the time-period 1996-2008. Four lithium use patterns were defined: continuation, add-on, switch and discontinuation. Differences in lithium use patterns were assessed for four age groups: 40-49, 50-59 ,60-69 and 70 years or older. The youngest group was termed the reference group. Baseline patient characteristics and potential determinants of changes in lithium use patterns were ascertained. We identified 2081 incident lithium users. The frequency of discontinuation and switching of lithium did not differ between the age groups. Older patients were less likely to receive add-on of psychopharmacologic drugs to ongoing lithium therapy ($P < 0.05$). Concomitant use of antidepressants was not different at baseline between age groups, but elderly patients starting lithium treatment, less frequently used antipsychotics at

baseline than middle-aged patients ($P < 0.05$). We concluded that older patients were less likely to receive add-on of psychopharmacologic drugs next to ongoing lithium therapy. Despite pharmacokinetic and pharmacodynamic changes in the elderly, lithium was not more often discontinued and not more often switched in older than in middle-aged patients.

In chapter 2.2 we presented a case report of an elderly man with cluster headache who was treated for many years with lithium and who developed a lithium intoxication. Lithium is almost exclusively prescribed by psychiatrists but sporadically lithium is prescribed by neurologist for the prevention of cluster headache. Guidelines for psychiatrists advise extensively on monitoring of lithium while the guidelines for neurologist are more restricted on this subject. The clinical symptoms, the treatment and possible irreversible neurotoxicity of lithium intoxication were discussed. We emphasized that every clinician who prescribes lithium should know the importance of monitoring and should be familiar with the symptoms of intoxication.

In chapter 2.3 we studied if age was a determinant of instability of the SLC. A retrospective study (1995-2004) was conducted using SLC from the laboratories of three hospitals in the Netherlands; 759 patients treated with lithium, 40 years or older, with at least two years of follow-up were identified. They were divided into four age groups: 40-49 years, 50-59 years, 60-69 years and 70+; the youngest group was used as a reference group. Several parameters, considered a proxy for instability, were compared between the age groups. These parameters were derived from studies involving oral anticoagulants, because these drugs have, just like lithium, a small therapeutic window and need regular monitoring. The parameters consisted of the variance growth rate and percentage of time below, in and above treatment range. We found no significant difference for these variables between the reference group and the older age groups. In a subgroup of 454 patients the parameters considered a proxy for instability during the titration phase, number of days and number of SLC measurements during titration, were evaluated; no significant difference was found between the age groups. In a small group of 117 patients titration and maintenance treatment for at least two years could be analyzed separately. Also in this group, there was no difference between the age groups. We concluded that age was not a determinant of SLC instability. Therefore, age is not a reason to not initiate or to discontinue lithium therapy.

Somatic adverse effects of lithium use in older patients

In chapter 3 the studies on the adverse effects of lithium use in older patients were presented. To determine the effect of long-term lithium therapy on glomerular filtration rate (GFR) and maximum renal concentrating capacity (Umax) in the elderly, we conducted a cross-sectional study with 48 outpatients of 65 years or over (mean 74,8 years), who were treated with lithium for at least six months (mean 9,2 years).(chapter 3.1) We also studied potential risk factors and the clinical impact of a reduced Umax in this population. In case of polyuria we tried to establish a diagnosis. The GFR was estimated using the Cockcroft-Gault formula (GFR-CG) and the Umax was measured in a urine sample collected between 3 and 5 hours after the patients received 40µg desmopressin (DDAVP) intranasally.
No relation was found between duration of lithium treatment and GFR-CG, but there was a significant relation between duration of lithium treatment and decrease in Umax (B -0.73; CI: -1.249/-0.212); 73% of the patients had a moderate to severe concentrating defect. No other risk factors than duration of lithium therapy were identified. A reduced Umax caused polyuria (> 2500mL/24h) in 33% but did not cause significant more thirst, incontinence or disturbed sleep. In case of polyuria other mechanisms beside nephrogenic diabetes insipidus were found to play a role in this age group.

Patients with an affective disorder are at increased risk for cardiovascular morbidity and mortality compared to the general population. The effect of lithium use is only sporadically studied. In chapter 3.2 we ascertained the prevalence of known cardiovascular risk factors (CVR) and the prevalence of cardiovascular disease (CVD) in older patients treated with lithium. We compared the prevalence of CVR and CVD in these patients with data from studies in the general population of the same age and determined the association with the duration of lithium use. A cross-sectional study of psychiatric patients visiting a specialised lithium ambulatory clinic for elderly patients was conducted. Patients underwent a comprehensive assessment and potential confounders of CVR and CVD were recorded. Based on duration of lithium treatment, patients were divided into four groups. The prevalence of diabetes in women and the prevalence of overweight and hypertension in both sexes were higher in our study population of lithium users compared to a 15 year older population study of the same age group. The prevalence of diabetes was lower in our study compared with a more recent population study. There was a striking lower prevalence of hyperlipidemia in our study compared with both population studies. The prevalence of ischaemic heart disease was lower and the prevalence of cerebrovascular disease was higher in our study than in the general population. There was no relation with duration of lithium use and CVR and CVD except for an increase in BMI in the first years of lithium use.

Because of the cross-sectional character of the study, causal relations could not be determined.

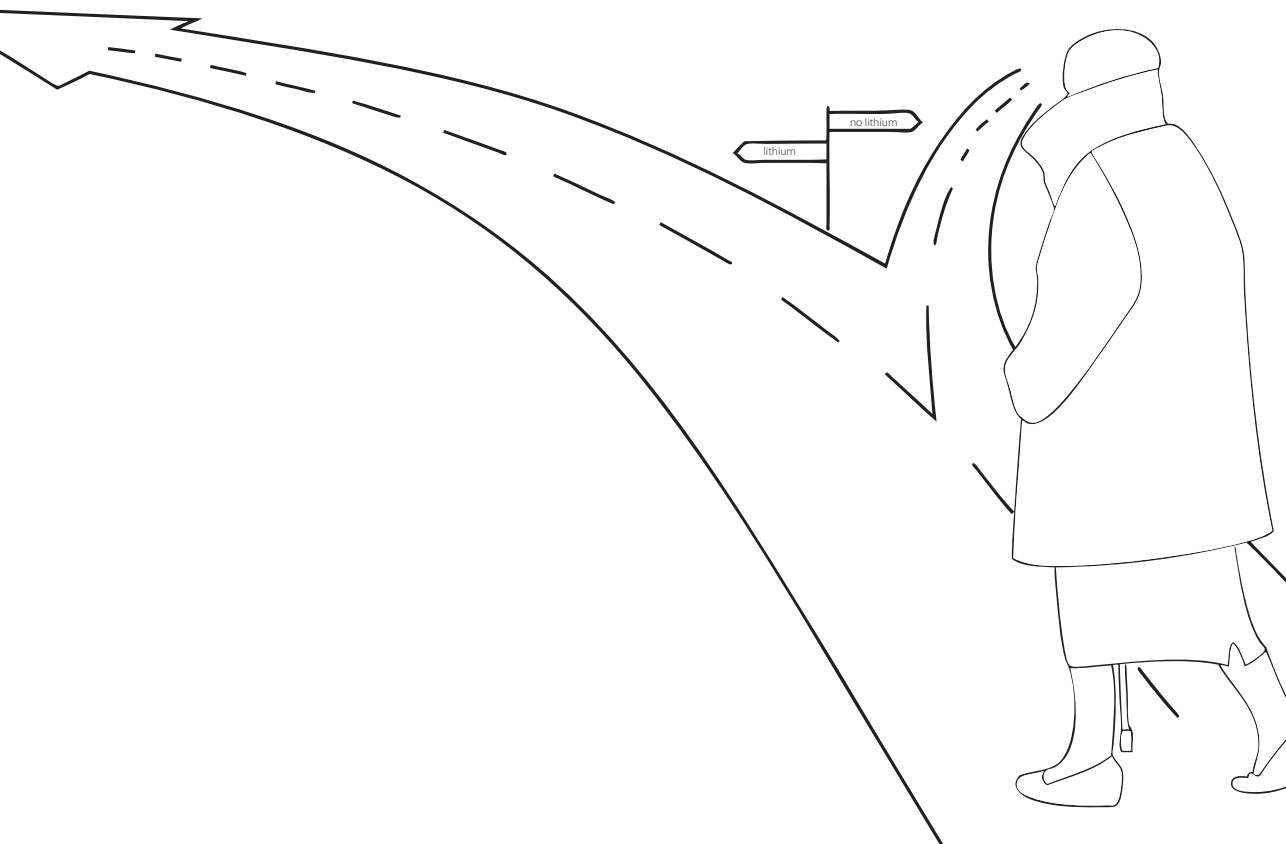
To determine the prevalence and determinants of thyroid dysfunction in older patients with an affective disorder a retrospective cross-sectional study was conducted in patients of 65 years and older with affective disorders according to DSM IV criteria (chapter 3.3). The patients were divided in lithium and nonlithium patients. The presence of thyroid disorders was determined on the index date (ID) defined as the date of the first available TSH in 2005. The presence of thyroid disorder was established according to defined criteria and in case of a prior diagnosis, confirmed by researching the medical files. In a subgroup of 45 lithium patients thyreoperoxidase and thyreoglobulin antibodies (TPO- and TG-ab) were determined.
A total of 79 lithium patients and 85 nonlithium patients were included. The prevalence of hypothyroidism (subclinical and clinical) was 35.4% among the lithium patients, with women having a prevalence as high as 41.3% and men 12.6%. In the nonlithium patients the prevalence was 7.1%; very close to that in the general population. No other determinant for the presence of thyroid disorder than female gender was identified. Seventeen of 26 lithium patients were diagnosed with hypothyroidism in the first three and a half year after the start of lithium.
The prevalence of thyroid antibodies was 27% in 45 lithium patients which was not different from the prevalence in the same age group in the general population.
We concluded that the prevalence of hypothyroidism during lithium treatment was very high in the elderly, especially in women. Autoimmunity did not seem to play a major part in lithium associated hypothyroidism in this age group. The timeframe between start of lithium and diagnosis of hypothyroidism suggests an individual susceptibility. The prevalence of hypothyroidism in nonlithium patients with affective disorders was not very different from the general population.

Lithium can influence calcium homeostasis resulting in changes in parathormone set point and renal calcium handling. The clinical significance of these changes in elderly patients is unknown. In chapter 3.4 we investigated the possible association between duration of lithium treatment and corrected calcium, parathormone and 24-h urinary calcium excretion in older psychiatric patients corrected for renal function and vitamin 25OH D. We also estimated the point prevalence of hypercalcemia and raised parathormone.
In a cross-sectional study of psychiatric outpatients visiting a specialized facility for elderly patients treated with lithium, patients underwent a comprehensive assessment and blood and urine testing. Potential confounders of calcium homeostasis were recorded. Based on duration of lithium treatment, patients were divided into four

groups; 111 patients were included, mean age 75.2 years. There was no significant association between the duration of lithium treatment and corrected calcium, parathormone and 24-h urinary calcium excretion. The point prevalence of hypercalcemia was 2.7% and 47.8% for raised parathormone. There was an unexpected but significant association between duration of lithium treatment and decrease in vitamin 25OH D, with 76.9% vitamin 25OH D deficiency (<50nmol/L) in the group using lithium for more than 10 years.
The conclusion was, that there was no association between duration of lithium treatment and calcium parameters in older psychiatric outpatients and that there was a high prevalence of raised parathormone, perhaps partly because of a high prevalence of vitamin 25OH D deficiency There was an unexpected association between duration of lithium treatment and decrease in vitamin 25OH D.

In chapter 4 the results of the individual studies and the clinical implications of these results are discussed. We state that a specialized lithium ambulatory clinic for the elderly could improve the quality of care for the older psychiatric patient and that this center can also be used to coordinate the cardiovascular screening for psychiatric patients, advised in the national guidelines. The discussion is ended with suggestions for future research and the conclusion that lithium treatment in the elderly can be safe, if the patient is monitored correctly.

Samenvatting



Lithium wordt al meer dan 60 jaar gebruikt in de psychiatrie en is nog steeds een van de voorkeursmiddelen bij de behandeling van een bipolaire stoornis. Daarnaast wordt het gebruikt als augmentatie naast antidepressiva bij de behandeling van een unipolaire depressie. Lithium is niet specifiek onderzocht in gerandomiseerde, placebo-gecontroleerde studies voor de behandeling van oudere patiënten. Geëxtrapoleerd vanuit studies met patiënten van alle leeftijden, wordt aangenomen dat lithium net zo effectief is bij oudere als bij jongere patiënten. Lithium heeft een smal therapeutisch venster, waarbij ineffectieve en toxische spiegels niet ver uit elkaar liggen. Leeftijdsafhankelijke veranderingen in de farmacokinetiek en farmacodynamiek van lithium zouden de gebruikspatronen van lithium in een ouder wordende populatie kunnen beïnvloeden, mede omdat er nieuwe medicijnen op de markt zijn gekomen. Tezamen met de leeftijdsafhankelijke veranderingen in de farmacologie van lithium, zouden toenemende multimorbiditeit en polyfarmacie adequaat doseren van lithium moeilijker kunnen maken.
Belangrijke bijwerkingen van lithium zijn afname van de nierfunctie; verminderde glomerulus filtratie snelheid (GFR) en afname van het maximaal concentrerend vermogen van de nieren (Umax), hypothyreoidie, hyperparathyreoidie en gewichtstoename. Bij het ouder worden nemen de homeostatische functies af en daarnaast is bij ouderen de prevalentie van cardiovasculaire en endocrinologische aandoeningen hoger dan bij de jongere bevolking. De laatst genoemde factoren zouden ouderen kwetsbaarder kunnen maken voor de mogelijke bijwerkingen van lithium.
Het doel van dit proefschrift is om bij oudere patiënten de gebruikspatronen van lithium te onderzoeken en de somatische bijwerkingen met hun mogelijke determinanten te bestuderen.

Farmaco-epidemiologische en klinisch farmacologische aspecten van lithium gebruik

In hoofdstuk 2 werden farmaco-epidemiologische en klinisch farmacologische aspecten van lithium gebruik bij ouderen bestudeerd. In hoofdstuk 2.1 vergeleken we de lithium gebruikspatronen bij poliklinische patiënten van middelbare en van oudere leeftijd in Nederland. Data voor deze studie werden verkregen uit de Dutch PHARMO Record Linkage System. Incidente lithium gebruikers van 40 jaar of ouder werden geïdentificeerd in de periode 1996-2008. Vier gebruikspatronen werden gedefinieerd: continueren, add-on, switch en stoppen. Verschillen in lithium gebruikspatronen werden onderzocht voor vier leeftijdsgroepen: 40-49 jaar, 50-59 jaar, 60-69 jaar en 70 jaar of ouder. De jongste leeftijdsgroep was de referentiegroep. Patiëntkarakteristieken bij de start met lithium en mogelijke determinanten van veranderingen

in lithium gebruikspatronen werden bestudeerd. We identificeerden 2081 incidente lithium gebruikers. De frequentie van stoppen en switchen verschilde niet tussen de leeftijdsgroepen. Oudere patiënten kregen minder vaak add-on van een ander psychofarmacon tijdens lithium therapie ($P < 0.05$). Reeds aanwezig gebruik van antidepressiva bij de start met lithium verschilde niet tussen de leeftijdsgroepen, maar oudere patiënten die startten met lithium gebruikten minder vaak antipsychotica ten opzichte van patiënten van middelbare leeftijd ($P < 0.05$). De conclusie was, dat oudere patiënten minder vaak add-on van psychofarmaca kregen tijdens behandeling met lithium. En ondanks farmacokinetische en farmacodynamische veranderingen bij ouderen, werd lithium niet vaker gestopt en was er niet vaker sprake van switch naar een ander psychofarmacon bij oudere dan bij middelbare patiënten.

In hoofdstuk 2.2 bespraken we een case report van een oudere patiënt met cluster hoofdpijn, die gedurende vele jaren werd behandeld met lithium en vervolgens een lithium intoxicatie ontwikkelde. Lithium wordt bijna uitsluitend voorgeschreven door psychiaters, maar incidenteel wordt het ook voorgeschreven door neurologen voor de preventie van cluster hoofdpijn. De klinische symptomen, de behandeling en de mogelijke irreversibele neurologische schade van een lithium intoxicatie werden besproken. We benadrukten dat elke arts die lithium voorschrijft ook op de hoogte moet zijn van het belang van goede monitoring en de symptomen van (dreigende) intoxicatie moet kunnen herkennen.

In hoofdstuk 2.3 bestudeerden we of leeftijd een determinant is van instabiliteit van de serum lithium concentratie (SLC). Er werd een retrospectieve studie (1995-2004) uitgevoerd, waarbij gebruik werd gemaakt van SLC metingen van drie ziekenhuis laboratoria in Nederland; 759 patiënten, die behandeld werden met lithium en die 40 jaar of ouder waren met ten minste twee jaar follow up, werden geïdentificeerd. Ze werden verdeeld in vier leeftijdsgroepen: 40-49 jaar, 50-59 jaar, 60-69 jaar en 70 jaar of ouder. De jongste groep was de referentie groep. Verschillende parameters, die beschouwd werden als een proxy voor instabiliteit, werden vergeleken tussen de leeftijdsgroepen. Deze parameters waren afkomstig van studies met orale anticoagulantia, die net als lithium een smal therapeutisch venster hebben en voor welke ook regelmatige monitoring noodzakelijk is. Deze parameters bestonden uit de variance growth rate en het percentage tijd onder, in en boven de therapeutische range. We vonden geen significant verschil voor deze variabelen tussen de referentie groep en de oudere leeftijdsgroepen. De parameters die beschouwd werden als een proxy voor instabiliteit tijdens de titratiefase, namelijk het aantal dagen dat de titratiefase duurde en het aantal metingen van de SLC tijdens deze fase, werden geëvalueerd in een subgroep van 454 patiënten. Er werden geen significante verschillen gevonden

tussen de verschillende leeftijdsgroepen en de referentiegroep. In een kleine groep van 117 patiënten konden de titratiefase en een onderhoudsfase van tenminste twee jaar apart worden geanalyseerd. Ook in deze groep werden geen verschillen gevonden tussen de leeftijdsgroepen en de referentiegroep. We concludeerden dat leeftijd geen determinant is van SLC instabiliteit. Daarom kan leeftijd op zich nooit een reden zijn om lithium therapie niet in te stellen en evenmin om een bestaande lithium behandeling te staken.

Somatische bijwerkingen van lithium gebruik bij oudere patiënten

In hoofdstuk 3 werden de studies over de somatische bijwerkingen van lithium gebruik bij ouderen besproken. Een cross-sectionele studie met 48 poliklinische patienten van 65 jaar en ouder (gemiddeld 74.8 jaar) en lithium gebruik van zes maanden of langer (gemiddeld 9,2 jaar) werd uitgevoerd om het effect te bepalen van lithium gebruik op de GFR en de Umax (hoofdstuk 3.1). We bestudeerden ook de potentiële risicofactoren en de klinische betekenis van een verminderde Umax in deze patiënten groep. Indien er sprake bleek van een polyurie probeerden we de mogelijke diagnose vast te stellen. De GFR werd berekend middels de Cockcroft-Gault formule (GFR-CG) en de Umax werd gemeten in een urine monster afgenomen 3-5 uur nadat de patiënt 40 µg desmopressine (DDAVP) intranasaal had toegediend gekregen.
Er werd geen relatie gevonden tussen de duur van het lithium gebruik en de GFR-CG, maar er werd een significante relatie gevonden tussen de duur van het lithium gebruik en de afname van de Umax (B -0.73; CI: -1.249/-0.212); 73% van de patiënten had een matige tot ernstige concentratie stoornis. Geen andere risicofactoren behoudens de duur van het lithium gebruik werden geïdentificeerd. Een verminderde Umax veroorzaakte polyurie (> 2500ml/24h) in 33% van de patiënten, maar veroorzaakte niet meer dorst, incontinentie of verstoorde slaap. Wanneer er sprake was van polyurie bleken, behalve nefrogene diabetes insipidus, ook andere mechanismen een oorzakelijke rol te spelen in deze leeftijdsgroep.

Vergeleken met de algemene populatie hebben patiënten met affectieve stoornissen een verhoogd risico op cardiovasculaire morbiditeit en mortaliteit. Het effect van lithium hierbij is slechts sporadisch onderzocht. In hoofdstuk 3.2 bepaalden we de prevalentie van bekende cardiovasculaire risicofactoren (CVR) en de prevalentie van cardiovasculaire aandoeningen (CVD) in oudere patiënten, die behandeld werden met lithium. We vergeleken de prevalentie van CVR en CVD bij deze patiënten met data van studies in de algemene populatie van dezelfde leeftijdsgroep en we bepaalden

de associatie met de duur van het lithium gebruik. Een cross-sectionele studie werd verricht bij psychiatrische patiënten die een gespecialiseerde lithium polikliniek voor ouderen bezochten. Patiënten werden uitgebreid onderzocht en potentiële confounders van CVR en CVD werden vastgelegd. Aan de hand van de duur van het lithiumgebruik werden de patiënten verdeeld in vier groepen. De prevalentie van diabetes bij vrouwen en de prevalentie van overgewicht en hypertensie in beide geslachten waren hoger in de studie groep van lithium gebruikers dan in een populatie studie in dezelfde leeftijdscategorie. Deze populatie studie dateerde echter van 15 jaar eerder. De prevalentie van diabetes was lager in de lithium groep vergeleken met een meer recente populatie studie. Er was een opvallend lagere prevalentie van hyperlipidemie in onze studie groep vergeleken met beide populatiestudies. De prevalentie van coronairlijden was lager en de prevalentie van cerebrovasculair accident was hoger in de lithium groep dan in de studies in de algemene populatie. Er was geen relatie met CVR en CVD en de duur van het lithium gebruik, behalve een toename van de BMI in de eerste jaren van de lithium behandeling. Vanwege het cross-sectionele karakter van de studie konden geen causale relaties worden bepaald.

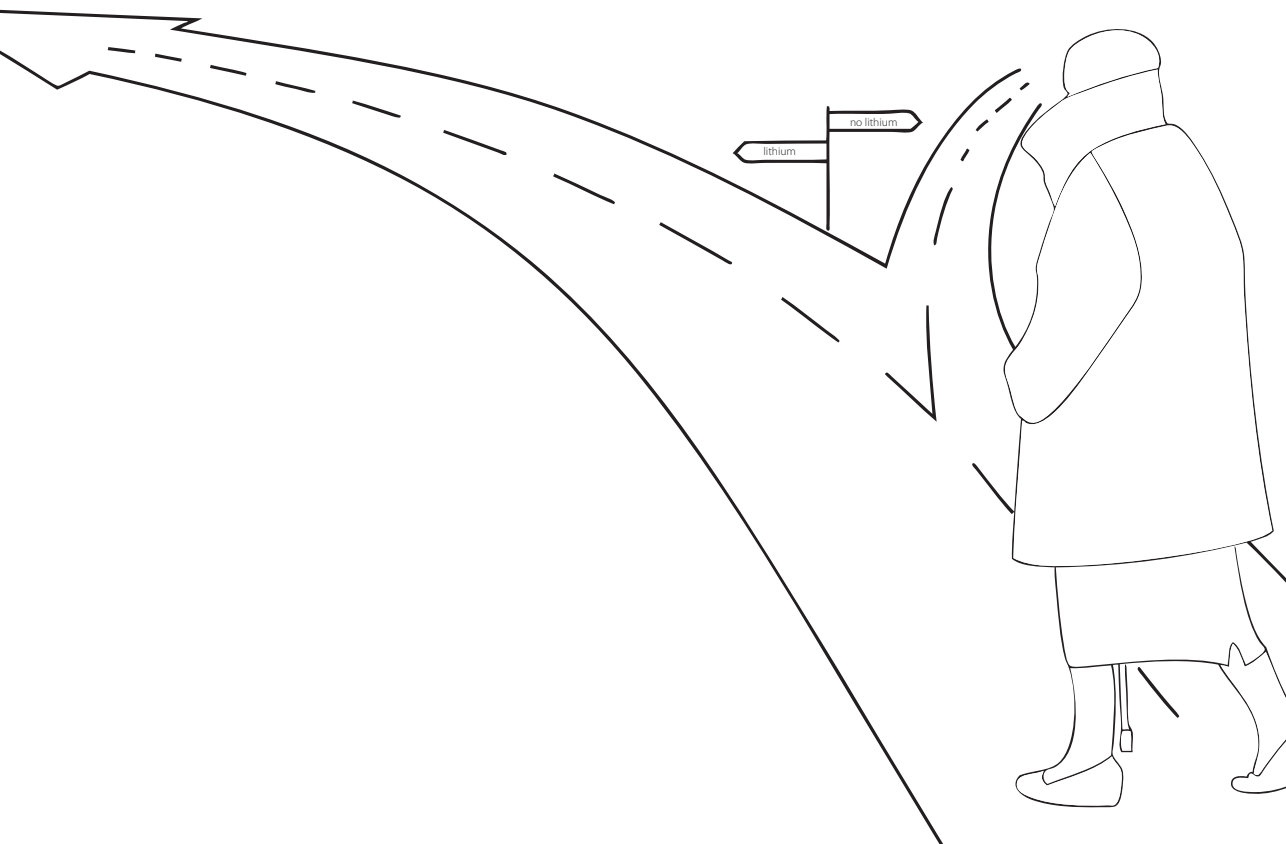
Om de prevalentie en determinanten van schildklier dysfunctie in oudere patiënten met affectieve stoornissen te bepalen werd een retrospectieve cross-sectionele studie uitgevoerd in patiënten van 65 jaar en ouder met affectieve stoornissen volgens de DSM IV (hoofdstuk 3.3). De patiënten werden verdeeld in lithium en niet-lithium patiënten. De aanwezigheid van een schildklieraandoening werd bepaald op de index datum (ID), dit was de datum van de eerste TSH die werd gemeten in 2005. De schildklieraandoening werd vastgesteld aan de hand van duidelijk gedefinieerde criteria. In geval van een eerdere diagnose, werd deze diagnose opnieuw getoetst aan de gedefinieerde criteria met de gegevens uit het medisch dossier. In een subgroep van 45 lithium gebruikers werden thyreoperoxidase en thyreoglobuline antilichamen (TPO- en TG-al) bepaald.
In totaal werden 79 lithium patiënten en 85 niet-lithium patiënten geïncludeerd. De prevalentie van hypothyreoïdie (subklinisch en klinisch) was 35.4% in de lithium patiënten, vrouwen hadden een prevalentie van 41.3% en mannen 12.6%. In de groep van niet-lithium patiënten was de prevalentie 7.3%, wat vrijwel overeen komt met dat in de algemene bevolking. Het vrouwelijk geslacht was de enige determinant van schildklier aandoeningen, die in de studie werd geïdentificeerd. Van 26 lithium patiënten met hypothyreoïdie, werden 17 gediagnostiseerd in de eerste 3.5 jaar na de start met lithium.
De prevalentie van schildklier antilichamen was 27% in 45 lithium patiënten, wat niet verschilde van de prevalentie in eenzelfde leeftijdsgroep in de algemene populatie.
We concludeerden dat de prevalentie van hypothyreoïdie erg hoog is tijdens lithium behandeling bij ouderen met name bij vrouwen. Autoimmuun mechanismen leken

geen belangrijke rol te spelen in lithium geassocieerde hypothyreoïdie in deze leeftijdscategorie. De korte tijdsduur tussen de start met lithium en het ontwikkelen van een hypothyreoïdie suggereert een individuele gevoeligheid. De prevalentie van hypothyreoïdie in niet-lithium patiënten met affectieve stoornissen verschilde niet echt van die in de algemene bevolking.

Lithium kan de calcium homeostasis beïnvloeden met als gevolg verandering in parathormoon set-point en in de calciumuitscheiding in de nieren. De klinische significantie van deze veranderingen bij ouderen is onbekend. In hoofdstuk 3.4 bestudeerden we de mogelijke associatie tussen de duur van het lithium gebruik en voor albumine gecorrigeerd calcium, parathormoon en 24 uurs calcium uitscheiding in de urine bij oudere psychiatrische patiënten, waarbij gecorrigeerd werd voor nierfunktie en vitamine 25OH D. We bepaalden tevens de punt prevalentie van hypercalciëmie en verhoogd parathormoon.
In een cross-sectionele studie werden psychiatrische patiënten die een gespecialiseerde lithium polikliniek voor ouderen bezochten uitgebreid onderzocht. Potentiële confounders van de calcium homeostasis werden geregistreerd. Gebaseerd op de duur van het lithium gebruik, werden de patiënten verdeeld in vier groepen; 111 patiënten werden geïncludeerd, de gemiddelde leeftijd was 75.2 jaar. Er was geen significante associatie tussen de duur van het lithium gebruik en het gecorrigeerde calcium, het parathormoon en de 24 uurs calcium uitscheiding in de urine. De punt prevalentie van hypercalciëmie was 2.7% en van verhoogd parathormoon 47.8%. Er was een onverwachte, maar significante associatie tussen de duur van het lithium gebruik en een verlaging van het vitamine 25OH D met 76.9% vitamine 25OH D deficiëntie (< 50nmol/L) in de groep die langer dan 10 jaar lithium gebruikte.
Er werd geconcludeerd, dat er geen associatie was tussen de duur van het lithium gebruik en calcium parameters in oudere poliklinische psychiatrische patiënten, maar dat er een hoge prevalentie was van verhoogd parathormoon, mogelijk deels door de hoge prevalentie van vitamine 25OH D deficiëntie. Er was een onverwachte associatie tussen de duur van het lithium gebruik en een daling van het vitamine 25OH D.

In hoofdstuk 4 worden de resultaten van de individuele studies en de klinische implicaties van deze resultaten besproken. We stellen dat een gespecialiseerde lithium polikliniek voor ouderen de kwaliteit van zorg voor de oudere psychiatrische patiënt kan verbeteren en dat dit centrum ook gebruikt kan worden voor de cardiovasculaire screening voor psychiatrische patiënten, die in richtlijnen wordt geadviseerd. De discussie is afgesloten met suggesties voor toekomstig onderzoek en de conclusie dat lithium behandeling bij ouderen veilig is, mits de patiënt correct wordt gemonitord.

Dankwoord



Bij het schrijven van dit dankwoord moet ik terug naar waar het begon en dat is ruim 10 jaar geleden. Tijdens het voorbereiden van de lessen voor de arts-assistenten psychiatrie in Parnassia Psycho-medisch Centrum, raakte ik geboeid door de werking en bijwerkingen van psychofarmaca. Bij de bijeenkomsten van het Endegeest Convent, een werkgroep van internisten werkzaam in de psychiatrie, stonden deze onderwerpen regelmatig op de agenda en ging het met name vaak over de bijwerkingen van lithium. Dit leverde boeiende en interessante discussies op en het werd duidelijk dat er nog vele onbeantwoorde vragen waren over lithium, zeker op het gebied van de ouderen. Alle toenmalige leden van het Endegeest Convent wil ik hartelijk danken voor deze stimulerende bijeenkomsten. Zij vormden de basis voor het starten van deze thesis. Met steun van mijn toenmalige collega dr.R.Sival werd met Parnassia afgesproken dat ik een halve dag per week onderzoek mocht gaan doen. Rob bedankt dat je daaraan hebt meegewerkt. Dr.J.Oomen, een van de internisten van het Endegeest Convent, was enthousiast over mijn plannen. Janus, jij wees mij er op dat je voor een promotietraject ook een promotor nodig hebt en jij wist wel iemand die interesse had in onderzoek naar lithium. Zo kwam ik terecht bij Prof.dr.T.C.G.Egberts. Na een korte mailwisseling over mijn wens onderzoek te doen naar lithium en de nieren, werd ik uitgenodigd naar Utrecht te komen voor een gesprek.

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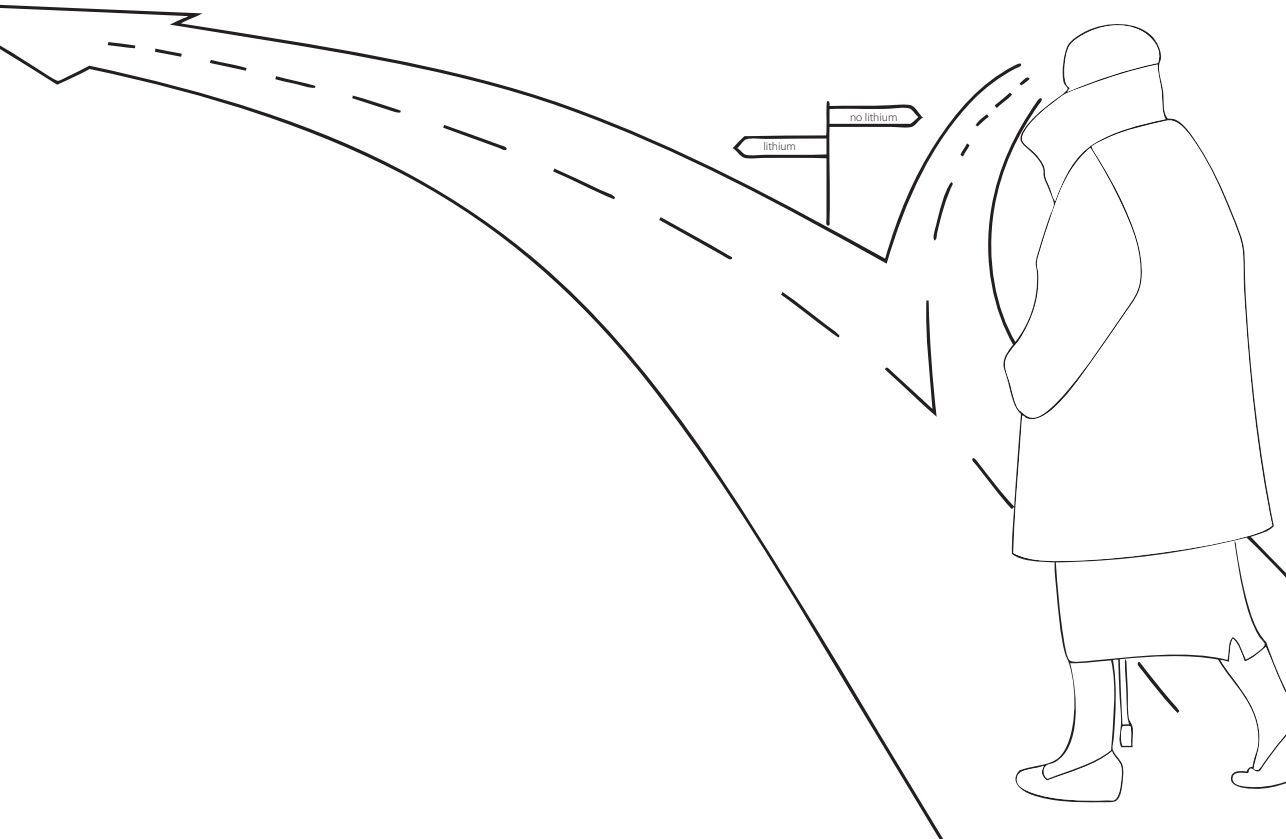
List of co-authors



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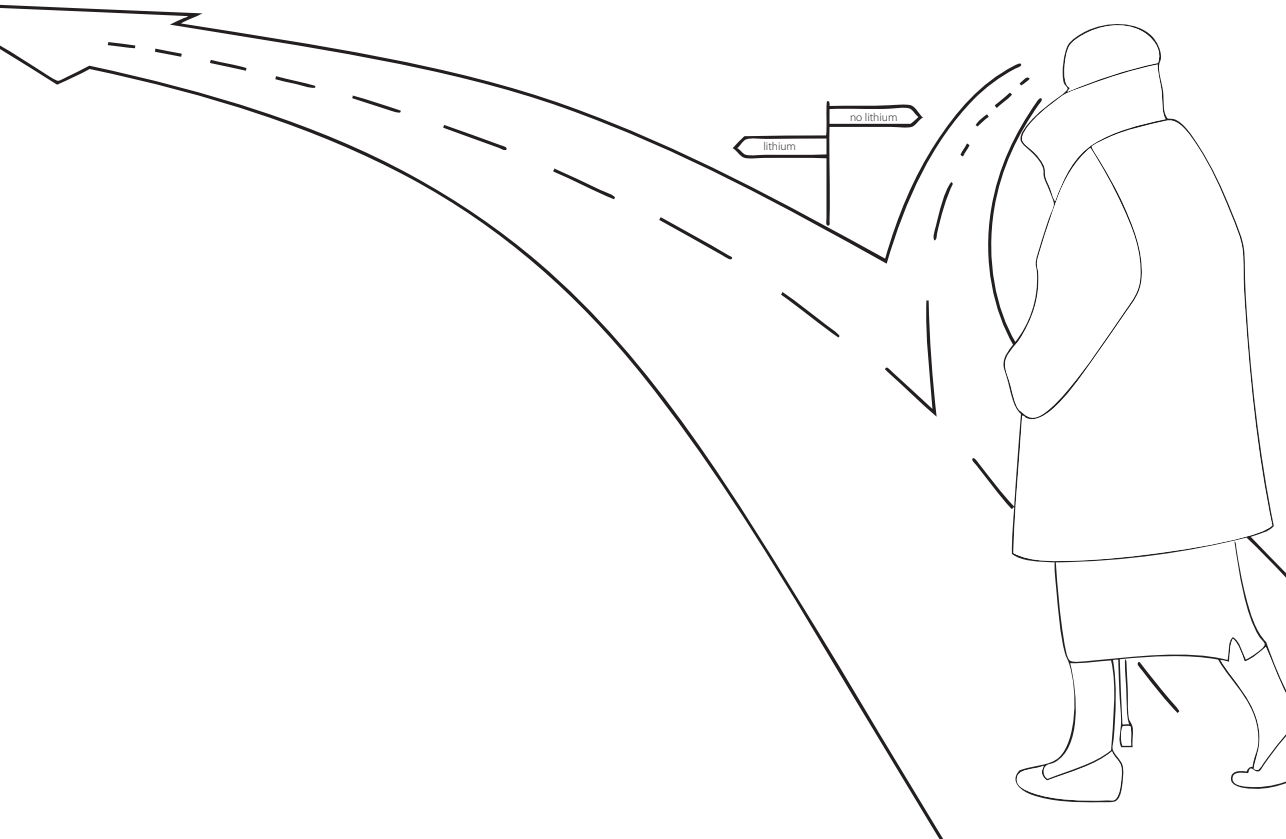
List of publications



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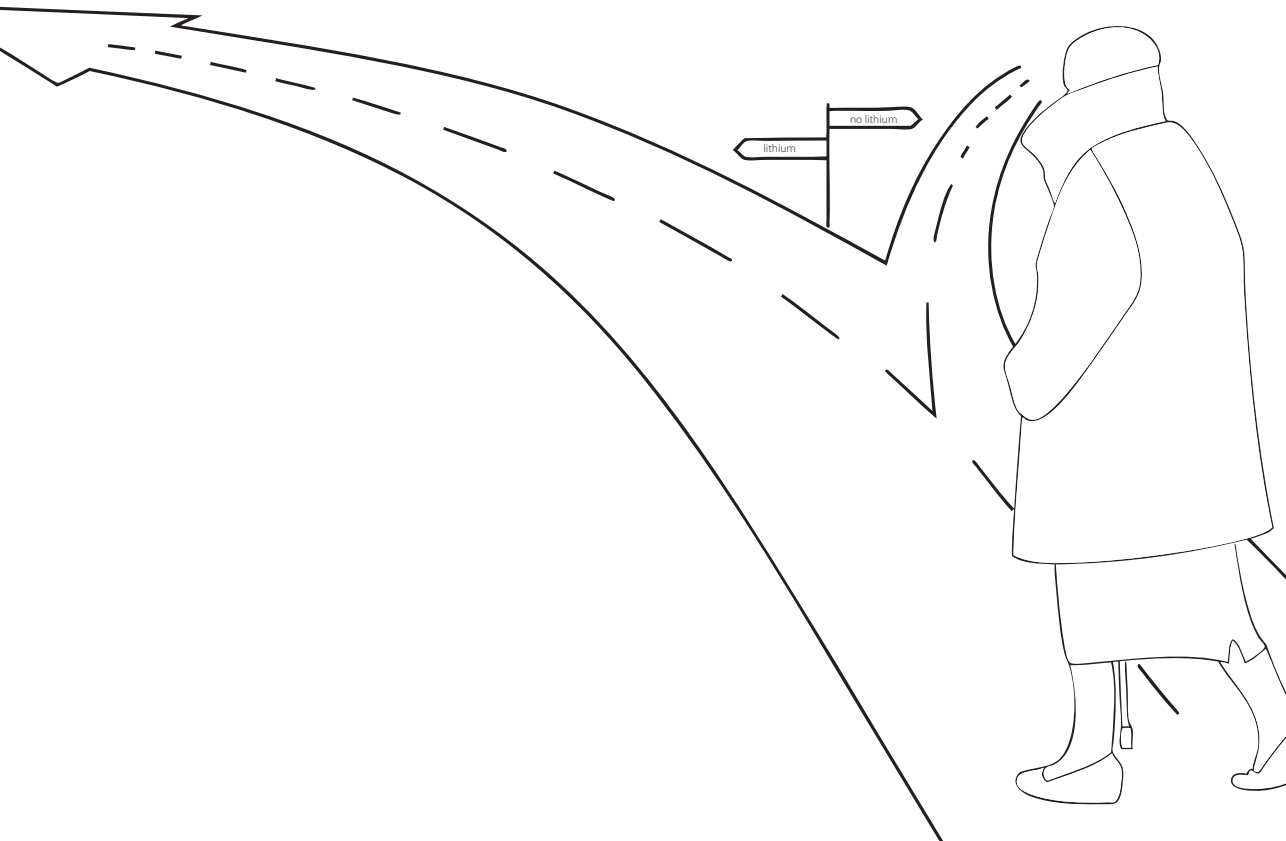

Els Jacoba Maria van Melick was born on the 3th of October 1956 in Roermond. After gymnasium β she studied Medicine in Utrecht from 1975 to 1982. From 1982 to 1987 she specialized in internal medicine in Leyenburg hospital in The Hague. Because her first son had been born in 1986 and at that time the part time jobs in internal medicine were almost non-existing, she started working part time as internist on the geriatric ward from the psychiatric hospital Rosenburg in The Hague. In 1996 she was registered as clinical geriatrician and became deputy trainer in geriatric medicine. After the merger between the psychiatric hospitals Rosenburg and Bloemendaal and the RIAGG's, she worked in the geriatric department of Parnassia until 2009. From august 2009 until October 2013 she worked in the geriatric department of the Havenziekenhuis in Rotterdam and since October 2013 she works is the geriatric department of the Reinier de Graaf Gasthuis in Delft. She has always had a great interest in pharmacology and this has resulted in this thesis.
Els van Melick is married to Martin Janssen and has three children, Dirk (1986), Nico (1989) and Mai (1992).