Patterns and clinical outcomes of lithium treatment

Ingeborg Wilting

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PATTERNS AND CLINICAL OUTCOMES OF LITHIUM TREATMENT

GEBRUIKSPATRONEN EN KLINISCHE UITKOMSTEN VAN LITHIUM GEBRUIK
(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. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 9 april 2008 des middags te 4.15 uur

door

INGEBORG WILTING

geboren op 2 oktober 1975 te Utrecht

PROMOTOREN:
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voor
mijn
ouders
en
Jeroen

COVER

The *statue* represents two faces and is made out of serpentine stone; a stone that has been ascribed to possess curing properties among which diminishing mood swings (August 2007, African Art Promotion, Zimbabwe).

The *leaves* are full of symbolic associations:

- in the autumn, leaves are falling from the trees which can cause melancholic moods and might even predispose to winter depressions (in Dutch, we know the saying of 'falling leaves');
- then there is the saying of 'turning like a leave on a tree' symbolizing bipolar depression (manic-depressive mood state);
- lastly, stormy weather with turbulent movements of leaves symbolizing the manic (stormy) mood state encompassing a tremendous amount of energy, turbulence and chaos.

CONTENTS

Scope, objectives and outline of the thesis

1

INTRODUCTION

Lithium is the best proven pharmacotherapeutic management option for the treatment of bipolar disorders, today.[1-3] Lithium is a remarkable psychotropic agent in many aspects. First, it is the smallest therapeutic agent available in today's pharmacotherapeutic armamentarium. Second, its entrance into psychiatric pharmacotherapy is a classical example of serendipity.[4]

The age in which lithium entered psychopharmacotherapy has resulted in an enormous gap between lithium's life cycle and today's drug approval requirements. The latter consists of an extensive pathway of pre-clinical and clinical testing followed by formal approval for registration and subsequent continued benefit-risk evaluation based upon use in clinical practice.

BIPOLAR DISORDERS

The plural term bipolar disorders refers to a spectrum of disorders: bipolar I disorder (defined by manic episodes and severe depression), bipolar II disorder (defined by hypomanic episodes and severe depression), as well as more milder forms such as cyclothymia (a chronic pattern of hypomanic episodes and only mild depressions), and bipolar disorders 'not otherwise specified'.[5,6] In this thesis both the more general term bipolar disorders and the more precise term bipolar disorder are used but should be considered interchangeable.

Mania is a state characterized by elevated mood or euphoria, increased speed of thinking, increased speech, over activity and a lack of need for sleep and an extreme optimism by definition resulting in psychosocial dysfunctioning. Hypomania is characterized by the same symptoms, but without psychosocial dysfunctioning.[7] The productivity of many famous artists like the Dutch painter Vincent van Gogh, the Spanish painter Salvador Dali, the German composer Robert Schumann, the American writer Virginia Woolf and the American poet Edgar Allan Poe has been attributed to the extreme creativity during their manic episodes. During periods of depression patients usually experience low self-esteem, extreme sadness, disrupted social functioning and diminished enjoyment of life with an increased risk to commit an attempt for suicide. Patients with bipolar disorders usually spend a relatively longer period in the depressive than in the manic phase.[8] Bipolar disorders, in addition, carry the risk of increased

morbidity (including somatic diseases like diabetes and cardiovascular morbidity) and increased mortality (e.g. due to suicide),[9,10] rendering it one of the worlds ten most disabling conditions.[11] The life-time prevalence of bipolar disorders is about 2%.[10,12-14]

Some 2300 years ago it was the Greek Hippocrates who was the first to conceptualise the concepts of mania and melancholia. In modern times (1921) the German Emil Kraeplin recognized the quantitative and qualitative variability in symptoms amongst those suffering from bipolar disorder, which he called 'Manisch-Depressive Irresein'. His concept, however, included also recurrent depression without (hypo)manic episodes. Next, the Swede Carlo Perris and the Swiss Jules Angst introduced the term bipolar disorder referring to the specific facet of the illness of alternating (hypo)manic, euthymic and depressive episodes.

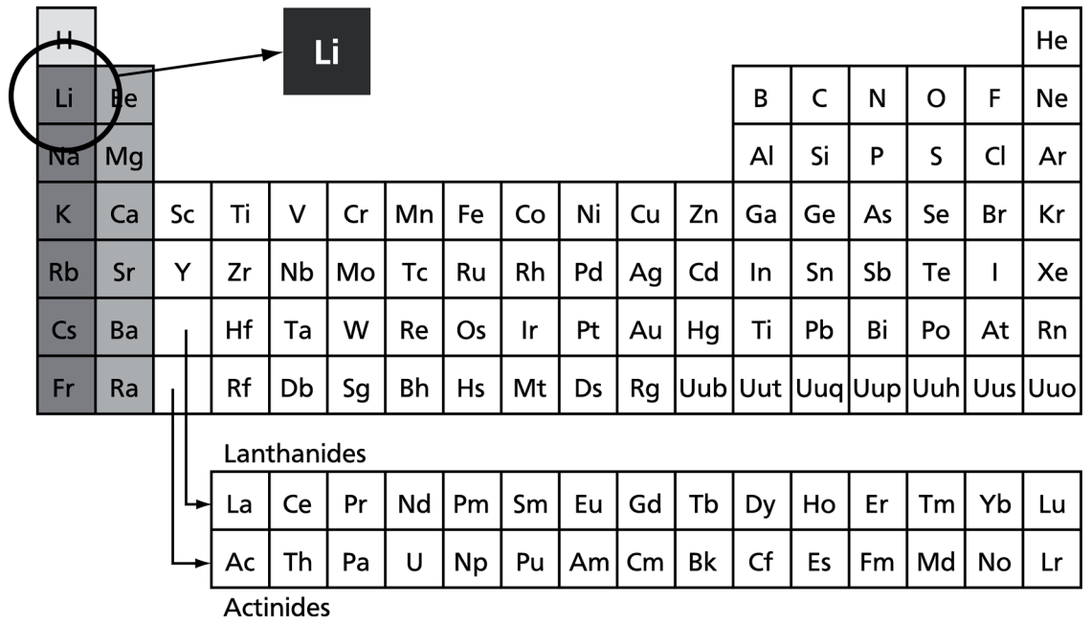
The exact pathophysiology of bipolar disorders has still not been elucidated. Hyperexcitability of neurons resulting in a disbalance of certain neurotransmitters is considered important.[15] Multiple studies have investigated the presence of abnormalities in the metabolism of among others the neurotransmitters noradrenaline, serotonine and dopamine. Anatomic studies have suggested structural abnormalities in brains of bipolar patients, like reduced regional brain volumes particularly in the ventral frontal cortex.[16] The knowledge that about 50 percent of the patients suffering from bipolar disorders have a positive family history of the disorder, resulted in a search for genetic factors predisposing to the disorder.[17] No strong associations linking genetic make-up to susceptibility for bipolar disorders have, however, been found.[18] There is not much evidence that specific personality traits are distinctive of patients with bipolar disorders. Stressful life events, like death of a loved one or a first love relationship, however, are often associated with the emergence of a first acute episode of bipolar disorders.

Up to present, no specific biomarkers have been discovered to diagnose bipolar disorders nor to evaluate effects of treatment. Therefore, in addition to the criteria as stated in the current edition of the diagnostic and statistical manual of mental disorders (DSM IV)[6] several rating scales like for example the Young Mania Rating Scale (YMRS) and instruments to assess follow-up like the Life-Chart Method are used in diagnosing and follow-up of patients with bipolar disorders.

THE HISTORY OF LITHIUM IN PSYCHIATRIC PHARMACOTHERAPY

Lithium is used in the treatment of bipolar disorders since about 1950,[19] and is one of oldest treatments that is still used today. It was in 500-600 A.D. that Soranus of Ephesus, although unknowingly, already recommended the use of lithium by promoting the use of alkaline waters to treat manic excitement. Later it was demonstrated that alkaline waters carry a high content of lithium.[20] In 1817 the element lithium was first discovered by the Swedish chemist Johan August Arfwedson,[19] after which lithium was included in the periodic table (Figure 1).

Figure 1: The periodic table



Lithium as a name originates from the Greek term 'lithos' meaning stone. This name was deemed suitable since lithium is not freely available in nature but can only be retrieved from ingeneous rocks and mineral springs. Today, lithium is mostly recovered from brine pools, being isolated from minerals like spodumene, lepidolite, petalite and amblygonite.

The actual story of the pharmacotherapeutic use of lithium began in 1859 when Garrod introduced its use in the treatment of gout and rheumatism.[20] The dissolving properties of lithium urate led to this introduction. Beginning 1890,

this same lithium urate resulted also in its first 'dissolution' into psychiatric pharmacotherapy. The Danish brothers Fredrik and Carl Lange focussed upon urate as an endogenous neurotransmitter periodically causing reduction and overstimulation of neurotransmission resulting in recurrent manic and depressive episodes. The Lange brothers hypothesized that use of lithium would be potentially useful as a therapeutic agent in the treatment of bipolar disorders, due to its urate dissolving effects.[21] The psychiatrist Fredrik Lange actually recommended use of lithium in his book on the most important psychiatric disorders,[22] which is thought to be the first written advocacy of lithium in psychiatric pharmacotherapy. After the death of Frederik Lange, in 1907, use of lithium faded.

The story of lithium repeated itself since the first re-emerging of lithium was when it was added to a drink created by the American Charles Leiper Grigg. Grigg came up with the formula for a lemon lime soda in 1929. The product's name, originally named 'Bib-Label Lithiated Lemon-Lime Soda', was soon changed to the better known name Seven-Up. Seven-Up originally contained lithium citrate. It was one of many medicine-like products popular in the late-19th and early-20th centuries; making claims similar to today's health foods.

Finally, the true establishment of lithium in psychiatry started with the serendipitous rediscovery of its sedative properties in mice, by the Australian John Cade.[3] His hypothesis was that mental illnesses are caused by an intoxication with an unknown compound and that this unknown compound would be found in patient urine. Investigation of the urine of manic patients led him to believe that this unknown compound was urate, leading him to inject soluble lithium urate in mice with the purpose of establishing urate toxicity. The observation, that mice became lethargic when being injected lithium urate, was followed by experimenting with lithium in ten manic patients, overall resulting in patient improvement of manic excitement. The promising results of this case series were published in 1949.[3] In the same year the use of lithium was expanded on a completely different level, namely as a substitute for sodium in salt for patients with hypertension, resulting in deaths and subsequently banning by the Food and Drug Administration (FDA). In 1954 the lithium story continued with the publication of the first randomised controlled clinical trial in bipolar patients, by the Danish chemist Mogens Schou, showing that lithium was superior to placebo in the treatment of mania.[23] This trial resulted in the evidence based introduction

of lithium in psychiatry. Finally, after further publications establishing lithium's efficacy in manic-depressive illness,[24,25] lithium was approved for the use in bipolar disorders by the FDA in 1970, followed by among other countries the Netherlands in 1971.

During the last decades the pharmacotherapeutic armamentarium for bipolar disorders has significantly widened. In addition to lithium (and the typical antipsychotics since the 1950s and 1960s) various other medications became available for the treatment of mania, starting with the anticonvulsants carbamazepine in the 1980s,[26,27] valproic acid in the 1990s.[28] During the last decade several atypical antipsychotics, olanzapine,[29] risperidone and quetiapine, have become available, while there is also an increasing place for second generation antidepressants,[30] and the anticonvulsant lamotrigine[31] in the treatment of bipolar depression. Lithium, however, up to present has remained the 'gold standard' in bipolar disorders.

DRUG LIFE CYCLE: FROM HISTORY TO TODAY

The story of lithium reaching daily clinical practice, as described above (Figure 2), is clearly very different from many other drugs in today's medicine.[4,32] Regardless of the developmental process, a drug usually enters daily clinical practice after having been evaluated in a relatively small selected number of patients for a relatively short time-period and under close monitoring of use patterns (as was done for lithium by Cade and next by Schou). Next a drug is studied under controlled conditions in large randomised controlled trials to assess the drug's efficacy and safety profile, finally resulting in it's approval by regulatory agencies such as FDA and EMEA (European Medicines Agency). The process of benefit-risk evaluation continues after approval using pharmacoepidemiologal methods to study the use and effects of drugs within large unselected populations in daily clinical practice. Patients in daily clinical practice often largely differ from patients in clinical studies both with respect to their health status as well as with respect to their drug utilisation patterns.[33-36]

Figure 2: History of lithium: from element to first-line treatment of bipolar disorder

500 - 600 A.D.	Siranus	Unknown advocacy of lithium
1817	Arfwedson	Discovery of the element lithium
1859	Garrod	First therapeutic use of lithium: gout and rheumatism
1894	Lange	First mentioning of lithium use in Bipolar Disorder
1929	Geriger Lipp	Lithium put in Seven-Up
1949	Cade	Serendipitous rediscovery of lithium
	FDA	Banning of lithium due to fatalities
1954	Schou	First trial proving lithium efficacy
1970	FDA	US approval of lithium use
1971	CBG	Dutch approval of lithium use

A.D. = Anno Domini; FDA = Food and Drug Administration; CBG = College ter Beoordeling van Geneesmiddelen

Assessment of drugs in daily clinical practice after the drug has been launched onto the market is an essential step required to further improve the general

practice of pharmacotherapeutic treatment as well as to improve the knowledge in the area of pharmacovigilance and drug safety as well as in the field of effectiveness to support innovation in the decision-making process for when and how to institute specific drugs.[37,38] Studying of drugs in daily clinical practice both requires adequate identification of unsuspected drug effects[39,40] as well as the development and testing of hypothesis in large population databases[41] filled with drug dispensing information and within small patient groups originating from daily clinical practice who are using the drug.[42-45] Investigating drug utilisation and effects of both drugs and disease post-approval in large groups of patients in daily clinical practice became more feasible with the development of several databases, like PHARMO[46] and GPRD (General Practice Research Database), encapturing prescription and disease information from general and hospital practice.[47] These databases can, however, clearly not be used to investigate pharmacological mechanistic aspects of drug outcome effects. For this purpose it is necessary to further approach the individual patient and to actually measure parameters that could provide information regarding specific pharmacological mechanistical aspects.

USE OF LITHIUM: A DELICATE BALANCE BETWEEN SAFETY AND EFFICACY

Lithium pharmacology

Lithium fits in the periodic table (Figure 1) within the group of alkali metals together with sodium and potassium, with which lithium shares certain chemical characteristics resulting in comparable handling (e.g. kidney handling) by the body. Physiologically lithium more resembles calcium and magnesium[48] resulting in comparable effects on specific second messenger systems with these two ions, probably more explaining its therapeutic effects. Lithium interferes amongst others with the glycogen synthase kinase-3 (GSK3), Wnt,[49] cyclic guanosine monophosphate (cGMP), 3'-5'-cyclic adenosine monophosphate (cAMP), inositol triphosphate (ITP3) systems, serotonin, noradrenaline, gamma-aminobutyric acid (GABA) and glutamic acid release.[20] Lithium, however, up to present has remained one of the mysteries of pharmacotherapy. The reason why

such a small metal ion exerts such profound psychopharmacological effects remains a hitherto unresolved mystery.[50]

Narrow therapeutic range: endogenous and exogenous factors and treatment of patients with lithium intoxication

The balance between efficacy and safety in case of lithium is very delicate, requiring sufficient knowledge and effort of both patient[51] and physician[52] to increase the likelihood of beneficial and safe use. Besides its apparent positive effects in the treatment of bipolar disorders, there are certain limitations to the safe use of lithium. A relationship between lithium serum levels and both its efficacy and its toxicity has been established.[53] Due to high affinity of lithium for many organ and cellular mechanisms, subtherapeutic, toxic and therapeutic serum levels lie very close together. It is very important to be aware of the very narrow therapeutic range of lithium with (0.4-)0.6 to 0.8 mmol/l in prophylaxis and 0.8-1.2 mmol/l in acute manic episodes,[54,55] meaning that relatively small changes in lithium serum level can either result in therapeutic inefficacy or toxicity. This fact, together with the large inter- and intraindividual variability in pharmacokinetics and sensitivity to its effects, render regular monitoring of lithium serum levels imperative.[54,55] Conditions affecting lithium serum level include both patient related effects and environmental factors, disease factors and healthcare worker factors. Knowledge of these influencing factors by both patient and physician can, providing sufficient effort, result in prevention of subtherapeutic and toxic serum levels. Patient related factors comprise of both kidney disturbances (being associated with ageing e.g.), disease induced behavioural changes and conditions predisposing to disturbances in water and electrolyte balance (induced by excessive fluid and electrolyte loss during periods of excessive physical activity, fever or induced by diarrhoea or vomiting or induced by inadequate fluid intake, especially endangering those patients suffering from nephrogentic diabetes insipidus [NDI]). Environmental factors include factors associated with changes in body salt and water homeostasis induced by hot weather, sauna or massive sporting activity. Disease factors influencing lithium's serum level represent direct alterations of lithium pharmacokinetics during periods of mania, as well as influences on patient behaviour regarding suicide risk and compliance. Healthcare worker factors include for example starting and stopping of concomitantly used drugs,

interacting with lithium excretion, as well as providing adequate information and optimalisation of integrating multidisciplinary knowledge. Lithium intoxication carries the risk of mortality and long-term morbidity e.g. the development of irreversible neurological damage mostly of cerebellar origin (ataxia, dysarthria e.g.).[56] This can –at least greatly– be prevented by adequate recognition and timely treatment which requires adequate knowledge on what treatment to institute. Easy access to complete and employable information to treat a patient with a lithium intoxication is in this matter imperative to increase the change of full recovery.

In this thesis we investigate the influence of potentially interacting co-medication and environmental temperature on lithium serum level and we investigate the completeness and employability of information on the management of a patient with a lithium intoxication as presented in available practice guidelines.

Long-term lithium use: adverse drug reactions (ADRs), disease influence and usage patterns during follow-up

Despite the fact that the story of lithium began in the late 19th century its establishment in psychiatry and its widespread use date from the 1970s. Since then multiple drugs have been licensed for the treatment of bipolar disorders especially over the last decade and the knowledge on safe use of lithium and prevention and treatment of its adverse reactions has increased. The emerging of alternatives to lithium treatment resulted in some countries in a decrease in the use of lithium whereas in other countries use of lithium did not appear much affected, or did even increase, probably partly resulting from an increased use of lithium in combination with other drugs as well.[57-60]

Despite paying adequate attention to safe use of lithium, adverse effects are frequently encountered, especially, during long-term treatment. Occurrence of at least one adverse effect during long-term treatment has been reported to vary between 75-90%.[61] The most prevalent adverse effects of lithium at initiation of treatment are GI-disturbances like diarrhoea and nausea. During long-term treatment most prevalent adverse effects are polydipsia with mean rates in different studies varying between 38-70%, polyuria (15-40%), resulting in NDI in about 12%,[62] thyroid disorders (5-35%), hyperparathyroidism (5-25%), weight gain (11-65%), psoriasis and acne (7%), ECG alterations (mostly lowering of T-top), neutrophilic leukocytosis,[63] tremor (28-45%), and disturbances in cognition

and concentration (10-43%). Adverse reactions are an important reason for discontinuation of lithium[64] with tremor and concentration deficits being the most important adverse reactions resulting in patient initiated discontinuation[65] and kidney and thyroid adverse reactions being the most feared ADRs by physicians. The prevalence of lithium-induced adverse effects has primarily been investigated in naturalistic studies. Due to differences in study design and changes in dosing recommendations over the years, the reported ranges of mean prevalence rates vary widely. Many studies on adverse reactions to lithium treatment have mainly focused on establishing prevalence. Only few studies have focused on the association between serum level of lithium and adverse reactions[66,67] revealing an association between serum level and tremor and nausea. Taking into account the burden of ADRs (in addition to the burden of the disease itself), it is important to be aware of determinants of adverse drug effects. In addition to specific effects related to the drug (including intake frequency and plasma level), also illness related factors may play a role. Regarding adverse reactions to tricyclic agents, also severity of depression has been associated to the reported prevalence rates of adverse effects.[68] In studying ADRs timing of exposure is very important to be able to adequately interpret potential ADRs. For some ADRs an association with duration of use has been established like for polyuria, polydipsia and tremor.[69,70] Some adverse reactions have been shown irreversible like adverse reactions associated with cerebellar damage.[56] Whereas others, like gastro-intestinal disturbances are known to subside after a decrease in serum level or discontinuation of lithium treatment.

In this thesis we investigate the influence of emerging alternatives for the treatment of bipolar disorders on use of lithium in the Netherlands. In addition we investigate the existence of an association between patient reported presence and severity of ADRs and mood state. Next, the reported association between lithium use and the risk of fractures is further explored taking into account timing of lithium use.

Lithium and the kidney: drug-drug interactions and molecular aspects

In about half of the patients using lithium polyuria develops, eventually resulting in about 12% of the patients in a true NDI.[62,71] Polyuria can be very disabling but is usually not a very dangerous ADR. However, it might become potentially life-threatening in case of inadequate compensatory fluid intake, like in elderly or in

case of some somatic illnesses resulting in an increased risk of dehydration and lithium intoxication.[72] Much research is still needed into the exact nature of this ADR and into defining risk factors for developing this ADR.

Many patients who use lithium are subjected to polypharmacy, they usually also use other medication; psychotropic drugs as well as somatic medication. In a previous study from our group it was found that the concomitant use of serotonergic antidepressants increased the risk for lithium induced polyuria.[39] As this was not the a priory aim of that study, there remained the risk that the finding was a chance finding resulting in a type II error (a false positive finding).

Some of the adverse reactions to lithium treatment, like reduced kidney urine concentrating capacity, are related to its body handling related to its physical properties. Lithium is handled by the body analogous to calcium, magnesium, sodium and potassium like for instance the role of the second messengers cAMP in causing nephrogenic diabetes insipidus. With respect to the mechanism of lithium induced polyuria multiple mechanisms have been proposed, like interference with cAMP formation or aquaporin-2 (AQP-2) synthesis or release, or other mechanisms interfering with the kidney urine concentrating cascade.[73-78] None, however, has definitely been proven to underlie the lithium induced urine concentrating deficit. Knowledge of the mechanism whereby lithium influences the kidney urine concentrating capacity might eventually result in new insight with respect to especially susceptible patients or improved treatment modalities.

In this thesis we re-evaluate the previously reported secondary finding of the increased risk of polyuria in patients using serotonergic antidepressants next to lithium. Lastly, we undertake a study with the purpose of further unravelling the molecular mechanism of NDI, a well-known lithium nephrogenic ADR.

OBJECTIVES OF THIS THESIS

The main objectives of this thesis were A) to investigate treatment patterns and the adverse reaction profile of lithium during follow-up, B) to investigate the endogenous and exogenous influences on lithium serum level and its toxicity, and C) to investigate molecular mechanistic aspects of lithium associated polyuria and nephrogenic diabetes insipidus.

OUTLINE OF THIS THESIS

This thesis comprises of three distinct parts: focusing on aspects of the use of lithium, on some clinical consequences of its narrow therapeutic window and lastly on its influence on kidney urine concentrating deficits.

The first part of this thesis entitled '*Patterns and consequences of lithium use*' focuses on the use of lithium. In *chapter 2.1* we focus on the follow-up of patients who had started using lithium within the last decade when more psychotropic drugs became available for the treatment of bipolar disorders. In *chapter 2.2* we concentrate on the association between mood ratings as well as lithium serum levels and ADRs as reported by patients attending an outpatient lithium clinic during the period of 1973 to 2000 in the Netherlands. In *chapter 2.3* we investigate the importance of timing of lithium use during follow-up with respect to the interpretation of a certain unwanted outcome in this case the risk of fractures.

The second part of this thesis entitled '*Determinants and treatment of potential lithium intoxications*', focuses on the consequences of the narrow therapeutic range of lithium. In *chapter 3.1* with a focus on drug-drug interactions as a determinant of the risk of elevated serum levels. In *chapter 3.2* we explore the association between environmental temperature and lithium serum level. And lastly in *chapter 3.3* we focus on what to do when encountering a patient with a lithium intoxication by focusing on the completeness and employability of treatment guidelines for the management of a patient with a lithium intoxication.

The third part of this thesis entitled '*Nephrogenic complications of lithium*' concerns lithium ADRs. In *chapter 4.1* a study into the influence of concurrently used psychotropic medication focusing on serotonergic antidepressants on the risk of lithium induced polyuria is presented. In *chapter 4.2* a further step into the molecular mechanistic aspects of lithium induced NDI is undertaken by looking into the urine concentrating capacity of patients using lithium with and without polyuria.

Finally in *chapter 5* the results of our studies are placed in a broader perspective in relation to both daily clinical practice and clinical research practice also providing future lessons to learn and challenges to come for this fascinating element.

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Patterns and consequences of lithium use

2

2.1

Changes in outpatient lithium treatment in the Netherlands during 1996-2005

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J Affect Disord (in press)

ABSTRACT

Background

During the past decade several atypical antipsychotics, additional second generation antidepressants, and antiepileptic mood stabilizers such as lamotrigine became available, that have changed treatment options of patients with bipolar disorders.

Objectives

The objectives of the present study were to investigate in outpatients in the Netherlands between 1996 and 2005, changes in 1) the incidence and prevalence of lithium use and 2) lithium use patterns (discontinuation, add-on, and switch).

Methods

Incidence and prevalence of lithium use were determined for each year between 1996 and 2005. In addition, we determined cumulative changes in lithium use (discontinuation, add-on, and switching) at three, six, 12 and 24 months for three separate time-cohorts (1998-1999, 2000-2001 and 2002-2003). Lastly, concomitant use of other drugs used in the treatment of bipolar disorders next to lithium during the 24 months after the first lithium prescription was determined for the three time-cohorts.

Results

Incidence of lithium use was found to be constant at approximately 0.2 per 1000 person-years, prevalence showed a 26% increase from 0.95 to 1.2 per 1000 persons between 1996-2005. The percentage of patients receiving an add-on drug used in the treatment of bipolar disorders was found to be constant over the three time-cohorts, with a significant decrease in use of tricyclic antidepressants. Within the patient group that stopped using lithium, more patients were found to switch from lithium to another agent used in the treatment of bipolar disorders over calendar time, and fewer patients were found to discontinue lithium. There was a significant increase in the use of atypical antipsychotics and valproic acid next to lithium.

Conclusion

The changes we observed in use of concomitant drugs next to lithium were in line with the increase in availability of alternatives during the last decade and in line with Dutch guidelines for the treatment of bipolar disorders.

INTRODUCTION

From 1960 onwards, lithium salts have been used in the long-term maintenance treatment of bipolar disorders, as an alternative or add-on to antipsychotics in the treatment of mania, and as add-on to antidepressants in the treatment of unipolar depression. The range of pharmacotherapeutic options for the treatment of bipolar disorders has widened significantly, especially during the recent 10-20 years. Between the 1960s and 1990s (typical) antipsychotics, antidepressants, carbamazepine and valproic acid were the major treatment options besides lithium.[1-7] During the past two decades several atypical antipsychotics[8-12] and additional second generation antidepressants became widely available, as well as antiepileptic mood stabilizers such as lamotrigine.[13,14] Especially in acute mania, (atypical) antipsychotics have the advantage of a faster onset of action compared to lithium and offer the possibility of parenteral administration. This broadening of therapeutic options together with the necessity of frequent serum level measurements in lithium users, its adverse drug reaction profile,[15-18] and the lack of marketing of lithium by a pharmaceutical company may have resulted in a shift to the use of other drugs instead of or next to lithium. Indeed, there have been reports of a decline in lithium prescription rates over the past years, especially in the U.S., but also in Europe.[15,19,20] In contrast, a study in Spain reported an increase in lithium use.[21] Besides changes in treatment options, the prevalence of psychiatric polypharmacy in bipolar patients has also been reported to increase over the past years.[22-25]

The objectives of the present study were to investigate in outpatients in the Netherlands between 1996 and 2005, changes in 1) the incidence and the prevalence of lithium use and 2) lithium use patterns (discontinuation, add-on, and switch).

METHODS

Setting and study population

Data for this study were obtained from the PHARMO record linkage system (PHARMO RLS) (www.pharmo.nl).[26] The PHARMO record linkage system has since its establishment in 1985, regularly been expanded regarding the participating population defined-areas, with important updates with respect to

our study period in 1998 and in 2003. The PHARMO RLS currently includes the demographic details and complete medication history of more than two million community-dwelling residents of more than twenty-five population-defined areas in the Netherlands, further linked to hospital admission data (with the exception of psychiatric hospital admissions) as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data. Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs.

For this study, drug dispensing data were used. The computerized drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. 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. The study period was from January 1996 until December 2005. From the PHARMO RLS, we identified all prescriptions for lithium (ATC-code N05AN01). For each prescription, the theoretical end date of lithium use was calculated using information on the date of dispensing, the amount of tablets dispensed and the daily dose instruction.

Our study population comprised all patients from the PHARMO system having at least one prescription dispensed for lithium between 1996 and 2005 at an age of 18 years or older.

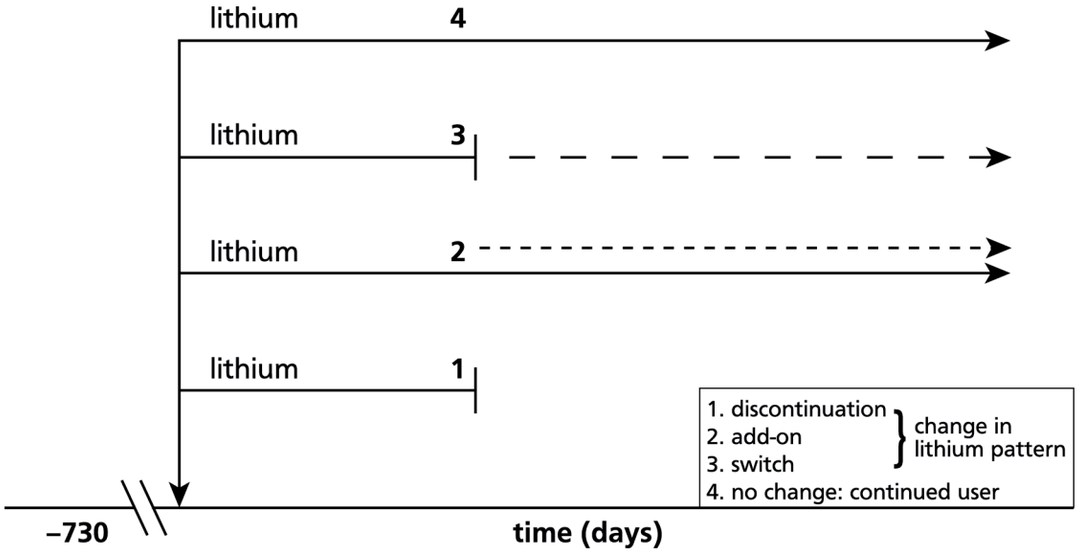
Prevalence and incidence of lithium use

The prevalence of lithium use was ascertained by dividing the number of users of lithium on the second Wednesday in March, June, September and December (to assess potential seasonal influences) of each calendar year between 1996-2005 (nominator) by the total number of people living in the catchment area (denominator) and was expressed per 1000 persons. Prevalent lithium users were defined as patients for whom the date of the prevalence estimation fell between the dispensing date and the theoretical end date of the lithium prescription.

The incidence of lithium use was calculated by dividing the total number of incident users per calendar year from 1998-2005 (nominator) by the total number of people living in the catchment area (denominator) in the same year

and expressed per 1000 person-years. Incident lithium users were defined as patients having received a first prescription of lithium between 1998 and 2005 while not having received a prescription for lithium during at least the preceding two years. In addition, patients had to have visited the pharmacy for at least one prescription for another drug than lithium in these two years to ensure eligibility.

Figure 1: Changes in lithium use assessed at three, six, 12 and 24 months in patients starting using lithium



Changes in lithium use patterns

Based on the year in which patients received their first lithium prescription, the incident lithium users were divided over three time-cohorts: 1998-1999, 2000-2001 and 2002-2003, rendering at least a 24-month follow-up period possible for all patients. Changes in lithium use were assessed for each of the three time-cohorts at three, six, 12 and 24 months for all eligible patients (Figure 1) and reported as cumulative changes. The following changes in lithium use were defined: 1) discontinuation, without switching; 2) add-on to continuing lithium treatment; and 3) switching from lithium to another drug. Discontinuation was defined as not having refilled a lithium prescription within six months after the theoretical end date of the last lithium prescription but having been non-institutionalised (having at least one drug dispensing event for any other drug

within the six months after their last lithium dispensing). Add-on was defined as continuing lithium use and starting another drug used in the treatment of bipolar disorders (anticonvulsants, antidepressants or antipsychotics). Switching was defined as the discontinuation of lithium followed by the start of another drug used in the treatment of bipolar disorders (anticonvulsants, antidepressants or antipsychotics) within three months after the theoretical end date of the last lithium prescription.

Data analysis

Linear regression analysis was conducted on the prevalences (1996-2005) and incidences (1998-2005) of lithium use to explore changes in prevalence and incidence in lithium use. In order to investigate differences in characteristics of patients starting to use lithium, baseline patient (age, gender), lithium (prescriber, kinetic profile, salt and daily intake frequency) and co-medication characteristics (baseline use of concomitant drugs used in the treatment of bipolar disorders (anticonvulsants, antidepressants or antipsychotics)) were compared between three separate time-cohorts (1998-1999, 2000-2001, and 2002-2003).

The cumulative frequency of the occurrence of any of the outcome events (Figure 1) was determined for each of the three different time-cohorts at three, six, 12 and 24 months after the first lithium prescription. Differences in lithium outcome events between the three time-cohorts at three, six, 12 and 24 months were assessed and expressed as relative risks (RRs) and 95% confidence intervals (CIs).

Lastly, concomitant use of other drugs used in the treatment of bipolar disorders next to lithium at any point during treatment follow-up was assessed at 24 months for the three different time-cohorts.

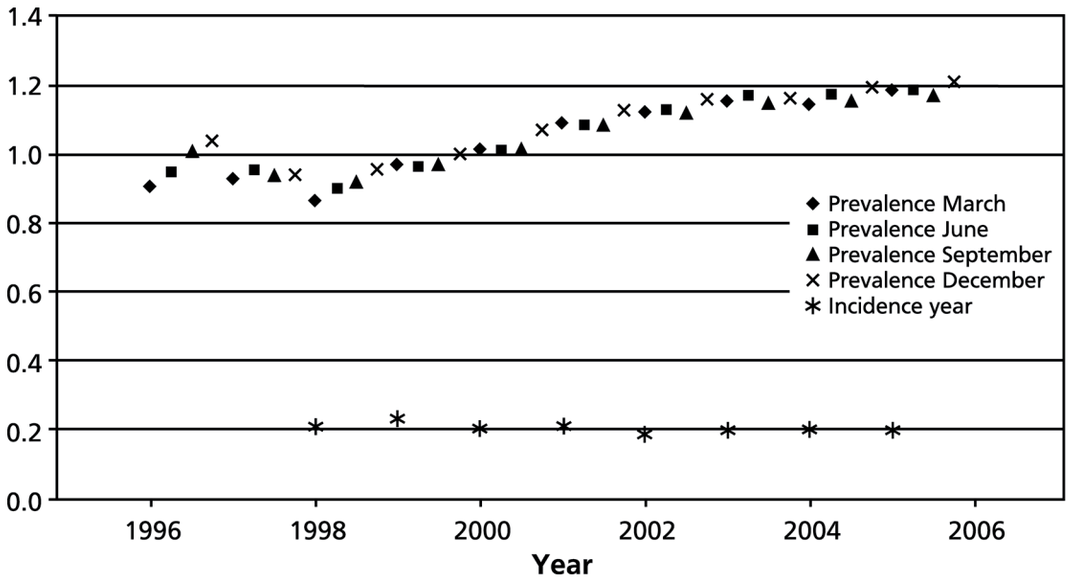
All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 13.0.

RESULTS

The prevalence and incidence estimations of lithium use in our study period are shown in Figure 2. Between 1998 and 2005 a total of 2426 patients were identified as incident lithium users out of the total study population consisting of 6711 patients. The incidence of lithium use between 1998 and 2005 was found

to be consistent at about 0.2 patients per 1000 persons per year. The prevalence of lithium use increased with 26% (from 0.95 to 1.2 patients per 1000 persons) over the study period; no differences in prevalence estimations were observed between seasons.

Figure 2: The prevalence and incidence of lithium use expressed per 1000 persons/person-years during 1996-2005



The baseline characteristics of the patients and of the first lithium prescriptions for the patients starting lithium treatment during 1998-2003 (n=1626) are shown in Table 1, both overall and for the three time-cohorts separately.

The number of first lithium prescriptions being a regular release preparation decreased within the time-cohorts from 38.9% to 30.0% ($p<0.05$). Approximately 70% of the incident lithium prescriptions was found to be prescribed by a psychiatrist, about 10% by a general practitioner (GP) and about 20% by physicians other than psychiatrists or GPs, these percentages did not significantly differ between the three time-cohorts.

The percentage of patients only using lithium as drug used in the treatment of bipolar disorders decreased between the first and the second time-cohort together with a significant increase in baseline antipsychotic use ($p<0.05$).

Table 1: Baseline characteristics of the incident lithium users in the three time cohorts

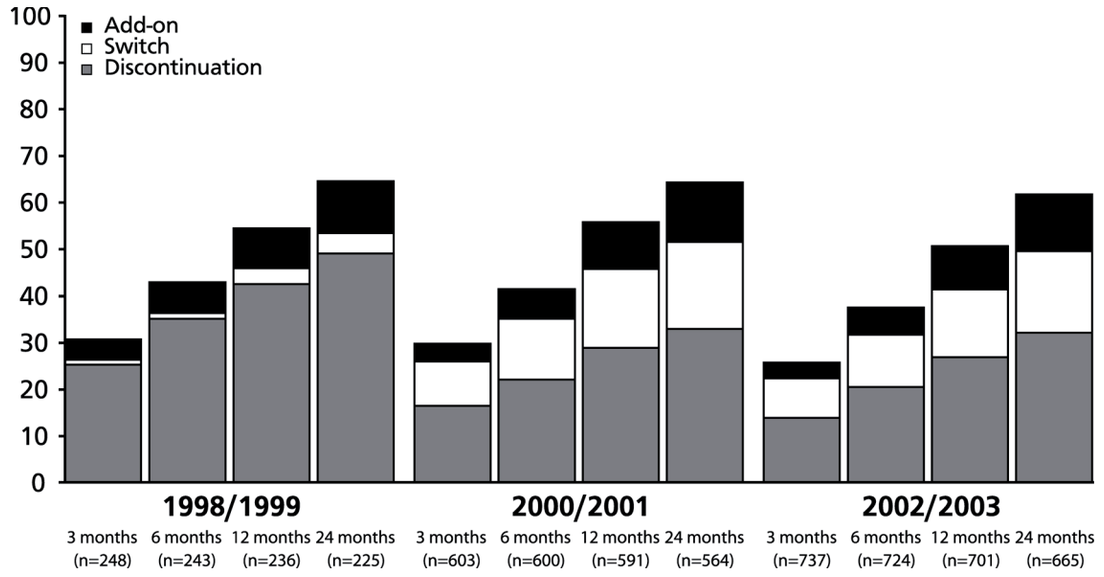
Characteristics	Time-cohort I 1998-1999	Time-cohort II 2000-2001	Time-cohort III 2002-2003	Overall 1998-2003
	n=254 (100%)	n=619 (100%)	n=753 (100%)	n=1626 (100%)
Patient demographics				
Gender (male); n (%)	90 (35.4)	205 (33.1)	296 (39.3)	591 (36.3)
Age; *mean (sd)*	*47.1 (16.0)*	*45.8 (14.5)*	*48.4 (14.9)*	*47.2 (15.0)*
Lithium first prescription characteristics[a]; n (%)				
Psychiatrist as first prescriber	175 (73.5)	442 (74.0)	503 (69.4)	1120 (71.8)
Regular release preparation	96 (38.9)	227 (36.7)	226 (30.0)	549 (33.9)
Carbonate salt	246 (99.6)	610 (98.5)	745 (98.9)	1601 (98.9)
Once daily intake frequency	195 (89.9)	518 (91.4)	635 (91.2)	1348 (91.1)
Concomitant use at baseline of drugs used in the treatment of bipolar disorders; n (%)				
None (lithium only)	143 (56.3)	297 (48.0)	382 (50.7)	822 (50.6)
Antipsychotics	44 (17.3)	170 (27.5)	195 (25.9)	409 (25.2)
typical	28 (11.0)	89 (14.4)	68 (9.0)	185 (11.4)
atypical	16 (6.3)	87 (14.1)	130 (17.3)	233 (14.3)
Antidepressants	89 (35.0)	213 (34.4)	247 (32.8)	549 (33.8)
TCA	50 (19.7)	113 (18.3)	140 (18.6)	303 (18.6)
SSRI	25 (9.8)	55 (8.9)	60 (8.0)	140 (8.6)
other	15 (5.9)	47 (7.6)	49 (6.5)	111 (6.8)
Mood stabilisers				
valproic acid	3 (1.2)	14 (2.3)	28 (3.7)	45 (2.8)
carbamazepine	3 (1.2)	5 (0.8)	13 (1.7)	21 (1.3)
lamotrigine	1 (0.4)	2 (0.3)	3 (0.4)	6 (0.4)

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor
a) Data not available for all patients.

Baseline use of atypical antipsychotics was found to increase whereas baseline use of typical antipsychotics was found to decrease over the three time-cohorts ($p<0.05$).

Overall, 147 patients (9.0%) filled only one prescription for lithium during follow-up. The number of patients receiving only one prescription for lithium did not significantly differ between the three time-cohorts with 1998-2003, 21 (8.3%) in the first time-cohort, 55 (8.9%) in the second time-cohort and 71 (9.4%) in the third time-cohort.

Figure 3: Percentage of patients having encountered one of the outcome events at three, six, 12 and 24 months for the three time-periods



The cumulative percentage of patients having encountered an outcome event at three, six, 12 and 24 months in the three time-cohorts as well as overall is presented in Figure 3. There was no difference with respect to the proportion of patients being prescribed add-on drugs between the three time-cohorts, with a RR of 1.15 (95% CI 0.75-1.76) in 2000-2001 and a RR of 1.10 (95% CI 0.72-1.67) for add-on at 24 months. Within the drugs used as add-on, there was a significant decrease in add-on of tricyclic antidepressants (TCAs) ($p<0.05$) and an increase in selective serotonin reuptake inhibitors and other second generation antidepressants. The proportion of patients switching from lithium to another drug used in the treatment for bipolar disorders at three, six, 12 and 24 months increased over the three time-cohorts ($p<0.05$) with a RR of 4.19 (95% CI 2.23-7.87) in 2000-2001 and a RR of 3.92 (95% CI 2.09-7.36) for switching at 24 months. There was a significant increase in switching from lithium to antipsychotics and antidepressants over the three time-cohorts. The percentage of patients having discontinued lithium at three, six, 12 and 24 months decreased over the three time-cohorts ($p<0.05$) with a RR of 0.67 (95% CI 0.56-0.80) in

2000-2001 and a RR of 0.66 (95% CI 0.55-0.78) for discontinuation at 24 months (Figure 3).

Table 2: Number of patients being prescribed concomitant drugs used in the treatment of bipolar disorder next to lithium during the 24 months after having started lithium

Concomitant drug use	Time-cohort I 1998-1999	Time-cohort II 2000-2001	Time-cohort III 2002-2003	Overall 1998-2003
	n=225 (100%)	n=564 (100%)	n=665 (100%)	n=1454 (100%)
Antipsychotics; n (%)	101 (44.9)	274 (48.6)	344 (51.7)	719 (49.4)
typical	65 (28.9)	160 (28.4)	159 (23.9)	384 (26.4)
atypical	51 (22.7)	157 (27.8)	234 (35.2)	442 (30.4)
Antidepressants; n (%)	159 (70.7)	386 (68.4)	456 (68.6)	1001 (68.8)
TCA	93 (41.3)	206 (36.5)	240 (36.1)	539 (37.1)
SSRI	66 (29.3)	151 (26.8)	181 (27.2)	398 (27.4)
other	33 (14.7)	112 (19.9)	122 (18.3)	267 (18.4)
Mood stabilisers; n (%)				
valproic acid	8 (3.6)	43 (7.6)	62 (9.3)	113 (7.8)
carbamazepine	7 (3.1)	18 (3.2)	21 (3.2)	46 (3.2)
lamotrigine	0 (0.0)	6 (1.1)	11 (1.7)	17 (1.2)

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor

Within the group of patients who stopped using lithium (discontinuation and switching) there was a significant change from discontinuation to switching ($p<0.05$). The proportion of patients switching from lithium to another drug used in the treatment of bipolar disorders increased from 8.3% at 24 months in the time-cohort 1998-1999 to 35.3% at 24 months in the time-cohort 2002-2003 and the number of patients discontinuing lithium without switching at 24 months was found to decrease from 91.7% in the time-cohort 1998-1999 to 64.7% at 24 months in the time-cohort 2002-2003.

The number and the percentage of patients having concurrently used another drug used in the treatment of bipolar disorders next to lithium at any time during the first 24 months of follow-up is presented in Table 2. The number of patients having concomitantly used atypical antipsychotics and those having concomitantly used valproic acid increased significantly over the three time-cohorts ($p<0.05$).

DISCUSSION

The results of the present study indicate that the prevalence of lithium use in outpatients in the Netherlands increased in the period 1996-2005. The incidence of lithium use was found to be constant at 0.2 per 1000 patient years. We found that characteristics of patients starting lithium treatment did not change over the years. We did find, however, that the treatment patterns in patients using lithium during follow-up changed over time. We found an increase in baseline atypical antipsychotic use over the three time-cohorts. We found an increase in switching from lithium to another drug used in the treatment of bipolar disorders, along with a decrease in discontinuation of lithium treatment. In addition, there was an increase in the use of other drugs used in the treatment of bipolar disorders next to lithium over the years. Especially atypical antipsychotics and valproic acid were increasingly prescribed next to lithium, whereas TCAs were less frequently used as add-on.

Our finding that the prevalence of lithium use increased over time is in line with data from the council of Dutch health insurers (www.Gipdatabank.nl), which show an increase of about 6% in the prevalence of lithium use as compared to about 5% in our data in the same time period. The incidence of lithium use was found to be constant at 0.2 per 1000 patient years, which indicates that in this period lithium was used for a longer time-period when started. An alternative explanation is that the increase in prevalence of lithium use over the years might be explained by the increasing effort to treat patients as outpatients rather than to have them institutionalised. In addition, in the Dutch guidelines,[27] use of lithium was re-established as first choice treatment for the prophylaxis of bipolar disorders, as also in the CANMAT[28] and NICE[29] guidelines.

Baseline characteristics of incident lithium users were not found to differ between the three time-cohorts, only use of atypical antipsychotics at baseline next to lithium was found to increase. Within the drugs used as add-on or in switching there were no significant changes other than a decrease in concomitant prescription of TCA as add-on to lithium. The latter could be the result of an increased number of publications on the risk of induction of mania when prescribing TCA to patients suffering from bipolar disorders,[30,31] and is in line with the Dutch guidelines for the treatment of bipolar disorders.[27] On the other hand it could be the result of a decrease in lithium co-prescription next to

antidepressants.[32] Our results indicate a shift from discontinuation with lithium towards switching from lithium to another drug used in the treatment of bipolar disorders over the past years. The increase in the number of patients switching from lithium to antipsychotics and antidepressants is in line with the increase in available drugs for the treatment of bipolar disorders over the past decade. Between the 1960s and 1990s (typical) antipsychotics, antidepressants, carbamazepine and valproate/valproic acid were the major treatment options besides lithium.[1-7] During the last decade more second generation antidepressants have become available for the treatment of depression, several atypical antipsychotics (olanzapine, risperidone and quetiapine) have become available for the treatment of mania as well as for the prophylaxis of bipolar disorders,[8,9,11,12,33] followed more recently by the introduction of lamotrigine for the treatment and the prophylaxis of bipolar depression.[13,14] In the Netherlands, lithium, carbamazepine and olanzapine are nowadays officially licensed for the treatment of mania and the prophylaxis of bipolar disorders. The typical as well as most atypical (risperidone and quetiapine) antipsychotics are approved for the treatment of mania. Valproic acid is frequently used for the treatment of bipolar disorder, and is officially recommended in the Dutch guideline.[27] Finally, lamotrigine is increasingly being used for the treatment and the prophylaxis of bipolar depression. In line with the increasing availability of newer drugs we found an increase in the concomitant use of newer drugs used in the treatment of bipolar disorders. When disregarding the strict definitions for add-on, switching and discontinuation we found that there was a decrease in concomitant prescription of typical antipsychotics next to lithium and a significant increase in the use of atypical antipsychotics next to lithium when comparing the three time-cohorts in line with the emerging new alternatives over the past decade. In addition, we found a significant increase in the concomitant prescription of valproic acid.

Our study is limited since we did not know the specific diagnosis for which lithium treatment was instituted. Our study is based on medication dispensing records and lithium can be instituted for bipolar disorder and for augmentation therapy of depression.

Additionally, we did not have information on psychiatric hospital admissions. This could have influenced our results in four essential ways. Firstly, patients being more severily ill are more likely to be admitted. An increase in out-patient

care would result in relatively more severely ill out-patients, influencing e.g. use of co medication. We did, however, not find a change in the percentage of add on. Secondly, some patients could actually have been admitted to a psychiatric hospital instead of having discontinued using lithium. Therefore, we decided to include an active dispensing pattern into the definition of discontinuation. Thirdly, trends in institutionalisation could have influenced incidence and prevalence of lithium use. Incidence of lithium use was found to be rather constant. Fourthly, the definition of incident lithium users could have resulted in an underestimation of incident users especially of young people for whom lithium could actually have been the first prescription ever. In order to prevent, however, including incident lithium users for whom lithium had actually been initiated during a psychiatric hospital admission we decided to take into account an active drug dispensing history into the definition of incident user.

In conclusion, the changes we observed in use of concomitant drugs next to lithium as well as the changes in lithium use were in line with the increase in availability of alternatives during the past decade and in line with the Dutch guidelines for the treatment of bipolar disorders.

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2.2

Association between lithium serum level, mood state and patient reported adverse drug reactions during long-term lithium treatment: a twenty-six year naturalistic follow-up study

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ABSTRACT

Background

Adverse drug reactions (ADRs) have been identified as a major reason for patients to discontinue lithium. Approximately 75%-90% of patients on long-term lithium treatment experience one or more ADRs.

Aim

The aim of our study was to assess the association between lithium serum level, mood state and the prevalence and the severity of ADRs in a large naturalistic sample of patients during long-term treatment with lithium.

Methods

A 26-year follow-up study was conducted among patients ≥ 18 years treated at the outpatient 'lithium clinic' of the University Medical Center Groningen, the Netherlands, between November 1973 and December 2000. At each monthly scheduled visit, patients were questioned by a research nurse in a standardized manner about the presence and the severity of nine specific ADRs, that frequently occur as a consequence of lithium treatment and that can be identified by the patients themselves. In addition, lithium serum level was measured and mood state was rated at each visit.

Results

A total of 186 patients participated and the median duration of follow-up was 5.7 years (interquartile range 2.2-11.8 years). We observed an increased prevalence and severity of ADRs with increased lithium serum level ($p<0.05$), also when adjusting for mood state. The prevalence and the severity of ADRs increased with decreasing mood state into the depressive range and decreased with mood state increasing into the manic range ($p<0.05$), also when adjusting for lithium serum level. Taking into account the intraindividual dependency of the data resulted in a statistically significant ($p<0.001$) association between respectively lithium serum level, mood state and the prevalence and severity of ADRs.

Conclusion

Both physicians and researchers need to be aware that lithium serum level and mood state are independently associated with patient reporting and severity scoring of ADRs, which may complicate objective assessment of ADRs.

INTRODUCTION

Lithium is frequently used in the management of bipolar disorders.[1-3] Compared to the results from randomized controlled studies,[4] its effectiveness in naturalistic follow-up studies is less pronounced.[5-8] Non-adherence to lithium treatment is one of the major problems interfering with the effectiveness of lithium in daily clinical practice.[5,9] Adverse drug reactions (ADRs) have been identified as a major reason for patients to discontinue lithium.[9-12] Approximately 75%-90% of patients on long-term lithium treatment experience one or more ADRs.[13] Early recognition and treatment of ADRs may therefore be an important factor in improving persistence with lithium treatment.

Because of the large inter- and intraindividual differences in both lithium pharmacokinetics and pharmacodynamics, lithium dose is not a good predictor of its effectiveness and occurrence of ADRs. However, there is ample evidence for a correlation with lithium serum levels, making – together with the likelihood of toxicity – serum level monitoring imperative. In the maintenance treatment of bipolar disorder a commonly advised target therapeutic lithium serum level is 0.6-0.8 mmol/l, whereas for the treatment of acute manic episodes the generally recommended target therapeutic lithium serum level is 0.8-1.2 mmol/l.[14,15] Likewise, an association between lithium serum level and the occurrence of several type A ADRs (e.g. tremor, nausea) has been demonstrated.[16-20] In addition to the degree of exposure to lithium, the underlying psychiatric disorder may influence the occurrence of ADRs. Some studies on depression found that the prevalence[21] and severity[22-24] of ADRs of tricyclic antidepressants was correlated with the severity of depression, whereas others did not find such an association.[25] One study in patients with schizophrenia reported a decrease in the prevalence of ADRs associated with both improvement of psychotic symptoms and decrease in polypharmacy.[26]

To our knowledge no studies have specifically focused on the association between severity of illness and prevalence and severity of ADRs in patients using lithium.

Therefore, we decided to assess the association between lithium serum level, mood state and prevalence and severity of ADRs in a large naturalistic sample of patients during long-term treatment with lithium.

METHODS

Setting

This study was performed as a prospective naturalistic follow-up study. Data were gathered from patients attending the specialized outpatient 'lithium clinic' of the Department of Psychiatry of the University Medical Center Groningen (UMC Groningen), Groningen, the Netherlands between November 1973 and January 2001. The psychiatric clinic of the UMC Groningen was the first in the Netherlands to start a specialized 'lithium clinic' focusing specifically on patients treated with lithium.

Study population

All patients of 18 years or older attending the outpatient 'lithium clinic' of the UMC Groningen already on or starting treatment with lithium between November 1973 and December 2000 were eligible for participation. Patients were included in the study starting from the date of the completion of the first ADR questionnaire and followed up until the date on which the last ADR questionnaire had been completed.

Data collection

Data on the presence and the severity of ADRs, mood state and lithium treatment were gathered as a routine procedure for all outpatients attending the lithium clinic. In monthly scheduled face-to-face standardized interviews, a research nurse practitioner gathered information. The same research nurse performed more than 95% of all interviews. Patients were asked about both the presence and the severity of nine specific ADRs that frequently occur as a consequence of lithium treatment and that could be identified by the patients themselves: diarrhea, nausea, vomiting, stomach ache, tiredness, concentration deficits, tremor, polyuria and polydipsia. The severity of the ADRs was scored by the patient on a three point scale (1 = mild, 2 = moderate, 3 = severe).

The same research nurse assessed mood state, during the past month, using a nine-point mood state rating scale ranging from 1 (severely depressed) through 5 (euthymic) to 9 (severely manic). In addition, she collected information on patient characteristics, lithium use (dose and daily intake frequency) and concomitantly used medication. Blood samples were drawn for lithium serum level measurement on the day of the interview.

Table 1: Follow-up taking into account all measurements for which concurrently an ADR questionnaire and a lithium serum level and/or a mood state rating had been completed for the included patients (n=186)

	median (interquartile range)	measurements (n)
ADR (n):		
- any	3 (2-5)	8056
- at least moderate	2 (1-3)	8056
- at least severe	1 (0-1)	8056
Lithium serum level in mmol/l	0.70 (0.60-0.82)	7250
Mood state rating	5 (5-5)	7940

Data analysis

The association between lithium serum level and mood state versus the mean number and severity of ADRs, and the prevalence of each of the nine ADRs as reported by the patients was evaluated using linear regression analysis. The residuals method was used to identify the impact of lithium serum level on the mean number and mean severity of ADRs adjusted for mood state and the impact of mood state on the mean number and mean severity of ADRs adjusted for lithium serum level and expressed as r^2. Additionally, we investigated the existence of within patient dependency on the association between lithium serum level, mood state and the number and the mean severity of present ADRs by performing a linear mixed model analysis. The coefficients of lithium serum level, mood state, gender, age at study inclusion and duration of lithium use while in study, were defined as fixed effects (assuming that all variables of interest are represented in the data). To allow for differences in intraindividual number and mean severity of present ADRs a random intercept was used. The association between lithium serum level, mood state and the prevalence of the different ADRs was assessed using logistic regression analysis. The prevalence of each of the nine ADRs was defined as the percentage of people scoring positive on the presence of a particular ADR divided by the total number of patients for whom an ADR questionnaire had been completed for that specific ADR in that particular lithium serum level category or mood state segment.

All analysis were carried out using the Statistical Package for the Social Sciences (SPSS) version 13.0.

Figure 1: Lithium serum level versus (A) the prevalence of the different reported ADRs, and (B) the mean number and severity of patient reported ADRs

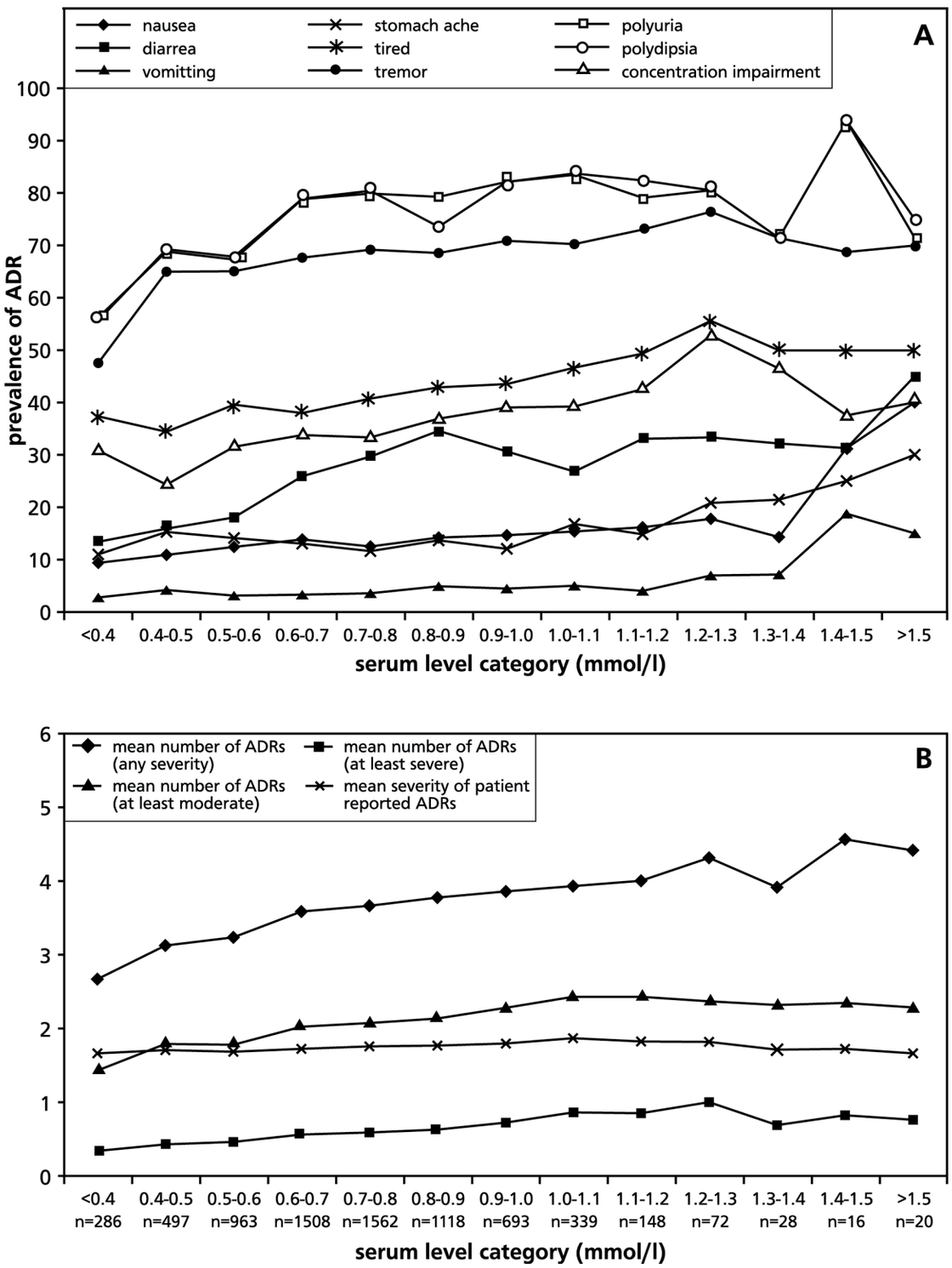
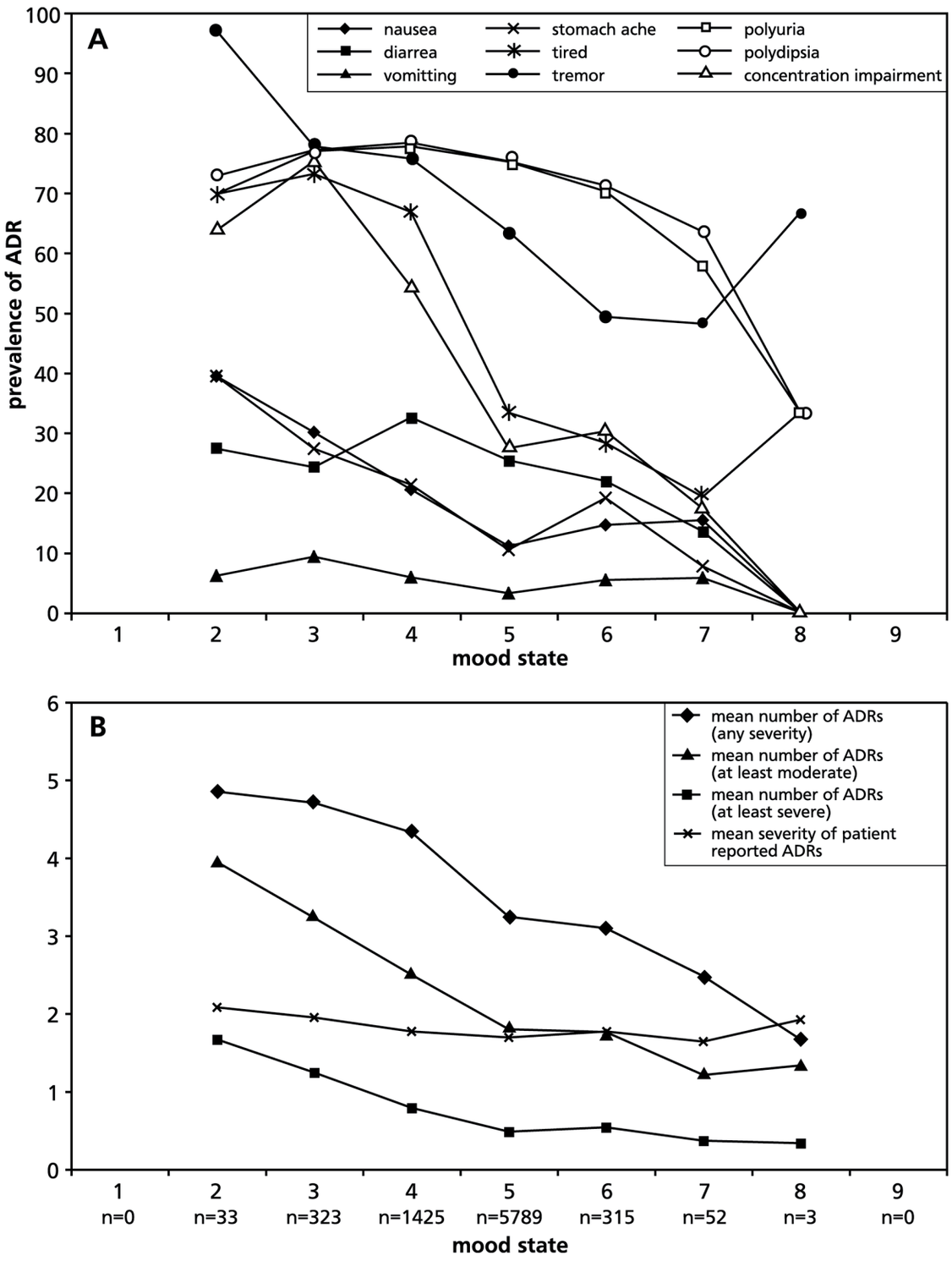


Figure 2: Mood state versus (A) the prevalence of the different ADRs, and (B) the mean number and severity of patient reported ADRs



RESULTS

Between November 1973 and December 2000, a total of 186 patients participated in our study. Overall, we included slightly more women 105 (56.5%) than men; mean age at inclusion was 42.1 years (sd 14.7). Most (98.5%) patients used lithium carbonate; median daily lithium dose at study inclusion was 32 mmol (interquartile range 24-43 mmol).

For 176 (94.6%) patients, at least two ADR questionnaires were completed during follow-up. A total of 8056 ADR questionnaires were completed during follow-up (Table 1). Median duration of patient follow-up was 5.7 years (interquartile range 2.2-11.8 years). All but two patients reported the presence of at least one ADR during follow-up. For the majority of patients (62.5%) the lithium serum level at each moment of interviewing fell within the therapeutic range as recommended for the prophylaxis of bipolar disorder and in most cases (73.4%) mood state was rated euthymic (mood state = 5). All other mood state ratings varied between 2 and 8.

In Figure 1A the relation between lithium serum level category and the prevalence of the different ADRs is shown and in Figure 1B lithium serum level category (n=7250) is plotted versus the mean number of patient reported ADRs, taking into account ADR severity as scored by the patient. Linear regression analysis for lithium serum level versus the number of present ADRs resulted in a statistically significant association ($p<0.05$; $r^2=0.031$), and it remained significant after adjusting for mood state ($p<0.05$; $r^2=0.021$). Adjustment for mood state was performed since lithium serum level and mood state were found to be significantly associated ($p<0.05$). A statistically significant association was also observed between lithium serum level and the mean severity of all present ADRs ($p<0.05$; $r^2=0.007$) again also when adjusting for mood state ($p<0.05$; $r^2=0.005$). Taking into account the intraindividual dependency of the data a statistically significant ($p<0.001$) association between respectively lithium serum level and the number and the mean severity of reported ADRs was established, also persisting when including mood state, age at study inclusion, gender and duration of lithium use while in study. The association between lithium serum level and the number of present ADRs resulting from the linear mixed model analysis, resulted in a mean number of present ADRs of 3.3, 3.6 and 3.8 in patients displaying a lithium serum level of 0.6 mmol/l, 0.9 mmol/l and 1.2 mmol/l respectively.

Figure 2A displays mood state versus the prevalence of the different ADRs. In Figure 2B mood state (n=7940) is plotted against the mean number of patient reported ADRs taking into account ADR severity as scored by the patient. Linear regression analysis for mood state versus the number of present ADRs resulted in a statistically significant association ($p<0.05$; $r^2=0.073$), also when adjusting for lithium serum level ($p<0.05$; $r^2=0.063$). A statistically significant association was observed between mood state and the mean severity of all present ADRs ($p<0.05$; $r^2=0.009$) also when adjusting for lithium serum level ($p<0.05$; $r^2=0.005$). The association between mood state and the number of ADRs, taking into account intraindividual dependency of the data resulted in a mean number of ADRs of 3.3 in patients being euthymic (mood state = 5) and a mean number of ADRs of 4.6 and 2.0 in patients being depressed (mood state = 2) and patients being manic (mood state = 8), respectively.

Logistic regression analysis was performed to assess the association between lithium serum level, mood state and the different ADRs (Table 2). Tiredness and concentration deficits were found to be most strongly associated with mood.

Table 2: Odds ratio per unit change in lithium serum level and of mood state for the different adverse drug reactions

	Lithium serum level	Mood state
	OR[a] (95% CI)	OR[b] (95% CI)
Nausea	1.51 (1.07-2.11)	0.61 (0.55-0.67)
Diarrhea	3.66 (2.81-4.77)	0.90 (0.83-0.98)
Vomiting	2.06 (1.16-3.67)	0.71 (0.60-0.84)
Stomach ache	0.95 (0.67-1.33)	0.63 (0.57-0.69)
Tiredness	1.33 (1.04-1.70)	0.37 (0.34-0.41)
Concentration deficits	1.82 (1.42-2.35)	0.43 (0.39-0.47)
Tremor	1.96 (1.52-2.53)	0.63 (0.58-0.69)
Polyuria	4.63 (3.47-6.18)	0.92 (0.84-1.01)
Polydipsia	4.99 (3.73-6.68)	0.91 (0.83-1.00)

a) Odds ratio per unit change in lithium serum level.
b) Odds ratio per unit change of mood state.

DISCUSSION

Our study reveals the presence of an association between lithium serum level as well as mood state and the prevalence as well as the severity of patient-reported lithium associated ADRs. These results indicate a dose response relationship for lithium and the occurrence of ADRs and show that both the reporting and the severity of lithium ADRs can at least partially be explained by either differences in patient-perception of ADRs associated with the different mood states (being manic, depressed or euthymic) and/or vice versa that mood state can at least partly be influenced by the occurrence of ADRs. We also observed an association between lithium serum level, mood state and the prevalence of most of the different individually studied ADRs.

To our knowledge our study is the first in which lithium serum level, mood state and ADRs have been systematically collected for such a long time-period and the first to reveal an association between mood state and the patient reported prevalence and severity of ADRs in patients using lithium. Lithium serum level and mood state, were found to explain a relatively small percentage of the variation in the prevalence and severity of ADRs. The latter most likely can be explained by the naturalistic design of our study. In a naturalistic setting both patients and physicians are free to act upon the presence and the severity of ADRs, lithium serum level and mood state during follow up. ADRs considered bothersome by the patient (e.g. tremor and concentration deficits)[27] or severe by the physician (e.g. nephrogenic or thyroid complications) might result in lowering the dose or even discontinuation of lithium. This may especially explain the more strong association between lithium serum level and the prevalence of ADRs in the lower lithium serum level ranges. In addition, the facts that lithium is an independent causal factor of ADRs,[13] and that most patient mood states were reported to be euthymic, may explain the relatively small percentage in variation in prevalence and severity of ADRs that can be explained by mood state.

In our study relatively few mood state ratings were reported to be in the manic range. In accordance with this observation most lithium serum level measurements were found in the therapeutic range as recommended for the prophylaxis of bipolar disorder. Patients being severely manic are at an increased

risk for non-compliance,[28] potentially also resulting in non-compliance with the monthly scheduled visits.

There are several strong points of our study. First of all, reporting of ADRs was based on completing ADR questionnaires in which patients were asked a in standardized manner about the presence and severity of nine ADRs that frequently occur during lithium treatment and that are identifiable by patients themselves. Actively asking patients about the presence of specific ADRs generally results in higher and consistent reporting of ADRs than when relying on spontaneous reporting alone. In addition, the fact that the interviewing of patients was done almost exclusively by one single person, minimizes inter-interviewer differences. Furthermore, in patients' reporting of ADRs, a simple 3-point measure of severity of present ADRs was used. Lastly our study encompasses follow-up over a very long period of time.

There are also limitations to our study. First of all we only have information on reporting of presence and severity of ADRs by patients. We do not have objective laboratory measures (e.g. urine concentrating capacity) nor physician observations (e.g. of tremor) of the presence of ADRs, nor information about other well-known ADRs of lithium, like hypothyroidism. In addition, we were not able to establish whether it was a decreased mood state or an increased number and severity of ADRs, which was first to occur. An increased awareness of ADRs in patients being more depressed might be an explanation for the observed association between mood state and the number and the severity of ADRs. On the other hand occurrence of ADRs might also increase the risk for depression.

Moreover, we have established the existence of an association between mood state and the number and the severity of frequently occurring ADRs during lithium treatment, we cannot completely ascertain if the nature of this association is causal (lithium induced) or casual (perceived by the patient and not related to the use of lithium),[29] Furthermore, we do not have information on factors influencing lithium exposure like clearance capacity (renal functioning impairment or other situations resulting in diminished lithium clearance e.g. disturbances in water and salt homeostasis) or intake (compliance). Another issue is the validity of the assessments. Both presence and severity of ADRs, as reported by the patients, as well as mood state were not assessed using a formal validated scale. Nevertheless we assume that that the assessments were reliable as

comparable measures, like VAS (visual analog scale) score used in itch or pain assessment, have been and are being used in many other studies.[30] In addition patient reporting of ADRs has been reported to be valid.[31] Furthermore, we might not have been able to adequately adjust for use of concomitant medication, especially with respect to medication not prescribed by the psychiatrist. In our study, registration of the use of medication was based on patients' reporting alone, possibly introducing the risk of no registration due to non-reporting by the patient which may especially apply to non-psychotropic drugs including over the counter medications.

In conclusion, we found that both mood state and lithium serum level are independently associated with the prevalence and the severity of patient reported ADRs in patients on lithium treatment. Prevention of ADRs is especially important since lithium treatment generally is intended for long-term and presence of ADRs increases disease burden and has been shown to result in discontinuation of lithium treatment.[5,12] In preventing ADRs in patients on long-term treatment with lithium, physicians need to try and keep the lithium serum level as low as clinically possible. Since ADRs are an important cause for patient initiated discontinuation, early recognition and treatment of ADRs may be an important factor in improving persistence with lithium treatment. Both physicians and researchers need therefore be aware that also mood state is a factor that is independently associated with patient reporting and severity scoring of ADRs, complicating assessing true ADRS and their severity.

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Lithium use and the risk of fractures

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ABSTRACT

Background

A recent study reported a decreased risk of fractures among lithium users.

Objective

To further explore the association between lithium use and the risk of fractures, taking into account the timing of lithium use.

Methods

We conducted a case-control study within the UK General Practice Research Database, comparing never, ever, current, recent and past lithium use in 231 778 fracture cases to matched controls. In addition, the risk of fractures was assessed in relation to cumulative duration of use and time since discontinuation.

Results

Current use of lithium was associated with a decreased risk of fractures (adjusted odds ratio [OR] 0.75, 95% confidence interval [CI] 0.64-0.88), which did not vary with cumulative duration of use. Among past users an increased risk of fractures was observed (adjusted OR 1.35, 95% CI 1.01-1.79), increasing with time since discontinuation.

Conclusion

Our results support the role of the underlying mental disorders in the aetiology of fractures and do not support a pharmacological effect of lithium based on lack of an association with cumulative duration of use.

INTRODUCTION

Bipolar disorder is characterised by (hypo)manic and depressive episodes alternated with periods of euthymia. Mania is associated with uncontrolled behaviour that may lead to accidents,[1] while depression is associated with an increased risk of suicide and suicide attempts,[2,3] thereby possibly increasing the risk of fractures. Lithium salts are one of the first choice agents for the long-term treatment of bipolar disorder and have been demonstrated to be effective in the treatment of acute mania and depression and to attenuate further manic and depressive episodes.[4-6] Moreover, lithium protects against suicide, which is possibly independent of its effects on mood.[5,7] Discontinuation of long-term lithium treatment has been shown to result in recurrence of both depression as well as mania,[8-10] and this risk of recurrence is larger after abrupt discontinuation.[9]
Lithium has been reported to affect bone density. Observational studies have shown a decrease in bone mineral content within six months of initiation of lithium treatment.[11] Reduced bone resorption in patients on long-term lithium treatment was suggested, based on a decrease in 24-hour urinary calcium excretion.[12] However, two other studies reported no effect of long-term lithium treatment on bone mineral density.[13,14] The reasons for the different results are not clear. Recently, a large population-based case-control study reported a decreased risk of fractures in users of lithium further decreasing with cumulative dose.[15] However, this study did not take into account the timing of lithium use. Any patient who ever received at least one lithium prescription in the four years prior to the date of fracture was considered to be exposed to lithium.
It is unclear whether the association between lithium use and risk of fractures is due to a direct effect of lithium, or can also be attributed to the therapeutic effects of lithium on the underlying mood disorder. In order to elucidate which of these two potential influencing factors predominates, investigating timing of lithium exposure is important. Therefore the objective of our study was to further explore the association between lithium and fractures, taking into account the timing of lithium use.

METHODS

Setting

General practitioners (GP) play a key role in the public health care system in the United Kingdom, being responsible for primary health care as well as being the gatekeepers for secondary care. The information in this study was obtained from the General Practice Research Database (GPRD), which contains the computerised medical records of about 650 general practitioner practices. Approximately five million of the total registered population of England and Wales is represented in this database. The GPRD includes demographic information about the patient, diagnoses, prescription details, preventive care provided, referrals to specialist care, hospital admissions and their major outcomes. Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OXMIS) and Read codes for diseases or causes of morbidity and mortality that are cross-referenced to the International Classification of Diseases (ICD-9). Several independent validation studies have shown that the GPRD database has a high level of completeness and validity.[16] A validation study by Van Staa et al. reported a high validity of the GPRD with respect to fractures.[17] In this study, data assembled in the GPRD from January 1987 to July 1999 were used. All patients aged 18 years or older registered in the GPRD were eligible for participation. Within this study base, a case-control study was conducted.

Study population

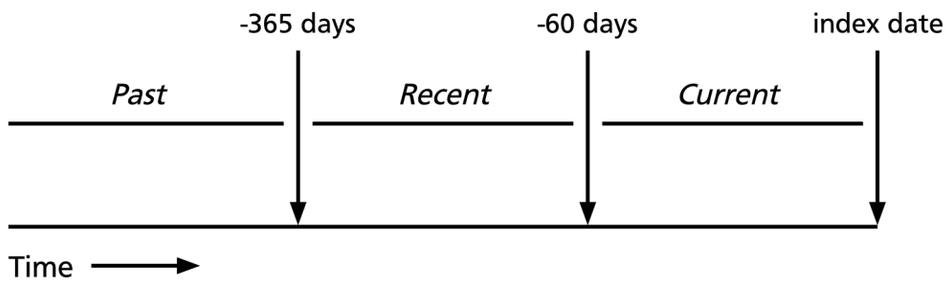
In this study, cases were patients aged 18 years or older with a first record of any fracture during GPRD follow-up. The first occurrence of a fracture during follow-up was identified through relevant OXMIS and Read codes, which were converted to ICD-9 codes. The index date was defined as the date of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

Exposure patterns

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

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

Figure 1: Timing of lithium use



Potential confounders

Potential confounders in this study were prior medical conditions and concomitant use of medications known to be associated with falls, fractures or known to be associated with either bone anabolic or catabolic effects. Medical conditions included diabetes mellitus, psychotic disorders, cerebrovascular accidents, anaemia, congestive heart failure, hypothyroidism, hyperparathyroidism, history of falls and renal impairment, evaluated within one year prior to the index date. Concomitantly used medications were evaluated within a six-month period prior to the index date. Concomitantly used medication assessed included non steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antireumatic drugs (DMARDs), hormone replacement therapy (HRT), thyroid hormones, thiazide diuretics, anxiolytics/hypnotics, antipsychotics, antidepressants, anticonvulsants, antiparkinsonian drugs, calcitonin, oral and inhaled glucocorticoids, and bronchodilators. In addition, we also included body mass index (BMI) (<20, 20-24.99, ≥25 kg/m^2, or unknown) and smoking status (history, no history of smoking, or unknown). Lastly, we also considered severity of the mood disorder as potential confounder, as patients with more severe forms might be more prone to fracture risk-increasing behaviour. As a measure for severity of disease we considered whether patients had been admitted to a psychiatric hospital or ward during the year prior to the index date.

Data analyses

Patients who had ever been on lithium treatment were compared to never users. In addition, ever use was stratified to current, recent and past use. The strengths of the associations between lithium exposure and fractures were evaluated using conditional logistic regression and were expressed as odds ratios (OR) and 95% confidence intervals (CI). Final regression models were determined by backward elimination of potential confounders using a significance level of $p<0.05$. In order to differentiate between the effect of lithium itself and the underlying mood disorder two separate analysis were performed, on cumulative duration of use in current users and on time since discontinuation of lithium treatment in ever users. Cumulative duration of lithium use in current users was investigated as the onset of an effect of lithium on bone may only be several months after start of treatment. Time since discontinuation of lithium was investigated to evaluate the offset of any lithium effect. Smoothing spline regression analysis was used in

these analyses. The group of current lithium users was subdivided into ten subgroups based on deciles of the cumulative duration of use (or time since discontinuation). An OR was calculated for each of the subgroups. Spline regression was then used to smooth these estimates and to visualise any trends. This method has been advocated as an alternative to categorical analysis.[18] In addition, a linear trend analysis (r^2) was performed on these ORs.

In order to determine any effects of disease severity, we determined whether current lithium users had been on concurrent psychotropic medication (antipsychotics, antidepressants, valproic acid or carbamazepine; agents that are frequently used in the treatment of bipolar disorders) within six months prior to the index date or had been admitted to a hospital because of a mental disorder within one year prior to the index date. Current users were subsequently stratified according to concurrent use of antipsychotics, antidepressants of valproic acid/carbamazepine or recent hospitalisation for a mental disorder.

All analyses were performed using SAS 9.1.3.

RESULTS

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

Ever use of lithium was associated with a decreased risk of fractures (adjusted OR 0.85, 95% CI 0.74-0.96) (Table 2). The timing of prior use of lithium was found to be important: current lithium users had a decreased risk of fractures (adjusted OR 0.75, 95% CI 0.64-0.88), whereas an increased risk was observed in patients who discontinued lithium at least one year ago (adjusted OR 1.35, 95% CI 1.01-1.79). The risk of fractures increased with time since discontinuation in patients who had discontinued their lithium treatment (linear regression coefficient; r^2=0.66) (Figure 2). A similar trend was observed when separately

Table 1: Baseline characteristics

Characteristic	Cases	Controls
	231 778 (100%)	**231 778 (100%)**
Patient characteristics		
age in yrs; mean (sd)	51 (22)	51 (22)
gender (female); n (%)	121 615 (52.5%)	121 615 (52.5%)
Lithium use characteristics		
ever use of lithium; n (%)	538 (0.2%)	489 (0.2%)
average daily use of lithium in mmol; mean (sd)	16.4 (14.1)	16.6 (9.6)
cumulative duration of lithium use in yrs; median	1.3	1.3
Medical history before the index date; n (%)		
bipolar disorder (ever prior)	850 (0.4%)	665 (0.3%)
depression (1 yr prior)	11 791 (5.1%)	8 121 (3.5%)
psychotic disorders (1 yr prior)	946 (0.4%)	763 (0.3%)
hospitalisations for psychiatric disorder (1 yr prior) ≥1	1 775 (0.8%)	1 083 (0.5%)
renal impairment (ever prior)	2 339 (1.0%)	1 730 (0.7%)
hyperparathyroidism (ever prior)	116 (0.1%)	95 (0.0%)
anaemia (1 yr prior)	4 117 (1.8%)	3 004 (1.3%)
cerebrovascular disease (1 yr prior)	10 846 (4.7%)	8 291 (3.6%)
heart failure (1 yr prior)	9 636 (4.2%)	8 239 (3.6%)
epilepsy (1 yr prior)	5 186 (2.2%)	2 707 (1.2%)
diabetes (1 yr prior)	7 101 (3.1%)	6 331 (2.7%)
hypothyroidism	4 144 (1.8%)	3 466 (1.5%)
BMI: ▪ 0-19.99 kg/m2	13 439 (5.8%)	11 316 (4.9%)
▪ 20-24.99 kg/m2	65 457 (28.2%)	60 283 (26.0%)
▪ ≥25 kg/m2	87 161 (37.6%)	97 228 (41.9%)
▪ not recorded	65 721 (28.4%)	62 951 (27.2%)
Smoking: ▪ yes	49 059 (21.2%)	40 419 (17.4%)
▪ no	106 014 (45.7%)	101 892 (44.0%)
▪ missing	76 705 (33.1%)	89 467 (38.6%)
Co-medication 6 months prior; n (%)		
anticonvulsants	5 282 (2.3%)	2 682 (1.2%)
HRT	5 685 (2.5%)	6 164 (2.7%)
anxiolytics/hypnotics	22 328 (9.6%)	16 577 (7.2%)
antipsychotics	6 157 (2.7%)	4 564 (2.0%)
antidepressants	16 449 (7.1%)	11 545 (5.0%)
levothyroxin/liothyronin	5 941 (2.6%)	5 166 (2.2%)
calcitonin	30 (0.0%)	12 (0.0%)
thiazid diuretics	13 373 (5.8%)	13 532 (5.8%)
DMARDs	1 660 (0.7%)	1 225 (0.5%)
NSAIDs	32 209 (13.9%)	23 617 (10.2%)
anti-parkinsonian drugs	2 808 (1.2%)	1 846 (0.8%)
oral corticosteroids	7 704 (3.3%)	4 692 (2.0%)
inhaled bronchodilators/corticosteroids	19 579 (8.4%)	14 554 (6.3%)

BMI = body mass index; HRT = hormone replacement therapy; DMARDs = disease-modifying antireumatic drugs; NSAIDs = non steroidal anti-inflammatory drugs

Table 2: Exposure patterns to lithium in cases and controls

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

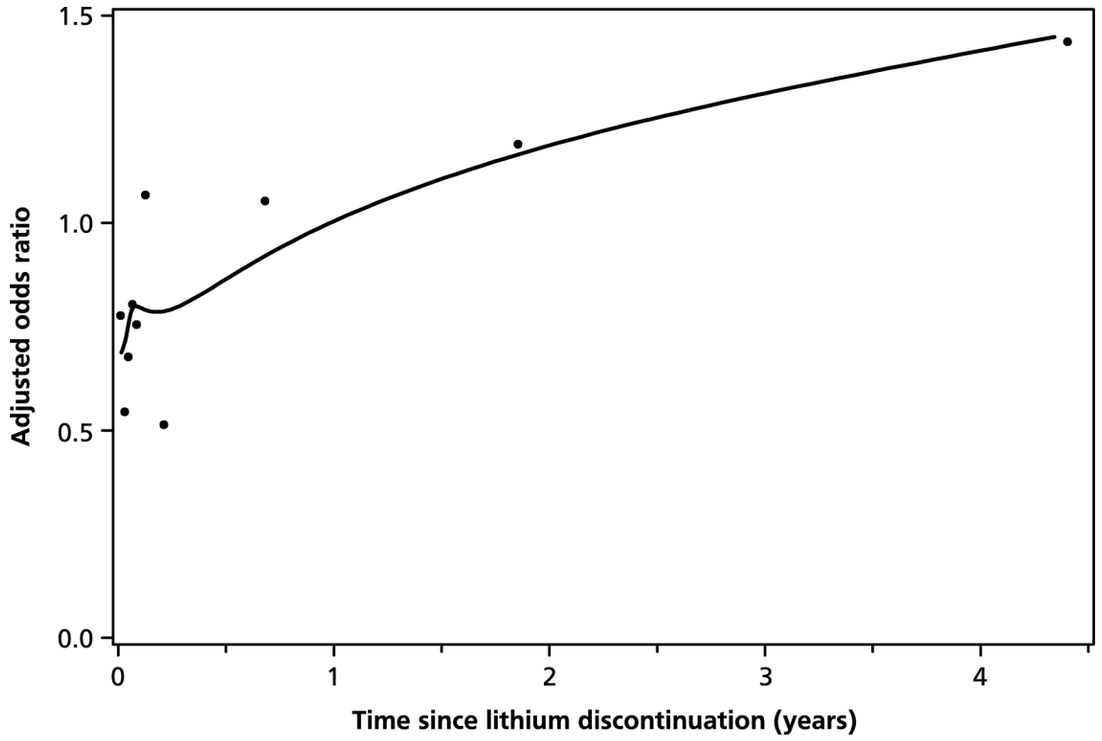
a) Adjusted for: Heart failure, anaemia, cerebrovascular disease, diabetes, and renal impairment (one year prior). Thiazid diuretics, history of falls, hormone replacement therapy (HRT), non steroidal anti-inflammatory drugs (NSAIDs), anxiolytics/hypnotics, antidepressants, anti-convulsants, antiparkinsonian drugs, inhaled bronchodilators/corticosteroids, oral corticosteroids, antypsychotics, thyroid drugs, smoking, and quetelet index (six months prior).

b) Adjusted for: Heart failure, anaemia, cerebrovascular disease, renal impairment, and psychotic disorders (one year prior). History of falls, thiazid diuretics, HRT, disease-modifying antireumatic drugs (DMARDs), NSAIDs, anxiolytics/hypnotics, antidepressants, anti-convulsants, antiparkinsonian drugs, inhaled bronchodilators/corticosteroids, oral corticosteroids, antipsychotics, thyroid drugs, smoking, and quetelet index (six months prior).

c) Adjusted for: Heart failure, anaemia, cerebrovascular disease, diabetes, renal impairment, psychotic disorders (one year prior). History of falls, thiazid diuretics, HRT, DMARDs, NSAIDs, anxiolytics/hypnotics, antidepressants, anticonvulsants, antiparkinsonian drugs, inhaled bronchodilators/corticosteroids, oral corticosteroids, antypsychotics, smoking, and quetelet index (six months prior).

performing the analysis for those who did not use an antipsychotic, an antidepressant, valproic acid or carbamazepine in the six months prior to the index date and those who did receive at least one prescription for any of these drugs. However, the overall risk in those not having been prescribed one of these drugs in the six months prior to the index date was smaller (results not shown).

Figure 2: Risk of fracture (any type) and time since lithium discontinuation



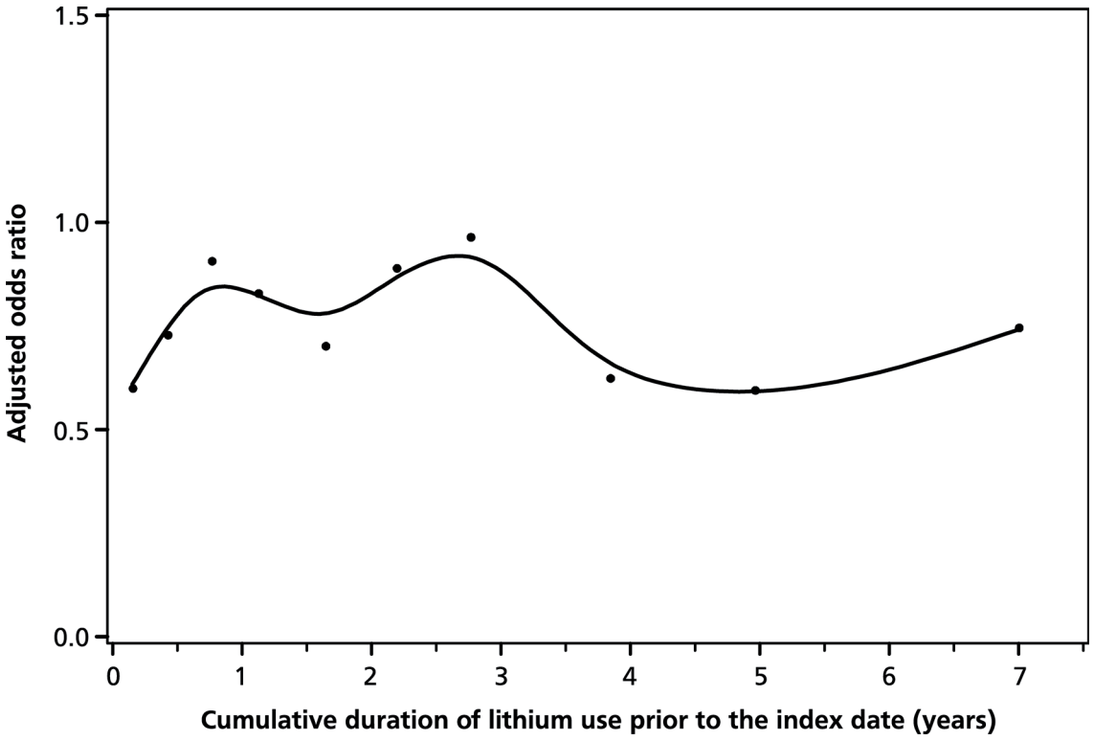
Time since discontinuation of lithium was investigated to evaluate the offset of any lithium effect. Smoothing spline regression analysis was used. The group of ever lithium users was subdivided into ten subgroups, based on deciles of time since discontinuation. An OR was calculated for each of the subgroups.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

A similar trend was observed for osteoporotic fractures (results not shown). The risk of hip/femur fracture was increased in ever users of lithium (adjusted OR 1.97, 95% CI 1.24-3.12). This effect persisted when taking into account timing of lithium use resulting in an adjusted OR of 1.39 (95% CI 0.80-2.43) for current lithium users that further increased after lithium discontinuation to an

adjusted OR of 3.14 (95% CI 0.84-11.8) for recent users and to an adjusted OR of 4.29 (95% CI 1.39-13.2) for past users. No differences were found in the risk estimates of lithium use and fractures across age and gender.

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

Figure 3: Risk of fracture (any type) and cumulative duration of lithium use



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

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

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

We observed a decreased risk of fractures in ever users of lithium, with the largest reductions at the highest cumulative doses (cumulative dose <250 DDD: adjusted OR 0.84 [95% CI 0.50-1.39]; cumulative dose 250-849 DDD: adjusted OR 0.85 [95% CI 0.72-0.99]; cumulative dose 850 DDD or more: adjusted OR 0.59 [95% CI 0.45-0.77]). These results changed, however, when taking into account the timing of lithium use. No association was found between cumulative dose and the risk of fractures in recent and past lithium users. In our study, 75% of the lithium users with the highest cumulative dose (≥850 DDD) could be classified as current users, whereas those with the lowest cumulative dose (<250 DDD) were recent or past lithium users (73%).

Table 3: The risk of fractures (any type) and concurrent use of psychotropic medication or a history of psychiatric hospitalisation in current lithium users (n=625)

	Current lithium users		
	Cases (n)	Controls (n)	Adj OR[a] (95% CI)
Antipsychotics			
yes	134	109	0.86 (0.66–1.12)
no	179	203	0.72 (0.58–0.88)
Antidepressants			
yes	185	141	1.02 (0.82–1.28)
no	128	171	0.61 (0.48-0.77)
Valproic acid/carbamazepine			
yes	24	21	0.90 (0.50–1.65)
no	289	291	0.75 (0.64–0.89)
Hospitalisations			
yes	44	40	0.80 (0.51–1.24)
no	269	272	0.75 (0.63–0.89)

a) Adjusted for: Heart failure, anaemia, cerebrovascular diseases, diabetes, renal impairment, psychotic disorders, and hyperparathyroidism (one year prior). Calcitonin, thiazid diuretics, hormone replacement therapy (HRT), disease-modifying antireumatic drugs (DMARDs), non steroidal anti-inflammatory drugs (NSAIDs), anxiolytics/hypnotics, antiparkinsonian drugs, inhaled corticosteroids and bronchodilators, oral corticosteroids, thyroid drugs, smoking status, and quetelet index (six months prior).

DISCUSSION

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

In line with the results from the previous case-control study conducted by Vestergaard et al.,[15] we observed in ever lithium users an association between risk of fracture and cumulative dose. However, this study did not consider the timing of lithium exposure and only considered ever use before of lithium. When taking into account the timing of lithium use in our study, the results of the cumulative dose based stratified analysis changed substantially, resulting in a disappearance of the association between cumulative lithium dose and the risk of fractures. Thus, it is likely that the finding of cumulative dose response on fractures in lithium users in the study performed by Vestergaard et al. can be explained by confounding by timing of lithium exposure. Epidemiological studies should therefore take into account the timing of exposure.

Several physiological mechanisms have been proposed for bone catabolic or anabolic effects of lithium. Long-term lithium treatment has been associated with the risk of secondary hyperparathyroidism that occurs in about 12-25% of long-term users.[11-14] Hyperparathyroidism may cause hypercalcaemia, thus stimulating bone resorption. Levels of ionised calcium were found to increase from baseline after three months of lithium treatment.[19,20] Another study found that

administration of lithium to healthy volunteers resulted in an acute increase in ionised parathyroid hormone, without concurrent alterations in ionised calcium levels.[21] On the other hand, lithium treatment may have bone anabolic effects through stimulating Wnt signalling. Wnts are glycoproteins that can initiate a signal transduction cascade, ultimately resulting in initiation of Wnt-responsive gene transcription. Through this mechanism Wnt is involved in the proliferation of bone-marrow derived mesenchymal stem cells, thereby controlling proliferation of osteoprogenitor cells which are the precursors to the bone mineralising osteoblasts. Lithium is a known Wnt mimic and has, in vitro, at low concentration been shown to stimulate the proliferation of bone-marrow derived mesenchymal stem cells.[22,23]

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

Besides the possible effects of lithium on bone, the disorders for which lithium was prescribed may also affect the risk of fractures. Lithium is predominantly prescribed for long-term treatment of bipolar disorders and depression. During manic episodes, patients may show a more dangerous life style with more accidents and thus an increased risk of fractures, while depressive episodes are associated with a higher risk of suicide and suicide attempts.[2,7] In this study, we observed an increased risk of fractures in patients who had discontinued lithium treatment, increasing with time since discontinuation. This finding supports a role of the underlying mental disorder in the aetiology of fractures in past lithium users. Following discontinuation of lithium treatment, its mood stabilising effects may have disappeared.

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

increased risk of fractures [24–29] and it may be possible that any beneficial effects of lithium on fractures is counteracted by these drugs.

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

In conclusion, it remains to be elucidated why current users of lithium display a decreased risk of fractures independent of duration of use. Based on the increasing risk of fractures with time since discontinuation of lithium treatment and the increased risk of fractures in those that used concomitant psychotropic medication or having been hospitalised for a mental disorder, our findings support a role of the underlying mental disorders in the aetiology of fractures in past lithium users. However, in order to fully unravel the association between the drug, the underlying mental disorder and the risk of fractures, a prospective

cohort study in which patients suffering from bipolar disorder are followed in time would be desirable. Patients with bipolar disorder treated with lithium could then be compared, with respect to bone quality parameters, fractures and disease severity/patterns, to patients with bipolar disorder not using lithium. A complicating factor, however, is that the main pharmacological alternatives for lithium in bipolar disorder, e.g. carbamazepine, (also) have influence bone quality and fracture risk.[27]

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Determinants and treatment of potential lithium intoxications

3

3.1

Drug-drug interactions as a determinant of elevated lithium serum levels in daily clinical practice

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ABSTRACT

Background

Lithium is a drug with a narrow therapeutic window. Concomitantly used medication is a potentially influencing factor of lithium serum concentrations.

Objective

We conducted a multicentre retrospective case-control study with the aim of investigating lithium-related drug interactions as determinants of elevated lithium serum levels in daily clinical practice.

Methods

Cases were patients with an increase of at least 50% in lithium serum concentrations resulting in an elevated lithium serum level of at least 1.3 mmol/l, and who were not suspected of a suicide attempt. Controls were patients who showed stable lithium serum levels within the therapeutic range. Use and start of nonsteroidal anti-inflammatory drugs, diuretics, renin-angiotensin inhibitors, theophyllin and antibiotics were investigated as potential determinants of the elevated lithium serum levels. Irregularity in lithium dispensing pattern, change in lithium dosing regimen, age, gender, prescribing physician and laboratory parameters were investigated as potential confounders.

Results

We included 51 cases and 51 controls in our study. Five (9.8%) controls and 15 (29.4%) cases used potentially interacting co-medication (OR of 3.83; 95% CI 1.28-11.48). Start of potentially interacting co-medication was observed in eight (15.7%) cases and in zero (0%) controls resulting in an OR of 20.13 (95% CI 1.13-359). After adjustment for co-medication, irregularity in lithium dispensing pattern, change in lithium dosing regimen, and age the statistically significant association was lost. We report an OR of 2.70 (95% CI 0.78-9.31) for use of concomitant medication, with a large contribution of antibiotic agents, and an OR of 3.14 (95% CI 1.15-8.61) for irregularity in lithium dispensing pattern.

Conclusion

Use of potentially interacting co-medication, especially antibiotics, tends to be associated with elevated lithium serum levels.

INTRODUCTION

Lithium salts are first choice agents for the long-term prophylaxis and acute treatment of several psychiatric disorders.[1-3] A strong relationship between lithium serum levels and both its efficacy and its toxicity has been established.[4-8] The narrow therapeutic window together with the high inter- and intraindividual variability in pharmacokinetics and sensitivity to its effects, necessitates regular therapeutic drug monitoring of patients receiving lithium.[8-10] Guidelines for monitoring lithium serum levels have been developed worldwide. In the Netherlands, for example, it is recommended to measure lithium serum levels at a frequency of two to four times a year after stable therapeutic lithium serum levels (0.6-1.2 mmol/l) have been reached.[11]

A large part of the intraindividual variability in lithium pharmacokinetics is due to the high susceptibility of lithium excretion to changes in renal blood flow and water and salt homeostasis. Influencing factors include somatic co-morbidity (e.g., water and electrolyte changes induced by fever, diarrhoea or vomiting) and concomitantly used drugs (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics and renin-angiotensin (RAS) inhibitors). For most of these drugs a mechanism explaining the interaction with lithium excretion has been either proposed or fully elucidated.

Nonsteroidal anti-inflammatory drugs increase lithium serum concentrations by inducing a decrease in glomerular filtration rate as a result of inhibition of prostaglandin synthesis. Diuretics influence lithium serum concentrations by inducing sodium depletion and thereby stimulating proximal sodium and therefore lithium reabsorption. RAS inhibitors induce volume depletion and in this manner reduce glomerular filtration rate, which may lead to a reduction in lithium clearance. Up to now, theophyllin has been implicated in lowering lithium serum concentrations by inducing lithium clearance through an unknown mechanism. The interaction between antibiotics and lithium is most likely not directly related to the drug itself but probably related to the fever, vomiting, diarrhoea and poor food and water intake associated with the underlying infection.

Most of the drug-drug interactions mentioned in textbooks and other sources of clinical information originate from case reports and small controlled studies.[12-38] The actual relevance of drug-drug interactions with lithium in daily clinical

practice, to our knowledge, is unknown. Therefore, relying on the established relationship between lithium serum concentrations and risk of (toxic) side-effects, we conducted a study to determine the influence of potentially interaction concomitant medication on the development of elevated lithium levels.

METHODS

Setting

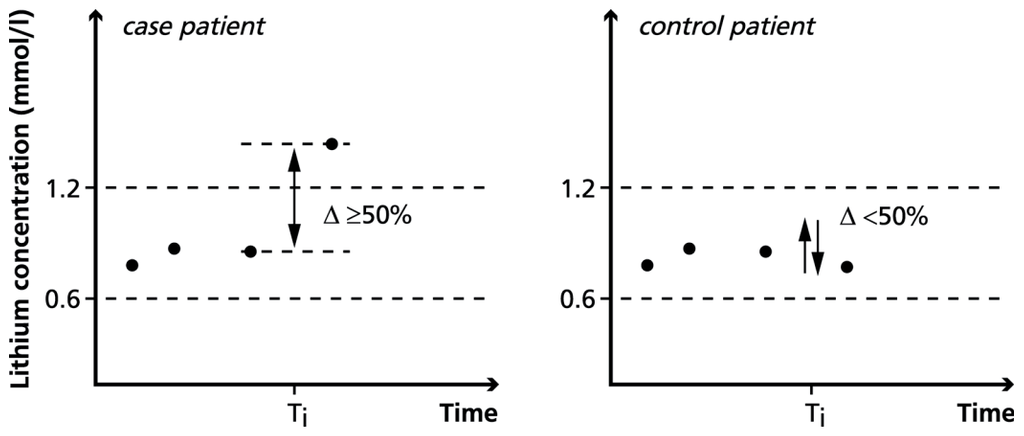
A multicentre retrospective case-control study was conducted among patients receiving long-term treatment with lithium for whom the lithium serum concentrations were under hospital laboratory control, during the time period of January 1997 until January 2003. Lithium serum concentrations of both inpatients and outpatients in the Netherlands are usually monitored by hospital laboratories. A total of 12 teaching hospitals participated in the study.
The medical ethics committee of the St Radboud University Hospital in Nijmegen, the Netherlands, approved the study protocol.

Study population

The study base consisted of patients who were at least 18 years of age and on lithium treatment for at least three months. To be eligible for participation all participants (cases and controls) had to have at least two subsequent lithium serum concentrations within the therapeutic range (0.6-1.2 mmol/l). Blood samples had to be drawn at least ten hours after the last lithium intake. Both inpatients and outpatients were eligible for participation. Patients were excluded if they were suspected of a suicide attempt.
From this study base we identified all cases and sampled controls as displayed in Figure 1. Cases were defined as all patients with a lithium serum level of ≥1.3 mmol/l, in combination with an increase in lithium serum level of at least 50% compared with the previous lithium serum level. The date on which the elevated lithium serum level was encountered was termed the 'index date'. For each case one control was randomly selected from the aforementioned study base. Controls had to have a lithium serum level on the case index date (± 1 week) within the therapeutic range (0.6-1.2 mmol/l). In addition, the difference between the lithium serum level on the index date and the previous lithium serum level had to be <50%. For both cases and controls, the time

window between the index date and the date of lithium serum level determination prior to the index date had to be <6 months.

Figure 1: Case and control definition



Ti = index date

Case: patient with an elevated lithium serum concentration (≥1.3 mmol/l) resulting from an increase of at least 50% compared with the previous lithium serum concentration. The date on which this lithium serum concentration was encountered is termed the index date.

Control: patient who on the index date had a lithium serum concentration within the therapeutic range (0.6-1.2 mmol/l), encompassing a difference of <50% compared with the lithium serum concentration prior to the one encountered on the index date.

Exposure definition

Exposure to potentially interacting concomitant medication in both the cases and the controls was assessed. From the literature, four drug classes (NSAIDs, diuretics, RAS inhibitors and antibiotics) and theophyllin, were *a priori* identified as potentially interacting with lithium. Although strictly speaking the interaction with antibiotics is not a drug-drug interaction, but a drug-disease interaction antibiotics were included.

Information on the study groups' exposure to these potentially interacting drugs was collected from drug dispensing data obtained from the 'community pharmacy', hospital pharmacy or the general practitioner's medical record. Drug dispensing data were obtained for a period starting at least one year prior to the index date. For each drug dispensing event, the prescription filling date, the drug name, the daily amount of drug prescribed and the total amount of drug per

prescription was provided. In order to determine the theoretical exposure time window, the total amount of drug dispensed per prescription was divided by the daily amount of drug prescribed. Patients were considered users if the medication was started before the index date and the index date fell within the theoretical exposure window. Starting and stopping of potentially interacting drugs are considered the most critical events on the subject of drug-drug interactions. Therefore we also looked into a subpopulation of users of medication, specifically those who had recently started on concomitant medication. Starting was defined as having had a first prescription in the 30-day period before the index date and not having had a prescription for the same medication in the 120 days before this 30-day period. For use of NSAIDs and antibiotics, starting was defined as having had a first prescription for the medication in the 30 days prior to the index date and not having had a prescription for a drug of the same drug class in the 14 days prior to the start of the drug before the index date. This difference in definition for starting on NSAIDs and antibiotics was chosen because influences of NSAIDs or antibiotics are known to appear and disappear rather quickly. Both NSAIDs and antibiotics can be used for relatively small periods, whereas diuretics and RAS inhibitors often are used for longer periods.

Potential confounding factors

In order to adjust for any factor that may confound the association between the use of concomitant medication and the occurrence of elevated lithium serum levels, the following data were gathered from the medical record and laboratory history: patient characteristics (age, gender), prescribing physician (psychiatrist or other), change in lithium dosing regimen (type of salt, daily dose and dose frequency) and laboratory parameters (serum creatinine, sodium, thyroid-stimulating hormone and potassium concentrations). In addition, irregularity in lithium dispensing pattern per patient was estimated using the pharmacy dispensing data for a time period encompassing at least three different dispensing occurrences before the index date.[39] Dispensing was termed irregular if the calculated ratio – days for which medication was dispensed according to dispensing data (the total dispensed amount divided by the prescribed daily dose) divided by the total number of days encompassing the time period – was <90% or >110%.

Table 1: Characteristics of the study population

	Controls n=51 (100%)	Cases n=51 (100%)
Patient characteristics		
female gender; n (%)	30 (58.8%)	36 (70.6%)
age; mean (sd)	49.8 (13.8)	54.9 (15.0)
Lithium characteristics		
prescribing physician (psychiatrist); n (%)	32 (68.1%)[a]	32 (72.7%)[a]
irregularity in lithium dispensing pattern >110% or <90%; n (%)	**9 (20.9%)[a]**	**19 (47.5%)[a]**
change in lithium dosing regimen; n (%)[b]	8 (15.7%)	9 (17.6%)
Index date parameters		
lithium dose in mmol/24h; median (range)	27.0 (10.8–43.2)	27.0 (10.8–43.2)
lithium serum level in mmol/l; median (range)	**0.80 (0.59–1.08)**	**1.55 (1.28–2.78)**
Date prior to the index date parameters		
lithium dose in mmol/24h; median (range)	27.0 (10.8–43.2)	27.0 (10.8–43.2)
lithium serum level in mmol/l; median (range)	0.83 (0.59–1.18)	0.78 (0.56–1.16)
Change between index date and date prior to the index date		
lithium serum level elevation in %; median (range)	**–2.39 (–30.6–42.3)**	**107 (50–369)**
number of days; median (range)	**90 (7–168)**	**42 (3–197)**
Concomitantly used medication; n (%)		
use of interacting medication	**5 (9.8%)**	**15 (29.4%)**
NSAID user	2 (3.9%)	2 (3.9%)
diuretic user	2 (3.9%)	6 (11.8%)
RAS inhibitor user	3 (5.9%)	4 (7.8%)
antibiotic user	0 (0.0%)	7 (13.7%)
starting of concomitant medication	**0 (0.0%)**	**8 (15.7%)**
NSAID starter	0 (0.0%)	1 (2.0%)
diuretic starter	0 (0.0%)	1 (2.0%)
RAS inhibitor starter	0 (0.0%)	1 (2.0%)
antibiotic starter	0 (0.0%)	7 (13.7%)

NSAID = nonsteroidal anti-inflammatory drug; RAS = renine-angiotensin
Values in bold indicate a statistically significant difference between cases and controls established in a univariate logistic regression analysis.
a) Data not for all patients available; see Results section.
b) Change in daily intake frequency and/or change in lithium salt and/or change in prescribed daily dose.

Data analysis

Differences in baseline population characteristics between case subjects and controls were evaluated with Mann-Whitney and with Chi-square analysis where appropriate.

The primary determinants (use and starting of potentially interacting concomitant medication) and all variables considered to be potentially confounding factors were assessed for the presence of a statistically significant association with elevated lithium serum levels by performing a univariate logistic regression analysis.

Those variables that were univariately significantly associated with elevated lithium serum levels ($p<0.10$) and that caused a change in point estimate of ≥10%, were incorporated into our multivariate model.

In order to assess the OR for determinants or potential confounding factors for which zero was included in the 2×2 table for either the cases or the controls, 0.5 was added to all data.

Data were analysed using SPSS version 11.0.

RESULTS

Fifty-one cases and 51 controls were included in the study. Population characteristics (age, gender) as well as the distribution of variables among cases and controls are presented in Table 1.

Although cases were slightly older than controls and females were represented more frequently, age and gender were not shown to differ statistically significant between cases and controls. For cases the increase in lithium serum level between the index date and the date prior to the index date was 107% (range: 50–369%). For controls this change was –2.39% (range: –30.6% to 42.3%). The lithium serum level on the index date was 1.55 mmol/l (range: 1.28–2.78 mmol/l) versus 0.80 mmol/l (range: 0.59–1.08 mmol/l) for cases and controls respectively. No statistically significant changes in lithium salt and change in lithium dosage were found. Cases and controls differed significantly for the number of days that had elapsed between the index date and the date prior to the index date.

Irregularity in lithium dispensing pattern, according to our definition (based on pharmacy dispensing data), was determined for 83 of the 102 patients in our study population. The remaining 19 of the 102 patients in our study population

were inpatients for whom medication was delivered to the ward, exclusively based on prescription refill data.

For 13 patients in our study population, the prescribing physician could not be identified based on medication dispensing data. Laboratory parameters measured within a range of three days prior to or after the index date were not broadly available. Therefore data on laboratory parameters could not be taken into account for in our analysis.

Five (9.8%) controls and 15 (29.4%) study subjects used potentially interacting co-medication resulting in an OR of 3.83 (95% CI 1.28-11.48). Starting of potentially interacting co-medication was observed in zero (0%) controls and eight (15.7%) study subjects resulting in an OR of 20.13 (95% CI 1.13-359) (Table 2).

As can be seen in Table 1 the largest contribution of potentially interacting concomitant medication in both users and starters can be attributed to the class of antibiotics. Seven cases and no controls were users of antibiotics. Within the cases six different antibiotics were used. No specific antibiotic, thus seemed to be more associated to elevated lithium serum levels. Irregularity in lithium dispensing pattern, calculated for 83 of the 102 patients in our study population, was clearly associated with elevated lithium serum levels (OR 3.42; 95% CI 1.31-8.94).

Table 2: Univariate and multivariate logistic regression analysis

	Univariate analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
Use of concomitant medication	3.83 (1.28–11.48)	2.70 (0.78–9.31)
Starting of concomitant medication	20.13[a] (1.13–359)	n.e. n.e.
Irregularity in lithium dispensing pattern	3.42 (1.31–8.94)	3.14 (1.15–8.61)
Age (continue)	n.e. n.e.	n.e. n.e.
Change in lithium dosing regimen	1.15 (0.41–3.27)	1.38 (0.45–4.24)

n.e. = not able to estimate

a) In order to assess the OR for determinants or potential confounding factors for which zero was included in the 2×2 table for either the cases or the controls, 0.5 was added to all data.

Potential confounding for the calculated OR for use of potentially interacting concomitant medication was dealt with in our multivariate analysis. Irregularity in lithium dispensing pattern, change in lithium dosing regimen (both significant

confounding agents according to our definition) and age were incorporated into our multivariate analysis. The association between the use of concomitant medication and elevated lithium serum levels lost statistical significance upon performing the multivariate analysis (OR 2.70; 95% CI 0.78-9.31). Irregularity in lithium dispensing pattern was found to be statistically significant when associated with elevated lithium serum levels (OR 3.14; 95% CI 1.15-8.61).

DISCUSSION

Our results show that the use and start of potentially interacting concomitant medication is associated with elevated lithium serum levels in daily clinical practice. Unfortunately in our multivariate analysis the statistical significance of the association is lost. Within the drug groups no specific drug seemed to be more associated with elevated lithium serum levels.

As there were no starters among our controls, performing a multivariate analysis on starting of concomitant medication was not possible.

Our results further indicate that irregularity in lithium dispensing pattern is an important risk factor for elevated lithium serum levels, as we found a statistically significant association between elevated lithium serum levels and an irregular lithium dispensing pattern.

There are certain limitations to our study. We only gathered data on elevated lithium serum levels and no data on the actual appearance of (toxic) side-effects of lithium. However, a strong relationship does exist for lithium serum concentrations and the risk of appearance of (toxic) side-effects. Furthermore, we did include an increase in lithium serum level of at least 50% relative to the prior measured level, which for an individual stabilized on lithium is associated with a high risk of the appearance of (toxic) side-effects.[4-10]

We had no access to information on possible concomitant use of over-the-counter medication. Such information could be important, particularly in case of NSAIDs,[12,15,16,26,27,32-36] which are, in the Netherlands for example freely accessible.

Besides use and start of potentially interacting co-medication, the withdrawal of these agents could also influence lithium serum levels. However it has been reported that withdrawal is more likely to result in a decrease[12-38] rather than in an increase in lithium serum level. As our focus is on the appearance of elevated

lithium serum levels, data on withdrawal of potentially interacting drugs was of lesser importance to this report.

The most plausible explanation for the association between the use of antibiotic agents and elevated lithium serum levels lies with the underlying infection, associated fever and poor fluid intake. Therefore, missing data on somatic co-morbidity associated with fever and poor fluid intake could be of great importance.

Laboratory parameters are known to fluctuate rather quickly. Therefore we allowed a maximum of only three days between the index date and the date at which the laboratory parameter was determined. Our rather stringent criteria may have resulted in the lack of laboratory parameters. As lithium clearance is largely influenced by disturbances in electrolyte and fluid homeostasis and renal function, missing data on laboratory parameters could be of considerable importance.

We do not have any information on environmental temperature. Besides the influence of endogenous temperature (provided for example by fever), there is also evidence for the influence of exogenous temperature (environmental temperature) on lithium serum levels.[40]

Finally the small sample size is a limitation. It might be possible that the appearance of elevated lithium serum levels (according to our definition) and the use of potentially interacting concomitant medication are not as frequently present as thought in advance.

The strength of our study is that we evaluated the importance of lithium related drug-drug interactions on elevated lithium serum levels, not in a research setting, but in daily clinical practice. To our knowledge, this study is the first to evaluate drug-drug interactions with lithium as a determinant for elevated lithium serum levels in daily clinical practice. Drug prescribing physicians, knowledge of drug dispensing pharmacists and patient's experience on handling of potential drug-drug interactions and symptoms is as such taken into account. Moreover, as our study was performed as a multicentre study we are not constrained by regional differences in prescription and treatment guidelines.

For both use and start of potentially interacting concomitant medication, the class of antibiotics is shown to be the most important contributor. Within the group of antibiotics no specific antibiotic seemed to be more associated to elevated lithium serum levels. In the Netherlands the 'community pharmacy' performs

checks on concomitant prescription of potentially interacting drugs with lithium, it verifies concomitant prescription of diuretics, RAS inhibitors, NSAIDs and metronidazol.[41] One can imagine that the check on the concomitant prescription next to lithium, and the following warning signal generated by the 'community pharmacy' does lead to extra caution in both physician and patient. However, for concomitant prescription of antibiotics next to lithium no such warning signal is generated. In addition, it is possible that in case of use of antibiotic agents by the patient, some symptoms associated with lithium (toxic) side-effects can be misinterpreted and consequently be wrongly attributed to the infection.

The potential of several drugs to decrease lithium clearance has been shown. However, evidence for clinical relevance of lithium-related drug interactions resulting in either induction or inhibition of lithium clearance is inconclusive.[12,22]

In conclusion, in this population based case-control study we found that in daily clinical practice potentially interacting co-medication and especially antibiotic agents tend to be associated with a higher risk of elevated lithium levels. In addition, the association between irregularities in lithium dispensing pattern is a risk factor for elevated lithium serum levels. Based on the results of our study we would like to make two recommendations: first, careful monitoring of lithium dispensing characteristics at the 'community pharmacy' and of the prescribed amount of lithium by the prescribing physician; secondly, considering extra lithium serum concentration monitoring for those suffering from an infection. Use of antibiotics can, as such, be considered a proxy for the existence of an infection. Based on the large contribution of antibiotic agents, further studies on the effects of concomitant prescription of these agents next to lithium are warranted.

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3.2

The impact of environmental temperature on lithium serum levels

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ABSTRACT

Background

Three studies have reported a seasonal variation in lithium serum levels, with higher levels during summer.

Objective

Our objective was to investigate the impact of actual environmental temperature on lithium serum levels.

Methods

A retrospective study was conducted using available records of lithium serum levels for the period between January 1995 and July 2004, obtained from three large teaching hospitals in the Netherlands. Lithium serum levels were linked to season and average daily temperature data obtained from the Royal Netherlands Meteorological Institute. An analysis was performed on all lithium serum levels not accounting for the intra-individual dependency of lithium serum levels. The association between season, temperature and both absolute lithium serum level and the frequency of potentially toxic serum levels was investigated. A mixed model analysis, accounting for intra-individual dependency of lithium serum levels, was performed.

Results

A total of 41 102 records of lithium serum levels (3 054 patients) were included. A significant difference in mean lithium serum levels across seasons ($p<0.001$) and temperature categories ($p=0.001$) was found, with a peak in summer (0.761 mmol/l ± standard error of the mean [sem] 0.002) and at temperatures 15-20°C (0.762 mmol/l ± sem 0.005), and a minimum in winter (0.748 mmol/l ± sem 0.002) and at <0°C (0.741 mmol/l ± sem 0.005). The relative frequency of potentially toxic serum levels significantly differed between seasons ($p=0.023$; highest in winter), but not between temperature categories ($p=0.481$). A significant positive association for intra-individual lithium serum level and season ($p<0.001$), and temperature ($p<0.001$) was established.

Conclusion

Season and environmental temperature have a statistically significant but therapeutically irrelevant effect on lithium serum levels.

INTRODUCTION

Lithium is the most widely used drug in the management of bipolar disorder, both in acute mania as well as in maintenance treatment.[1] Its narrow therapeutic window (0.6–1.2 mmol/l), together with the high intra- and interindividual variability in pharmacokinetics and interindividual sensitivity to adverse drug reactions, necessitates regular monitoring of lithium serum levels.[2,3] Lithium serum levels above 1.3-1.5 mmol/l commonly result in toxic side-effects.[3,4] The severity of symptoms is generally proportional to both the degree and the duration of the elevation of lithium serum levels.[4]

Since about 80% of the renally excreted lithium is reabsorbed in the proximal tubule together with sodium,[5] any situation causing an increase in proximal reabsorption of sodium, such as a negative water or sodium balance (e.g., due to perspiration without adequate compensatory fluid and salt intake), will result in an increase in tubular lithium reabsorption, thereby elevating the lithium serum level and consequently the risk for lithium toxicity.[2-4] Higher rates of perspiration can be induced, for instance, by fever, sudden changes in amount of exercise or sudden substantial elevations in environmental temperature.[6-8]

To date, three studies have reported a seasonal variation in lithium serum levels, all reporting higher levels during summer. These studies were performed in different parts of the world, i.e., the Netherlands,[9] Italy,[10] and Michigan, USA.[11] The differences in the extent of seasonal variation of lithium serum levels in the three studies were attributed to differences in environmental temperature in these different parts of the world. For Italy the observed seasonal variation was about 10% in a total of 168 patients, whereas in the Netherlands a difference of about 5% was observed in a total of 68 patients. In two of these studies the mean lithium serum level per patient for each season was studied. The study in Michigan evaluated the mean lithium serum level per month for a total of 377 admitted patients.

To our knowledge, the impact of the actual environmental temperature on lithium serum levels, and the influence of season and actual environmental temperature on intra-individual lithium serum levels have never been studied. Therefore we decided to investigate the impact of actual environmental temperature and season on lithium serum levels, taking within subject dependency into account.

METHODS

Setting and study population

A retrospective study was conducted using available records of lithium serum levels for patients in whom lithium serum levels had been measured in the laboratories of three large teaching hospitals in different parts of the Netherlands, i.e. TweeSteden hospital, Tilburg; Altrecht Institute for Mental Health Care, Utrecht; and Reinier De Graaf Hospital, Delft. Data were gathered for the period between January 1995 until July 2004. Lithium serum levels for all patients of 18 years and older for whom at least two levels were available were included.

Data on average daily temperature were obtained from the nearest meteorological site of the Royal Netherlands Meteorological Institute, all situated within 30 kilometres of the respective laboratories.

Data

Data on patient gender, year of birth, lithium serum level and corresponding blood sampling date were gathered, along with a unique patient identification number. Approval to use anonymous patient data for this study was obtained from the scientific boards of the three participating institutions.

Lithium serum levels were linked to average daily temperature one day prior to blood sampling. Since blood samples are usually drawn in the morning and sodium and lithium serum levels can modify rapidly,[2,7,8] the average daily temperature of the day prior to blood sampling was considered to be the most appropriate. Temperature was taken both as a continuous variable, as well as a per five degrees Centigrade categorized variable with a lower category of temperatures below 0°C and an upper category of temperatures of 20°C and higher.

In order to put the results into perspective with the results from the studies reported previously, the impact of seasonal variation on lithium serum levels was also investigated. Therefore, lithium serum levels were also linked to the different seasons, with seasonal transitions defined as occurring on March 21, June 21, September 21 and December 21, as in the previous studies.

Potentially toxic lithium serum levels were defined as levels of ≥1.3 mmol/l, resulting from an increase of ≥50% in lithium serum level with at least two

preceding subsequent levels within the therapeutic range (0.6–1.2 mmol/l). Age was categorized as old (≥65 years) and young (<65 years).

Data analysis

All lithium serum levels below 0.2 mmol/l were excluded from analysis on account of uncertainty regarding the intake of lithium and analytical imprecision below this value.

The first data analysis included every lithium serum level obtained from the subjects described in the paper. It is pertinent to note that these analyses included several lithium serum levels for the same individual at different time-points and during different seasons of the year. Therefore, this analysis does not take into account within-subject (i.e., intra-individual) correlation in lithium serum levels. The mean lithium serum level, as well as the frequency of potentially toxic serum levels within each season and temperature category, were determined. The differences in mean lithium serum level between seasons and temperature categories were assessed by a one-way ANOVA analysis. Differences in the frequency of potentially toxic serum levels across seasons and temperature categories were analysed by chi-square analysis.

In order to account for within-subject dependency of the lithium serum levels, a linear mixed model analysis was subsequently performed. The coefficients of season, temperature and age were defined as fixed effects (assuming that all variables of interest are represented in the data). A random intercept was used to allow for differences in intra-individual lithium serum levels.

All analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 41 102 lithium serum levels from a total of 3 054 patients were included. More females (62.3%) than males were included and the mean age was 50.5 years (standard deviation [sd] 17.0). A large variation in the total number of lithium serum levels per person was observed, with a median of ten levels per patient (range of 2-100); 90% of the serum level measurements pertained to patients with up to 51 serum level measurements; 50% to patients with up to 28 serum level measurements; and 33% to patients with up to 14 serum level

measurements. Lithium serum levels were equally distributed across seasons. However, with regard to temperature about 75% of the levels was found between 5-20°C (Table 1).

Table 1: Lithium serum level and temperature characteristics

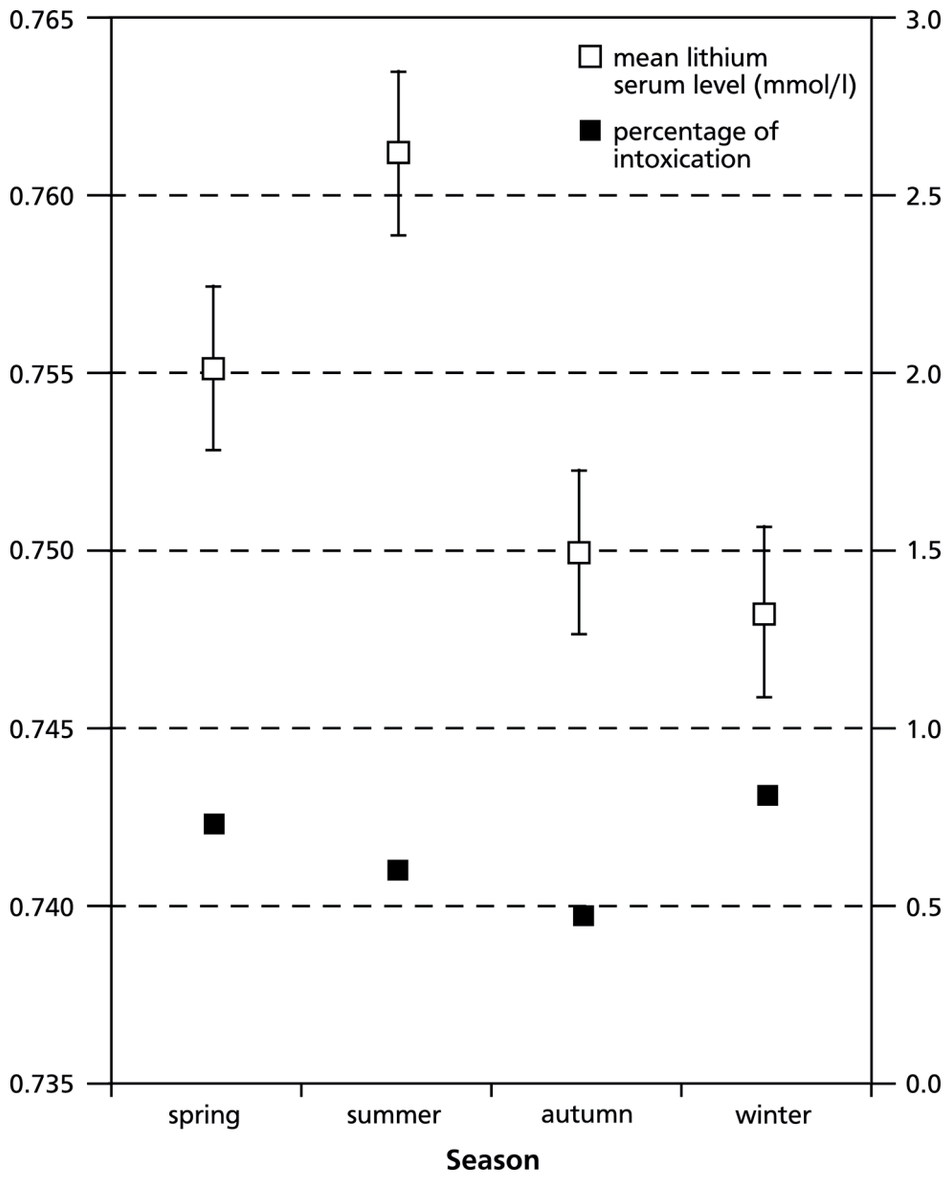
Lithium serum levels	n=41 102 (100%)	T mean (°C) ± sd
Seasonal distribution		
spring	10 538 (25.6%)	11.8 ± 4.5
summer	10 365 (25.2%)	17.4 ± 3.1
autumn	10 073 (24.5%)	8.1 ± 4.9
winter	10 126 (24.6%)	4.5 ± 4.2
Distribution per temperature category; T (°C)		
<0	2 218 (5.4%)	
0 – 5	5 993 (14.6%)	
5 – 10	11 091 (27.0%)	
10 – 15	10 617 (25.8%)	
15 – 20	8 946 (21.8%)	
≥ 20	2 237 (5.4%)	

T = temperature, sd = standard deviation

A statistically significant difference in mean lithium serum levels was found for seasons ($p<0.001$), peaking in summer (0.761 mmol/l ± standard error of the mean [sem] 0.002) and at a minimum in winter (0.748 mmol/l ± sem 0.002) (Figure 1). The maximal seasonal difference in lithium serum level was about 2%. A statistically significant difference in mean lithium serum level for temperature category ($p=0.001$) was observed, with higher lithium serum levels occurring at higher average daily temperatures (Figure 2). Mean lithium serum levels were 0.741 mmol/l (± sem 0.005) at temperatures <0°C and 0.762 mmol/l (± sem 0.005) at temperatures of 15-20°C, again resulting in a maximal difference of about 2%.

A statistically significant difference in the frequency of potentially toxic serum levels ($p=0.023$) across seasons was established (Figure 1), with the highest frequency in winter, and the lowest in autumn. No significant ($p=0.481$) difference was found in the frequency of potentially toxic serum levels across temperature categories (Figure 2).

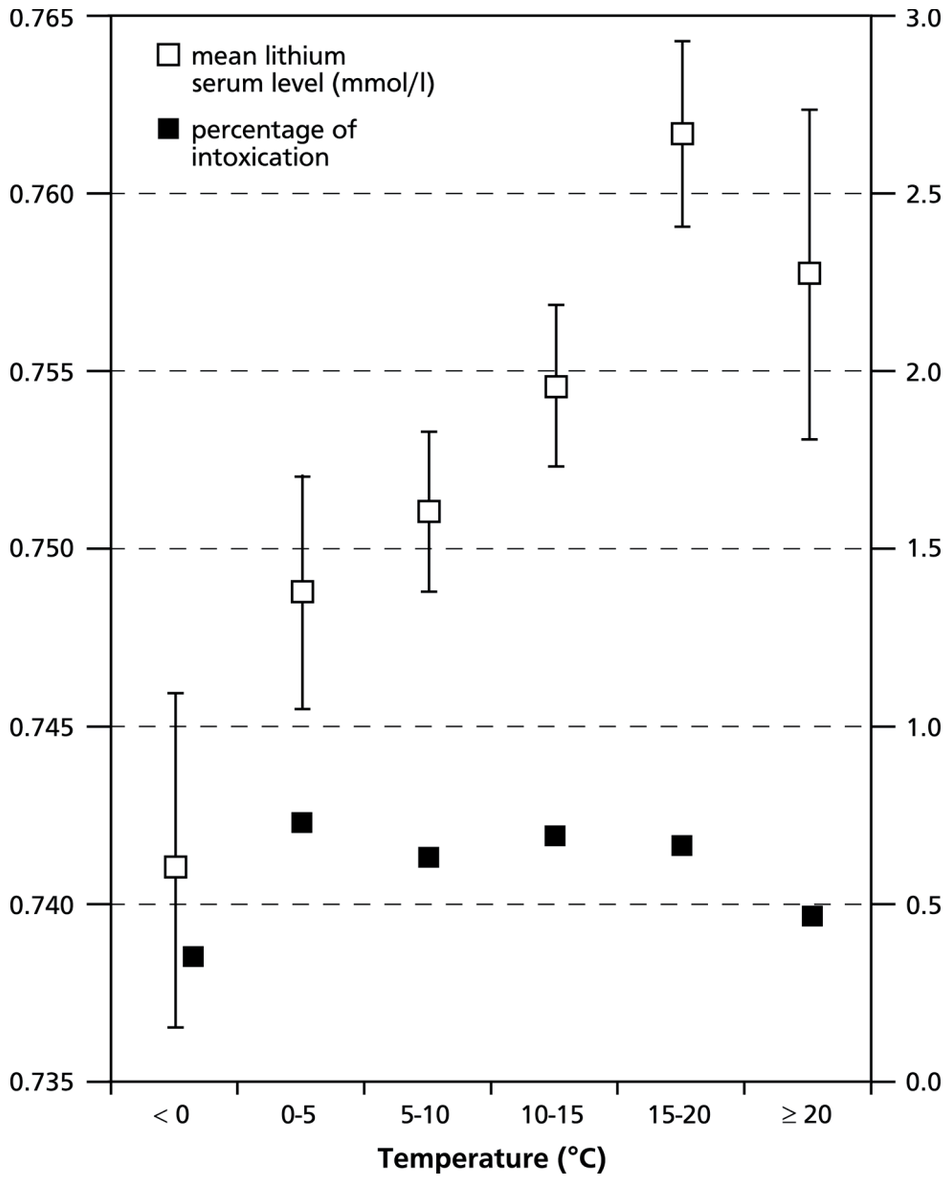
Figure 1: Mean overall lithium serum levels and frequencies of potentially toxic serum levels[a] per season



Bars represent standard errors of the mean.
There was a statistically significant difference in mean lithium serum levels across seasons ($p<0.001$, one-way ANOVA) and frequencies of potentially toxic serum levels ($p=0.023$, χ^2) significantly differed between seasons.

a) Defined as a lithium serum level ≥1.3 mmol/l resulting from an increase of ≥50% in lithium serum level with at least two preceding subsequent levels within the therapeutic range (0.6–1.2 mmol/l).

Figure 2: Mean overall lithium serum levels and frequencies of potentially toxic serum levels[a] per temperature category



Bars represent standard errors of the mean.
There was a statistically significant difference in mean lithium serum levels across temperature categories (p=0.001, one-way ANOVA). Frequencies of potentially toxic serum levels (p=0.481, χ^2) did not significantly differ between temperature categories.

a) Defined as a lithium serum level ≥1.3 mmol/l resulting from an increase of ≥50% in lithium serum level with at least two preceding subsequent levels within the therapeutic range (0.6–1.2 mmol/l).

Taking into account the intra-individual dependency of the data, a statistically significant ($p<0.001$) effect of both season and environmental temperature on lithium serum level was established by performing a mixed model analysis. Equation 1 and 2 represent the effect of season and temperature on lithium serum level, respectively:

Lithium serum level (mmol/l) =
0.00544 (se 0.00095) × season[a] + 0.722 (se 0.0036) (1)

[a] substituting 1 for winter, 2 for autumn, 3 for spring and 4 for summer

Lithium serum level (mmol/l) =
0.000793 (se 0.000166) × temperature[b] + 0.727 (se 0.00321) (2)

[b] average daily temperature in °C at one day prior to blood sampling

Equation 1 results in lithium serum levels of 0.727 mmol/l and 0.744 mmol/l for winter and summer, respectively. Equation 2 results in lithium serum levels of 0.727 mmol/l at 0°C and 0.743 mmol/l at 20°C.

A sub-analysis on lithium serum levels was performed on a subset of patients for whom more than six, more than ten and more than 12 lithium serum levels were available. In these sub-analyses, the same trends were observed for the relationships between lithium serum levels and both temperature and season, respectively (results not shown). In order to investigate the influence of age on the effect of temperature on lithium serum level, age category was included in the mixed model for temperature and lithium serum level. The effect of environmental temperature on lithium serum level was about twice as great in those aged ≥65 years (0.014 mmol/l elevation in lithium serum level per 10°C increase) than in those aged <65 years (0.006 mmol/l elevation in lithium serum level per 10°C increase). This difference, however, was not statistically significantly different ($p=0.065$).

DISCUSSION

We found that lithium serum levels in daily clinical practice in the Netherlands showed statistically significant differences across seasons and temperatures. Higher lithium serum levels were observed at higher temperatures as well as during warmer seasons, the latter in accordance with results from previous studies.[9-11]

The effect of temperature and season on lithium serum level persisted when accounting for the within-subject dependency of lithium serum levels.

Although statistically significant, the reported effects are not of clinical importance. A temperature increase of ten °C, for example, results in an elevation in lithium serum level of only 0.008 mmol/l (Equation 2). Although our finding that a warmer season is related to higher lithium serum levels is in accordance with results from previous studies, we report a maximal difference in lithium serum levels between seasons of about 2%, in contrast to the previously reported variation of about 5% in the Netherlands.[9] This discrepancy may be explained by the fact that we included lithium serum levels for about 3 000 patients in contract to the 68 patients included in the study by Beersma et al.[9] It may be possible to explain the observed difference in minimum and maximum serum level per season of 10% for Italy and 2% for the Netherlands in this study by the difference in climate between the two countries. Italy has a Mediterranean climate, characterized by a dry, hot summers and mild winters. Compared to Italy, the Netherlands experiences overall lower temperatures without a dry season, due to lower summer temperatures and greater influence of the sea.

In addition, the frequency of potentially toxic serum levels did not differ statistically significantly between temperature categories. A possible reason for this is that patients can avoid the consequences of high temperatures in summer, via climate control measures (e.g., air conditioning) and through compensatory fluid and salt intake, as is recommended in information leaflets for patients taking lithium.

However, the frequency of potentially toxic serum levels did differ with statistical significance across seasons but, in contrast to our hypothesis on the impact of temperature on lithium serum levels, did not follow the order of coldest to warmest season. The observed peak during colder seasons may reflect a seasonal variation in the prevalence of intentional overdosing. Depression in bipolar disorders has, in some studies, been shown to arise mostly in autumn and winter.[12-15] The observed peak of potentially toxic serum levels may therefore possibly reflect a rise in suicide attempts corresponding with a higher prevalence of depression in winter. In the literature conflicting results are reported with respect to seasonal variation of intentional overdosing; most studies, however, report a peak in spring and summer.[16-22] We cannot entirely explain the discrepancy between the peak in suicide attempts reported in the literature and

the higher prevalence of potentially toxic serum levels in winter observed in this study. However, the reports in the literature with respect to seasonal variation and suicide frequency are conflicting and we have no information regarding the reasons for the observed potentially toxic serum level. It may be possible that, in our study, we missed several instances of intentional overdose and the corresponding lithium measurements, since one of the included hospitals is a psychiatric facility and patients with severe somatic problems due to intentional overdosing may have been transported to another (general) hospital.

Due to a less adequate responding thirst centre and a decreased glomerular filtration rate, elderly people are presumed to be more at risk for sudden elevation of lithium serum levels than younger people are.[23,24] Accordingly, we did establish a trend towards a larger impact of temperature on lithium serum levels in elderly subjects.

There are several limitations to our study. First, in accordance with our hypothesis that environmental temperature has a prompt, if any effect, we defined temperature as average daily temperature one day prior to blood sampling. In comparison with average daily temperature over a two, three and seven day period prior to blood sampling, temperature defined as average daily temperature one day prior to blood sampling actually provided the best fit. We obtained data on average daily temperature, but maximal daily temperature, apparent temperature,[25] or average daily temperature between dawn and sunset, instead of 24 hour measurements, could also be of importance. Furthermore, it may be hypothesized that longer periods of elevated environmental temperature (e.g. heat waves) may have greater impact than short periods of elevated temperature.

Secondly, we had no information on lithium dosage. Bipolar disorders have been shown to display seasonal variation, possibly leading to prescriber initiated dose changes and patient-initiated differences in adherence to treatment. Previous research has demonstrated evidence for seasonal variation in the course of bipolar disorder, with mania arising more frequently in spring and summer, while depression tends to arise more in autumn and winter.[12-15,22,26-30] Higher lithium serum levels in summer could therefore also be partly attributed to increases in lithium dose. On the other hand, it has been demonstrated that even at stable lithium doses, lithium serum levels fall during periods of mania and rise throughout periods of depression.[31-34]

Third, we have no information on the specific reasons for lithium serum measurements. Measurements initiated because of suspected high levels caused by deliberate overdosing could therefore not be excluded. It is possible that this may falsely influence the observed higher frequency of potentially toxic lithium serum levels. Fourth, information on the time interval between blood sampling and the last lithium intake was unspecified in most cases (93%). Time intervals <10 hours distort correct interpretation of measured lithium serum levels by presenting falsely high values due to an incomplete distribution phase.[2] This could also falsely have influenced the observed higher frequency of potentially toxic lithium serum levels since it can be expected, that, in cases of suspected overdose the regime of a 12 ± 0.5 hour time interval is often not followed. However, because all laboratories claimed to have structured a 12 ± 0.5 hour time interval regime in accordance with the guideline,[35] most time intervals are probably >10 hours.

Finally, we have not been able to correct for other important patient characteristics that have previously been demonstrated to be related to lithium serum levels, such as comorbidity, current mood phase of bipolar disorder, diarrhoea, vomiting, infections or renal insufficiency, concomitantly used medication, pregnancy, changes in diet, alcohol use or weight and higher rates of perspiration due to exercise or visits to saunas.[2,34,36-38]

In conclusion, our results show that environmental temperature has a statistically significant but therapeutically irrelevant impact of on lithium serum levels. The lack of a clinical relevant impact of both season and temperature may possibly be explained by adequate measures taken by both clinicians and patients in response to changes in environmental temperature.

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3.3

Evaluation of treatment guidelines for the management of lithium intoxication

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submitted

ABSTRACT

Background

An intoxication with lithium is a potentially very serious event carrying considerable risk for long-term morbidity and even mortality. Providing instant adequate care is therefore imperative upon presentation of a patient with a suspected lithium intoxication. Patients with a lithium intoxication are most likely presented to the emergency ward and to be treated by physicians not very familiar with lithium. Therefore, a complete and employable treatment guideline needs to be available preferably guiding the physician step by step through the management of the intoxicated patient.

Objective

The objective of our study was to assess the completeness and employability of different treatment guidelines available for the management of patients with a lithium intoxication and to provide recommendations for improvement.

Methods

Treatment guidelines were searched through internet, online databases, textbooks and by requesting different poison information centres and university medical centers. A list of potential items that may be encountered while treating a patient suffering from a lithium intoxication including the information per item was composed based on a literature search.

Treatment guidelines were scored with respect to the presence of information on the identified relevant items. In addition, the presence of potentially hazardous information in the treatment guidelines was scored. Lastly, employability of the treatment guidelines was assessed using part of the AGREE (Appraisal of Guidelines Research and Evaluation) instrument.

Results

Nineteen treatment guidelines originating from seven different countries were taken into account. Overall, most items were present in the treatment guidelines. In some treatment guidelines, however, essential information was missing or potential hazardous information was present. In most treatment guidelines clarity and presentation and applicability (according to AGREE) were poor.

Conclusion

Several treatment guidelines on the management of lithium intoxication are currently used. Treatment guidelines show profound variability regarding completeness and employability. Various recommendations with respect to content of information and employability are given. Clinicians should be aware of the limitations of various guidelines.

INTRODUCTION

Lithium is one of the first choice agents for the long-term prophylaxis and treatment of acute episodes of bipolar disorders. In addition, lithium is frequently instituted as augmentation therapy to antidepressants in case of treatment-resistant unipolar depression.[1] Its use and effectiveness, however, are hampered by its narrow therapeutic window and the susceptibility of its clearance to changes in among others patient-related and environmental factors. In daily practice regular therapeutic drug monitoring is imperative to maximize benefits and minimize toxicity from lithium therapy.[2,3] Although large inter- and intraindividual patient differences exist with respect to the probability and severity of toxic symptoms, a lithium serum level of ≥1.5 mmol/l is generally considered the lower limit of the toxic range. An intoxication with lithium, intentionally or unintentionally, is potentially very harmful, since it may result in permanent sequelae, especially neurologic, or even death.[4] The vast majority (82%) of the 5559 patients with a suspected lithium intoxication reported to the American Association of Poison Control Centres Toxic Exposure Surveillance System (TESS) in 2005 required hospitalisation.[5] Five (0.1%) of these patients died, 312 (6.9%) had a major adverse outcome (defined as signs or symptoms that are life-threatening or resulted in significant residual disability or disfigurement), while only 943 (17.0%) had no adverse outcomes.[6,7]

Patients treated with lithium are at a relatively high risk of intoxication, given the drug's pharmacological profile as well as the nature of the underlying disease. The frequency of encountering a patient with a lithium intoxication is for most physicians, however, too low to really gain experience with its management. Taken that together with the potential severe consequences of a lithium intoxication, it is necessary to have complete and employable information readily available at the emergency department. Several protocols and toxicology textbooks are currently available and may guide the clinician. Since the management of an intoxication is obviously not a liable subject for performing clinical trials, recommendations within these treatment guidelines are mostly based on evidence originating from animal studies, pharmacokinetic studies, small observational studies (including case reports/series) combined with expert opinions,[8] consequently introducing the potential for large differences between them.

The primary objective of the present study is to evaluate available treatment guidelines for the management of lithium intoxications, with respect to the completeness and employability of their content and to provide recommendations for improvement.

METHODS

Treatment guideline retrieval

In order to identify relevant treatment guidelines for the management of a lithium intoxication we searched Medline, Toxnet, National Guideline Clearinghouse, Guideline International Network, E-guidelines, NeLh, NICE, NHS, SIGN, toxicology.org, Google® and Google Scholar® using the terms 'lithium' and 'intoxication' and 'guideline' or 'protocol'. In addition, we contacted different poison control centres by e-mail, requesting for a copy of their most recent treatment guideline for the management of patients with a lithium intoxication. We contacted centres in Europe (The European Association of Poisons Centres and Clinical Toxicologists; eapcct.org), The United States (The American Academy of Clinical Toxicology; clintox.org), New Zealand (The New Zealand Poison Information Centre) and Australia (The Australian Poison Control Centre). Finally, six university medical centres in different countries of Europe and different parts of the US were contacted with a request for a copy of their lithium intoxication treatment guideline. In case of no response to our first e-mail request, a second e-mail request was sent after about six weeks. In addition, we included some treatment guidelines originating from toxicology textbooks that are frequently used at the emergency room, and that contain a chapter on the management of lithium intoxications. Treatment guidelines were only included in our study, if they were completely available, including references used for the provided information and were developed with the intention to be used in daily clinical practice. The final selection of the treatment guidelines was made based on above mentioned inclusion criteria following a meeting discussion between all authors.

Information in the treatment guidelines

Before discussing the other aspects of our methods we will first discuss the most important issues that in our opinion should be dealt with in a treatment guideline

for the management of patients with lithium intoxication. These consist of certain aspects which are important for the adequate management of an intoxication with lithium. Important aspects determining the outcome of a lithium intoxication consist of a certain number of factors, which were associated with pharmacological properties of lithium itself, in addition to certain pharmacodynamic factors and individual patient's risk factors. Other factors relevant for outcome of a lithium intoxication, are intoxication type, lithium pharmaco(toxico)kinetics, extracorporal elimination, somatic anamnesis, pharmaceutical anamnesis, and post-treatment issues (Addendum 1). We determined these factors after having evaluated the retrieved treatment guidelines, available literature and after having discussed the various issues in two consensus meetings with all authors.

To be able to appreciate the potential severity of a lithium intoxication there are two important factors to consider. Firstly, the potential life threatening complications of an intoxication with lithium, determined by a combination of the lithium serum level itself and the actual clinical symptoms. Secondly, the risk of long-term morbidity, i.e. neurologic sequelae,[4] especially increases with long-term exposure to relatively high lithium serum levels.

It is important to realize that lithium shares certain important properties with other small cations in the body. Together with sodium, lithium is – after being excreted in the glomeruli – reabsorbed in the proximal tubuli, with a ratio depending upon the body's sodium balance. Lithium is, like potassium, ultimately largely distributed intracellular. This makes the nature of the intoxication very important with respect to the risk for long-term neurologic sequelae. There are different types of a lithium intoxication, i.e. an acute intoxication in lithium naïve patients, an acute on chronic intoxication in patients who are on long-term lithium treatment, and a chronic intoxication due to gradual accumulation of lithium during chronic exposure.

For correct interpretation of the obtained lithium serum levels it is crucial to understand lithium pharmaco(toxico)kinetics. The initial process of lithium distribution after ingestion, takes at least six hours to be completed.[9] Decisions on treatment should not only be based on lithium serum levels determined in blood drawn within six hours after ingestion, in case of an acute or an acute on chronic lithium intoxication. Early determined serum levels can, however, be helpful for the clinician in anticipating on what to expect in a patient. Pharmacokinetic

differences between the various lithium preparations are important. The prolonged time of absorption in case of slow- of delayed release preparations, or (in case of ingestion of large amounts due to bezoar formation) results in a longer time before the initial distribution phase is completed. In these cases multiple serum levels are required. In this framework it is good to realize that the therapeutic window of lithium is based on serum levels determined 12 hours (± 30 minutes) after the last lithium intake.[9]

There are several treatment aspects that are essential to maximize the likelihood for a good outcome. With respect to extracorporal elimination, haemodialysis is the technique of choice, being the technique for which most experience has been collected world wide. Haemodialysis is not free of – particularly haemodynamic – adverse events. On the other hand, not instituting haemodialysis when indicated, exposes the patient to an increased risk of long-term neurologique sequelae.

In patients with lithium induced nephrogenic diabetes insipidus (NDI) careful monitoring of sodium and water balance is imperative. In nephrogenic diabetes insipidus the kidney is no longer able to adequately respond to antidiuretic hormone resulting in production of large amount of diluted urine rendering adequate compensatory fluid intake imperative. The institution of large amounts of 0.9% NaCl to restore fluid depletion, poses those patients at risk for hypernatraemia, worsening their condition. Based on the relative water or sodium disbalance institution of an isotonic, hypertonic, halfsodium/halfglucose, isotonic glucose or oral water infusion may be indicated. In case of profound serum sodium disturbances restoring of sodium balance should be undertaken carefully to allow gradual adjustment of especially cerebral electrolyte concentration.

In the assessment of a lithium intoxication, as with any drug, it is important to be extra alert for the possibility of other ingested drugs.

Since lithium is used for severe and recurrent psychiatric illnesses, most patients surviving the intoxication will be in need for further psychiatric treatment including pharmacotherapy. One may argue whether, advices on and how to reinstitute lithium, should be addressed in a treatment guideline on the treatment of a lithium intoxication or should be addressed in more general treatment guidelines on the treatment of bipolar disorder or depression. Nevertheless it is

useful to pay attention both treatment guidelines when therapeutic treatment with lithium should be instituted again.

Composition of item list to assess completeness of treatment guidelines

During a first consensus meeting with all authors a draft list of various items (including those described above) that we consider of importance when managing a patient with a lithium intoxication was composed (first column, Addendum 1). Available information concerning the treatment of lithium intoxications was retrieved searching Medline using the terms lithium, intoxication, treatment, management, dialysis both using MeSH and word-terms. The search was limited to articles involving humans, written in English, French or German. The retrieved 636 publications were initially screened by title, leaving 179 potentially usable publications, which were further screened. References of included articles were also screened for usefulness. Finally a total of 91 articles were taken into account. Based on these articles the selected item list, as presented in Addendum 1, was further refined and finalized after consensus between all authors. (column 2, Addendum 1).

Subsequently, all selected items were categorized into five main categories: general information (7 items); direct supportive care (2 items); anamnesis (8 items); treatment (6 items); and discharge and follow-up (2 items) (Addendum 1). The final item list was used to assess completeness with respect to presence of information in the different treatment guidelines.

Assessment of the treatment guidelines

First, the presence of all selected items was scored for each treatment guideline independently by two of the authors: IW and TE. Aspects on which IW and TE could not reach consensus were discussed with the other authors. Items were scored as present or absent (column 1, Addendum 1). For each of the selected items the number of treatment guidelines scoring present or scoring absent was determined. In addition, the percentage of items that were scored as present was calculated, for each of the five main categories. Second, information encountered in the treatment guidelines that was either not mentioned in the item list or was in contradiction with current literature was assessed with respect to its potential harmfulness. Retrieved potentially harmful information was separately gathered and discussed.

Finally, the employability of reporting in the treatment guideline was explored using parts of the AGREE instrument (Appraisal of Guidelines Research and Evaluation Instrument (www.agreecollaboration.org)).[10] The treatment guidelines were therefore evaluated on two of the six different domains (4 = clarity and presentation, and 5 = applicability) consisting together of seven out of the total 23 AGREE items. Scoring was based on a four-point scale (Table 1). Final scores were calculated as a percentage of the maximum score (12 and 9) possible. The assessment of all treatment guidelines using the AGREE instrument was performed by IW and RH.

Table 1: Domains present in the AGREE instrument[a]

AGREE
1. Scope and purpose
2. Stakeholder involvement
3. Rigour of development
4. Clarity and presentation
I. The recommendations are specific and unambiguous
II. The different options for management of the condition are clearly presented
III. Key recommendations are easily identifiable
IV. The guideline is supported with tools for application
5. Applicability
I. The potential organisational barriers in applying the recommendations have been discussed
II. The potential cost implications of applying the recommendations have been considered
III. The guideline presents key review criteria for monitoring and/or audit purposes
6. Editorial independence

a) The AGREE (Appraisal of Guidelines for Research & Evaluation) instrument is intended to provide a framework for assessing the quality of clinical guidelines. Scoring of each of the items is performed on a 4-point scale as follows: 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = strongly agree.

RESULTS

Our search resulted in a total of 27 treatment guidelines. Eight treatment guidelines were excluded due to incompleteness of the treatment guidelines (four), due to non availability of used references (two), due to not actually being a treatment guideline (one) or a combination of not providing used references

and not actually being a guideline (one). A total of 19 treatment guidelines originating from seven different countries and from four different sources were taken into account for further assessment. Five treatment guidelines were retrieved from online databases (no. 1-5), six from poison information centres (no. 6-11), one from a university medical centre (no. 12) and seven from widely used toxicology textbooks (no. 13-19). Each treatment guideline was assessed for the presence or absence of the different items (Addendum 1) (Table 2).

Although most items were present in most of the 19 treatment guidelines, only three (12%) of 25 selected items were present in all treatment guidelines (clinical symptoms of the intoxication, different types of the intoxication and extracorporal elimination technique). In addition, in all but one treatment guideline information was present on the different causes of lithium intoxication and the indication for lithium use. Information was least present on: (long-term) prognosis, psychiatric assessment, monitoring during haemodialysis; discharge criteria; and information on post-treatment issues. None of the treatment guidelines mentioned psychiatric anamnesis.

In almost every treatment guideline (17 out of 19) the risk for permanent neurologic sequelae was mentioned, the potentially acute lethal consequences for a patient with a lithium intoxication was mentioned in 15 of the 19. In some treatment guidelines important aspects within the different items, like practical instructions for lithium serum level assessment (e.g. the need to take into account the time since intake of lithium) (present in 15) and the need to repeat lithium and electrolyte serum assessments (present in 16) were missing or were insufficiently emphasized. Only few treatment guidelines advised on interpretation of lithium serum levels with respect to the different pharmacokinetic formulations (n=2). Although criteria for the institution of extracorporal elimination techniques were found to differ amongst the treatment guidelines, they were, in most treatment guidelines, concrete and based on both clinical as well as laboratory parameters. Only few treatment guidelines paid specific attention to differences in needs for specific populations, like elderly (with respect to their increased sensitivity to toxic symptoms) (n=1), children (with respect to the chance of having an acute intoxication) (n=2), patients suffering from nephrogenic diabetes insipidus (with respect to their special needs regarding fluid infusion and water and electrolyte balance monitoring) (n=1), and being aware of and how to act upon multiple drug involvement (n=2).

Table 2: Distribution of the assessed treatment guidelines (n=19) with respect to the presence or absence of information on the items in Addendum 1

Items	Present	Absent
1. Description of general information		
– clinical symptoms of intoxication	**19**	0
– causes of intoxication	**18**	1
– indication for lithium use	**18**	1
– different lithium preparations	**17**	2
– pharmaco(toxico)kinetic parameters	**17**	2
– outcome of intoxication	**15**	4
– long-term prognosis of intoxication	4	**15**
2. Direct/initial supportive care		
– admission criteria	8	**11**
– initial symptomatic treatment	**16**	3
3. Anamnesis and assessment		
– determining intoxication type	**19**	0
– determining symptoms	**15**	4
– pharmaceutical anamnesis	6	**13**
– somatic anamnesis	**14**	5
– somatic assessment	**13**	6
– psychiatric anamnesis	0	**19**
– psychiatric assessment	1	**18**
– laboratory evaluation	**16**	3
4. Treatment		
– initial treatment	**16**	3
– prevention of absorption	**16**	3
– enhancing elimination	**13**	6
– extra corporal elimination	**19**	0
– monitoring during haemodialysis	2	**17**
– different treatment aspects	5	**14**
5. Follow-up		
– discharge issues	3	**16**
– post-treatment issues	5	**14**

Presence of information on items (Addendum 1) that may be needed as general information or encountered during supportive care, anamnesis, treatment and follow-up of patients suffering from acute, acute on chronic or chronic intoxication with lithium.
Information on these items is useful in treatment guidelines intended to be used for the management of patients suffering from intoxication with lithium anticipating on physicians not very familiar with lithium. The number of treatment guidelines scored respectively as present or absent was counted for each of the 25 assessed items. In bold the categories with the majority of the guidelines are indicated.

Table 3: The relative percentage of scoring for the five main categories

Practice guideline	Type of guideline	Description of general information	Direct/initial supportive care	Anamnesis & assessment	Treat-ment	Follow-up	Overall mean
1	Database	71.4	50	62.5	**83.3**	0	53.4
2	Database	71.4	50	50	**100**	0	54.3
3	Database	71.4	**100**	62.5	50	50	**66.8**
4	Database	28.6	**50**	37.5	**50**	**50**	43.2
5	Database	71.4	**100**	87.5	83.3	**100**	**88.4**
6	PIC	71.4	**100**	50	**100**	**100**	**84.3**
7	PIC	71.4	50	37.5	**83.3**	0	48.4
8	PIC	**57.1**	50	37.5	50	0	38.9
9	PIC	71.4	50	62.5	**100**	0	56.8
10	PIC	71.4	50	50	**83.3**	50	**60.9**
11	PIC	57.1	**100**	50	50	0	51.4
12	UMC	57.1	50	62.5	**83.3**	0	50.6
13	Textbook	85.7	50	75	**100**	0	**62.1**
14	Textbook	71.4	**100**	37.5	50	0	51.8
15	Textbook	71.4	50	62.5	**83.3**	0	53.4
16	Textbook	71.4	50	75	**100**	50	**69.3**
17	Textbook	**71.4**	50	50	**83.3**	0	50.9
18	Textbook	**85.7**	50	62.5	83.3	0	56.3
19	Textbook	42.9	50	37.5	**100**	0	46.1
Overall mean per scoring category		**63.6**	**60.0**	52.5	**75.8**	20.0	

PIC = poison information centre; UMC = University Medical Centre
An overview is given of the relative percentage of the total scoring for presence of the different items for each treatment guideline within the five main categories (general information, supportive care, anamnesis, treatment and discharge/follow-up). Each of the items in the five main categories was scored either as present or not present.
In bold the best represented categories per practice guideline are indicated. In addition, in the last row the categories with the highest scores and in the last colomn the highest scoring treatment guidelines are indicated in bold as well.

Generally, treatment guidelines were found to start at the point when it is clear that the patient admitted is suffering from a lithium intoxication and to end when enhancement of elimination if finished. Only a minority of the treatment guidelines was found to advise in the setting of pre-hospital care and to provide specific advise for discharge and follow-up especially regarding neurologic sequelae. One treatment guideline very briefly mentioned the continued need for

the treatment of a patient for the underlying psychiatric disorder after recovery from the intoxication and included advice on what considerations are important in decision making if and how to reinstitute lithium.

Potentially harmful advices were retrieved in five treatment guidelines; advocacy of use of ipecac syrup (n=2), the dangerous recommendation to perform fluid diuresis with fluid infusion and diuretics to enhance lithium clearance (n=2), the incorrect statement that acute (overdosing in a lithium naïve person) and acute on chronic (overdosing in a patient using lithium) lithium intoxication are equally severe (n=1), the incorrect mentioning of a positive strong relation between lithium serum level and toxicity (n=1) and the incorrect mentioning of peritoneal dialysis as the extra corporal elimination technique of second choice (n=2). The relative percentage of the maximal scoring (100%) for each of the five main categories is presented in Table 3.

Items from the category 'treatment' were found to be most frequently present throughout the treatment guidelines, whereas the category 'anamnesis and assessment' and 'follow-up' (including items like criteria for discharge and follow-up in case of neurological sequelae) were least present. In general, treatment guidelines originating from poison information centres provide a detailed description on how to treat the intoxicated. Thereby, guiding the clinician through each step, with much emphasis on enhancement of elimination and on additional symptomatic treatment e.g. of convulsions. Text books generally were found to focus more on the need for lithium treatment and on the specific symptoms encountered in toxicity, and are less extensive in providing a detailed description of supportive care. Overall, treatment guidelines no. 3, 5 (two online databases), 6, 10 (two poison's information centre guidelines) and 13, 16 (two text books) were most complete in their information.

The quality assessment on the employability of the treatment guidelines, using the two domains of the AGREE instrument is presented in Tables 4 and 5. The treatment guidelines were generally found to score very poorly, with respect to both used domains of the AGREE instrument. Most of the treatment guidelines do not provide an easy overview providing their key recommendations. None of the treatment guidelines mentioned anything on costs of treatment.

Table 4: Scoring of the individual treatment guidelines according to two main domains of the AGREE instrument

Practice guideline number	Type of guideline	Clarity and presentation	Applicability
1	Database	**50.0**	11.1
2	Database	33.3	0
3	Database	**58.3**	22.2
4	Database	33.3	0
5	Database	33.3	11.1
6	PIC	**50.0**	44.4
7	PIC	**50.0**	11.1
8	PIC	41.7	11.1
9	PIC	41.7	0
10	PIC	41.7	0
11	PIC	41.7	0
12	UMC	33.3	0
13	Textbook	33.3	0
14	Textbook	16.7	11.1
15	Textbook	**50.0**	11.1
16	Textbook	41.1	11.1
17	Textbook	33.3	11.1
18	Textbook	41.7	11.1
19	Textbook	25.0	11.1

AGREE = Appraisal of Guidelines for Research & Evaluation; PIC = poison information centre; UMC = University Medical Centre
Percentages of maximal scoring for the treatment guidelines (n=19) on two of the six main domains in the AGREE instrument (as presented in Table 1) are shown. Each of the items within the six domains was scored as follows: 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = strongly agree. In bold the highest scoring treatment guidelines per domain are indicated.

DISCUSSION

The majority of the treatment guidelines for the management of lithium intoxications we retrieved were found to be reasonable complete with respect to most of the items (i.e. especially those items considering immediate care). However, they were rather inconsistent with respect to other aspects of the treatment of a patient with a lithium intoxication (i.e. especially items of pre-hospital care, anamnesis concerning specific somatic aspects, items requiring collaboration between different disciplines and items considering discharge and

guidelines originating from poison information centres were found to provide more detail on how to treat (e.g. extracorporal elimination), whereas text books generally were found to provide more complete information on items concerning general information (i.e. indication for lithium use, different lithium preparations).

Five of the 19 (26%) treatment guidelines contained potentially hazardous information. Two treatment guidelines advocated use of ipecac in order to prevent absorption of ingested lithium. In addition to this false and potentially harmful advice, gastric lavage was found to be advocated in nine treatment guidelines. Since 2005 gastric lavage has been abandoned.[11] Fluid infusion and use of diuretics in patients intoxicated with lithium are beneficial with the purpose of restoring fluid balance. Institution of either fluid or diuretics does not increase lithium clearance but rather aggravates the intoxication due to disturbing water- salt homeostatis. Two different guidelines were found to recommend forced diuresis by infusion of fluids and diuretics with the purpose of enhancing lithium clearance. In the treatment decision process the type of intoxication (acute, acute on chronic and chronic intoxication), the serum level as well as the clinical symptoms of the patient are very important. With respect to the severity of a lithium intoxication the duration of exposure to lithium is particularly important. Therefore acute, acute on chronic and chronic intoxications need a different approach. One of the treatment guidelines stated that the acute and the acute on chronic intoxication are equally severe. Serum level only, can not predict the severity of the intoxication but should be considered in combination with the clinical symptoms. One of the guidelines stated that only looking at lithium serum level is adequate for decision making regarding institution of extracorporal elimination techniques. Taking lithium serum level alone may unnecessarily predispose patients to haemodialysis. On the other hand if institution of extracorporal elimination is deemed necessary the technique used should be able to quickly eliminate lithium. Two guidelines, however, recommended the use of peritoneal dialysis in case haemodialysis is not feasible. Peritoneal dialysis is able to lower lithium serum level, however, only at a speed approximating the body's normal lithium clearance. Continuous venovenous haemodiafiltration (CVVHDF) on the contrary can lower lithium serum level at an enhanced rate and is therefore deemed appropriate if haemodialysis is either not available or if the patient is haemodynamically unstable.

Table 5: Scoring of the individual treatment guidelines according to the specific items of two main domains of the AGREE instrument

Treatment guideline number	Clarity and presentation[a]				Applicability[b]		
	4.I	4.II	4.III	4.IV	5.I	5.II	5.III
1	2	**4**	2	2	1	1	2
2	2	**3**	1	2	1	1	1
3	**3**	**3**	**3**	2	2	1	2
4	2	2	2	2	1	1	1
5	**3**	2	2	1	2	1	1
6	**3**	**3**	**3**	1	**3**	1	**3**
7	**3**	**3**	**3**	1	1	1	2
8	2	2	**3**	2	1	1	2
9	**3**	**3**	1	2	1	1	1
10	**3**	2	2	2	1	1	1
11	**3**	2	2	2	1	1	1
12	2	2	2	2	1	1	1
13	**3**	**3**	1	1	1	1	1
14	2	2	1	1	1	1	2
15	**3**	**3**	**3**	1	1	1	2
16	2	**3**	**3**	1	1	1	2
17	**3**	**3**	1	1	1	1	2
18	2	**3**	**3**	1	2	1	1
19	2	2	2	1	1	1	2
Overall mean percentage	**50.9**	**54.4**	36.8	15.8	8.8	0.0	19.3

AGREE = Appraisal of Guidelines for Research & Evaluation

a) 4.I The recommendations are specific and unambiguous
   4.II The different options for management of the condition are clearly presented
   4.III Key recommendations are easily identifiable
   4.IV The guideline is supported with tools for application

b) 5.I The potential organisational barriers in applying the recommendations have been discussed
   5.II The potential cost implications of applying the recommendations have been considered
   5.III The guideline presents key review criteria for monitoring and/or audit purposes

In the last row the best represented items for the treatment guidelines overall are indicated in bold. In addition, the highest scoring treatment guidelines per item are indicated in bold as well.

follow-up). In general, treatment The methodological quality of reporting in the treatment guidelines and of the developmental process (as defined by AGREE), was explored. The AGREE instrument[10] is developed for the quality of guidelines assessment. The AGREE instrument consists of six different domains (scope and purpose, stakeholder involvement, rigour of development, clarity and

presentation, applicability and editorial independence), consisting together of 23 separate items. The AGREE instrument can not be used on all aspects of treatment guidelines for patients with a lithium intoxication. For example, information on who participated in the treatment guideline development, was not found to be addressed. With respect to the main category in AGREE, the rigour of the development of treatment guidelines were not found to provide insight into their literature selection process. The major reason for that probably is that the field of how to address and treat a patient with a lithium intoxication cannot be based on results of randomised controlled trials. Literature therefore mainly consists of small observational studies and expert opinions. With respect to editorial independence no information was found. We decided to use only two of the domains (i.e. clarity and presentation and applicability) of the AGREE instrument: to assess the employability of the treatment guideline in daily clinical practice. These items were generally found to score poorly. Those who develop treatment guidelines should provide specific and unambiguous recommendations where possible, instead of providing a summary of evidence as was done in some guidelines. Information on different management modalities if present should be presented. We had expected treatment guidelines to provide key recommendations for the treatment of a patient with a lithium intoxication allowing for an easy and quick overview on what to do and on what to expect. The items providing organisational barriers (minimal required treatment facilities) as well as key criteria for monitoring and audit (concrete mentioning of e.g. treatment targets and treatment duration) purpose were found to score low. Regarding organisational barriers (minimal required treatment facilities), it could be helpful to clearly state when there is, for example need for an ICU unit and haemodialysis equipment and to provide criteria for ending the haemodialysis session. We had expected the items on providing tools for application (i.e. computer assistance tools) and on potential cost implications to score relatively low, as they did.

There are several limitations to our study. First, we have included treatment guidelines based on response to our request. With respect to treatment guidelines this caries the risk of selection of possibly the better treatment guidelines, since centres being more convinced of the content of their treatment guideline might be more willing to respond to a request to share their information. In addition we can not provide information about the origin of the provided treatment

guidelines, since we have not formally asked the owner of the treatment guideline to publish this information. The purpose of our study was, however, not to point out the best and the worst treatment guideline available, but instead to find out which information was best and which information was least covered in available treatment guidelines and to provide general recommendations.

Second, specific issues as being extra alert for co-ingestion of other drugs in case of intentional intoxication, or information regarding discharge and follow-up in some centres and handbooks are addressed in another treatment guideline describing the general assessment and treatment of those presenting themselves with an intoxication. This might especially be true for poison information centres treatment guidelines, thereby resulting in relatively low scoring on these items.

Third, we have scored all items without weighing them and calculated an overall score based on five main categories which are containing not an equal number of items.

Lastly, our composition of the list of items one may encounter in the treatment of a patient with a lithium intoxication (Addendum 1) may be considered arbitrary or may even be criticized. Nevertheless, the evaluation in this article provides an adequate impression of available treatment guidelines with respect to their strengths and weaknesses regarding completeness and employability.

In conclusion, treatment guidelines show profound variability regarding completeness and employability and some guidelines contain wrong information. Clinicians using these guidelines should be aware of these limitations. We found most items of our selected items list on the treatment of a lithium intoxicated patient to be addressed in the assessed different treatment guidelines. Some items requiring collaboration between different disciplines were not well addressed (i.e. correct interpretation of serum levels taking into account exposure aspects, monitoring during haemodialysis, co-morbidity, multiple drug intake and reinstitution of lithium therapy). Regarding employability, treatment guidelines can be improved by providing key management issues, providing specific and unambiguous recommendations and multiple management options, where possible. Furthermore it could be helpful to specify more clearly minimal required treatment facilities such as intensive care observation, haemodialysis, and psychiatric aftercare following the treatment of the lithium intoxication.

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Addendum 1: Items relevant for the management of a patient with a lithium intoxication

Treatment guideline item	Essential content of item
1. General information	
Clinical symptoms of toxicity[12-18]	▪ Description of symptoms encountered in intoxication: ⇨ early (GI) symptoms ⇨ late (renal and neurologic) symptoms ▪ Acute, acute on chronic, and chronic intoxication: ⇨ acute: initially GI symptoms, followed by CNS depression, renal and cardiac involvement and eventually neurotoxic symptoms[19] ⇨ acute on chronic: initial symptoms as described in acute intoxication and more rapidly neurotoxic symptoms ⇨ chronic: intoxication evolving over weeks or even months starting with a prodromal phase; involving GI symptoms, coarse tremor, drowsiness, muscle twitching, lethargy, tinnitus, nystagmus, slurred speech/dysarthria followed later on by CNS depression, profound neurologic symptoms (ataxia, dysarthria, confusion, convulsions, coma) and alterations in renal functioning (renal failure)
Causes for intoxication[3,12,13,17,18,20-24]	▪ Diminished renal clearance (capacity) (e.g. as result of dehydration, fever, elective surgical procedure, change to low salt diet, renal failure, drug-drug interactions, pregnancy close to delivery[25]) ▪ Intentional overdose (suicide attempt) ▪ Accidental/non-intentional overdose[26]
Indication of lithium treatment[1]	▪ Bipolar disorders: acute or maintenance treatment ▪ Unipolar depression (augmentation to antidepressant)
Available lithium preparations[17]	▪ Route of administration: oral ▪ Preparations: tablets liquids capsules ▪ Kinetic properties: immediate, slow, delayed release[27] ▪ Types of salt: citrate, carbonate ▪ Lithium content: 2.7 mmol lithium in 100 mg lithiumcarbonate, 6 mmol lithium in 564 mg lithiumcitrate
Pharmaco(toxico)kinetic parameters[9,12,17,24,27,28]	▪ Therapeutic serum level ▪ Toxic serum level ▪ Time to absorption for the different formulations: in overdoses absorption may be prolonged due to bezoar formation[29-32] ▪ Time to completion of initial distribution phase

Treatment guideline item	Essential content of item
	▪ Volume of distribution ▪ No protein binding ▪ Elimination route: predominantly kidney, largely proximally reabsorbed in the nephron; lithium is handled in the kidney as sodium[21] ▪ Plasma half-life; dependency on intact kidney functioning, and type of intoxication[33,34] ▪ In chronic intoxication more lithium is deposited intracellularly;[34] measuring serum/RBC ratio[34]may be useful
Outcome of intoxication[17,19,35]	▪ Defining an intoxication with lithium as a potentially very serious intoxication requiring immediate adequate care ▪ Acute consequences: indicating that lithium intoxication is potentially fatal[15,23,36-39] especially in case of acute intoxication in patients with long-term lithium therapy ▪ Long-term consequences: indicating that a lithium intoxication has potential irreversible neurologic consequences, especially in case of chronic intoxication. Neurologic sequelae mainly consists of cerebellar disfunctioning[40,41] (e.g. dysarthria, ataxia, nystagmus, tremor); if still present after 12 months, symptoms are likely to be permanent.[4,13,15,23,36,42-46]
Factors associated with (long-term) outcome of intoxication[19,27,35]	▪ Prognostic factors: ⇨ co-morbidity: cardiovascular morbidity (sick-sinus syndrome),[13] diabetes and renal impairment (including nephrogenic diabetes insipidus [NDI])[4,47,48] ⇨ lithium: duration of maintenance lithium treatment, the duration of the intoxication, type of preparation, type of intoxication; acute, acute on chronic and chronic ⇨ risk population: prior suicide attempt, abuse of/dependence on drugs or alcohol[13,48] ⇨ treatment: instant adequate care, institution of extra corporal elimination technique[35]

2. Initial supportive care

Admission and hospitalisation criteria	▪ Any (GP) suspicion for lithium intoxication should lead to referral to a hospitalfor further assessment[48] ▪ Criteria for admission to a specific ward: ⇨ admission to a general ward is required in case of minor toxic symptoms and/or specific lithium serum level criteria ⇨ admission to ICU is indicated in case of severe/life-threatening toxic symptoms (e.g. cardiac dysrhytmias (AV-block, QTc- prolongation, flattening of T-top accompanied by U-wave)[13], respiratory depression,

Treatment guideline item	Essential content of item
	serious neurologic symptoms, hyperthermia, supportive fluid and electrolyte management, renal failure or nephrogenic diabetes insipidus)[49] and/or high lithium serum levels
Initial symptomatic treatment[8,13,50]	▪ Respiratory depression requiring intubation[51] ▪ Serious neurologic symptoms (e.g. seizures,[52] symptoms due to cerebellar damage, basal ganglia symptoms)[13] ▪ Cardiac dysrrhytmias,[53,54] hypertension,[55] or hypotension ▪ Hyperthermia requiring immediately cooling

3. Anamnesis

Determination of the type of intoxication	▪ Acute, acute on chronic or chronic intoxication[15] ▪ Mono or multiple drug ingestion (especially to be considered in acute (intentional) overdose)
Determination of presence clinical symptoms[12-18]	▪ Early and late symptoms[13,15] as described above ▪ Symptoms in acute, acute on chronic or chronic intoxication[13,15] as described above
Pharmaceutical anamnesis	▪ Lithium: ⇨ reason for lithium use ⇨ duration of use, dose, dose changes, previous lithium levels ⇨ amount, type of preparation and salt ingested ⇨ time of last intake, probable duration of intoxication ▪ Concomitant medication: ⇨ type, dose and duration of use ⇨ pharmacokinetic/dynamic interactions with lithium[56-58] ⇨ additionally ingested medication in overdose[33]
Somatic anamnesis[20]	▪ Renal function, nephrogenic diabetes insipidus, renal impairment[59] ▪ Cardiovascular morbidities compromising renal function/flow; heart failure, hypertension
Somatic assessment	▪ Temperature: hyperthermia ▪ Blood pressure (hypo or hypertension), heart rate (ECG) and QTc prolongation[53,54] ▪ Respiratory functioning: respiratory depression[51] ▪ Neurological examination focussing on cerebellar functioning: ataxia, dysarthria, confusion[13,15,23,36,42-46] ▪ Renal functioning: renal failure, polyuria[59]
Psychiatric anamnesis	▪ Psychiatric co-morbidities (e.g. abuse of/dependence on alcohol or drugs, personality disorder)

Treatment guideline item	Essential content of item
	▪ Additional risk factors[13,48] (prior suicide attempts, suicidal ideation)
Psychiatric assessment	▪ Psychiatric assessment current delirious, psychotic, manic, depressed status or suicidal ideation ▪ Attention and concentration, orientation, memory, perception, thinking, mood, affect, cooperativeness
Laboratory evaluation	▪ Lithium: [9] ⇨ timing of blood sampling: in acute, acute on chronic, or chronic intoxication ⇨ sampling instructions (non haemolysed blood, not pushed out of vein, not collected in lithium heparin tube)[60,61] ⇨ sampling within six hours of ingestion can not be considered conclusive, however, it can be useful to allow anticipation on what to expect ⇨ interpretation of serum level in relation to time of ingestion, type of intoxication, type of preparation and treatment, suitable interpretation is possible after initial distribution at least six hours post-intake, adequately interpretable in case of blood sampling 12 hours post dosing.[62] Additionally stating that even at therapeutic level toxicity may occur[63] ⇨ frequency of blood sampling during treatment: repeatedly post dosing (<4 hours), 6-8 hours post dialysis and repeated 12-hourly after completion of haemodialysis ▪ Other: [8] ⇨ electrolytes (sodium, potassium, and in addition in case of nephrogenic diabetes insipidus: calcium, magnesium) ⇨ renal function (serum and urine urea and serum and urine creatinine and concentration and urine volume to estimate creatinine clearance, followed by creatinine clearance based on urine obtained during a 24 hour time-period in order to measure creatinine clearance more appropriately) ⇨ type and frequency of monitoring of electrolytes and renal functioning,[21] sodium and creatinine should be measured 2-hourly during treatment in case of severe intoxication ⇨ collecting and storing serum for possible later determinations

4. Treatment

Initial treatment[17]	▪ Restoring of electrolyte-fluid balance disturbances using 0.9% NaCl or 0.45%/2.5% glucose or even 5% glucose dependent on kidney functioning and presence of

Treatment guideline item	Essential content of item
	nephrogenic diabetes insipidus/polyuria/disturbances in water/salt homeostasis, in addition to repeated monitoring of serum sodium concentration[64-68] ▪ Restoring of renal blood flow by using vasopressor agents in addition to fluid infusion
Prevention of absorption[8,50]	▪ Criteria for institution of absorption preventive measures in case of acute intoxication; based on time and amount of lithium intake and type of lithium preparation ⇨ induction of emesis, Ipecac is contraindicated ⇨ gastric lavage[11] within an hour after intake ⇨ whole bowel irrigation[8,13,21,69,70] treatment of choice especially in case of extended release preparation within 6-12 hours post dosing. ⇨ charcoal not useful in lithium mono-intoxication,[21] but potentially useful in case of multiple drug ingestion ⇨ resonium can increase lithium excretion, in relation to risk of induction hypokalaemia,[12,70-84] not currently recommended
Enhancing elimination[8,17,33,35,85,86]	▪ Enhancing body lithium clearance without extracorporal elimination technique ⇨ restoring kidney function by increasing renal blood flow using volume/electrolyte suppletion and vasopressor agents[8,59] ⇨ intake of salt (bouillon or salt tablets) is not an adequate treatment for those with a suspected lithium intoxication ⇨ fluid infusion is only recommended in case of demonstrated fluid depletion,[12] with regular monitoring of serum electrolytes to prevent severe hypernatremia[21] ⇨ forced diuresis; diuretics or fluid infusion contra-indicated because of the risk of inducing/aggravating water-/electrolyte disturbances and lack of demonstrated efficacy[8,23,70] ⇨ theophylline increasing lithium elimination rate by altering the proximal reabsorption of sodium by inhibiting carbonicanhydrase.[21] This treatment is currently not advised[70,87] ▪ Enhancing body lithium clearance using extracorporal elimination modalities[21,88-90] ⇨ criteria for institution of extracorporal elimination technique, include clinical criteria: type of intoxication, toxic symptoms (especially renal function, cardiac and neurologic effects),[88] and pharmacokinetic criteria: serum level, terminal half-life,[49,86,91] type of intoxication and a preferred timing (as soon as possible, preferably within 8-12 hours of intake) of decision making[12,91]

Treatment guideline item	Essential content of item
	⇨ criteria for discontinuation of extracorporal elimination technique based on lithium serum level criteria and risk for high intracellular depot levels (inducing rebound-phenomenon 6-8 hours after ending of dialysis)[15,21,92,93] ⇨ criteria to institute and terminate extracorporal elimination technique are essential to guide inexperienced physicians ⇨ haemodialysis (preferred method even if transportation to a nearby centre is required)[86,90,94] clearance 60-150 ml/min[24,70,90] ⇨ risk of rebound after haemodialysis (due to redistribution of lithium from intra to extracellular spaces or by ongoing absorption from GI-tract [due to bezoar formation]),[12,21,90,95] with an indication for redialysis if lithium serum levels rapidly increase (>1.0 mmol/l measured in serum taken 6-8 hours after dialysis)[13] ⇨ dialysate: bicarbonate is possibly preferred over acetate because use of acetate could possibly by acidification of intracellular spaces promote intracellular accumulation of lithium by stimulating the Na/H+ antiporter[21,96] ⇨ continuous venovenous haemodiafiltration (CVVHDF) is the second preferred method after haemodialysis and first preferred in patients who are haemodynamically unstable following initial supportive intensive care treatment. It precipitates less hypotension and in addition it is not dependent on patients' arterial pressure (contrary to continuous arteriovenous haemodiafiltration [CAVHDF]) since it is pump driven[92,97,98] ⇨ continuous venovenous haemofiltration(CVVH): lithium clearance of 42-60 ml/min,[91,96,98] not indicated[99] ⇨ continuous arteriovenous haemofiltration (CAVH): lithium clearance of 42-60 ml/min,[92,99] not indicated ⇨ Haemodiafiltration: not indicated ⇨ peritoneal dialysis: clearance 9-15 ml/min, not indicated[21,100,101] ▪ Monitoring in haemodialysis ⇨ description of the pharmaco(toxico)-kinetic monitoring of efficacy of extracorporal elimination technique, including pharmacokinetic formulas allowing monitoring of efficacy[29,34,90,93,94,102-104] ⇨ monitoring of efficacy of elimination technique (4 h after initiation of extracorporal elimination technique (measuring lithium dialysate or serum level) ⇨ risks involved in prolonged duration of dialysis (bleeding (activation of coagulation cascade)) indicating that in case prolongation is required monitoring of coagulation is necessary)[21,105]

Treatment guideline item	Essential content of item
	⇨ monitoring of effectiveness of membrane since after a certain time of use membranes could become overfilled with lithium reducing the efficacy of the extracorporal elimination
Differentiating between different aspects of treatment throughout the treatment section	▪ Acute versus acute on chronic versus chronic intoxication[14,16,19,59,91,106] ▪ Elderly have increased sensitivity for toxic effects of lithium,[16,107] children have higher plausibility of an acute intoxication[18] ▪ Advice on cessation of interacting medication, including both pharmacokinetic (influencing lithium excretion, such as NSAIDs, RAS inhibitors and diuretics) and pharmacodynamic interacting medication (medication increasing the risk of neurotoxicity or other CNS or cardiovascular toxic reactions to lithium, such as neuroleptic agents or medication causing QTc prolongation or electrolyte disturbances).[9,14,16,19,20,28,59,91,106] These medication should if possible be discontinued ▪ Nephrogenic diabetes insipidus: fluid replacement should be induced taking into account water/salt homeostasis[108]
5. Follow-up	
Discharge	▪ Discharge criteria: status of the intoxication with lithium, the risk of sequelae, recurrence of suicide attempts
Post-treatment issues	▪ Follow-up instructions with respect to neurologic sequelae (cerebellar) and prevention[103] ▪ Reinstitution of lithium: considering evaluation of suicide attempt risk, recovery of intoxication, efficacy of other treatments ▪ Providing adequate education for patients to prevent recurrence of the lithium intoxication. Patients and relatives education to recognize prodromal lithium toxicity symptoms.[109] Bouillon might be beneficial for prevention of lithium intoxication during anticipated periods of excessive perspiration (e.g. sports or heat induced)[48,103,110]

Nephrogenic complications of lithium

4

4.1

The association between concomitant use of serotonergic antidepressants and lithum induced polyuria A multicentre medical chart review study

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ABSTRACT

Background

A previous study aimed at revealing the prevalence and determinants of lithium induced polyuria suggested an increased risk of polyuria (urine volume ≥ 3 l/24 h) in those using serotonergic antidepressants next to lithium.

Objective

The objective of our study was to re-evaluate this secondary finding in another study population.

Methods

We performed a multicenter medical chart review study in patients using lithium in whom a 24-hour urine volume had been determined.

Results

We included 116 patients, twelve (26%) of the 46 patients with polyuria used serotonergic antidepressants compared to ten (14%) of the 70 patients without polyuria. We found an increased risk of polyuria in lithium users concurrently using serotonergic antidepressants (odds ratio 2.86; 95% confidence interval 1.00-8.21), adjusted for age, gender, use of antiepileptics and thyreomimetics.

Conclusion

Our results confirm the previous secondary finding of an increased risk of polyuria in patients using serotonergic antidepressants next to lithium. Physicians should take this into account when evaluating polyuria in patients using lithium and when choosing an antidepressant in patients using lithium.

INTRODUCTION

Long-term use of lithium salts, one of the first choice agents for the long-term treatment of bipolar and other mood disorders, is complicated by adverse drug reactions in more than half of the patients.[1] The wide variation in prevalence of ADRs is amongst others due to differences in study design, lithium dosing regimen and the increase in use of multiple drugs for the treatment of bipolar disorders. One of the most frequently occurring complications is polyuria with a prevalence estimated to vary between 15 and 40% of all patients on long-term lithium treatment.

Polyuria in those on lithium treatment can be the result of either acquired nephrogenic diabetes insipidus (NDI), i.e. an inadequate response of the kidneys to antidiuretic hormone (ADH) induced water reabsorption, or the consequence of psychogenic polydipsia. Although polyuria is usually harmless, it can have a large impact on activities of daily living. In patients predisposed to inadequate compensatory fluid intake (e.g. the elderly, those undergoing surgery or those suffering from an infection), polyuria may become potentially life-threatening, resulting in both dehydration as well as in an increase in the risk for the development of lithium toxicity.

In a previous study aimed at revealing the prevalence and determinants of lithium induced polyuria, our group found that use of serotonergic antidepressants and especially clomipramine and paroxetine, next to lithium was strongly associated with polyuria (adjusted odds ratio [OR] 4.25; 95% confidence interval [CI] 1.15-15.86).[2] Since this was a secondary finding of that study, it deserves evaluation in another study population. Therefore, we decided to conduct a cross-sectional medical chart review study among patients treated with lithium, with the primary objective to determine whether use of serotonergic antidepressants (selective serotonin reuptake inhibitors (SSRI), clomipramine or venlafaxine) next to lithium indeed increases the risk of lithium induced polyuria.

METHODS

Setting and design

The study was conducted as a multicenter cross-sectional medical chart review among patients treated with lithium. The source population consisted of patients

attending one of three participating clinics for mental health care in the Netherlands: 1) The Department of Psychiatry of the University Medical Center Groningen, in Groningen, 2) the 'Geestgronden' Specialists in Mental Health, in Bennebroek, and 3) Mental Health services North–Holland North, in Heiloo and Alkmaar. Written approval for acquiring the necessary information from the patients' psychiatric and somatic medical charts was obtained from all centres. Data were obtained from patients treated with lithium at one of these clinics within the time period from 1995 to 2005.

Study population

In order to be included in this study, patients had to be at least 18 years old and at least one 24-hour urine volume measurement had to have been carried out after a minimum duration of lithium use of one month. In case of availability of multiple 24-hour urine volume measurements information on the most recent measurement was gathered. Patients were excluded if they had a known history of kidney disease (Glomerular Filtration Rate < 50 ml/min estimated using the Jellife II formula), if they had proteinuria (> 0.3 g/l) or if they were pregnant at the time of the urine volume measurement.

The necessary sample size was calculated based on the results of the afore mentioned study performed by Movig et al.[2] In that study a prevalence of 33% of concomitant use of serotonergic antidepressants and a prevalence of polyuria of 37% in patients receiving long-term lithium treatment was observed. Given this prevalence estimate it was calculated that a study population of at least 96 evaluable patients was required to be able to detect a relative risk of at least 2.0 with a power of at least 80% and $p \leq 0.05$.

Outcome

The relevant outcome of this study was the presence of polyuria. Based on their most recent 24-hour urine volume measurement, patients were classified as either 'with polyuria' (in case of a 24-hour urine volume ≥ 3.0 l) or 'without polyuria' (in case of a 24-hour urine volume < 3.0 l).[2] The date of this 24-hour urine volume measurement was defined as the index date.

Exposure

The relevant determinant under investigation was use of serotonergic antidepressants next to lithium. Patients were termed 'users' of serotonergic antidepressants if they were currently receiving a SSRI or clomipramine or

venlafaxine (at a daily dose ≤ 150 mg),[3] or if they had discontinued using such an antidepressant within one month before the index date. The cut-off value for venlafaxine was chosen since venlafaxine at a dose of less than 150 mg daily is considered to be an SSRI. Patients were termed 'no users' if they had discontinued using serotonergic antidepressants more than one month prior to the index date or if they had never used such antidepressants.

Additional data

Additional data obtained in this study were patients' characteristics (age, gender), concurrent medical conditions and concomitant use of (psychotropic) medication known to influence renal function or urinary output, lithium use characteristics and laboratory parameters. All additional data were gathered from the patients' psychiatric and somatic medical charts.

Medical diseases assessed were diabetes mellitus, hypertension and hypothyroidism. Medications assessed were other antidepressants (i.e. non-serotonergic antidepressants), antipsychotics, benzodiazepines, antiepileptic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, renin-angiotensin inhibitors (RAS) inhibitors, anticholinergic agents and thyreomimetics. Use of concurrent medication was defined as either use or no use according to medication use on the index date. Information on concurrent (somatic) medication is usually registered when measuring 24-hour urine volume.

The following characteristics on lithium treatment were gathered: current dose (mmol/24 hours), daily intake frequency (once daily, more than once daily), duration of lithium treatment (years) and most recent lithium serum level (on the index date ± ten days). The following laboratory parameters were obtained: serum creatinine (to calculate creatinine clearance using Jellife II), thyroid stimulating hormone (TSH), calcium, sodium and potassium serum levels (on the index date ± seven days).

Data analysis

The frequencies of concurrent use of serotonergic antidepressants, patients' characteristics, concurrent medical conditions, concomitant use of (psychotropic) medication, lithium use characteristics and laboratory parameters were compared between lithium users with and without polyuria, using chi-square and t-test analysis.

Table 1: Characteristics of the study population

	All patients (n=116)	Polyuria (n=46)	No polyuria (n=70)
Patient characteristics			
age in yrs; mean (sd)	52.7 (12.8)	51.4 (11.9)	53.6 (13.4)
female gender; n (%)	75 (64.7)	27 (58.7)	48 (68.6)
Lithium characteristics			
use in yrs; median (range)	7.9 (0.1-32.5)	7.3 (0.1-30.9)	8.0 (0.3-32.5)
current dose in mmol; mean (sd)	23.0 (8.4)	24.5 (9.6)	22.0 (7.3)
serum level in mmol/l; mean (sd)	0.74 (0.21)	0.73 (0.17)	0.74 (0.24)
once daily intake[a]; n (%)	86 (90.5) n=95	35 (92.1) n=38	51 (89.5) n=57
Concurrent medical conditions; n (%)			
diabetes mellitus	5 (4.3)	0 (0.0)	5 (7.1)
hypertension	15 (12.9)	4 (8.7)	11 (15.7)
hypothyroidism	19 (16.4)	10 (21.7)	9 (12.9)
Concurrently used medication; n (%)			
psychotropic medication	80 (69.0)	36 (78.3)	44 (62.9)
serotonergic antidepressants	22 (19.0)	12 (26.1)	10 (14.3)
other antidepressants	13 (11.2)	5 (10.9)	8 (11.4)
antipsychotic agents	31 (26.7)	14 (30.4)	17 (24.3)
benzodiazepines	48 (41.4)	21 (45.7)	27 (38.6)
anticholinergic agents	1 (0.9)	1 (2.2)	0 (0.0)
antiepileptic agents[b]	24 (20.7)	14 (30.4)	10 (14.3)
diuretics, ACE-inhibitor, ATII antagonist	9 (7.8)	2 (4.3)	7 (10.0)
thyreomimetics[b]	14 (12.1)	8 (17.4)	6 (8.6)
Laboratory parameters; median (range)			
creatinine clearance in ml/min	83 (51-139)	80 (51-139)	84 (51-132)
TSH in mu/l[c]	1.90 (0.0-44.5) n=53	1.43 (0.01-44.5) n=23	2.07 (0.0-10.6) n=30
sodium in mmol/l[c]	140 (135-147) n=66	140 (137-147) n=28	140 (135-144) n=38
potassium in mmol/l[c]	4.3 (3.6-5.4) n=66	4.5 (3.6-5.4) n=28	4.3 (3.6-4.8) n=38
calcium in mmol/l[c]	2.4 (2.2-2.7) n=42	2.43 (2.3-2.7) n=17	2.5 (2.2-2.7) n=25

ACE-inhibitor= angiotensin-converting enzyme inhibitor; ATII antagonist= angiotensin II receptor antagonist

a) Data available for part of patients; number is shown after n (%).
b) Univariately ($p \leq 0.2$) associated with polyuria in users of lithium.
c) Data available for part of patients; number is shown after median (range).

The strength of the association between use of serotonergic antidepressants in patients using lithium and polyuria was evaluated using logistic regression analysis and was expressed as an OR with 95% CI. Variables univariately associated ($p \leq 0.2$)[4] with polyuria as well as age and gender were incorporated into the final model.

The risk of polyuria in patients using serotonergic antidepressants next to lithium was furthermore evaluated in a post-hoc analysis stratified for duration of lithium use. The latter analysis was performed because it has been reported that the risk of polyuria increases with longer duration of lithium use.[5]

In order to summarize the available evidence on this association we calculated a pooled risk estimate using the data of both the current study and the study performed by Movig et al., estimating the influence of concomitant use of serotonergic antidepressants on the risk of polyuria in patients using lithium.[2]

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 12.0.

RESULTS

The medical charts of in total 153 patients were assessed; 37 patients were excluded from the analysis, because of insufficient data mostly due to lack of or inconsistency with respect to the data on renal function, lithium use, and concomitant medication or because of inexplicable time-gaps in their medical charts. Thus, the final study population consisted of a total of 116 patients. Patient characteristics are summarized in Table 1. Overall, more females (65%) than males were included; the mean age was 53 years, the median duration of lithium use was 7.9 years. Median 24-hour urine volume in the study population was 2.63 l, for patients 'with polyuria' median 24-hour urine volume was 3.80 l (ranging from 3.00 to 10.0 l), and for patients 'without polyuria' median urine volume was 2.10 l (ranging from 1.20 to 2.95 l). A total of 46 patients (40%) were identified as suffering from polyuria. Gender (p=0.28), age (p=0.35), duration of lithium use (p=0.91) and lithium serum level (p=0.93) and creatinine clearance (p=0.23) did not statistically significantly differ between patients 'with' and patients 'without polyuria'. Concurrent use of thyreomimetics (p=0.16) and

antiepileptic agents (p=0.04) were found to be univariately associated ($p \leq 0.2$) with polyuria in those using lithium.

On the index date, thirty percent of the patients were using antidepressants of whom 22 (19% of the study population) were using serotonergic antidepressants. Twelve (26%) of the 46 patients suffering from polyuria were users of serotonergic antidepressants compared to ten (14%) of the 70 patients not suffering from polyuria (OR 2.15; 95% CI 0.83-5.59). Five (11%) of the 46 patients with polyuria were users of other antidepressants compared to eight (11%) of the 70 patients without polyuria (not statistically significantly different; p=0.93).

After adjustment for age, gender and concurrent use of thyreomimetics and antiepileptic agents, we observed and an association (OR 2.86; 95% CI 1.00-8.21) between use of serotonergic antidepressants and polyuria in lithium users (Table 2).

Table 2: Association between current use of serotonergic antidepressants next to lithium and polyuria

Current use of antidepressants	Polyuria n (%)	OR (95% CI)	Adj[a] OR (95% CI)
None (n=81)	29 (35.8%)	reference	reference
Serotonergic (n=22)	12 (54.6%)	2.15 (0.83-5.59)	2.86 (1.00-8.21)
Other (n=13)	5 (38.5%)	1.12 (0.34-3.74)	1.66 (0.43-6.34)

a) Adjusted for age, gender, current use of antiepileptic and thyreomimetic agents.

The risk of polyuria in users of serotonergic antidepressants next to lithium was also investigated separately for each of the three participating centres, in order to reveal any heterogeneity between the three centres. The results of this analysis revealed the same pattern for the increased risk for polyuria in users of serotonergic antidepressants next to lithium for each of the three centres separately.

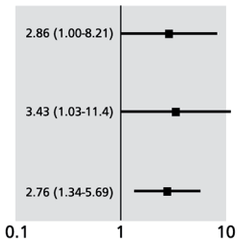
In a post-hoc performed analysis, we investigated the risk op polyuria in users of serotonergic antidepressants next to lithium stratified for duration of lithium use (with short-term use ≤ 4 years, median duration > 4-10 years and long-term > 10 years). We found the highest risk for polyuria in those users of serotonergic

antidepressants having used lithium for less than 4 years yielding an OR 10.7 (95% CI 1.45-79). However, no evidence for effect modification of duration of lithium use on the risk of polyuria was found in the total group of lithium users (for product term in logistic regression analysis p=0.71).

Lastly we investigated the risk for polyuria in users of serotonergic antidepressants next to lithium for the pooled data of the current study and the data of the study performed by Movig et al. The results of this analysis are together with the results of both studies separately presented in Table 3. We observed an overall increased risk of polyuria OR 2.76 (95% CI 1.34-5.69) in patients using serotonergic antidepressants next to lithium for the pooled data of both studies.

Table 3: The risk of polyuria in patients using serotonergic antidepressants next to lithium compared to patients not using serotonergic antidepressants next to lithium

	Number of patients with polyuria / total number of patients using lithium with respectively:			Adj[a] OR (95% CI)
	serotonergic antidepressants	non-serotonergic antidepressants	no antidepressants	
Current study (n=116)	12/22 (54.6%)	5/13 (38.5%)	29/81 (35.8%)	2.86 (1.00-8.21)
Movig et al. (n=75)	14/25 (56.0%)	4/16 (25.0%)	10/34 (29.4%)	3.43 (1.03-11.4)
Pooled data (n=191)	26/47 (55.3%)	9/29 (31.0%)	39/115 (33.9%)	2.76 (1.34-5.69)



a) Adjusted for age, gender, current use of antiepilectic and thyreomimetic agents.

DISCUSSION

We found an increased risk of polyuria in patients using serotonergic antidepressants next to lithium, in line with the previous results of the study performed by Movig et al.[2] The results of the analysis of the pooled data of both studies as shown in Table 3 accordingly reveal an increased risk of polyuria in users of serotonergic antidepressants next to lithium. Polyuria is a well known complication with a prevalence estimated to vary between 15 and 40% in those

on long-term lithium treatment.[6] Polyuria in those on lithium treatment can be the result of either acquired NDI, i.e. an inadequate response of the kidneys to ADH induced water reabsorption,[7] or can be the consequence of psychogenic polydipsia.[8,9] Although polyuria is usually harmless, it can have a large impact on activities of daily living. In patients suffering from polyuria as a results of NDI, who in addition find themselves in a situation predisposing them to inadequate compensatory fluid intake (e.g. the elderly, those undergoing surgery or those suffering from an infection), polyuria may become potentially life-threatening, resulting in both an increase in the risk for dehydration and for the development of lithium toxicity.[10] It remains to be elucidated what the mechanism is behind the increased risk of lithium associated polyuria in those concomitantly using serotonergic antidepressants next to lithium. Serotonin pharmacologically stimulates cholinergic neuromuscular transmission in isolated detrusor muscle.[11,12] It is suggested that this effect, by activation of 5HT4 receptors, can induce minor urinary leakage or incontinence.[2,3,13-16] This pharmacological effect, however, is not expected to influence urinary volume, but is rather expected to increase urinary frequency. An increase in urinary frequency in those using serotonergic antidepressants has indeed been observed.[17,18] Serotonergic antidepressants have, also been associated with the syndrome of inappropriate release of antidiuretic hormone (SIADH).[19,20] The latter is more likely to result in an increase in water retention, consequently resulting in a diminished 24-hour urine volume instead. Possibly the pharmacological effect of serotonergic antidepressants induced SIADH in those with an existing lithium induced kidney urine concentrating deficit might be less, or a distinctly different pharmacological effect of serotonergic antidepressants may become more important.

Surprisingly, we did not observe an association between duration of lithium use and the risk of polyuria, in contrast to previous reports.[21] This may be explained by the cross-sectional design of our study, resulting in both depletion of susceptibles and lack of information on the moment of development of polyuria, as explained later on. Stratification for duration of lithium use indicated the highest risk of polyuria in users of serotonergic antidepressants being relatively short-term users of lithium in contrast with the results observed by Movig et al.[2] who found the highest risk of polyuria in users of serotonergic antidepressants in relatively long-term users of lithium.

Similar to the results of previous studies,[22] concurrent use of other psychotropic medication showed a trend towards an increased risk of polyuria. Use of antipsychotic agents, anticholinergic agents or benzodiazepines were not found to be associated to an increased risk in polyuria in patients using lithium. We observed an increased risk for polyuria in patients using antiepileptic agents next to lithium, which was unexpected since carbamazepine, for example, is known for its risk to induce hyponatraemia,[19] a condition thought to result from SIADH, resulting in diminished urine output.[23,24] No difference in the risk for polyuria was observed between the different antiepileptic agents used. Diuretics, especially thiazides and amiloride, are often instituted to alleviate the symptoms of lithium induced kidney urine concentrating deficit, which possibly explains the observed higher prevalence of concurrent use of diuretics in the patients 'without polyuria'.

There are several limitations to our study. First of all, our study is based on the information as available from the psychiatric and somatic charts of the patients included from the three participating centres. Other concurrent medical conditions not diagnosed as well as use of other medication not instituted at these centres are possibly not fully documented in the medical charts. It is, however, not very likely that either the presence or the absence of polyuria influences availability of such information in the medical charts. Next, we cannot exclude selection bias with respect to availability of a 24-hour urine volume measurement in our study, i.e. it can be expected that especially patients complaining of polyuria are more likely to be assessed for a 24-hour urine collection than those not complaining of polyuria. We accordingly observed a relatively high prevalence of 40% of polyuria in those on lithium treatment. Reported prevalences of polyuria in lithium users in literature vary widely.[6,22] This selection is, however, not very likely to influence the observed association between use of serotonergic antidepressants and polyuria in users of lithium.

In addition, because of the nature of our study, we were not able to distinguish between polyuria resulting from psychogenic polydipsia or polyuria as a consequence of acquired diminished urine concentrating capacity (or even a combination of these two factors) within those classified as 'with polyuria'. In order to differentiate between these two factors we would have needed more detailed information on fluid intake, or response to water deprivation or vasopressin administration. It is conceivable that the pharmacological effect of

serotonergic antidepressants in those with kidney urine concentrating deficit differs from the pharmacological effect of serotonergic antidepressants in psychogenic polydipsia.

We were limited by the design of our study. Since we designed our study as a cross-sectional study we were not able to adequately study the association between duration of lithium use and the risk of lithium induced polyuria. We had no possibility to determine the actual moment of development of polyuria, not allowing us to determine the duration of lithium use at the moment this complication emerged. Furthermore, the cross-sectional design of our study resulted in possible selection bias primarily resulting in inclusion of patients relatively good responding and relatively well tolerating lithium, a type of selection bias also referred to as 'depletion of susceptibles'. Poor responders to lithium treatment are more likely to discontinue earlier in the treatment, whereas later complications of lithium treatment, like polyuria, may be the predominant factor for discontinuation later in the treatment. Therefore, long-term lithium users in our naturalistic population setting, are likely to represent a selection of good responding patients, who in addition do tolerate lithium relatively well. This assumption of relatively good response is also illustrated by the fact that we observed concurrent use of antidepressants predominantly in those on shortest duration of lithium use.

In addition, the design of our study did not allow us to establish whether the observed association between use of serotonergic antidepressants and lithium induced polyuria is actually a causal association. Lastly, this study is limited by its sample size. Sample size calculations were based on the prevalence of use of antidepressants as detected in the previously conducted study.[2] However, it appeared that the prevalence of antidepressant use observed in our study was lower than expected from the study performed by Movig et al, which can be explained by differences in mental disorders for which lithium was instituted in the two study populations, being primarily depression in the previous study and being predominantly bipolar disorders in ours.

In conclusion, our results show an increased risk for lithium induced polyuria in those concurrently using serotonergic antidepressants. The pharmacological mechanism whereby concurrent use of serotonergic antidepressants next to lithium increases the risk of lithium induced polyuria remains to be elucidated. Physicians need to take into consideration the increased risk of polyuria in users

of serotonergic antidepressants next to lithium in their decisions making for what drug to prescribe their patient in need for concurrent use of antidepressant treatment next to lithium. In case of existing polyuria or increasing urine volume since lithium initiation the clinician could decide to institute another drug for the treatment of bipolar depression. In case of emergence of polyuria or increasing urine volume after having added a serotonergic antidepressant to ongoing lithium treatment the clinician can decide to switch to another drug used in the treatment of bipolar depression. In addition, physicians should be extra alert for the development of polyuria in patients using serotonergic antidepressants next to lithium. It remains also to be determined whether discontinuation of serotonergic antidepressants or switching from serotonergic antidepressants to another treatment modality results in reversal of this increased prevalence of polyuria in users of lithium.

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4.2

Urine osmolality, cyclic AMP and aquaporin-2 in urine of patients under lithium treatment in response to water loading followed by vasopressin administration

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ABSTRACT

Background

Lithium is the drug that is most frequently associated with acquired nephrogenic diabetes insipidus (NDI). The exact mechanism of lithium-induced NDI in man is unknown.

Objective

The objective of the present study was to investigate the kidney response to minimal and maximal stimulation of the kidney urine concentrating mechanism by measuring urine osmolality, and urine levels of 3',5'-cyclic adenosine monophosphate (cAMP) and aquaporin-2 (AQP-2) in urine of patients under long-term lithium treatment.

Methods

Twenty patients under long-term lithium treatment were included. The kidney urinary cAMP, AQP-2 levels and urine osmolality were determined during a situation of minimal kidney urine concentrating activity (induced by water loading) and during a situation following maximal stimulation of kidney urine concentrating activity (induced by 1-desamino-8-D-arginine-vasopressin [dDAVP]).

Results

Patients were classified as NDI, partial NDI and non-NDI based on maximal reached urine osmolality. The partial correlation (*r*) between urinary cAMP levels (mol/l) and urine osmolality was 0.94 ($p<0.001$). No significant correlation was observed between urinary AQP-2 levels (mol/mol creatinine) and osmolality nor between urinary cAMP and AQP-2 levels. The rise in urinary cAMP but not AQP-2 levels upon dDAVP administration after water loading significantly differed between the three categories, decreasing with increasing NDI category.

Conclusion

In conclusion we found that in lithium-induced kidney urine concentrating deficit in man, the cAMP generation in response to dDAVP administration after water loading, is impaired. It remains to be elucidated whether principal cells, G-proteins or adenylate cyclase e.g. are the major targets for the mechanism underlying lithium-induced NDI in man.

INTRODUCTION

Long-term use of lithium salts, one of the first choice agents for the treatment of bipolar disorders, is often complicated by adverse reactions such as tremor, hypothyroidism and nephrogenic diabetes insipidus (NDI), often resulting in polyuria (24-hour urine volume ≥3 l). A diminished kidney urine concentrating ability in response to adequate release of the antidiuretic hormone arginine vasopressin (AVP) occurs in approximately 54% of the long-term lithium users,[1] whereas in about 12% forthright NDI (maximal urine osmolality <350 mosm/kg) develops.[2,3] Although the exact mechanism of lithium-induced NDI is at present unknown, it has been demonstrated that the risk for lithium-induced NDI is associated with duration of treatment, serum level and cumulative dose.[4]

In normal physiology AVP, that is released from the posterior pituitary gland in response to an increased serum osmolality or a decreased effective circulating volume, stimulates the basolaterally located kidney vasopressin 2 receptor. Vasopressin 2 receptor stimulation subsequently results in G-protein induced activation of adenylate cyclase, stimulating 3',5'-cyclic adenosine monophosphate (cAMP) formation. Next, cAMP stimulates protein kinase A, followed by activation of its catalytic subunit, in turn resulting in phosphorylation of AQP-2 in the cytoplasmic vesicles. Finally, the cytoplasmic vesicles containing AQP-2 protein fuse with the apical membrane of the ductal tubular cells, rendering this normally water tight membrane permeable for water. As a consequence of the osmotic force of the hypertonic interstitium, water is then reabsorbed from pro-urine. Finally, water flows into the main circulation through basolaterally located aquaporin-3 and aquaporin-4 channel proteins.[5-7] Studies have demonstrated that both AQP-2 and cAMP are detectable in urine of healthy volunteers.[8-14] Urinary excretion of AQP-2 has been suggested to be a surrogate marker of AVP stimulated insertion of AQP-2 in the ductal tubular apical membrane.[9-11,15] In healthy volunteers a correlation was established between AQP-2 and both an increased AVP plasma level and exogenous vasopressin 2 receptor stimulation.[8,15] Small studies with patients with either central diabetes insipidus or patients with congenital or lithium-induced NDI, demonstrated either minimal or no 1-desamino-8-D-arginine-vasopressin (dDAVP) induced AQP-2 excretion in urine.[10,11,14]

Presently, it is unknown which mechanism is exactly responsible for the occurrence of NDI in patients under long-term lithium treatment and what is exactly the target for lithium. Some studies on the mechanism of lithium-induced NDI in animal models have shown that lithium can impair cAMP generation, possibly by modulating the interaction between G-proteins and adenylate cyclase.[6,16-18] Other studies have implied the involvement of other mechanisms such as down-regulation of the vasopressin 2 receptor,[19] a direct effect on AQP-2,[20] or on the principal cells.[21]

In order to investigate which part of the vasopressin 2 receptor–cAMP–AQP-2 cascade is involved in the mechanism of lithium-induced NDI in man, we investigated the kidney response to minimal and maximal stimulation of the kidney urine concentrating mechanism by measuring urine osmolality, and urine levels of cAMP and AQP-2 in urine of patients under long-term lithium treatment.

METHODS

Setting

The study was conducted at the psychiatric department of the St. Elisabeth Hospital, in Tilburg; a large teaching hospital located in the South of the Netherlands. The study was performed in accordance with the current revision of the Declaration of Helsinki International Conference on Harmonization guidelines and Good Clinical Practice guidelines.[22]

The medical ethics committee of the St. Elisabeth Hospital approved the study protocol. Each patient gave written informed consent after full explanation of the study, both verbally and in writing.

Study population

Participants of at least 18 years of age who were under long-term lithium treatment (defined as having been maintained on lithium for at least two years prior to inclusion) were selected from a population of 75 patients, in whom the presence of polyuria (24-hour urine volume ≥3 l) had been determined in a previously reported study.[23] In order to obtain representatives in all of the three respective categories (NDI, partial NDI and non-NDI) we included ten patients with polyuria and ten patients without polyuria.

Patients were not included in the present study if they had kidney function impairment (Glomerular Filtration Rate <80 ml/min or proteinuria (>0.3 g/l), diabetes mellitus, cardiac disease, hypertension, known pregnancy, or if they were using carbamazepine, oxcarbazepine, nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen (more than 3g/24h for a long period of time). Carbamazepine and oxcarbazepine can cause hyponatreamia.[24] NSAIDs frequently interfere with renal function,[25] as does long-term use of high dose acetaminophen.[26]

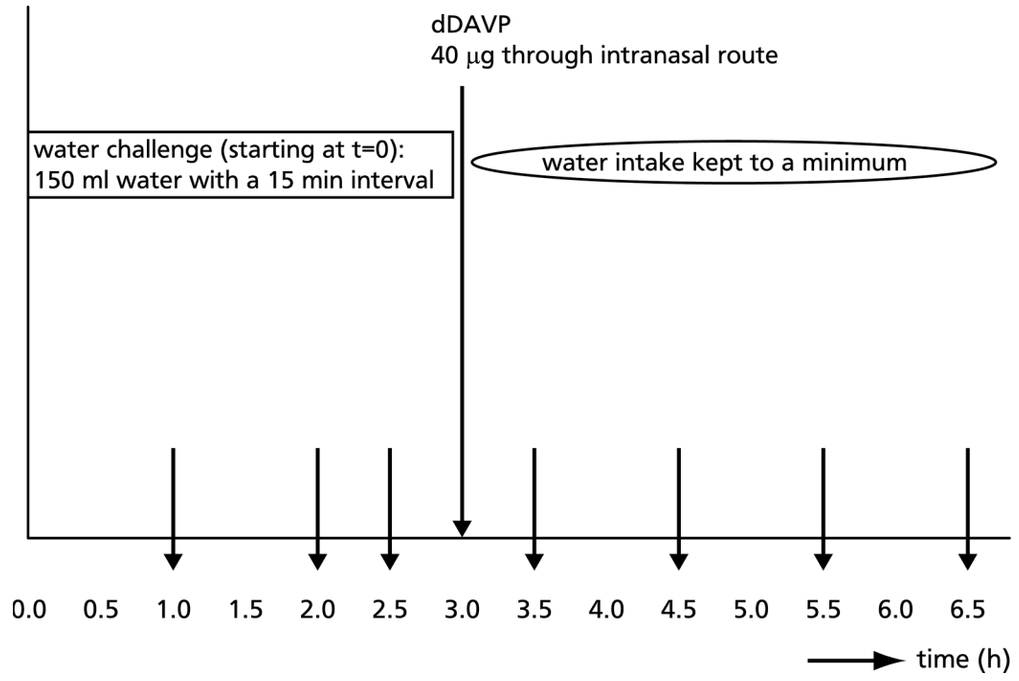
Experiment

Patients were instructed not to drink coffee or tea and not to smoke starting from six PM prior to the study day. Caffeine has natriuretic properties in man.[27] Nicotine induces endogenous AVP secretion.[28] On the study day patients were first subjected to water loading by drinking 150 ml of water every 15 min for 2.5 hours in order to completely block endogenous AVP-mediated renal vasopressin 2 receptor stimulation. Half an hour after this period of water loading patients were administered 40μg of dDAVP intranasally; in order to induce maximal stimulation of the renal vasopressin 2 receptor. Following dDAVP administration, patients were asked to restrict their fluid intake to a minimum. Throughout the study day patients had to urinate seven times according to the study day schedule (Figure 1). No blood sampling was performed on the study day. Absence of protein in urine was confirmed for all patients.

Biochemical analysis

Each urine sample was collected separately and after urine-volume determination, samples were, after a two step concentrating procedure, immediately stored at –80°C until further analysis. Protease inhibitors were added to the concentrated urine samples, before storage, as previously described.[29] Urine osmolality, creatinine, urinary cAMP (principally expressed in mol/l) and AQP-2 (expressed in mol/mol creatinine) levels were determined in each sample. Urine osmolality was determined by measuring freezing point depression.[30] Creatinine was determined by standard automated laboratory techniques. In accordance with current literature urinary cAMP levels were expressed per volume urine and urinary AQP-2 levels were expressed per mol creatinine.[31,32]

Figure 1: Schematic representation of the study day



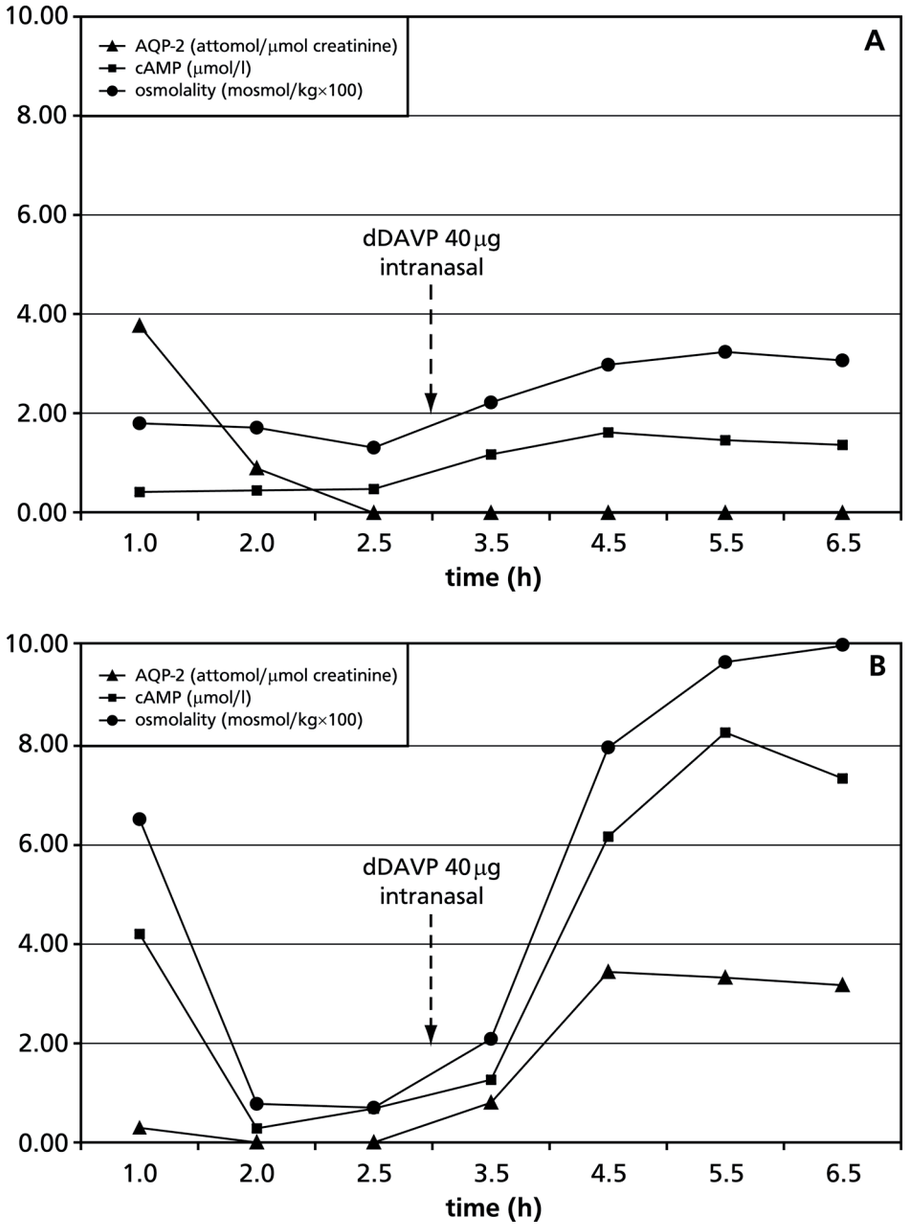
Upon presentation at the lithium clinic patients were asked to urinate. Subsequently patients were asked to drink 150 ml of water every 15 min for two and a half hours. Half an hour after the water loading was terminated, patients were administered 40 μg of 1-desamino-8-D-arginine-vasopressin (dDAVP) through intranasal route (**long arrow**). Starting from three hours prior to dDAVP administration until three and a half hours after dDAVP administration patients were asked to urinate at specific times (**small arrows**). For each urine sample separately volume, osmolality, creatinine, cAMP and AQP-2 levels were determined.

Quantification of cAMP was performed in a competitive protein-binding assay using a Radio Immuno Assay (RIA) for quantification and was performed according to the instructions provided by the manufacturer (DPC).

AQP-2 was measured according to a previously described method involving semi-quantitative immunoblot analysis, after sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE).

The only adaptation from the original method was substitution of the primary antibody into a commercially available rabbit anti-AQP-2 antibody (BDPharmingen).[29]

Figure 2: Example of a typical NDI patient (A) and a non-NDI patient (B)



NDI = nephrogenic diabetes insipidus; dDAVP = 1-desamino-8-D-arginine-vasopressin

A. A typical NDI patient displaying both inadequate response of urinary cyclic AMP (cAMP) and aquaporin-2 (AQP-2) levels to maximal stimulation of kidney urine concentrating activity.

B. A typical non-NDI patient displaying both adequate response of urinary cAMP and AQP-2 levels to maximal stimulation of kidney urine concentrating activity.

Additional clinical data

For each patient a pharmacy drug dispensing record, starting at least one year prior to the study day, was obtained. From this record concomitant drug use and lithium dose were determined. For each patient the cumulative lithium dose, the most recent lithium serum level prior to the study day and duration of lithium use were obtained from the medical record.

Data analysis

For each patient we obtained seven different urine samples at seven different time-points during the experiment. Subsequently we determined in each of these samples separately urine osmolality, creatinine, urinary cAMP (principally expressed in mol/l) and AQP-2 (expressed in mol/mol creatinine) levels. All seven different observations for urine osmolality, urinary cAMP and AQP-2 levels were plotted in time for each patient separately. For each individual patient the correlation between urinary cAMP levels and urine osmolality, respectively between urinary AQP-2 levels and urine osmolality, correspondingly between urinary cAMP levels and urinary AQP-2 levels was determined using the results from the analysis of the seven different urine samples obtained in time during the experiment. Furthermore the partial correlation *r* for the pooled study population data, taking into account the within subject dependency of the seven separate observations per patient was determined.

In order to evaluate the kidney's urine concentrating response, the maximal rise in urinary cAMP and AQP-2 levels were determined for each individual by comparing the situation of maximal vasopressin 2 receptor stimulation (induced by nasal administration of 40 μg dDAVP) to the situation under minimal AVP-mediated endogenous vasopressin 2 receptor stimulation (induced by water loading). Furthermore the kidney's maximal urine concentrating capacity was evaluated using the maximal reached urine osmolality under exogenous vasopressin 2 receptor stimulation. A linear regression analysis was performed for both the maximal rise in urinary cAMP and AQP-2 levels and the individual maximal reached urine osmolality.

Patients were, based on the maximal reached urine osmolality, categorized to one of the following categories; NDI, partial NDI or non-NDI.[3]

Patients exhibiting a maximal urine osmolality <350 mosm/kg upon dDAVP administration were assigned to the NDI class. Patients showing a maximal urine

osmolality between 350 and 750 mosm/kg in response to dDAVP administration were assigned to the partial NDI category. Patients displaying a maximal urine osmolality ≥750 mosm/kg upon dDAVP administration were assigned to the non-NDI group. Whether the maximal rise in urinary cAMP and urinary AQP-2 levels differed significantly between the three groups; NDI, partial NDI and non-NDI, was established by performing the non-parametric Kruskal-Wallis test. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 12.0.

RESULTS

Based on maximal urine osmolality after administration of dDAVP, five patients were assigned to the NDI group, ten patients to the partial NDI group and five patients to the non-NDI group. A typical example of a patient suffering from lithium-induced NDI and a typical example of a patient not suffering from lithium-induced NDI are shown in Figure 2A and B.

Table 1: Patient characteristics

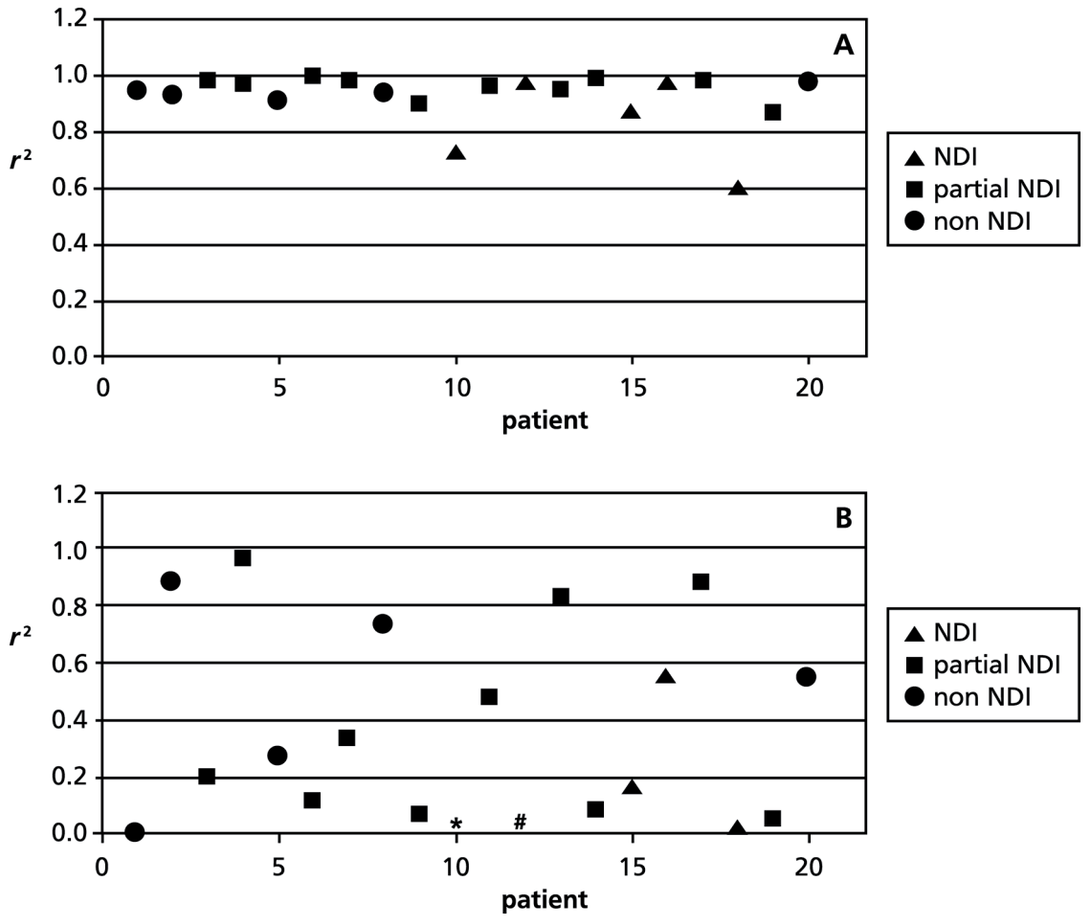
Patient characteristics	NDI n=5 (100%)	Partial NDI n=10 (100%)	Non-NDI n=5 (100%)
Age in yrs; *mean (range)*	58 (50–62)	52 (40–65)	49 (35–68)
Female gender; n (%)	4 (80%)	8 (80%)	3 (60%)
Polyuria; n (%)	4 (80%)	5 (50%)	1 (20%)
Smoking; n (%)	0 (0%)	5 (50%)	2 (40%)
Lithium characteristics			
Use[a] in yrs; *mean (range)*	17 (12–32)	3.5 (2.5–6.0)	3.9 (2.3–5.4)
Dose in mmol/day; *mean (range)*	23 (16–42)	25 (16–38)	22 (11–32)
Serum level[b] in mmol/l; *mean (range)*	0.90 (0.7–1.0)	0.74 (0.5–1.0)	0.68 (0.5–1.0)
Total dose[a] in mmol; *mean (range)*	154 101 (255 949)	31 231 (43 648)	36 544 (46 948)

NDI = nephrogenic diabetes insipidus

a) Duration of use (years) ($p<0.05$) and cumulative dose (mmol) ($p<0.05$) were shown to differ statistically significant between the three categories (Krushkal-Wallis).

b) Most recent prior to the study day.

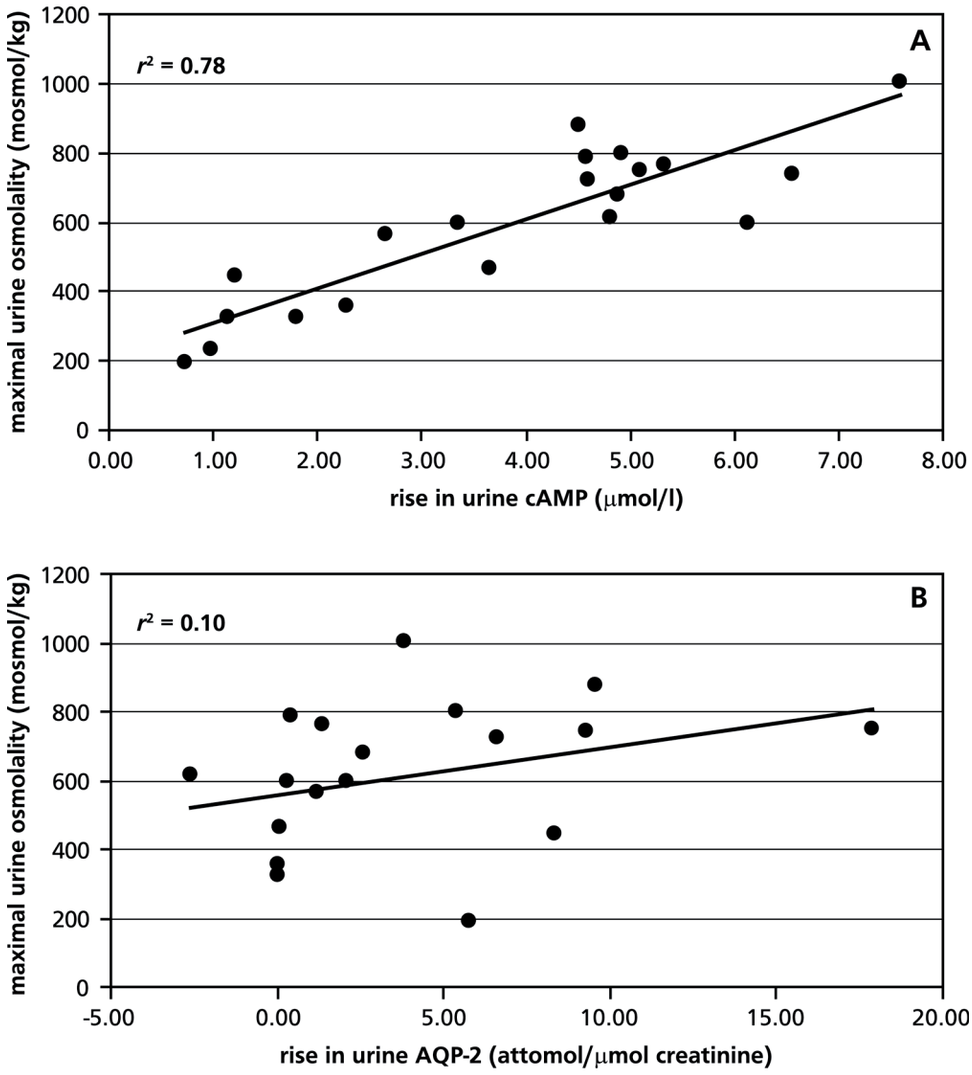
Figure 3: Correlations between urinary cyclic AMP levels and urine osmolality (A) and between urinary aquaporin-2 levels and urine osmolality (B) for all individual patients



A. For each patient the correlation between urinary cyclic AMP (cAMP) levels and urine osmolality was determined. Correlations (r^2) between urinary cAMP levels and urine osmolality, for the subsequent urine samples on the study day, in each individual patient are shown.

B. For each patient the correlation between urinary aquaporin-2 (AQP-2) levels and urine osmolality was determined. Correlations (r^2) between urinary AQP-2 levels and urine osmolality, for the subsequent urine samples taken on the study day, in each individual patient are shown.
For patient 10 (see ∗) it was not possible to determine the correlation since no AQP-2 could be determined because of analytical disturbance in the urine samples. For patient 12 (see #) it was not possible to determine the correlation because of lack of AQP-2.

Figure 4: Overall correlation (r^2) between rise in urinary cyclic AMP and maximal reached urine osmolality (n=20) (A) and between rise in urinary aquaporin-2 levels and maximal reached urine osmolality (n=19) (B)



A. For each patient the maximal rise in urinary cyclic AMP (cAMP) levels was determined by taking the difference between the minimal urinary cAMP levels in the situation of minimal kidney urine concentrating activity (induced by water loading) and the maximal urinary cAMP levels under the situation following maximal stimulation of kidney urine concentrating activity (induced by 1-desamino-8-D-arginine-vasopressin [dDAVP]).

B. For each patient the maximal rise in urinary aquaporin-2 (AQP-2) was determined by taking the difference between the minimal urinary AQP-2 levels in the situation of minimal kidney urine concentrating activity (induced by water loading) and the maximal urinary AQP-2 levels in the situation following maximal stimulation of kidney urine concentrating activity (induced by dDAVP). For patient 10 no AQP-2 was determined because of analytical disturbances in the urine samples.

Patient characteristics are reported in Table 1. Duration of lithium use as well as cumulative lithium dose significantly differed between the three categories (Krushkal-Wallis $p<0.05$).

Table 2: Kidney urinary concentrating parameters

	NDI (n=5)	Partial NDI (n=10)	Non-NDI (n=5)
Maximal urine osmolality in mosm/kg; mean (sd)	287 (70)	617 (108)	846 (97)
Rise in urinary cAMP[a] level in μmol/l; mean (sd)	1.39 (0.64)	4.29 (1.61)	5.39 (1.27)
Maximal urine cAMP level in μmol/l; mean (sd)	1.88 (0.62)	4.55 (1.54)	5.70 (1.49)
Rise in urinary AQP-2[a] level in attomol/μmol creatinine; mean (sd)	1.45 (2.89)[b]	4.58 (6.06)	4.10 (3.63)
Maximal urine AQP-2 level in attomol/μmol creatinine; mean (sd)	1.45 (2.89)[b]	5.77 (6.32)	4.72 (3.88)

NDI = nephrogenic diabetes insipidus; cAMP = cyclic AMP; AQP-2 = aquaporin-2
For each urine sample separately volume, osmolality, creatinine, cAMP and AQP-2 levels were determined. For each patient maximal reached urine osmolality upon 1-desamino-8-D-arginine-vasopressin (dDAVP) administration was determined. For each patient the maximal rise in urinary cAMP and AQP-2 levels was determined by taking the difference between the minimal urinary cAMP and AQP-2 levels in the situation of minimal kidney urine concentrating activity (induced by water loading) and the maximal urinary cAMP and AQP-2 levels in the situation following maximal stimulation of kidney urine concentrating activity (induced by dDAVP). For each of the three categories NDI, partial NDI and non-NDI the mean and standard deviation of the rise in and the maximum urinary cAMP and AQP-2 levels were determined as well as the mean and standard deviation of the maximal reached urine osmolality.

a) Rise in urinary cAMP level ($p<0.001$) but not urinary AQP-2 level ($p=0.675$) was shown to differ statistically significant between the three categories (Krushkal-Wallis).
b) For one individual in the NDI category no AQP-2 could be determined due to analytical disturbances.

For each individual patient urinary cAMP levels and osmolality measured during the study day were significantly correlated ($p<0.05$). In 18 of the 20 enrolled patients this correlation r^2 exceeded 0.8 (Figure 3A). The partial correlation *r* between urinary cAMP levels and osmolality was 0.94 ($p<0.001$). The partial correlation *r* for the cAMP corrected for creatinine was 0.229 ($p=0.007$).
For urinary AQP-2 levels no significant correlation with urine osmolality (Figure 3B) nor urinary cAMP levels could be established neither for the individual data nor for the pooled data (partial correlation *r* for urinary AQP-2 levels and urine osmolality 0.028; $p=0.750$).

The partial correlation *r* between urinary AQP-2 levels and urinary cAMP levels was –0.021 (p=0.813).

In order to investigate whether maximal kidney urine concentrating capacity was correlated to maximal rise in kidney cAMP and/or AQP-2 production, we investigated the correlation between the individual maximal reached urine osmolality and the individual maximal rise in urinary cAMP and AQP-2 levels. Overall, individual maximal reached urine osmolality was statistically significantly (p<0.001) correlated to the individual maximal rise in urinary cAMP levels (r^2=0.783) (Figure 4A). When expressing rise in cAMP mol/hour or corrected for urinary creatinine excretion a correlation of r^2=0.769 (p<0.001) and r^2= 0.002 (p=0.858) were obtained.

The rise in individual urinary AQP-2 levels showed a high interindividual variability (Table 2). No significant (p=0.187) overall correlation (r^2=0.100) could be established for the individual rise in urinary AQP-2 levels and the individual maximal reached urine osmolality (Figure 4B).

In addition we investigated whether there was a statistically significant difference in dDAVP-induced rise in urinary cAMP and AQP-2 levels between the three respective NDI categories. We performed a Kruskal-Wallis test of which the results indicated that the dDAVP induced rise in urinary cAMP levels for the three categories was statistically significantly different (p=0.006). Expressing cAMP as mol/hour instead of mol/l did not change the results (p=0.007)

DISCUSSION

A statistically significant correlation was observed between urinary cAMP levels but not urinary AQP-2 levels and urine osmolality in response to water loading followed by stimulation with dDAVP in patients under long-term lithium treatment. The severity of the kidney urine concentrating deficit was clearly linked to the degree of diminished dDAVP induced cAMP generation.

To our knowledge our study is the first in which, in man, long-term lithium-induced kidney urine concentrating deficits, are linked to an impaired dDAVP-induced cAMP generation. Both duration of lithium use and cumulative lithium dose were significantly higher in those classified as NDI, consistent with the

reported association between exposure to lithium and the occurrence of kidney urine concentrating deficits in literature.[1,3,4,33,34]

In a previous study by Walker et al, it was established that four weeks of lithium treatment in healthy volunteers resulted in a small but significant reduction in dDAVP induced kidney urine concentrating capacity, in concurrence with both reduced urinary cAMP and AQP-2 levels.[32] In their study both cAMP and AQP-2 were expressed in the same manner as in our study with cAMP as mol/l and AQP-2 as mol/mol creatinine. In our study, we investigated the long-term effects of lithium treatment on kidney urine concentrating capacity and urinary cAMP and AQP-2 levels, in patients under long-term lithium treatment in daily clinical practice. The observed rise in urinary cAMP levels in our study was statistically significantly less in those exhibiting kidney urine concentrating deficits. Analysing our results expressing cAMP and AQP2 respectively as mol/l, mol/mol creatinine or mol/hour resulted in a similar trend, revealing significant correlations for urinary excretion of cAMP but not for AQP2. However, the correlation between urinary excretion of cAMP and urine osmolality was less pronounced when expressing cAMP as mol/mol creatinine (results not shown).

It has previously been suggested that lithium acts by inhibiting adenylate cyclase activity in the collecting duct principal cells thereby preventing cAMP formation,[6,16-18,35] which was shown to involve activation of G-inhibitory (Gi) subunits in rats treated with lithium for a long-time period.[18] Furthermore, it has more recently been found, that lithium exhibits a direct toxic effect on the principal cells in animal studies,[21] resulting in a direct loss of vasopressin 2 receptor.[19] This could be in accordance with previous reports,[3,4,33-35] that show that both duration and total cumulative dose are correlated to the degree of lithium-induced urinary concentrating defect. A significantly higher exposure to lithium (duration of use as well as cumulative dose) was in accordance with previous results established in our NDI group compared to the partial NDI and the non-NDI group in accordance with previously reported studies.[3,4,33-35] Both a direct toxic effect of lithium on the principal cells or direct toxic effects on the G-protein or adenylate cyclase could explain these phenomena.

Various other effects of lithium treatment have been found: reduced levels of AQP-2-mRNA, next to low Na-K-ATPase mRNA levels,[36] and also altered expression of specific acid-base transporters in response to long-term lithium

treatment.[37] The kidney, in lithium-induced NDI, has been shown to be resistant to AVP stimulation of the vasopressin 2 receptor.[11]

Based on the limited knowledge of its central therapeutic effects (involving among others effects on the level of the second-messenger cAMP)[38] and the above reported renal effects in lithium-treated rats, we hypothesized that lithium is more likely to cause direct interference with the vasopressin 2 receptor–cAMP part of the cascade, rather than to have a direct effect on the AQP-2 gene or protein in man. Our results, accordingly, show a diminished urinary cAMP excretion in relation to diminished kidney urine concentrating capacity in patients under long-term lithium treatment. Our findings, which are in accordance with the results described for studies in animals.[6,16-18,21,35,39] indicate that an impaired cAMP generation is, at least in part, responsible for lithium-induced NDI in man. In man low urinary AQP-2 levels upon dDAVP administration in lithium-induced NDI have been described,[29] however, without concurrent information on urinary cAMP levels.

The overall results of our study do not show a statistically significant diminished AQP-2 generation in those with lithium-induced kidney concentrating deficits. The results of our study therefore do not indicate AQP-2 as the primary target in the mechanism underlying lithium-induced NDI. On the other hand, in light of the good correlation established between urine cAMP levels and urine osmolality in both individuals with impaired concentrating capacity and individuals with intact concentrating capacity, we presume that the established large inter- and intraindividual variability indicates that urine AQP-2 level is not a good marker of activation of the vasopressin 2 receptor–cAMP–AQP-2–urine osmolality cascade, in conflict to what has been suggested previously in other studies.[9-11,40] Based on our results it is therefore not possible to entirely exclude a direct involvement of AQP-2 (by means of production, phosphorylation, release or insertion in the apical membrane). There are certain limitations to our study. We did not include a healthy control group. Including a healthy control group in our experiment could have revealed important information on actual differences in the urinary cAMP and AQP-2 levels, in response to water loading and administration of dDAVP between those not exposed to long-term lithium treatment and those under long-term lithium treatment not suffering from a kidney urine concentrating deficit and those under long-term lithium treatment suffering from a kidney urine concentrating deficit. We only followed patients

for three and a half hours post dDAVP administration. Possibly a follow-up period of three and a half hours is insufficient to assure full recovery of the medullary hyperosmolal status, which could have been diminished due to water loading. We were not able to discuss the influence of concomitantly used medication, due to the relatively small population size. Further research is warranted to investigate the effects of concomitant use of medication on the occurrence of lithium-induced NDI.

In conclusion, our findings are the first indication that NDI induced by long-term lithium use in man is caused by a mechanism leading to inadequate production of cAMP, thus implicating that the mechanism of lithium-induced kidney urine concentrating deficits is to be found at the vasopressin 2 receptor or within the vasopressin 2 receptor–cAMP part, rather than in the cAMP–AQP-2 part of the kidney urine concentrating cascade. It remains to be elucidated, which specific part of the vasopressin 2 receptor–cAMP cascade (for instance G-proteins or adenylate cyclase) or perhaps the principal cells in general, are the major targets for renal lithium toxicity in man.

Additionally, variability, as reported in literature, in individual susceptibility for renal lithium-toxicity suggesting involvement of a genetic factor resulting in predisposition, remains the subject for future investigation.

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5 General discussion

INTRODUCTION

Bipolar disorder is one of the worlds ten most disabling conditions, literally depriving patients from years of healthy functioning.[1-3] Bipolar disorders often go underrecognized and consist of a psychiatric disease spectrum that, in addition to a high socio-economic disease burden[4] often shows severe somatic co-morbidity.[5-7] For the pharmacological treatment of bipolar disorders lithium has been the gold standard for over 50 years.[8] Lithium is a simple small anorganic element, that as pharmacotherapeutic agent requires a complicated and intensive monitoring shield in order to obtain a positive balance between intended and unintended effects.[9] This balance is difficult to obtain and easily disturbed in each individual patient. The latter because of the susceptibility of lithium effects to various factors.[10-12] Lithium influences many physiological systems potentially inducing many effects other than the intended one. This is probably due to its simple structure resembling potassium, sodium, magnesium and calcium. Several of these unintended effects, such as nephrogenic diabetes insipidus (NDI) and hypothyroidism are not regarded as beneficial but rather as adverse drug reactions (ADRs).[13] Some of the unintended lithium effects have, however, more recently gained interest as being potentially beneficial, for example its supposed neuroprotective and immune modulating effects.[14-16] Given that the mechanisms underlying lithium's pharmacological effects have up to present not been fully elucidated, it is very difficult to predict which patients are more likely to benefit from lithium and which patients are more likely to be merely susceptible to its debilitating effects. Therefore, targeted prescribing, taking into account individual susceptibility aspects, is difficult.

In this thesis, several studies have been conducted that focused on different outcomes of long-term treatment of patients with lithium. Lithium treatment outcomes, in this thesis, refer to both its beneficial intended therapeutic effects in the prophylaxis and the acute treatment of bipolar disorders and unipolar depression as well its unintended ADRs complicating its use. We have focused on treatment outcomes during long-term follow-up, studying influences of emerging alternatives on lithium utilization patterns and associations between disease phase and lithium treatment outcomes. Additionally, we studied factors (i.e. drug and environmental factors and healthcare professional performance) influencing the occurrence of supratherapeutic lithium serum levels and the

management of the lithium intoxicated patient. Lastly, we studied the long-term nephrogenic complications of lithium treatment: polyuria and NDI. The latter by studying the influence of concomitant drug use and investigating molecular mechanistic aspects.

In this final chapter the results of the individual studies will be placed in a broader perspective, focusing on the three major topics:

1. Susceptibility of lithium effects to variability in dynamic and fixed factors;
2. Challenges for improvement of the handling of a small therapeutic agent;
3. Differences between evidence based medicine (EBM) and medicine based evidence (MBE).

The chapter will conclude with some future perspectives for both clinical practice and research.

SUSCEPTIBILITY OF LITHIUM EFFECTS TO VARIABILITY IN DYNAMIC AND FIXED FACTORS

Lithium treatment outcomes can be regarded as one of the examples illustrating that outcomes of drug treatment can be highly sensitive to and dependent upon intraindividual dynamic and interindividual dynamic and fixed factors. Important dynamic factors comprise of pharmacodynamic and pharmacokinetic characteristics, patient behaviour, diet, drug utilization patterns, disease features, healthcare professional performance and environmental factors. On the other hand there is an increasing number of studies associating fixed factors like genetic predisposition and first-line family anamnesis to certain adverse and therapeutic intended drug effects of lithium treatment.[17-20]

Variability in lithium effects in relation to its pharmacological profile

An important factor that contributes to the high variability of lithium treatment outcomes is its pharmacological profile. Lithium is a drug with a very narrow therapeutic index, due to its high affinity for many organ systems and cellular processes. This makes its treatment outcomes very susceptible to relatively small changes in exposure. Moreover, lithium is intended for long-term use and its adverse reaction profile is known to change during the course of treatment. At initiation of lithium treatment gastro-intestinal ADRs are most prominent,

whereas the incidence of nephrogenic and thyroid complications increases during long-term treatment. During the course of treatment the focus on different treatment outcomes therefore has to change. Additionally, the considerable inter- and intraindividual differences in lithium pharmacokinetics largely influence exposure of the human biosystem to lithium. For this reason, lithium dose itself is not a good predictor of treatment outcomes,[21] rendering regular lithium serum level monitoring imperative.[22] This need for regular TDM contributes to the total burden of lithium treatment for both patients and healthcare professionals. Several efforts have been undertaken into prediction of the lithium dose needed to obtain the target lithium serum level on an individual patient level.[23,24] A valid dose requirement prediction method without serum level monitoring, captivating all potentially influencing factors is, however, still not available. The fact that so many factors potentially determine lithium serum levels, makes it highly unlikely that lithium serum level monitoring will ever be avoidable.

In this thesis several studies are brought together focussing on factors influencing lithium serum level. In our study (Chapter 3.1) we found that antibiotic use next to lithium was relatively most frequent in patients presenting with elevated lithium serum levels.[25-33] In the Netherlands patients are often registered to one single community pharmacy, clustering all prescriptions for drugs being prescribed to them in an out-patient situation. This enables the community pharmacist to adequately react on the occurrence of drug-drug interactions and thereby to anticipate on the negative consequences thereof. Monitoring for lithium-drug interactions mainly refers to drugs interacting with lithium through a direct pharmacokinetic mechanism such as the interactions with diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs). Antibiotics are not associated with alterations in lithium serum level through a direct pharmacokinetic mechanism, but are merely-as a proxy for infection- associated to endogenous heat i.e. fever induced changes in body handling of lithium. In addition, use of antibiotics is also a proxy for destabilisation of the patient's general condition.[34] Therefore, co-prescription of antibiotics next to lithium did, at the time we performed our study, not generate a warning signal in pharmacies. The latter possibly explains why these drugs had relatively the largest impact on elevated lithium serum levels in our study. The same water and salt depleting mechanism could be the reason for lithium serum levels being increased during periods of higher outdoor temperature. This led us to subsequently investigate exogenous

heat i.e. environmental temperature as a determinant of the height of lithium serum levels (Chapter 3.2). We found a statistically significant but clinically irrelevant association between higher outdoor temperature and elevated lithium levels. Possibly as a result of lack of information on other factors in addition to the relatively mild Dutch climate, the variation in lithium serum level that could be explained by environmental temperature was very small. These two factors, indirectly influencing lithium exposure through influencing the body's salt and water homeostasis, represent an example of new possibilities of more personalized monitoring for drug-interactions in patients using lithium. Implementation of this multifactorial knowledge can take medication surveillance in pharmacies to a higher level. This requires efforts of patients, physicians, pharmacists and other healthcare professionals.

In addition, efforts to decrease the burden associated with the intensive and complicated lithium monitoring shield are important. There are two major options to achieve this goal. First, by the development of point-of-care testing methods and implementing such testing methods into specialized outpatient lithium clinic facilities. This would lead to a decrease in the number of mandatory visits to laboratory facilities.[35] Implementing this testing method into daily clinical practice most likely preserves the need for intensive guiding by physicians or specialized nurse practitioners. Secondly, point-of-care lithium serum level methods could be used to have patient measure their own lithium serum level. The latter is common for a disease like diabetes and has been investigated for use of oral anticoagulants.[36] Patient initiated lithium dose adjustments based on lithium serum level could prove to be rather difficult because of its complicated pharmacokinetic properties.

In addition to blood sampling required for lithium serum level monitoring, there are certain frequently occurring ADRs that can be detected early through monitoring of certain laboratory parameters. In case of nephrogenic and thyroid complications, laboratory measurements can provide information prior to actual clinical symptom development, by measuring certain biomarkers. In addition, monitoring of renal function is essential for maintaining adequate lithium serum level. So, if point-of-care testing is to find its way into daily clinical practice, generating a complete lithium profile test allowing for simultaneous detection of nephrogenic or thyroid complications could prove useful.

The pharmacological properties of lithium render it highly unlikely that use of lithium will ever go without its current intensive and complicated monitoring shield in clinical practice.

With respect to the design of pharmacoepidemiological studies the absence of an association between lithium dose and lithium serum level makes it difficult to perform drug exposure association studies. Searching for a dose response association without information on lithium serum level is unfeasible. The latter highlights limitations to the use of traditional prescription databases mostly used in pharmacoepidemiological research. In addition, in evaluating occurrence of certain ADRs the importance of both additional laboratory measurements and the duration of use need to be considered.

Variability in lithium outcomes in relation to interindividual differences in patient pharmacodynamics

There are large interindividual differences with respect to patient susceptibility to lithium therapeutic beneficial outcomes and ADRs. About 30-40% of patients do not sufficiently respond to lithium treatment. Some factors associated to beneficial therapeutic response in patients treated with lithium have been recognized. An increased chance for beneficial clinical response exists for patients presenting with a classical bipolar I disorder[37,38] and patients with a positive therapeutic outcome of lithium treatment in a first-degree relative.[18-20]

About 75-90% of the patients encounter one or more ADRs during long-term lithium treatment. In addition, ADRs have shown to be an important reason for both patient as well as physician initiated discontinuation of lithium treatment. In this manner occurrence of ADRs can obstruct lithium beneficial therapeutic outcomes. Targeted prescribing can be refined by increasing knowledge on baseline patient susceptibility factors for the occurrence of ADRs. Some evidence has been found on factors explaining interindividual differences regarding susceptibility to thyroid ADRs. Women above 45 years of age and patients presenting with thyroid antibodies[39-41] are at increased risk for developing thyroid complications to lithium treatment. Fully implementing this knowledge into the therapeutic decision making process is still difficult. Increased comprehension of mechanistic pharmacological aspects of lithium can lead to elucidating baseline susceptibility factors and other influencing factors predisposing to occurrence of ADRs. The knowledge for example that about 15-40% of the patients on long-

term lithium treatment develop polyuria, which in about 12% results in a true NDI[42,43] reveals that not all patients are equally susceptible to the development of this ADR. However, this knowledge does not yet provide us information on who is more and who is less susceptible and therefore not on how to integrate this susceptibility knowledge into the daily therapeutic decision making process.
In our study (Chapter 4.2), we found that the mechanism of lithium induced NDI is more likely to be found within the first part of the kidney-urine concentrating mechanism. This had previously been established in a study investigating short-term lithium effects on urine concentrating capacity[44] in men. Further research could lead to the unravelling of the exact mechanism of lithium induced NDI, ultimately resulting in elucidating factors associated with baseline interindividual differences in susceptibility for the development of this lithium ADR. This information can then be taken into account in the decision making process regarding which long-term pharmacotherapeutic treatment to institute in the individual patient.
The assessment of lithium therapeutic outcomes, can in addition to the changing ADR profile over time, also be affected by the changing of population dynamics over the course of lithium treatment. In long-term treatment the potential importance of selection bias; i.e 'depletion of susceptibles', increases. During longer duration of treatment there is an increased chance of encountering patients with a relatively good response to the drug and relatively few ADRs.[45] This might have resulted in the large impact of use of serotonergic antidepressants on polyuria in relatively short-term lithium users in our study (Chapter 4.1). Lithium is often used long-term, whereas data available for research purposes generally do not allow for such long-term follow-up. In evaluating lithium effects in pharmacoepidemiological studies, duration of use can be considered an important factor when assessing potential determinants of therapeutic outcomes.

Lithium outcomes in relation to the underlying disease

Next to the pharmacological drug properties and the interindividual differences in patient pharmacodynamics, the underlying disease itself can also be considered an important factor in the evaluation of lithium effects. Bipolar disorder has an unpredictable episodic pattern, influencing lithium effects by influencing patient behaviour, judgement, suicidalilty,[46] efficacy of treatment, compliance,

perception of ADRs and even the drug's pharmacokinetic characteristics.[47] ADRs have shown to be an important factor in both patients initiated and physician initiated discontinuation of lithium treatment.[48-50] Actively asking patients about the occurrence of ADRs has been shown to increase reporting of ADRs.[51,52] Some studies on depression and schizophrenia have shown an association between disease and occurrence of ADRs.[53-55] We hypothesized that such an association also exists in bipolar disorders. Outpatients on long-term lithium treatment were asked during monthly visits about the presence and severity of ADRs well known to frequently occur during lithium treatment. During the same visit their mood state was scored and lithium serum level assessed (Chapter 2.2). Indeed, we observed that mood state was associated to the number and the severity of reported lithium ADRs, independent of serum level. Patients being more depressed overall reported more ADRs. In addition, present ADRs were scored as more severe. The observed association between mood state and ADRs might complicate evaluation of outcomes to lithium treatment in two essential ways. First of all, persistence with lithium might be influenced by the complication of the objective assessment, prevention and treatment of unintended effects. Secondly, occurrence of ADRs might, on the other hand also influence objective assessment of intended beneficial therapeutic lithium outcomes. Mood state might be influenced by occurrence of ADRs potentially altering the risk for depression. Awareness that ADR assessment is complicated by the underlying disease, and on the other hand ADRs might obstruct beneficial treatment outcome helps the clinician in the therapeutic decision making process regarding lithium treatment outcomes.

Mood state is on the other hand an important factor influencing patient behaviour. Patient discontinuing lithium are at an increased risk for recurrence of both manic and depressive episodes.[56] This may have been an important factor explaining the increased risk of fractures we observed in patients having discontinued lithium in our study (Chapter 2.3).

Patients suffering from bipolar disorders are at increased risk for somatic co-morbidities, especially cardiovascular risks.[57] This might also further complicate objective assessment of ADRs. Multiple drugs, like olanzapine and valproic acid, used in the treatment of bipolar disorders have been associated with an increased risk of metabolic syndrome.[58,59] Lithium use has also been associated with an increased risk for weight gain.[60,61] Since both drug and disease are associated with

an increased risk for cardiovascular risk factors it remains difficult to establish the exact contribution of each and to determine the best strategy to minimalise this risk in the individual patient. Alternatively, other factors like concomitant disease, interact with lithium effects i.e. heart-failure (e.g. minimising fluid intake instructions, concomitant drug use), changes in environment like admission to hospital (risking fluid deprivation), and re-entering of patients into bipolar disorder treatment facilities after having survived an intoxication with lithium (Chapter 3.3). Intensified communication throughout different medical specialities including psychiatrists, cardiologists, toxicologists, chirurgical specialists, general practitioners and (hospital) pharmacists is required to allow adequate acting upon these factors. Several efforts are currently being undertaken into further development of continuous safety monitoring regarding bipolar patients, in light of its increased risk for somatic co morbidity and especially long-term ADRs. Besides the underlying disease, disease severity is also an important factor of selection bias, regarding patient setting in pharmacoepidemiological studies. Patients being extremely ill are more likely to be admitted to the hospital, thereby, excluding them from an outpatient study population.

When evaluating lithium treatment outcomes in clinical practice and in (pharmacoepidemiologic) research, considering the potential influences of the episodic pattern of the disease, concomitant morbidities, disease severity and baseline risk factors associated with the disease are important. Time-varying covariates analysis may if feasible prove valuable to study certain lithium treatment outcomes.

Susceptibility in relation to healthcare professional performance and environmental factors

Besides patient and drug related factors, healthcare professional related factors as well as environmental factors can potentially influence lithium effects. Another issue involving selective prescribing regarding lithium ADRs, is concomitant drug prescription (pharmacodynamic drug-drug interactions). We found an increased risk of polyuria in patients using serotonergic antidepressants next to lithium (Chapter 4.1). This finding represents another issue that, prior to actually effectuating the prescription, needs to be considered. Pharmacodynamic drug-drug interactions can potentially be even more important since bipolar disorders

represent a disease spectrum for which polypharmacy is not uncommon.[62-64] Healthcare professional performance (concomitant prescription of medication; Chapter 3.1 and 4.1), providing intake instruction, adequate acting upon laboratory measurements and clinical outcomes (in handling a patient with a lithium intoxication (Chapter 3.3), integrating of multidisciplinary knowledge (Chapter 3.3) and environmental factors, as referred to earlier (temperature and humidity; Chapter 3.2) can influence an individual's body handling of lithium to an important extent.

In clinical practice knowledge on influences of co prescription beyond the well known pharmacokinetic interacting drugs and the increase in vulnerability to lithium toxicity during periods of warm weather, is important to stimulate proactive monitoring and to avoid toxicity. In pharmacoepidemiological research, these factors are important in assessing different outcomes. Information on these factors is, however, not always available for research purposes.

Therapeutic outcomes of lithium treatment can thus be considered the result of a very complex clustering of and interaction between influencing dynamic and fixed factors. This fact is important for both (pharmacoepidemiological) researchers as well as for clinical practice as has been demonstrated above.

CHALLENGES FOR IMPROVEMENT OF THE HANDLING OF A SMALL THERAPEUTIC AGENT

Given the high variability described in the previous section of this general discussion, complying to the established monitoring shield for lithium is absolutely mandatory. This monitoring shield has been established, but challenges for further improvement of the handling of this small therapeutic agent still exist.

Importance for clinical practice

Lithium treatment is one of the treatment modalities requiring continuous high care monitoring during patient follow-up. In clinical practice, lithium treatment consequently demands specific efforts and collaboration between different healthcare professionals and patients in optimising beneficial outcomes for the individual patient. Increasing knowledge and awareness of the impact of the influences of these factors and how to best anticipate on them has resulted in the

development, continuous updating and implementation of practice guidelines, monitoring for drug-drug interactions and the emergence of specialized lithium outpatient clinics. Transfer of knowledge between healthcare workers is facilitated by cooperation between healthcare professionals (psychiatrists, pharmacists and specialized nurse practitioners) and patients like for example in the Dutch 'Lithium plus working group', the 'International Society of Bipolar Disorders' (ISBD) and the 'International Group of Study of Lithium' (IGSLI). A more integrated multidisciplinary approach of continuous safety monitoring, in which both the underlying disease as well as the drug effects are taken into account is warranted. The latter is currently being evaluated by the ISBD safety monitoring committee which has resulted in the development of the ISBD safety monitoring guideline (currently under review). In the Netherlands the issue of safety monitoring is well represented in the Dutch Guideline of the Dutch association of Psychiatrists (NVvP) for the treatment of bipolar disorders of which the revision is currently in press.

Healthcare professional performance has been an important factor in creating the current lithium monitoring shield. Psychiatrists have increased the care for their patients using lithium by creating specialized lithium outpatient clinics. Pharmacists are able to proactively anticipate on drug-drug combinations potentially influencing lithium treatment outcomes. In line with the existing monitoring shield for oral anticoagulants the lithium monitoring shield could be further improved. This could be accomplished by increasing collaboration of healthcare professionals like has been done in the collaboration between the Scientific Institute Dutch Pharmacists (WINAP), the Dutch federation of anticoagulation clinics and pharmacists.[65] With this collaboration, an extensive handbook advising physician and pharmacist on acting on occurrence of the most common drug-drug interactions with oral anticoagulants has been prepared. Within this handbook specific advise on which healthcare professional should act at what moment on which drug-drug interaction is provided.

In addition to taking the monitoring of patients using lithium to a more integrated higher level, further exploring the impact of influencing factors on lithium treatment outcomes is required. Results should be translated into managing strategies regarding lithium treatment in daily clinical practice, resulting in further maximising the likelihood of intended therapeutic outcomes and minimising the likelihood of unintended adverse lithium outcomes. The full

elucidation of the impact and the interaction between these factors on outcomes could ultimately result in stimulating selective prescribing to those patients most likely to benefit from lithium treatment, while choosing an alternative treatment in patients at an increased risk for ADRs.

Importance for clinical research

In light of all above described influencing dynamic and fixed factors, it is essential to consider the possibilities and limitations of available data for research purposes. No conclusions regarding the traditional dose response assessment can be made, without information on lithium serum levels. In addition, duration of treatment is an important factor in ADR assessment. Lithium's ADR profile changes over time, especially concerning long-term effects. Researchers need to be aware of the influence of interindividual differences in pharmacodynamics resulting in the possibility of 'depletion of susceptibles'[45] with longer duration of use. The term 'depletion of susceptibles' refers to the fact that patients either not well tolerating lithium or not having a beneficial clinical response to lithium treatment are most likely to discontinue using lithium. Disease severity can on the other hand influence study-population dynamics by influencing patient setting. Patients being extremely ill are more likely to be institutionalised moving away from the out-patient population setting. In addition, in evaluating the underlying disease the timing of outcome assessment is important, since disease phase has been shown to influence outcomes. Lastly it is important to account for possible influences on lithium outcomes of healthcare professional performance factors and environmental factors. The latter influences are due to incompleteness of available data not always easy to account for. Utilising different data sources can aid in answering different research questions with each source having its own limitations. We were fortunate to be able to use patient-mood state-ADRs data that had been systematically gathered over a time-period of 26 years (Chapter 2.2). These data allowed us to investigate the existence of an ADRs-mood state association. Such detailed information on patients using lithium derived from daily clinical practice for such a long-time period is unfortunately not widely available. Registration of outcomes during long-term treatment increases possibilities to improve management strategies by increasing research possibilities. For the studies presented in this thesis we used different data sources differing on data type with respect to source, duration and expertise collaboration.

The first source used in this thesis comprised of a source most frequently used in pharmacoepidemiological research, i.e. the drug dispensing data base obtained from PHARMO (Chapter 2.1) and General Practitioner Research Database (GPRD) (Chapter 2.3).

Traditional drug dispensing databases generally contain large amount of anonymous medication dispensing data for a relatively long time-period. In case of GPRD, data also provide information on diagnosis. PHARMO data are currently linked to hospitalisation data, however, unfortunately hospitalisation data do not include psychiatric hospital admissions. Prescription data can help to elucidate patterns of use and to investigate certain effects related to timing of exposure. In case of lithium, traditional prescription databases do not allow to investigate dose-response associations. The second source, used to perform the studies in this thesis, consisted of short-term data. Data were obtained from small groups of psychiatric out-patients consisting of more detailed data originating from patient interviewing (Chapter 2.2), medical charts (Chapter 4.1) and data directly obtained from patients (Chapter 4.2). Using more detailed patient information in smaller settings can provide information on certain determinants of drug effects like on occurrence of ADRs and influences on serum level. Specifically measuring those parameters of interest in the individual patient can help to elucidate pharmacological mechanistic aspects (Chapter 4.2) of different effects. The third data source used in this thesis comprised of pharmacy laboratory data on lithium serum level (Chapter 3.1 and Chapter 3.2), and urine volume (Chapter 4.1). The last source consisted of information obtained from practice guidelines originating from online databases, textbooks, poison information centres and university medical centres (Chapter 3.3) used to evaluate advises regarding treatment of lithium toxicity.

Translating findings from research into daily clinical practice is not always straightforward. For example, in assessing lithium exposure both timing and the awareness of the lack of a correlation between dose and treatment outcomes need to be correctly interpreted (Chapter 2.3). Both misinterpretation of timing of lithium use as well as a presumed dose effect association were found to result in preliminary conclusions[66] regarding the effects of lithium on bone. Our results demonstrated that lithium anabolic effects on bone as found in laboratory research[67,68] are not in agreement with the actual outcome of bone-fractures in daily clinical practice. The latter illustrates that differences in interpretation of

outcome depend on availability and adequate interpretation of information. The number and the severity of patient reported lithium associated ADRs has been shown to be associated to mood state in clinical practice (Chapter 2.2). The fact that this association has been established from observation of lithium users for a time-period of 26 years does not advise us on how to interpret this knowledge and how to implement it in both research and daily clinical practice. Is it disease phase by means of mood state influencing patient perception and severity of ADRs, or could it be that the increased burden of disease by means of ADRs increases the likelihood of depression to occur? Or could it even be that part of the reported ADRs are rather associated to the particular mood state than that they are lithium-induced? In either way the established association between disease and adverse effects does complicate the objective assessment of lithium outcomes by means of objective assessment of both beneficial effects and ADRs. The association between mood state and the prevalence and severity of ADRs, is likely also to hold true within other fields of healthcare with respect to drug acceptance.

EVIDENCE BASED MEDICINE (EBM) VERSUS MEDICINE BASED EVIDENCE (MBE)[69]

Serendipity in drug discovery is probably not accidentally found especially within the field of psychiatry. Psychiatry is one of the least mechanistically comprehended fields with many diseases requiring long-term use of pharmacotherapy.[70] Lithium has since its serendipitous rediscovery been the gold standard for about half a century in the bipolar pharmacotherapeutic armamentarium. It is one of the few drugs currently still in wide-spread use with a set off in daily clinical practice (MBE) rather than the well controlled environment of a randomised clinical trial (EBM). Other examples of serendipitous discoveries consist of irreversible monoaminoxidase inhibitors (MAOI) and penicillin. Lithium has survived many barriers and is despite its safety issues still regarded to be the drug with still the best proven efficacy in the long-term prophylaxis of bipolar disorders. We found that baseline characteristics of out-patients being prescribed lithium for the first time did not change over time in the last decade in the Netherlands (Chapter 2.1). We did observe,

however, an increase in concomitant prescription of alternative drugs, emerging during the last decade. Moreover, we found an increase in use of these alternatives after discontinuation of lithium treatment.

In light of such an intensive and complicated monitoring shield and still ongoing research into solving some of the mysteries of lithium's pharmacological profile, one may wonder what would have happened if lithium's mood stabilising properties would have been discovered today. Would the bipolar patient ever have had access to today's gold standard in bipolar psychopharmacotherapy? Would there have been any company that would have further developed lithium use in an EBM manner, also in light of the fact that lithium's efficacy is best proven during long-term prophylaxis. Would there have been a company that would have marketed a drug requiring such an intensive and complicated monitoring shield that can not be patented?

When lithium re-entered psychopharmacotherapy, together with the experience gained with its use (MBE), drug regulations were less stringent than they are today. Today's drug approval consists of an extensive pathway of pre-clinical and clinical studies (EBM) followed by formal approval and post-marketing studies. Despite its well established position in bipolar pharmacotherapy, lithium treatment has remained the objective of considerable debate concerning both its efficacy[71,72] and its safety profile. The latter by means of causality of certain ADRs like nephrogenic complications[73,74] and the practical obstacles associated with its use. Lithium is one of the few drugs for which increasing knowledge from mostly observational studies (MBE) has dictated use in daily clinical practice, instead of regulatory authority approved registration files (EBM). For most drugs, results in daily clinical practice (MBE) do not approach the results obtained from highly selected and well controlled patient selection in randomised controlled clinical trials (EBM). For lithium, on the contrary, post marketing surveillance has proven to be essential for its use today. Ironically, lithium today serves as gold standard in RCTs with the purpose of investigating the efficacy-safety profile of newly available drugs in the long-term treatment of bipolar disorders in an evidence based manner. Also, most of the information regarding ADRs to lithium is the result of observational research. The fact that most information on lithium use is derived from daily clinical practice (MBE) where the different factors can not be separately assessed, complicates causality assessment. This we have shown in our own study (Chapter 2.2) on the association between mood

and the number and severity of reported ADRs and has been established for cognitive disturbances due to lithium use and due to bipolar disorders itself.[75] What is to come for lithium is still unknown since the efficacy safety profile for newer emerging alternatives versus lithium is not yet fully known. Will the increasing knowledge on lithium treatment and on how to further customize the approach to lithium prove sufficient to preserve its position as first-line treatment? Or will lithium use ultimately fade in light of the emerging alternatives currently attacking lithium as a first line treatment in the treatment of mania, depression as well as in prophylaxis. None of the alternatives has up to present succeeded in conquering lithium at all therapeutic entrances.

FUTURE PERSPECTIVES

Despite its proven efficacy and being the gold standard in the long-term treatment of bipolar disorder, lithium can not be considered an ideal treatment because of its required intensive complicated monitoring shield and ADR profile. Hence, more research is required into optimising its current use and into further understanding the mechanisms of its positive and unintended therapeutic outcomes. The latter also in order to facilitate the search for possible alternatives to lithium with similar or preferably better efficacy and a more beneficial ADR profile. Assuring further integration of knowledge from different medical disciplines in addition to alternative drug interaction monitoring is required. The latter to increase beneficial therapeutic outcomes in daily clinical practice, and to improve research strategies. Knowledge on baseline susceptibility factors with increased probability for beneficial as well as with increased chance for adverse outcome events should be considered when comparing lithium to potential alternatives. Additionally also beneficial and adverse response to prior pharmacotherapy should be accounted for in analysis of efficacy and safety comparison. This to allow for fair comparison between potential alternative treatments, thereby not risking discarding specific treatments from selected populations who are most likely to benefit from them.

Many lessons have been learned from lithium in its post-marketing era, with some immediately applicable to improving patient care. Most lessons learned from influences on lithium and lithium effects originate from the post-marketing

era, reinforcing the use and monitoring pattern of today's practice. One of the important lessons was that as the result of fatalities, the inter- and intraindividual differences in pharmacokinetics have learned to be appreciated. This has resulted in today's stringent serum level monitoring regimen. Both patient and physician behaviour have been forced to adapt to the demands of the drug in order to allow for safe use. The latter can be regarded as a form of personalized medicine by pre-selection of patients able to comprehend and likely to commit to such a stringent regimen. More research is, however, warranted into elucidating which patients are most likely to benefit from lithium and who most certainly are not.

Knowledge on baseline factors associated with beneficial as well as adverse outcomes needs to be increased in order to limit prescription of lithium to those patients most likely to benefit from lithium. Using the knowledge that during long-term treatment the patients still using lithium are more likely to be those well responding and relatively well tolerating lithium can possibly be used in elucidating baseline interindividual susceptibility factors. Regarding its ADR profile, our finding that the mechanism of lithium induced NDI lies within the first part of the kidney-urine concentrating mechanism needs to be further explored to eventually fully unravel lithium's pharmacological effects on the kidney. This pharmacological insight could then further lead to elucidating determinants for lithium induced NDI and to provide information on patients more and less at risk for the development of lithium induced NDI. Lithium monitoring needs to be taken to a higher level integrating knowledge on influencing factors into a more proactive approach regarding safety in the lithium using patient. Patients suffering from NDI need to be especially monitored for with respect to maintaining a positive fluid balance in situations where they can not preserve adequate compensatory fluid intake themselves. Patients having survived an intoxication with lithium deserve special attention and follow-up with respect to sequelae and reinstitution of pharmacotherapy.

At the moment, on the other hand, there is a growing interest in lithium pharmacological mechanistic properties. Especially concerning its possible neuroprotective and also its immunomodulating properties.[14-16,76] The latter, however, is more likely to increase pharmacological mechanistic insight into neuroprotection and possibly immunomodulation potentially leading to development of future drugs, than to provide a new indication for lithium prescription.

Lithium use is not likely to fade within the near future, even if other alternatives will ultimately prove to supersede lithium. Further research to elucidate factors predicting its efficacy and determining its safety remains necessary to optimise current use of lithium as the gold standard in bipolar disorders pharmacotherapy.

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summary

Lithium currently is the gold standard in the treatment of bipolar disorders. Lithium is, however, in light of its very narrow therapeutic range and its adverse drug reaction (ADR) profile, not considered the most ideal pharmacotherapeutic agent. With the studies performed in this thesis we anticipated to contribute to the current knowledge of the use and effects of lithium in daily clinical practice. The main objectives of this thesis were 1) to investigate treatment patterns and the ADR profile of lithium during follow-up, 2) to investigate the endogenous and exogenous influences on lithium serum level and its toxicity, and 3) to investigate molecular mechanistic aspects of lithium associated nephrogenic complications (polyuria and nephrogenic diabetes insipidus [NDI]).

The first part of this thesis entitled **'Patterns and consequences of lithium use'** focuses on different aspects of the use of lithium during long-term follow-up.

In *chapter 2.1* we studied patterns of use of lithium in out-patients who had started using lithium within the last decade. In this time-period the pharmacotherapeutic treatment armamentarium for bipolar disorders has widened significantly. The objectives of the study presented in *chapter 2.1* were to investigate in outpatients in the Netherlands between 1996 and 2005, changes in 1) the incidence and the prevalence of lithium use and 2) lithium use patterns (discontinuation, add-on, and switch). This study was performed using the PHARMO database. Incidence of lithium use was found to be constant during the study period at approximately 0.2 per 1000 person years. Prevalence, however, was found to increase with about 26% from about 0.95 to 1.2 per 1000 persons during 1996-2005. In addition, we determined cumulative changes in lithium use (discontinuation, add-on, and switching) at three, six, 12 and 24 months for three separate time-cohorts (1998-1999, 2000-2001 and 2002-2003). The percentage of patients receiving an add-on to ongoing lithium treatment of another drug used in the treatment of bipolar disorders was found to be constant over the three time-cohorts. Within the patient group that stopped using lithium, more patients were found to switch from lithium to another agent used in the treatment of bipolar disorders over calendar time, and fewer patients were found to discontinue lithium. There was a significant increase in the use of atypical antipsychotics and valproic acid next to lithium. Use of tricyclic agents decreased over time. The changes we observed in use of concomitant drugs next

to lithium were in line with the increase in availability of alternatives during the last decade and in line with Dutch guidelines for the treatment of bipolar disorders.

Approximately 75-90% of patients on long-term lithium treatment experience one or more ADRs. Previous studies in depression and schizophrenia showed an association between disease severity and prevalence of ADRs. We hypothesized that mood state in bipolar disorders might also be an important factor interfering with objective assessment of ADRs and potentially with lithium efficacy. Such an association might be important since ADRs are a known risk factor for both patient as well as physician initiated discontinuation of lithium. In *chapter 2.2* we assessed the association between mood state as well as lithium serum levels and prevalence and severity of ADRs as reported by a total of 186 patients attending an outpatient lithium clinic during the period of 1973 and 2000 in the Netherlands. The prevalence and the severity of ADRs increased with decreasing mood state into the depressive range and decreased with mood state increasing into the manic range ($p<0.05$), also when adjusting for lithium serum level. Taking into account the intraindividual dependency of the data resulted in a statistically significant ($p<0.001$) association between respectively lithium serum level, mood state and the prevalence and severity of ADRs. Both physicians and researchers need to be aware that lithium serum level and mood state are independently associated with patient reporting and severity scoring of ADRs. This may complicate objective assessment of ADRs.

In assessing determinants for outcomes to lithium treatment both timing and serum level may be very important. A recent study reported a decreased risk of fractures among lithium users and in addition reported a dose response association between use of lithium and the risk of fractures. This was in accordance with laboratory findings demonstrating lithium anabolic effects on bone in vitro. The study, however, did not account for timing of lithium use in relation to the occurrence of the fracture. Nor did this study take into account lithium serum level to assess a dose response association between use of lithium and the risk of fractures. In *chapter 2.3* therefore, we investigated the importance of timing of lithium use during follow-up with respect to the interpretation of the reported association between lithium use and the risk of fractures. We conducted a case-control study within the UK General Practice Research Database, comparing never, ever, current, recent and past lithium use in 231 778

fracture cases to matched controls. In addition, the risk of fractures was assessed in relation to cumulative duration of use and time since discontinuation. Current use of lithium was associated with a decreased risk of fractures (adjusted odds ratio [OR] 0.75, 95% confidence interval [CI] 0.64-0.88), that did not vary with cumulative duration of use. Among past users an increased risk of fractures was observed (adjusted OR 1.35; 95% CI 1.01-1.79), increasing with time since discontinuation. Our results support the role of the underlying mental disorders in the aetiology of fractures, but do not support a pharmacological effect of lithium based on lack of an association with cumulative duration of use.

The second part of this thesis entitled **'Determinants and treatment of potential lithium intoxications'** focuses on both determinants and consequences of the narrow therapeutic range of lithium. Despite knowledge that multiple drugs potentially interact with lithium, the actual impact of these drug-drug interactions in daily clinical practice is largely unknown. In *chapter 3.1* we explored drug-drug interactions as a determinant of the risk of elevated lithium serum levels. We conducted a multi-centre retrospective case-control study with the aim of investigating lithium-related drug-drug interactions as determinants of elevated lithium serum levels in daily clinical practice. We defined cases as patients with an increase of at least 50% in lithium serum concentrations resulting in an elevated lithium serum level of at least 1.3 mmol/l, and who were not suspected of a suicide attempt. Controls were patients who showed stable lithium serum levels within the therapeutic range. Use and start of nonsteroidal anti-inflammatory drugs, diuretics, renin-angiotensin inhibitors, theophyllin and antibiotics were investigated as potential determinants of the elevated lithium serum levels. Irregularity in lithium dispensing pattern, change in lithium dosing regimen, age, gender, prescribing physician and laboratory parameters were investigated as potential confounders. A total of 51 cases and 51 control patients were include in our study. Five (9.8%) controls and 15 (29.4%) cases used potentially interacting co-medication (OR of 3.83; 95% CI 1.28-11.48). Start of potentially interacting co-medication was observed in eight (15.7%) cases and in zero (0%) controls resulting in an OR of 20.13 (95% CI 1.13-359). After adjustment for co-medication, irregularity in lithium dispensing pattern, change in lithium dosing regimen, and age the statistically significant association was lost. We established an OR of 2.70 (95% CI 0.78-9.31) for use of

concomitant medication, with a large contribution of antibiotic agents, and an OR of 3.14 (95% CI 1.15-8.61) for irregularity in lithium dispensing pattern. We found that use of potentially interacting co-medication, especially antibiotics, tends to be associated with elevated lithium serum levels. Antibiotics are not associated with elevations in lithium serum level through a direct pharmacokinetic interaction. Antibiotics are rather expected to be a proxy for infection induced fever, a condition that can result in an increase in fluid and salt loss resulting in an increase in tubular sodium and lithium reabsorption.

The finding that antibiotics were most frequently prescribed to patients with elevated lithium serum levels led us to subsequently investigate exogenous heat by means of outdoor temperature as a determinant of the height of lithium serum level, in *chapter 3.2*. Our objective was to investigate the impact of actual environmental temperature on lithium serum levels. We conducted a retrospective study using available records of lithium serum levels for the period between January 1995 and July 2004, obtained from three large teaching hospitals in the Netherlands (TweeSteden hospital, Tilburg; Altrecht Institute for Mental Health Care, Utrecht; and Reinier De Graaf Hospital, Delft). Lithium serum levels were linked to season and average daily temperature data obtained from the Royal Netherlands Meteorological Institute. A total of 41 102 records of lithium serum levels (3 054 patients) were included. A significant difference in mean lithium serum levels across seasons ($p<0.001$) and temperature categories ($p=0.001$) was found, with a peak in summer (0.761 mmol/l ± standard error of the mean [sem] 0.002) and at temperatures 15–20°C (0.762 mmol/l ± sem 0.005), and a minimum in winter (0.748 mmol/l ± sem 0.002) and at <0°C (0.741 mmol/l ± sem 0.005). The relative frequency of potentially toxic serum levels significantly differed between seasons ($p=0.023$; highest in winter), but not between temperature categories ($p=0.481$). A significant positive association for intraindividual lithium serum level and season ($p<0.001$), and temperature ($p<0.001$) was established. Season and environmental temperature have a statistically significant but therapeutically irrelevant effect on lithium serum levels. Lithium toxicity is a condition that, unfortunately arises relatively easy due to its narrow therapeutic window and the large susceptibility of its clearance to multiple factors. Lithium intoxication is a very serious condition, carrying a high risk of mortality and long-term morbidity caused by its potential for irreversible cerebellar damage. A lithium intoxication, therefore, is a condition that requires

immediate adequate care. Since clinicians treating the patient intoxicated with lithium are not very likely to have much experience with lithium, it is imperative to have complete and available information easily accessible at the emergency ward. In *chapter 3.3* we investigated the completeness and employability of available practice guidelines for the treatment of patients with a lithium intoxication. Multiple practice guidelines on the treatment of a patient with a lithium intoxication are currently being used. Practice guidelines show profound variability regarding their completeness and employability. Various recommendations for improvement with respect to content of information and employability are given.

The third part of this thesis entitled **'Nephrogenic complications of lithium'** concerns determinants and molecular mechanisms of lithium's nephrogenic ADRs. Patient suffering from bipolar disorders are very likely to be treated with multiple drugs. In a previous study our group found that use of serotonergic medication next to lithium increased the risk of polyuria (urine volume ≥ 3 l/24 h). Since this was a secondary finding we decided to perform a study designed to investigate use of serotonergic medication next to lithium as a determinant of polyuria. In *chapter 4.1* we performed a multicentre medical chart review study in patients using lithium in whom a 24-hour urine volume had been determined. We included 116 patients, twelve (26%) of the 46 patients with polyuria used serotonergic antidepressants compared to ten (14%) of the 70 patients without polyuria. We found an increased risk of polyuria in lithium users concurrently using serotonergic antidepressants (OR 2.86; 95% CI 1.00-8.21), adjusted for age, gender, use of antiepileptics and thyreomimetics. Our results confirm the previous secondary finding of an increased risk of polyuria in patients using serotonergic antidepressants next to lithium. Physicians should take this into account when evaluating lithium associated polyuria and when choosing an antidepressant in patients using lithium.
Besides some factors influencing the risk of lithium induced polyuria there is not much known regarding the exact pharmacological mechanism of lithium induced NDI. In *chapter 4.2* we took a further step into the molecular mechanistic aspects of this frequently occurring lithium ADR. The objective was to investigate the kidney response to minimal and maximal stimulation of the kidney urine concentrating mechanism by measuring urine osmolality, and urine levels of

3',5'-cyclic adenosine monophosphate (cAMP) and aquaporin-2 (AQP-2) in urine of patients under long-term lithium treatment. We included ten patients with polyuria and ten patients without polyuria under long-term lithium treatment. The kidney urinary cAMP, AQP-2 levels and urine osmolality were determined during a situation of minimal kidney urine concentrating activity (induced by water loading) and during a situation following maximal stimulation of kidney urine concentrating activity (induced by 1-desamino-8-D-arginine-vasopressin [dDAVP]). Patients were classified as NDI, partial NDI and non-NDI based on maximal reached urine osmolality. The partial correlation between urinary cAMP levels (mmol/l) and urine osmolality was 0.94 ($p<0.001$). No significant correlation was observed between urinary AQP-2 levels (mol/mol creatinine) and osmolality nor between urinary cAMP and AQP-2 levels. The rise in urinary cAMP but not AQP-2 levels upon dDAVP administration after water loading significantly differed between the three categories, decreasing with increasing NDI category. We found that in lithium-induced kidney urine concentrating deficit in man, the cAMP generation in response to dDAVP administration after water loading, is impaired. It remains to be elucidated whether principal cells, G-proteins or adenylate cyclase e.g. are the major targets for the mechanism underlying lithium-induced NDI in man.

In *chapter 5* the results of the individual studies are discussed and put into a broader perspective. We thereby focus on the susceptibility of lithium effects to multiple dynamic and fixed factors. Additionally, we focus on remaining challenges for improvement of treatment of patients with lithium. Lastly we focus on important differences between evidence based medicine and medicine based evidence regarding lithium. We conclude with future perspectives for both clinical and research practice.

samenvatting

Lithium is momenteel de goud standaard voor de farmacotherapeutische behandeling van patiënten met een bipolaire stoornis. Lithium is, gezien zijn zeer smalle therapeutische breedte alsmede zijn bijwerkingenprofiel, echter niet het meest ideale geneesmiddel. Met de onderzoeken, die in het kader van dit proefschrift zijn uitgevoerd, was het de bedoeling om een bijdrage te leveren aan de kennis op het gebied van het gebruik van lithium in de dagelijkse praktijk. Het doel van dit proefschrift is drieledig: 1) de gebruikspatronen en het bijwerkingen profiel van lithium in de dagelijkse praktijk te onderzoeken, 2) de endogene en exogene invloeden op de lithium serum spiegel nader te bekijken, en 3) dieper in te gaan op determinanten en moleculair mechanistische aspecten van lithium geïnduceerde nefrogene diabetes insipidus (NDI).

Het eerste deel van dit proefschrift, getiteld **'Gebruikspatronen en consequenties van lithium gebruik'** concentreert zich op verschillende aspecten van langdurig lithium gebruik. In *hoofdstuk 2.1* hebben we het gebruik van lithium onderzocht in de afgelopen 10 jaar bij poliklinische patiënten, die kort tevoren gestart waren met een behandeling met lithium. In het afgelopen decennium zijn er vele alternatieven voor de behandeling van bipolaire stoornissen beschikbaar gekomen. Diverse atypische antipsychotica en anticonvulsiva worden momenteel ingezet voor de behandeling van patiënten met een bipolaire stoornis. Het doel van het onderzoek in *hoofdstuk 2.1* was om enerzijds het verloop van de incidentie en de prevalentie van lithium gebruik te bekijken en anderzijds om lithium gebruikspatronen (stoppen, additie en switchen) te onderzoeken. We hebben dit onderzoek uitgevoerd met behulp van de PHARMO database. In deze database zijn alle geneesmiddel leveringen door aangesloten openbare apotheken opgenomen. De incidentie van lithium gebruik lag rond de 0,2 per 1000 persoonsjaren en bleef gedurende de onderzoeksperiode nagenoeg constant. De prevalentie van lithium gebruik nam gedurende de jaren 1996-2005 met 26% toe van 0,95 tot 1,2 per 1000 personen. Vervolgens hebben we bekeken welk percentage patiënten stopte met lithium, een additie van een ander geneesmiddel bij lithium kreeg of switchte van lithium naar een ander geneesmiddel. We hebben onderzocht of het percentage van deze gebeurtenissen verschilde tussen drie verschillende tijdscohorten: 1998-1999, 2000-2001, 2002-2003. Het percentage patiënten, dat naast lithium een additie kreeg van een geneesmiddel dat wordt gebruikt bij de behandeling van bipolaire stoornissen,

was constant over de drie tijdscohorten; namelijk ongeveer 12% na 24 maanden. Van alle patiënten, die met het gebruik van lithium stopten, waren er meer patiënten die switchten van lithium naar een ander middel ten opzichte van het aantal patiënten, dat met het gebruik van lithium stopten en daarvoor in de plaats geen ander middel kreeg (een stijging van het aantal switchers van 4,4% naar 17,4% versus een daling van het aantal stoppers van 48,9% naar 32,0% na 24 maanden). Binnen de geneesmiddelen, die gebruikt werden als additief viel op, dat met name het gebruik van tricyclische antidepressiva naast lithium afnam. De veranderingen in het geneesmiddelgebruik bij lithium gebruikers waren in overeenstemming met de toename van de beschikbaarheid van alternatieven voor lithium, alsmede met de Nederlandse richtlijn voor de behandeling van bipolaire stoornissen.

Een behandeling met lithium gaat vaak gepaard met bijwerkingen. Ongeveer 75-90% van de patiënten, die langdurig lithium gebruiken, krijgt gedurende de behandeling te maken met één of meer bijwerkingen. Gebaseerd op de bevindingen bij depressieve en schizofrene patiënten ontstond ook de vraag of stemming ook een mogelijke verstorende factor zou kunnen zijn voor het objectief vaststellen van bijwerkingen en de effectiviteit van een behandeling met lithium. Bijwerkingen zijn een bekende risicofactor voor zowel door patiënt als door behandelaar geïnitieerd staken van een behandeling met lithium. In *hoofdstuk 2.2* hebben we de associatie tussen respectievelijk de stemming van patiënten en de lithium serum spiegel en het aantal, alsmede de ernst van de bijwerkingen onderzocht bij een totaal van 186 poliklinische patiënten, die behandeld werden in de periode van 1973-2000. De aanwezigheid alsmede de ernst van bijwerkingen werden gerapporteerd door de patiënten zelf. De prevalentie en de ernst van bijwerkingen nam toe met dalende stemming richting het depressieve en nam af met stijgende stemming richting manische toestand ($p<0,05$). Dit verband tussen stemming en bijwerkingen bleef ook bestaan, wanneer werd gecorrigeerd voor de hoogte van de lithium serum spiegel. Bij correctie voor de intra-individuele afhankelijkheid van de waarden bleef het verband tussen de lithium serum spiegel, de stemming en het aantal alsmede de ernst van de bijwerkingen significant ($p<0,001$). Zowel behandelaren, patiënten als onderzoekers moeten zich realiseren, dat de lithium serum spiegel en de stemming beiden zijn geassocieerd met de aanwezigheid en de ernst van de

bijwerkingen zoals gerapporteerd door patiënten. Dit gegeven kan het objectief vaststellen van bijwerkingen bemoeilijken.

Bij het vaststellen van determinanten voor uitkomsten van lithium-gebruik zijn zowel het moment van lithium gebruik in relatie tot de uitkomst als de lithium serum spiegel van belang. De resultaten van een recent onderzoek lieten een afname van het risico op botbreuken onder lithium gebruikers zien ten opzichte van mensen, die geen lithium gebruiken. In dit onderzoek werd echter niet gecorrigeerd voor het moment van lithium gebruik in relatie tot het krijgen van de botbreuk. Tevens vermeldde dit onderzoek een negatieve associatie tussen de dosis lithium en het risico op botbreuken. Deze bevinding was in overeenstemming met eerdere gepubliceerde resultaten van in-vitro onderzoek, waarin anabole effecten van lithium op bot werden aangetoond. Het onderzoek maakte echter geen gebruik van lithium serum spiegel waarden om de relatie tussen blootstelling en respons vast te stellen. De relatie tussen de dosis lithium en de bereikte serum spiegel lithium is zeer slecht. Daarom is het bij lithium noodzakelijk om bij het onderzoeken van een relatie tussen blootstelling en respons de lithium serum spiegel en niet de dosis als maat voor blootstelling te gebruiken. In *hoofdstuk 2.3* onderzochten we het belang van het moment van gebruiken van lithium in relatie tot het ontstaan van de botbreuk. We hebben een patiëntcontrole onderzoek uitgevoerd in de UK General Practice Research Database (GPRD). Dit is een database, waarin huisartspraktijk gegevens, zoals geneesmiddel recepten en diagnoses, zijn terug te vinden van alle bij GPRD aangesloten huisartspraktijken. We hebben in deze database het risico op botbreuk bekeken bij patiënten, die nooit lithium hadden gebuikt en dit vergeleken met het risico bij patiënten, die ooit lithium hadden gebruikt en met patiënten, die ten tijde van het onderzoek lithium gebruikten. Dit hebben we gedaan door het lithium gebruik te bekijken in een groep van 231.778 patiënten met een botbreuk en een gelijk aantal controle patiënten zonder botbreuk. Beide groepen waren vergelijkbaar wat betreft geslacht, leeftijd en huisartsenpraktijk. Tevens hebben we het risico op botbreuken bekeken in relatie tot de cumulatieve duur van lithium gebruik, alsmede in relatie tot de tijd na staken van lithium gebruik. Huidig lithium gebruik was geassocieerd met een afgenomen risico op botbreuken (gecorrigeerde odds ratio [OR] 0,75; 95% betrouwbaar-heidsinterval [BI] 0,64-0,88). Het risico nam echter toe na staken met lithium (gecorrigeerde OR 1,35; 95% BI 1,01-1,79). Onze resultaten ondersteunen de

rol van de onderliggende ziekte in de etiologie van botbreuken. Onze resultaten ondersteunen echter niet een farmacologisch effect van lithium op bot, gebaseerd op de afwezigheid van een associatie tussen het risico op botbreuken en de cumulatieve duur van lithium gebruik.

Het tweede deel van dit proefschrift getiteld **'Determinanten en behandeling van potentiële lithium intoxicaties'** concentreert zich op zowel de oorzaken als de consequenties van de smalle therapeutische breedte van lithium. Ondanks de huidige kennis van het bestaan van potentiële geneesmiddel-geneesmiddel interacties met lithium, is het daadwerkelijke belang ervan in de dagelijkse praktijk grotendeels onbekend. In *hoofdstuk 3.1* hebben we geneesmiddel-geneesmiddel interacties met lithium onderzocht als determinant voor verhoogde lithium serum spiegels. We hebben een multicenter retrospectief patiëntcontrole onderzoek uitgevoerd met als doel om lithium gerelateerde geneesmiddel-interacties als determinant voor verhoogde lithium serum spiegels te onderzoeken. Een lithium serum spiegel werd als verhoogd beschouwd als deze ten minste 1,3 mmol/l was en dit stijging van ten minste 50% betrof ten opzichte van de serum spiegel daarvoor. Patiënten, die ervan werden verdacht de gestegen serum spiegel te hebben gekregen ten gevolge van een auto-intoxicatie, werden uitgesloten van het onderzoek. Controle patiënten waren patiënten met stabiele lithium serum spiegels binnen het therapeutisch venster. Gebruik van en starten met niet-steroïde ontstekingsremmende pijnstillers (NSAIDs), diuretica, renine angiotensine remmers, theofylline en antibiotica werden onderzocht als mogelijke oorzaken voor verhoogde lithium serum spiegels. Een onregelmatig lithium afhaalpatroon, veranderingen in voorgeschreven lithium gebruik, leeftijd, voorschrijver en laboratorium parameters werden als potentieel verstorende variabelen meegenomen. Een totaal van 102 lithium gebruikers waarvan 51 patiënten met een verhoogde lithium serum spiegel en 51 patiënten zonder een verhoogde lithium serum spiegel werden meegenomen in ons onderzoek. Vijf (9,8%) controle patiënten en 15 (29,4%) case patiënten gebruikten co-medicatie die potentieel een interactie geeft met lithium (OR 3,83; 95% BI 1,28-11,48). Starten van gebruik van potentieel interacterende co-medicatie werd waargenomen bij acht (15,7%) patiënten en geen (0%) controles (OR 20,13; 95% BI 1,13-359). Na correctie voor onregelmatig afhaalpatroon, verandering in voorgeschreven lithium gebruik en leeftijd ging de gevonden associatie tussen

gebruik van potentieel interacterende co-medicatie en verhoogde lithium serum spiegels verloren. We vonden een OR van 2,70 (95% BI 0,78-9,31) voor gebruik van potentieel interacterende medicatie met een relatief grote bijdrage van gebruik van antibiotica. We vonden een OR van 3,14 (95% BI 1,15-8,61) voor een onregelmatig afhaalpatroon van lithium. Gebruik van medicatie, die potentieel een interactie geeft met lithium en met name gebruik van antibiotica, lijkt geassocieerd met toegenomen lithium serum spiegels. Antibiotica hebben geen directe farmacokinetische interactie met lithium, maar zijn een indicatie voor aanwezigheid van door infectie geïnduceerde koorts. Koorts en ziekte kunnen leiden tot een toename van verlies van vocht en zout. Dit kan leiden tot een toename van de proximale terugresorptie van zout om dit verlies te compenseren. Toegenomen terugresorptie van zout leidt tot een toename van de terugresorptie van lithium en daarmee tot een verhoging van de lithium serum spiegel. De bevinding van de relatief grote rol van gebruik van antibiotica bij patiënten met toegenomen lithium serum spiegels, bracht ons ertoe om vervolgens exogene hitte als determinant voor de hoogte van de lithium serum spiegel te onderzoeken, in de vorm van buitentemperatuur. In *hoofdstuk 3.2* hebben we een retrospectief onderzoek uitgevoerd, waarbij we gebruik hebben gemaakt van beschikbare lithium serum spiegels in een periode van tien jaar van drie grote ziekenhuislaboratoria (het TweeSteden ziekenhuis in Tilburg, de Reinier de Graaf groep in Delft en psychiatrisch ziekenhuis Altrecht in regio Utrecht). De lithium serum spiegels werden op datum gekoppeld aan seizoen en gemiddelde dagtemperatuur. Gegevens over de dagtemperatuur werden verkregen via het Koninklijk Nederlands Meteorologisch Instituut (KNMI). Een totaal van 41.102 lithium serum spiegels (afkomstig van in totaal 3.054 patiënten) werden meegenomen in ons onderzoek. We vonden een significant verschil in gemiddelde lithium serum spiegel over de seizoenen en temperatuurcategorieën met een piek in de zomer (0,761 mmol/l ± standaard afwijking van het gemiddelde [sem] 0,002) en bij dagtemperaturen van 15–20°C (0,762 mmol/l ± sem 0,005)), en een minimum in de winter (0,748 mmol/l ± sem 0,002) en bij temperaturen <0°C (0,741 mmol/l ± sem 0,005). De relatieve frequentie van potentieel toxische lithium serum spiegels verschilde significant (p=0,023) tussen de seizoenen (met de hoogste frequentie in de winter), maar niet tussen de temperatuurscategorieën (p=0,481). Een significant positieve associatie werd gevonden tussen lithium serum spiegels op individueel niveau en seizoen

(p<0,001) en temperatuur (p<0,001). De resultaten van dit onderzoek lieten zien, dat seizoen en omgevingstemperatuur statistisch significant geassocieerd zijn met de hoogte van de lithium serum spiegel. Het gevonden verband tussen de hoogte van de lithium serum spiegel en de buitentemperatuur werd echter als therapeutisch irrelevant geclassificeerd.
Een lithium vergiftiging is een conditie, die redelijk eenvoudig ontstaat, door de smalle therapeutische breedte van lithium alsmede de grote mate van gevoeligheid van onder andere de lithium klaring voor diverse factoren. Een lithium vergiftiging is een zeer ernstige gebeurtenis met een hoog risico op zowel mortaliteit als morbiditeit; dit laatste met name vanwege het risico op irreversibele hersenschade. Een patiënt met een lithium vergiftiging dient daarom bij presentatie snel en adequaat te worden behandeld. Clinici, die betrokken zijn bij de behandeling van een patiënt met een lithium intoxicatie, hebben over het algemeen niet veel ervaring met lithium gebruikende patiënten. Daarom is het noodzakelijk om complete en gemakkelijk toegankelijke informatie op de eerste hulp aanwezig te hebben. In *hoofdstuk 3.3* hebben we de mate van compleetheid alsmede de toegankelijkheid van diverse beschikbare praktijk richtlijnen voor de behandeling van een lithium intoxicatie onderzocht. Verscheidene praktijk-richtlijnen voor de behandeling van een lithium intoxicatie zijn momenteel in gebruik. Beschikbare praktijk richtlijnen laten een behoorlijke variatie in compleetheid en toegankelijkheid zien. Verschillende aanbevelingen ten aanzien van de inhoud en de toegankelijkheid van de praktijk richtlijnen worden gegeven.

Het derde deel van dit proefschrift, getiteld **'Nefrogene complicaties van lithium'**, gaat over determinanten van polyurie (urine volume ≥ 3 l/24 h) en het moleculair mechanisme van lithium geïnduceerde NDI. Veel patiënten met een bipolaire stoornis gebruiken meerdere geneesmiddelen. In een eerder gepubliceerd onderzoek van onze groep werd gevonden, dat gebruik van serotonerge antidepressiva het risico op lithium geïnduceerde polyurie verhoogt. Aangezien deze bevinding een secundaire bevinding betrof, besloten we in een vervolg onderzoek na te gaan of gebruik van serotonerge antidepressiva naast lithium echt een oorzaak is voor een verhoging van het risico op een lithium geïnduceerde polyurie. *Hoofdstuk 4.1* beschrijft een multicenter status onderzoek uitgevoerd bij lithium gebruikers bij wie, gedurende de behandeling met lithium,

ten minste één 24-uurs urine volume bepaling was uitgevoerd. Een totaal van 116 patiënten werd opgenomen in ons onderzoek. Als primaire uitkomst werd, op basis van het 24-uurs urine volume, bekeken of patiënten voldeden aan de definitie polyurie. Van de 116 deelnemende lithium gebruikers gebruikten 12 (26%) van de 46 patiënten met polyurie en 10 (14%) van de 70 patiënten zonder polyurie serotonerge antidepressiva. We vonden een verhoogd risico op polyurie bij lithium gebruikers, die tevens serotonerge antidepressiva gebruikten (OR 2,86; 95% BI 1,00-8,21), gecorrigeerd voor leeftijd, geslacht en gebruik van thyreomimetica en antiepileptica. Onze resultaten bevestigen daarmee de eerdere bevinding, dat gebruik van serotonerge antidepressiva naast lithium het risico op polyurie bij lithium gebruikers verhoogt. Behandelaren zouden dit verhoogde risico op polyurie bij lithium gebruikers door gelijktijdig gebruik van serotonerge antidepressiva in de overwegingen mee moeten nemen bij het maken van de keuze voor een antidepressivum voor het behandelen van een bipolaire depressie. Naast kennis over potentiële risicofactoren voor lithium geïnduceerde polyurie is er nog weinig bekend over het onderliggende mechanisme van lithium geïnduceerde NDI. In *hoofdstuk 4.2* zijn we dieper ingegaan op het mechanisme van deze frequent voorkomende bijwerking van lithium. Dit hebben we gedaan door het urine concentrerend vermogen van patiënten, die lithium gebruiken, te bekijken in een groep patiënten met NDI, een groep met gedeeltelijke NDI en een groep patiënten zonder NDI. Het doel van dit onderzoek was om het effect van minimale en maximale stimulatie van het nier urine concentrerend mechanisme te onderzoeken. Dit hebben we gedaan door de urine osmolaliteit en de urine spiegels van 3',5'-cyclisch adenosine monofosfaat (cAMP) en aquaporine-2 (AQP-2) te meten bij patiënten, die langdurig lithium gebruiken. Een totaal van 20 patiënten, die langdurig lithium gebruikten, werden in het onderzoek opgenomen. De urine spiegels van cAMP, AQP-2, alsmede de urine osmolaliteit werden bepaald onder minimale (door overmatig water drinken) en maximale (door 1-desamino-8D-arginine-vasopressine (dDAVP)) stimulatie van het urine concentrerend vermogen. Patiënten werden geclassificeerd als NDI, gedeeltelijk NDI of niet-NDI gebaseerd op de maximaal bereikte urine osmolaliteit (maximaal urine concentrerend vermogen). De partitiele correlatie tussen urine cAMP spiegels (mol/l) en urine osmolaliteit was 0,94 ($p<0,001$). Noch tussen de urine AQP-2 spiegels (mol/mol creatinine) en de urine osmolaliteit, noch tussen urine cAMP en AQP-2 spiegels werden significante

correlaties ontdekt. De stijging in urine cAMP, maar niet in urine AQP-2 spiegels als reactie op dDAVP toediening, verschilde significant tussen de groep met NDI, gedeeltelijke NDI en de groep zonder NDI en nam toe met toenemende NDI categorie. Onze resultaten laten zien, dat bij patiënten met een lithium geïnduceerde NDI, de aanmaak van cAMP als reactie op dDAVP toediening na water belasting gehinderd is. De resultaten geven aan, dat de kans groot is, dat het mechanisme van lithium geïnduceerde NDI ligt in het eerste deel van het nier urine concentrerend mechanisme. Verder onderzoek zal moeten uitwijzen of G-eiwitten, principal cellen of adenylaat cyclase het aangrijpingspunt zijn voor dit effect van lithium bij de mens.

In *hoofdstuk 5* besluiten we dit proefschrift door de resultaten van de individuele onderzoeken in een breder perspectief te plaatsen. We gaan in op de smalle therapeutische breedte van lithium en de vele dynamische en statische factoren, die van invloed zijn op de effecten van lithium. Vervolgens gaan we in op de mogelijkheden om de behandeling van patiënten met lithium te verbeteren. Tot slot bespreken we belangrijke verschillen tussen bewijs gestuurd behandelen en praktijk gestuurd bewijs voor wat betreft de therapie met lithium.

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