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## **Lithium and Renal Impairment**

*A Review on a Still Hot Topic*

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# Lithium and renal impairment: a review on a still hot topic

**Running title:** Lithium and renal impairment

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## Abstract

### Introduction

Lithium is established as an effective treatment of mania, of depression in bipolar and unipolar disorder, and in maintenance treatment of these disorders. However, due to the necessity of monitoring and concerns about irreversible adverse effects, in particular renal impairment, after long-term use, lithium might be underutilized.

### Methods

A narrative review of six large observational studies addressing the risk of impaired renal function associated with lithium treatment as well as methodological issues impacting interpretation of results.

### Results

An increased risk of renal impairment associated with lithium treatment is suggested. This increased risk may, at least partly, be a result of surveillance bias. Additionally, the earliest studies pointed toward an increased risk of end-stage renal disease associated with lithium treatment, whereas the later and methodologically most sound studies do not.

### Discussion

The improved renal outcome found in the more recent lithium studies may be a result of improved monitoring and focus on recommended serum levels (preferentially 0.6-0.8 mmol/l) as compared to poorer renal outcome in studies with patients treated in the 1960's to 1980's.

### Keywords

Lithium; Renal impairment; Epidemiology; Adverse events

## Introduction

Lithium was introduced as a potential treatment for mania by John Cade in 1949, and a few years later its antimanic potential was confirmed by the Danish researcher Mogens Schou [1]. Since then research into lithium's effects have established lithium as an effective treatment for bipolar disorder, both acutely as well as in maintenance treatment [2]. Moreover, it has been found effective in unipolar depression [3] and an antisuicidal effect independently from its mood stabilizing properties has been suggested [4,5]. Finally, recent data have indicated a possible role for lithium in preventing mild cognitive impairment and dementia [6]. However, due to a low therapeutic index necessitating frequent monitoring of serum levels and due to concerns about irreversible adverse effects, in particular renal impairment, after long-term use, lithium might be underutilized in clinical practice [7,8].

The acute renal toxicity and reversible diuretic action of lithium is well established [9]. Early biopsy studies demonstrated structural renal changes associated with lithium exposure [10,11]. The original concept of lithium nephropathy developed in the following years included tubular damage with interstitial fibrosis with only minor or no glomerular damage, and accordingly, the risk of decreased renal function was believed to be minimal. Later studies by Bendz et al [12–14] indeed indicated that lithium exposure for 15 years or more might lead to glomerular damage, but it was not until Bendz et al. [15] published a large scale study in 2010 based on the Swedish registry of renal replacement therapy reviewed below, that the magnitude of the problem was systematically estimated. Since then five more large scale observational studies, i.e. studies systematically covering whole regions or countries, have been published, addressing the risk of impaired renal function as a categorical outcome associated with lithium treatment [16–20]. We therefore found it timely to review these studies, focusing also on the methodological issues which might impact the interpretation of the study results.

## Study design issues

Randomized clinical trials (RCTs) evaluating drug effects are generally easy to interpret regarding causality due to the approximated even distribution of known and unknown confounders across study groups. However, RCTs are usually characterized by a relatively short duration of follow-up and by relatively small sample sizes. Therefore, RCTs are not appropriate for detecting and evaluating rare side effects occurring after years of treatment. Instead, large observational studies with long duration of follow up are needed [21]. Although selection bias and confounding cannot be avoided in non-randomized studies, various approaches in terms of design and analysis are available for balancing the comparative groups and/or for confounder control, e.g. case-control design, use of propensity score models or use of multivariate regression analysis. Numerous observational studies have investigated the association between lithium treatment and the risk of lowered glomerular filtration rates [22]. However, these studies may overestimate this association since lithium treated patients are expected to undergo repeated monitoring of thyroid, parathyroid, and renal function resulting in non-symptomatic renal impairment being detected more frequently in lithium exposed patients than in non-exposed controls [23]. To minimize this surveillance or detection bias some recent studies have included end-stage renal disease (ESRD) (e.g. renal transplantation or dialysis) as an outcome, either alone or in combination with other renal outcome measures, as this condition will produce severe symptoms resulting in detection of virtually all cases independently of repeated monitoring of renal function. When defining a population for an observational study, participants can be defined by a single psychiatric disorder, e.g. bipolar disorder as done by Close et al and by Hayes et al [17,20], or could be defined by exposure as done by Kessing et al [19], although Kessing et al also identified a bipolar cohort. A possibility is also identifying all ESRD cases, differentiated by previous exposure or non-exposure to lithium and then relating the numbers to lithium exposed and non-exposed in the general population as done by Bendz et al and Aiff et al [15,16].

Unless a study only comprises bipolar patients, controlling for the presence of the disorder is needed as bipolar disorder has been associated to decreased renal function independently of treatment, resulting in a

potential risk of confounding by indication [19,21,24]. Furthermore, inclusion of both lithium treatment-naïve (i.e. never exposed to lithium) patients as well as patients who have been treated with lithium previously could be of importance in the interpretation of study results since previous tolerance or intolerance to a study drug may influence the subsequent study group allocation and thereby outcomes of the study [25]. Moreover, in some clinical samples patients are followed for a brief period of time or data collection is cross-sectional by design [15,16], in contrast to other studies, primarily register-based, where patients are followed long-term or even lifelong allowing for follow-up on development of renal impairment in patients exposed never, only previously, or still/continuously [17–20,26]. Another advantage of register-based studies is that all cases can more easily be identified (regardless of severity, course of illness, comorbidity, etc.) and followed longer term, whereas in clinical follow-up studies, renal impairment after study withdrawal may not be identified. Lastly, the assessment of the magnitude of lithium exposure, e.g. time exposed or cumulative dosages is a challenge, in especially studies including non-treatment-naïve patients [25]; for a review of methodological aspects of register-based lithium studies see Kessing et al [27].

## **Review of the selected studies**

In 2010, Bendz et al published the first large epidemiological study of renal impairment in lithium exposed patients [15]. This cross-sectional study based on one third of the Swedish population, included 2,202 patients with ESRD from two regions of Sweden utilizing the Swedish Registry for Active Treatment of Uremia with a prevalence date of March 31, 2005. All included patients were interviewed regarding previous or present lithium treatment, with charts being examined in patients reporting lithium exposure. A total of 27 patient charts were examined resulting in confirmation of the exposure in 23 patients, with four patients being defined as false positives. For all true positives a diagnosis of lithium induced ESRD was determined utilizing a set of pre-hoc defined criteria, resulting in a total of 18 patients being defined as having a lithium induced ESRD. To estimate the ratio of the prevalence of lithium induced ESRD among lithium treated patients to the prevalence of ESRD in the general population, information on lithium treatment in the general

population at the same prevalence point was needed, and was established by contacting all psychiatric clinics as well as private psychiatrists regarding data on lithium treatment and demographics on patients exposed. The study showed a prevalence of 0.9 ‰ ESRD in the general population, and a prevalence of 5.3 ‰, 95% CI: (2.8 – 7.8‰) of ESRD in patients exposed to lithium, resulting in a six times increased prevalence of lithium induced ESRD as compared to the prevalence of ESRD in non-exposed. Due to the use of interviews to establish a possible lithium exposure among the ESRD cases, and the consequent investigation of only positive cases, recall bias could have affected outcome determination, as patients not disclosing a previous lithium treatment exposure would bias results towards a finding of a smaller difference between exposed and non-exposed [28]. In contrast, recall bias is less likely to occur in the identification of the lithium treated population due to the sampling method. Aiff et al [16] conducted a study similar to the investigation from Bendz et al in 2014, but with a prevalence date of December 31, 2010. End-stage renal disease patients were again interviewed regarding lithium treatment exposure, and patients responding positively towards previous exposure had their charts reviewed. Contrary to the previous study the prevalence of lithium treatment in the population was established utilizing the Swedish Prescribed Drug Register which should ensure a minimal risk of bias in the estimation of lithium treated persons in the population. The risk of recall bias in ESRD patients regarding lithium exposure was unaffected by the use of the drug register, as this information was based on interviews with all ESRD patients. The main finding of the study was a prevalence of 15.0‰, 95% CI: (9.7-20.3) lithium induced ESRD in patients exposed to lithium as compared to 1.9‰, 95% CI: (1.8 – 2.0) ESRD in the general population, resulting in a ratio of 7.8, 95% CI: (5.4 – 11.1) in an age restricted analysis only including patients  $\geq 55$  years. In both studies, the chosen model of analysis did not investigate for the effects of variables known to influence the risk of end-stage renal disease including other medications, physical co-morbidities and psychiatric disorders, as well as length of exposure nor cumulative dosages.

Both studies reviewed above calculated point prevalences at the prevalence dates defined, e.g. 2005 and 2010. The prevalence of lithium induced ESRD in the lithium exposed population was defined as the number of lithium induced ESRD patients divided by the number of patients exposed to lithium in the population at

the prevalence date. However, since lithium induced ESRD seemingly was most common in patients exposed for 15 years or more in both studies [15,16] and since lithium use has decreased over the last decades in Europe, the relatively low number of lithium exposed individuals in 2005 and in 2010 might result in an overestimation of the prevalences. The use of a time-adjusted prevalence rate of lithium exposure in the background population, would have resulted in a lower prevalence ratio of lithium induced ESRD in the studies.

In 2014 Close et al [17] conducted a study of primarily renal failure defined as chronic kidney disease stage 4 or 5 or renal replacement therapy (renal transplant or dialysis) (RRT) utilizing the UK General Practice Research Database (GPRD) encompassing more than two million patients registered with the general practitioners delivering data to the GPRD. All patients diagnosed with bipolar disorder were included, except for patients diagnosed previously with renal cancer, congenital renal abnormalities, renal conditions related to pregnancy, patients diagnosed outside the study period or patients who had less than one year of data in the GPRD. Crude analyses showed an increased occurrence of renal failure in 51 (2%) of 2,496 patients with bipolar disorders ever exposed to lithium treatment as compared to 26 (0.7%) of 3,864 patients never exposed to lithium treatment. Utilizing a Cox regression model adjusted for patient demographics, comorbidity and concomitant drug use the authors showed ever-use of lithium was associated with an increased risk of developing renal failure (Hazard rate ratio (HR) 2.7, 95%CI (1.7-4.3)) with diuretic use and diabetes also independently increasing the risk of renal failure, when adjusting for age and gender. The study investigated the validity of a registry diagnosis of renal failure and of ever-use of lithium in those with a record of renal failure in the GPRD. Of the 77 cases with renal failure the authors were able to gain access and confirm GPRD data in 44 (57%) of cases via their charts, among these, lithium use was confirmed in all 28 patients identified as lithium users. In the remaining 16 patients who were identified as lithium non-users the chart review revealed evidence of lithium treatment in two. There was no investigation of possible false negatives in lithium never-exposed patients, similar to a lack of investigation of patients being defined as not being diagnosed with bipolar disorder in the GPRD. As the GPRD only includes data from general practitioners



(GPs) an inherent risk of underestimating occurrence of bipolar disorder, use of lithium as well as occurrence of renal disease was present, if patients were solely treated in secondary care for their diseases or disorder. Secondly, the diagnosis of bipolar disorder is a specialist task, which might influence the validity of the diagnosis of patients solely diagnosed and followed by GPs.

Shine et al [18] investigated the long-term effects of lithium on renal, thyroid and parathyroid function utilizing the Clinical Biochemistry Departments laboratory database which performs routine tests in a catchment area of approximately 650.000 persons in the UK. All persons with creatinine, thyrotropin, calcium or glycated haemoglobin measurements in the study period were included. Lithium exposure was defined as at least two measurements of lithium, and with all other patients of the same sex and age group serving as controls. The dataset did not include information on indication for treatment, e.g. unipolar depression or bipolar disorder. The primary kidney outcome was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m<sup>2</sup>, corresponding to stage 3 (or higher) kidney disease, calculated utilizing laboratory results, age and sex. Applying a Cox regression model with lithium use, age in years, sex and diabetes as co-variables and kidney disease as outcome they showed that lithium treatment was associated with declining renal function (HR 1.93, 95% CI (1.76-2.12)). They also showed that increasing age, male sex and diabetes increased the risk of developing decreased renal function.

As the study was unable to adjust for previous treatment history, patients treated with lithium prior to the study period but discontinuing before the study period began may contaminate the never-exposed group. Secondly, there is an inherent risk of confounding by indication not only in the exposed group but also in the never-exposed group as indications for blood samples and corresponding laboratory work are unknown. Such indications including renal symptoms would most likely have resulted in more patients being identified with decreased renal function in the control group as compared to the lithium ever-exposed group. Further, also here, there is a risk of surveillance bias related to the renal monitoring in the lithium exposed group leading to an overestimation of the risk of kidney disease associated with lithium. Finally, it is not clear whether the

overall finding of a nearly two times increased rate of kidney disease associated with lithium use was driven by higher lithium dosing as the study went back to even 1982.

The first nationwide population-based study of the renal effects of lithium treatment was published in 2015 by Kessing et al[19]. Utilizing the extensive Danish healthcare registers including drug prescription register and register for regular dialysis and transplantation, they defined two cohorts: 1) A random sample of 1.500.000 individuals registered in Denmark January 1, 1995, and 2) all patients having their first psychiatric contact ever between 1994 to end of 2012 and receiving a main diagnosis of mania or bipolar disorder at that time. All with a known previous renal dysfunction were excluded. Utilizing a Poisson regression model with the number of lithium prescriptions, number of anticonvulsants prescriptions, number of antipsychotic prescriptions, number of antidepressants prescriptions, calendar year, bipolar diagnosis, age, sex, employment status, prescriptions for other medications (including for physical disease) as explanatory variables they investigated possible chronic kidney disease (CKD), definite CKD, and ESRD as outcomes, with the latter being relatively more resistant to surveillance bias, as described earlier.

Crude analyses showed a prevalence of 0.2% of end-stage renal disease in cohort 1 with a prevalence of 0.6% in the second cohort. Regression analyses showed that the risk of ESRD did not increase with an increasing number of lithium prescriptions (primary analysis to limit type one errors); additionally, for each prescription level, there was no statistically significantly increased risk as compared with the reference (1-2 prescriptions). However, for definite kidney disease there was an increasing HR with increasing number of prescriptions ( $p < 0.001$ , test for trend). The HR of ESRD and definite kidney disease were higher in patients with a bipolar diagnosis, in patients taking other medications, whereas female sex was associated with a lowered HR as compared to males.

In the second cohort of patients diagnosed with bipolar disorder, a similar pattern was seen with the HR of ESRD not increasing with an increasing number of lithium prescriptions ( $p = 0.30$  for trend). The HR of definite

kidney disease was increasing with increasing number of prescriptions ( $p < 0.001$  for trend). Contrary to the first cohort, HR of definite and end-stage kidney disease, respectively, increased with the number of prescriptions for anticonvulsants. As compared to the previous studies there is no risk of recall bias, and the inclusion of only patients diagnosed within the study period minimized the risk of bias due to previously exposed patients being included as never exposed. Further, previous studies may have overestimated the risks of chronic kidney disease, especially among older individuals, as the competing risk of death without chronic kidney disease was not considered, in contrast to the study by Kessing et al[19]. The use of ESRD as the primary renal outcome minimizes that part of the results being influenced by surveillance bias. However, as pointed out by Goodwin in an accompanying editorial, the risk of ESRD was numerically, albeit not statistically significantly, higher in the lithium exposed as compared to the non-exposed, and obviously type 2 errors cannot be excluded [29].

Lastly, Hayes et al investigated several long-term side effects of lithium treatment exposure including chronic kidney disease stage 3 and 4 defined as glomerular filtration rates below 60 or 30 mL/min/1.73m<sup>2</sup> respectively [20]. The study was conducted in the UK, and the population were all patients diagnosed with bipolar disorder in The Health Improvement Network database receiving at least one 28-day prescription of lithium, valproate, olanzapine, or quetiapine, in the period January 1, 1995 to December 31, 2013. All patients prescribed another study drug at start of follow-up, or a month before this, were excluded. The model of analysis was a Cox regression with renal outcomes as defined above, in cohorts divided by treatment (e.g. lithium, valproate, olanzapine or quetiapine). Patients were followed until the earliest of the following: first outcome record, quitting the drug plus three months since last prescription, switching to another study drug, leaving the physician's practice, death, or end of study period.

A propensity score was calculated utilizing baseline patient characteristics believed to influence prescription choice. Propensity score, age, calendar year and clustering by practice were used as explanatory variables in the Cox regression. The crude analysis showed 52 (2.42%) of 2,148 patients exposed to lithium experienced chronic kidney disease stage 3 or more. In the adjusted model, patients prescribed valproate, olanzapine and

quetiapine had reduced rates of CKD stage 3 or more severe as compared to those prescribed lithium, whereas there was no difference between drugs investigated with chronic kidney disease stage 4 or more as outcome. The inclusion of patients who have been treated with study drugs before the follow-up started may have influenced the between-group comparisons since previous tolerance or intolerance to a study drug may have influenced the subsequent study group allocation and thereby outcomes of the study. This methodological problem could have been minimized by the inclusion of only treatment naive patients and following these until end of study registering drug exposure and outcome, similar to the study by Kessing et al[19]. As with previous studies surveillance bias may have occurred, and this may, at least in part, explain the findings of valproate, olanzapine, and quetiapine exposed patients having a decreased rate of chronic kidney disease stage 3 or more, with no significant differences found between study drugs on the outcome kidney disease stage 4 or more. In line with this, it is noteworthy that lithium was associated with an increased risk of CKD even though the duration of treatment was relatively short.

## Discussion

In general, when renal impairment of a lower degree than ESRD was chosen as an outcome, lithium exposure was found to be associated with an increased diagnostic incidence of renal impairment as compared to non-exposure. Thus, a relatively high occurrence of stage 3 renal disease associated with lithium treatment was observed in the studies by Shine et al, Hayes et al, and Close et al [17,18,20]. Likewise, Kessing et al showed that possible and definite CKD were associated with an increasing number of lithium prescriptions[19], similar to the study by Hayes et al showing associations between lithium exposure and moderate kidney disease. Taken together, these findings might, at least partly, be a result of surveillance bias, i.e., due to the repeated renal monitoring of lithium treated patients.

When ESRD was chosen as outcome, the picture was more diverse. The studies by Bendz et al and Aiff et al found an increased frequency of ESRD associated with lithium as compared to the general population [15,16].

However, these studies are hard to interpret due to the risk of recall bias regarding lithium exposure in ESRD patients in both studies, and the methods used to determine lithium use in the initial study. Additionally, the cross-sectional design may have inflated the frequency of ESRD associated with lithium. Close et al [17] also showed an increased risk of renal failure associated with lithium use. Unfortunately, this latter study is also hard to interpret due to the lack of data from secondary treatment facilities and the lack of validation of the bipolar disorder diagnosis [17]. In contrast to these studies, Kessing et al found that ESRD was not associated with an increasing number of lithium prescriptions[19]. Also Hayes et al found no association between lithium exposure and severe kidney disease [20]. The study by Kessing et al[19], is so far the largest and methodologically the most sound study as it incorporated the use of end-stage disease as an outcome, utilized the extensive Danish healthcare registers for identifying exposure and outcome, and used a cohort exclusively of patients with bipolar disorders, thereby minimizing the risk of confounding by indication. Furthermore, Kessing et al included competing risk of death, added analyses according to age at start of lithium use, and controlled for a variety of potential confounders including somatic medication. The study could specifically though be criticized for lack of laboratory results, thereby relying only on clinical register based diagnosis regarding CKD.

The way of determining lithium exposure differed between studies; Close et al [17], Kessing et al [19] and Hayes et al [20] utilized prescription data to estimate drug exposure, whereas Shine et al [18] utilized lithium serum levels and lastly Bendz et al [15] and Aiff et al [16] interviewed all end-stage renal patient regarding previous lithium exposure. The use of prescription data allows for long-term follow-up and investigation of cumulative drug effects, albeit there is a lack of confirmation of all prescribed drugs being ingested by the patient. The use of serum levels for determining exposure is effective for a dichotomous definition of ever versus never exposure, but minimizes the possibilities of investigating cumulative drug effects. Lastly, an interview based determination of lithium exposure infers the risk of recall bias, and also makes it difficult to address cumulative exposure.

Regarding the discrepancy between results from the studies using ESRD as an outcome, an increased occurrence of ESRD was seen only in the studies including patients early in time. Thus, Bendz et al [15] and Aiff et al [16] mainly included patients who initiated treatment in the 1960's, 1970's and 1980's when serum lithium levels between 0.8 and 1.2 mmol/L were recommended, likely increasing the risk of renal impairment. A re-analysis of the Aiff et al [16] and Bendz et al [15], showed that no patient with ESRD had started lithium treatment later than 1980 [30]. Similarly, Close et al [17] included prevalent cases from 1990; they did not report time of lithium initiation, but presumably many of the cases were treated during earlier decades. The studies by Kessing et al [19] and Hayes et al [20] not finding an increased risk of ESRD associated with lithium, included treatment-naïve patients from 1994 and onwards and patients presumably not previously treated patients from 1995 and onwards, respectively. The different results over time might indicate that the modern guidelines for lithium treatment minimize the risk of lithium induced ESRD, as also proposed by Aiff et al [30], [30], and indirectly indicated the findings of Clos et al [31] showing that patients exposed to serum lithium levels above 0.8 mmol/L had an increased risk of decreasing estimated glomerular filtration rate as compared to those exposed to lower levels. Future studies with even longer follow-up periods on treatment-naïve patients will most likely be able to elucidate on this matter.

## Conclusion

In conclusion, this review of recent large observational data suggests an increased risk of decreased renal function associated with lithium treatment. This increased risk may however, at least partly, be a result of surveillance bias. In addition, data does not point toward an increased risk of end-stage renal disease associated with lithium treatment. The improved renal outcome found in recent lithium studies may be a result of improved renal monitoring and focus on recommended lithium serum levels (preferentially between 0.6 and 0.8 mmol/l) during maintenance treatment.

## Conflicts of interest

RE Nielsen has received research grants from H. Lundbeck and Otsuka Pharmaceuticals for clinical trials, received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, Lundbeck, Servier, Otsuka Pharmaceuticals, and Eli Lilly and has acted as advisor to Astra Zeneca, Eli Lilly, Lundbeck, Otsuka Pharmaceuticals, Takeda, and Medivir.

LV Kessing has within the preceding three years been a consultant for Sunovion.

WA Nolen has received research grants from Netherlands Organisation for Health Research and Development, European Union, honoraria for lecturing from Lundbeck and Aristo Pharma, and has acted as advisor to Daleco Pharma.

RW Licht has received research grant from Glaxo Smith Kline, honoraria for lecturing from Pfizer, Glaxo Smith Kline, Eli Lilly, Astra-Zeneca, Bristol-Myers Squibb, Janssen Cilag, Lundbeck, Otsuka, Servier and honoraria from advisory board activity from Glaxo Smith Kline, Eli Lilly, Astra-Zeneca, Bristol-Myers Squibb, Janssen Cilag, and Sunovion.

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