Predictors of severe kidney disease in long-term lithium treatment

Clinical studies on a still hot topic

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Do the best you can until you know better. Then, when you know better, do better.

Quote of uncertain origin, attributed to Maya Angelou

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ABSTRACT

The thesis aims to advance the understanding of severe chronic kidney disease in lithium-treated patients through four observational studies in which subjects were recruited from the Sahlgrenska University Hospital laboratory database.

The findings of **Paper I** revealed a gradual increase in adherence to lithium monitoring guidelines over 30 years, with mean lithium levels decreasing over time, within the recommended range. **Paper II** showed an almost sevenfold increased risk of severe chronic kidney disease in patients with moderately elevated serum creatinine, indicating pre-existent renal damage, prior to lithium initiation, compared to matched controls. **Paper III** indicated that a low (1%) risk of severe chronic kidney disease during the first ten years of lithium treatment remained unchanged over a time span of three decades. **Paper IV** highlighted age-dependent variations in the lifetime risk of severe chronic kidney disease, with the highest risk in patients starting lithium at age 65-74 years. Patients below 55 years of age at lithium start had negligible 10-year risk. Prolonged lithium exposure, especially over 20 years, was a significant risk factor.

The findings corroborate the notion that lithium treatment per se poses a certain risk of severe chronic kidney disease. While pretreatment renal impairment markedly elevates the risk, a normal serum creatinine level is associated with moderate excess risk and should not preclude lithium use in patients who could benefit from it. Key predictors of severe renal impairment include age, baseline creatinine and duration of lithium exposure, with no significant influence of sex.

Keywords: Lithium; Chronic Kidney Disease; Renal Insufficiency chronic; Guideline adherence

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SAMMANFATTNING PÅ SVENSKA

Litium är vårt äldsta läkemedel med specifik psykofarmakologisk verkan och rekommenderas alltfort som återfallsförebyggande förstahandsval vid behandling av patienter med bipolär sjukdom och som ett värdefullt behandlingsalternativ vid recidiverande och svårbehandlade depressioner. Dess användbarhet begränsas dock av biverkningar varav den mest allvarliga är att en del patienter som behandlas med litium i många år kan få bestående njurfunktionspåverkan, så kallad kronisk njursjukdom.

Denna avhandling syftar till att öka kunskapen om allvarlig njursjukdom hos patienter behandlade med litium. Den omfattar fyra forskningsartiklar baserade på observationsstudier av patienter som behandlats med litium mellan 1980 och 2017, utvalda från Sahlgrenska Universitetssjukhusets laboratoriedatabas.

Studie 1 visade att en kontinuerlig ökning i efterlevnaden av riktlinjerna för uppföljning av litiumbehandling ägt rum sedan de infördes i början av 1980-talet, med en samtidigt gradvis minskning av blodkoncentration av litium, inom det rekommenderade intervallet. **Studie 2** visade en nästan sju gånger högre risk för allvarlig njursjukdom hos patienter med förhöjda serumkreatininnivåer, tydande på nedsatt njurfunktion, redan när litiumbehandling inleddes. **Studie 3** visade att risken för allvarlig njurfunktionsförsämring under det första decenniet efter litiumbehandlingsstart inte förändrats sedan 80-talet. **Studie 4** visade att risken för allvarlig njursjukdom skiljer sig avsevärt beroende på när i livet litiumbehandlingen påbörjas och vilket tidsperspektiv som avses: 10-årsrisken för de som började behandlas med litium under 55 års ålder var försumbar, medan livstidsrisken intill 90 års ålder var högst för de som började behandlingen mellan 65 och 74 år. Förlängd behandlingstid, i synnerhet över 20 år, framstår som en signifikant riskfaktor.

Resultaten tyder på att litiumbehandling i sig medför en viss risk för allvarlig njursjukdom. Nedsatt njurfunktion redan innan behandlingen innebär en påtaglig riskökning, men behandlingen bör alltid erbjudas till patienter med normala serumkreatininnivåer, där överrisken är måttlig. Viktiga riskfaktorer för allvarlig njursjukdom inkluderar ålder, serumkreatininnivå innan behandlingen och behandlingstid, medan kön inte påverkar risken.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Golic M, Aiff H, Attman PO, Ramsauer B, Schön S, Svedlund J. Compliance with the safety guidelines for long-term lithium treatment in Sweden. J Psychopharmacol. 2018 Oct;32(10):1104-1109. doi: 10.1177/0269881118780014. Epub 2018 Jun 13. PMID: 29896998.

II. Golic M, Aiff H, Attman PO, Ramsauer B, Schön S, Steingrimsson S, Svedlund J. Starting lithium in patients with compromised renal function - is it wise? J Psychopharmacol. 2021 Feb;35(2):190-197. doi: 10.1177/0269881120936541. Epub 2020 Jul 14. PMID: 32660301.

III. Golic M, Aiff H, Attman PO, Ramsauer B, Schön S, Steingrimsson S, Svedlund J. The low risk for early renal damage during lithium treatment has not changed over time. J Psychopharmacol. 2023 Mar;37(3):318-324. doi: 10.1177/02698811221123054. Epub 2022 Sep 19. PMID: 36121029; PMCID: PMC10076338.

IV. Golic M, Aiff H, Attman PO, Ramsauer B, Schön S, Steingrimsson S, Svedlund J. Lifetime risk of severe kidney disease in lithium-treated patients: a retrospective study. Int J Bipolar Disord. 2023 Dec 9;11(1):39. doi: 10.1186/s40345-023-00319-2. PMID: 38070020; PMCID: PMC10710395.

CONTENTS

ABBREVIATIONS

ACE inhibitors	Class of antihypertensive drugs that act by inhibiting the angiotensin-converting enzyme (ACE)
AKI	Acute kidney injury
AQP(s)	Aquaporin(s)
AUC	Area under the curve
CIF	Cumulative incidence function
CKD	Chronic kidney disease
CV/CVD	Cardiovascular/cardiovascular diseases
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FSGS	Focal segmental glomerular sclerosis
GFR	Glomerular filtration rate
GSK3	Glycogen synthase kinase 3
HR	Hazard ratio
HT	Hypertension
IMP	Inositol monophosphatase
LYL	Life-years loss
MSA(s)	Mood stabilising antiepileptic(s)
MRI	Magnetic resonance imaging
NDI	Nephrogenic diabetes insipidus
NKF	National Kidney Foundation

NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
QoL	Quality of life
RCA	Renal concentration ability
RLM	Revised Lund-Malmö (formula/equation for estimating GFR)
RRT	Renal replacement therapy
s-creatinine	Concentration of creatinine in serum
SGA(s)	Second generation antipsychotic(s)
s-Li	Concentration of lithium in serum
SNR	Svenskt njurregister (Swedish Renal Registry)
TRD	Treatment resistant depression

DEFINITIONS IN SHORT

Bipolar Disorder	Psychiatric disorder characterised by an episodic course, manifesting as periods of depression and periods of abnormally elevated mood, energy and activity level, with various frequencies and durations (from days to months).
Chronic kidney disease (CKD)	Chronic progressive condition characterised by structural or functional kidney damage, lasting at least 3 months.
Distribution volume (V_d)	Pharmacokinetic measure, calculated as the amount of substance/drug in the body divided by its plasma concentration. Substances with large distribution volumes have a higher propensity to leave the plasma and enter extravascular compartments.
Elimination half-life ($T_{1/2}$)	Pharmacokinetic measure defining the time needed for a particular substance/drug to reduce its initial blood concentration by 50%.
End-stage renal disease (ESRD)	The most advanced stage of renal disease in which the kidneys cannot function at a level necessary to sustain life. Sometimes termed ‘end-stage kidney disease’ (ESKD).
Glomerular Filtration Rate (GFR)	Measure of the renal function, indicating the plasma volume filtered through the kidneys per unit of time.
Mood Stabilising Antiepileptics (MSAs)	Group of drugs with both anticonvulsant and mood-stabilising effects. Initially developed to treat epilepsy, these drugs were subsequently found to have mood stabilising properties as well.

Polydipsia	Excessive fluid intake (over 3 l daily).
Polyuria	Large volume of urine excretion (typically over 3 l daily).
(Renal) conservative management	Set of supportive therapeutic strategies used in advanced stages of CKD, either to postpone the initiation of RRT, or in those cases where RRT is opted against. It focuses on symptom management, slowing the disease progression and optimising quality of life.
Renal replacement therapy (RRT)	Medical treatments that substitute for the function of the kidneys, including haemodialysis, peritoneal dialysis and renal transplantation.
Second Generation Antipsychotics (SGAs)	Newer group of drugs primarily used to treat psychotic disorders and bipolar disorder. Also employed as adjunctive therapy to antidepressants in treatment resistant depression. Other (sometimes off-label) uses of SGA's include: severe agitation, aggression, behavioural disturbances in dementia, Tourette syndrome, and OCD.
Teratogenic effect	Teratogens are agents that negatively affect a foetus after exposure during pregnancy. Teratogenic effect is thus the property of teratogens to cause birth defects or malformations.
Treatment Resistant Depression (TRD)	Concept without a strict definition, usually designating depression episodes that have responded inadequately to at least two antidepressant treatment courses.

INTRODUCTION

BACKGROUND AND RATIONALE FOR THESIS

This thesis highlights epidemiological aspects of severe chronic kidney disease (CKD) in patients treated with lithium. Considered the first modern psychopharmaceutical, lithium has a specific effect in a core group of psychiatric disorders called mood, or affective, disorders in which its successful use has been established and documented since the mid-twentieth century.

Mood disorders encompass bipolar disorder and major depression, also termed unipolar depression. Bipolar disorder, a core psychiatric condition, manifests as recurrent manic or hypomanic episodes, alternating with depressive episodes, and separated by euthymic phases of normal mood and function. Manic episodes are characterised by heightened mood, energy and activity, irritability, accelerated thought processes, pressured speech, poor judgement, erratic or risky behaviour, and sometimes, psychotic symptoms. Depressive episodes, common to both bipolar and unipolar depression, are marked by low mood, lack of joy and motivation, energy loss, anhedonia, concentration difficulties, pervasive negative thoughts, and suicidal ideation. Episodes of mixed states, combining elements of both depression and manic excitement, are also described as part of the course of bipolar disorder. Psychotic features and suicidal behaviour may co-occur in all types of mood episodes.

Based on the severity of the heightened mood episodes, two main types of bipolar disorders are described: type I (bipolar I) with severe 'high' episodes called manic episodes (or manias) and type II (bipolar II), with less severe 'highs' called hypomanic episodes (hypomanias). The larger group of bipolar spectrum disorders also includes other conditions with mood dysregulation as core symptom, but which do not fulfil the strict mood episodes criteria.

According to conservative estimates, 'classic' bipolar disorder (I and II combined) has an aggregate lifetime prevalence of approximately 1% of the population, with a somewhat lower yearly prevalence of 0.7% (Merikangas et al., 2011). Bipolar disorder is a debilitating condition, associated with various degree of impaired functioning and disability, often with severe consequences

on the level of academic achievement and family life, leading to unemployment, substance abuse, psychiatric and somatic comorbidities, hospitalisations, suicidal behaviour and reduced life expectancy (Baldessarini et al., 2020). Individuals with bipolar disorder have the highest risk of suicide among psychiatric patients. The estimates, although not fully consistent, suggest a risk of suicide in bipolar patients approximately 20-30 times higher than in the general population. About 40% of bipolar patients will attempt suicide at least once in their lifetime. They tend to employ more lethal methods, and up to 15-20% of them may actually end up dying in suicide (Plans et al., 2019). The most important areas of psychiatric use for lithium today are the acute treatment of mania and prevention of bipolar mood episodes, while at the same time it reduces the risk of dying in suicide (Wilkinson et al., 2022).

Depression is a far more common psychiatric condition than bipolar disorder. Its reported prevalence may vary, depending on demographic characteristics, diagnostic instrument used, geographical area, and study period. A recent structured review and meta-analysis reported a trend towards increased likelihood to experience depression over time (Moreno-Agostino et al., 2021). A meta-analysis, which was based on studies covering 30 countries worldwide published between 1994-2014, reported an aggregate one-year prevalence of depression of 7.2% and an aggregate lifetime prevalence of 10.8%. There was a high level of heterogeneity between the studies, and a significantly higher prevalence was found for women (Lim et al., 2018). A recent study covering 27 European countries reported similar results (Arias-de la Torre et al., 2021) and found that, between 2013 and 2015, the overall 12-months-prevalence for current depressive disorder was 6.4%, with a higher prevalence in women (7.7%) versus men (4.9%). About 8-30% of depressive episodes qualify as treatment-resistant depression (TRD), in which a meaningful clinical response is not achieved after two or more adequate antidepressant treatment trials (Lundberg et al., 2023; Zhdanava et al., 2021). In the last two decades, TRD has gained significant attention in psychiatric research, a focus that is justified, given TRD's considerable contribution to the overall burden of disability and healthcare utilisation attributed to depression (Lundberg et al., 2023). Besides its classic use in bipolar disorder, lithium is a valuable treatment option in TRD (Vázquez et al., 2021).

Despite lithium's effectiveness in treating mood disorders, its usage appears to decline (Karanti et al., 2016; Lin et al., 2020). The introduction of newer mood-stabiliser agents around the turn of the century was expected to reduce the share of lithium prescriptions to some extent. However, experts currently view

lithium as greatly underused, considering its therapeutic benefits and its endorsement in bipolar management guidelines (Malhi et al., 2023; Post, 2018; Zivanovic, 2017). Often cited reasons for not prescribing lithium are the need for biochemical monitoring of the treatment and its side effects profile (Michael Gitlin, 2016). Even physicians who view lithium as their first choice for treating bipolar disorder may have concerns about the increased risk of renal adverse events, particularly chronic kidney disease (CKD), associated with long-term lithium treatment (Hidalgo-Mazzei et al., 2023).

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health (NKF, 2013). It is most often a progressive, irreversible condition. A variety of heterogeneous disease processes, some of them operating over many years, may end up altering the function and structure of the kidney irreversibly, and causing CKD. Continuous progress of CKD over years may lead to renal failure and end-stage renal disease (ESRD), in which the kidneys can no longer sustain their function, a condition that is not compatible with life in the long-term, unless renal replacement therapy (RRT) is instated.

The association between long-term lithium treatment and CKD continues to be a topic of debate. Although the weight of evidence suggests a link exists, recent large registry-based studies have challenged the consensus that singles out lithium as the sole nephrotoxic mood-stabiliser (Bosi, Clase, et al., 2023; Kessing et al., 2015b). These studies indicate that bipolar patients treated with other mood-stabilisers may develop CKD at rates similar to those treated with lithium, suggesting that detection bias could partially account for the perceived association between lithium use and CKD.

Despite extensive research on lithium-associated CKD, knowledge gaps persist, spanning epidemiology, pathophysiology, individual prognosis, and prevention. This thesis seeks to enhance the epidemiologic understanding of severe CKD in lithium-treated patients.

LITHIUM

DISCOVERY AND EARLY APPLICATIONS

Lithium, the lightest and smallest solid element, is naturally found only in an ionised state, within salts or solutions, and is highly reactive with water and negative ions at ambient temperature. Discovered in the early 19th century

within petalite, a mineral from a Swedish iron ore mine in Utö, lithium was first documented by Swedish chemist Johan August Arfwedson in 1817. Isolated via electrolysis in 1855, it was initially considered a rare and commercially unviable element. This opinion proved completely wrong: in the 1860s, spectral analyses revealed lithium's ubiquity in nature, present in trace amounts in soils, rocks, salt deposits, brines, natural waters, and living organisms. During the following centuries, lithium has become a vital element for modern life, its significance extending from early pharmaceuticals to modern applications in batteries (Larcher & Tarascon, 2017). In 2022, more than 95% of the world's lithium production came from Australia's mines (47.2%), Chile's brines (30.2%), China's mines (14.7%) and Argentina's brines (4.8%) (*Lithium facts*).

The mid-19th century saw lithium's introduction to medicine by London-based doctor Alfred Baring Garrod in 1859 (Shorter, 2009). He discovered that lithium salts added to water help dissolve uric acid salts, and recommended its use for gout. The late 1800s and beginning of 1900s witnessed an exaggerated medicinal craze for lithium, which was used for a wide array of ailments thought to be consequences of uric acid excess ('the uric acid diathesis'). A plethora of lithia-tablets and 'lithia waters' were marketed and indiscriminately advertised for various conditions ranging from dyspepsia to rheumatism and malaria, from typhoid fever to gallstones, and various blood and nerve diseases. For example, upon its introduction in 1929, the carbonated beverage 7-Up, originally named "Bib-Label Lithiated Lemon-Lime Sodas", contained lithium. It was promoted, among other things, as a cure for hang-over (Brown, 2019). While lithia tablets for uric acid disorders persisted for some time, the excitement over 'lithia waters' waned when analyses showed negligible to undetectable lithium content in many of them.

In 1948, lithium chloride briefly entered the U.S. market as a sodium chloride (table salt) substitute for patients with heart failure and hypertension (HT), but was soon withdrawn in 1949 due to toxicity reports (Strobusch & Jefferson, 1980). This setback likely contributed to the delayed acceptance and adoption of lithium in American psychiatric practice.

BRIEF HISTORY OF PSYCHIATRIC USE

The pivotal role of John Cade and Mogens Schou is central to any discussion about lithium's history. The Australian doctor John Cade, despite limited scientific training and research facilities but equipped with a keen observational eye, made a groundbreaking discovery: lithium's potential to

treat mania, which he detailed in a seminal 1949 report (Cade, 1949). His first patient, a 51-year-old man, with a years-long history of manic psychosis, exhibited such a remarkable improvement under lithium treatment that he was discharged after three months of treatment (Brown, 2019).

However, the early 1950s presented a challenging period for lithium, marred by reports of patients' deaths due to its toxicity. Cade himself nearly abandoned lithium, even banning its use at the Royal Park Mental Hospital in Melbourne, where he was superintendent, after a patient succumbed to lithium intoxication. Edward Trautner, a multifaceted German refugee, poet, writer, and medical graduate working at the University of Melbourne, brought a major, yet underappreciated, contribution to lithium's breakthrough. Together with his junior colleague Charles Noack, he employed flame photometry to measure serum lithium concentrations (s-Li) and engaged in research that established a safe and effective range for lithium's blood levels. Trautner's work reconfirmed lithium's efficacy in treating mania and demonstrated its safe administration with regular monitoring (Brown, 2019). Today, the routine measurement of s-Li concentrations is a foundational aspect of contemporary lithium treatment guidelines.

The Danish doctor Mogens Schou independently corroborated Cade's findings, through systematic studies, including one of the first (if not 'the first') randomised placebo-controlled study in psychiatry (Schou et al., 1954). Mogens Schou was the first to provide evidence for lithium's prophylactic effect in bipolar disorder and to highlight lithium's potential to reduce suicide rates in bipolar patients (Brown, 2019). Despite the sound methodology and unequivocal results in Mogens Schou's work, the psychiatric world was not prepared to listen and the use of lithium remained sporadic for a long time. It took almost two decades of dedicated, persevering, and resilient work by Schou, his collaborators, and his adepts before the European psychiatric community finally accepted lithium and the FDA approved its use in the US.

Before John Cade and Mogens Schou, other physicians were briefly connected with the early psychiatric use of lithium and are worth mentioning. Philadelphia-based neurologist Silas Weir Mitchell, as early as 1870, recommended lithium bromide for its anticonvulsant and hypnotic properties and later for treating 'general nervousness'. Additionally, William Hammond, a professor at Bellevue Hospital Medical College in New York, pioneered the use of lithium bromide for mania in 1871. Finally, Danish psychiatrist

Frederick Lange in 1894 described the effectiveness of lithium carbonate in treating melancholic depression (Shorter, 2009).

Cade's discovery is often heralded as the advent of the modern psychopharmacological era. The late 1960s and early 1970s marked a surge in the scientific interest in lithium, a trend that has been long-lasting, as illustrated in Figure 1. Although its initial medical use was speculative and transient, lithium's role in psychiatry has been solidly established and endures.

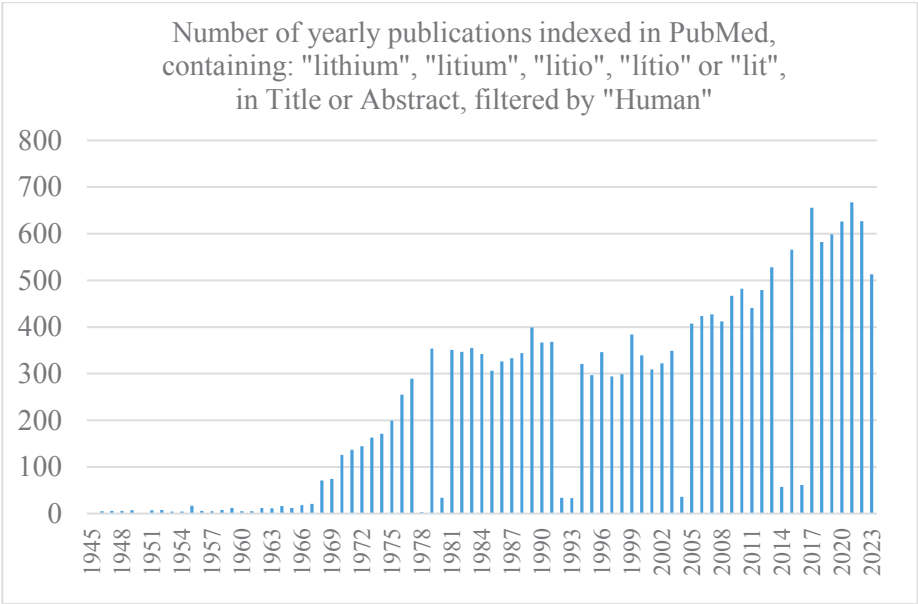

Figure 1 Number of yearly publications indexed in PubMed, obtained with search expression: "lithium" OR "litium" OR "litio" OR "lítio" OR "lit", contained in Title or Abstract, filtered by "Human". Date of PubMed Search: February 1, 2024

CURRENT USE OF LITHIUM

It is important to distinguish between officially registered (approved) indications of lithium and its practical (sometimes off-label) uses. Lithium's registered indications vary by country. In the United States, it is approved for acute and prophylactic treatment of mania (*Lithium carbonate prescribing information*), while in Sweden, its registration extends to prophylactic treatment of both depressive and manic phases of bipolar disorder, and the acute treatment of mania (*Lithionit FASS text*). In addition to these indications, in the UK, lithium's registered indications further encompass the acute

treatment of hypomania, recurrent treatment-resistant depression (TRD), and reduction of aggressive and self-harming behaviours (*Priadel package leaflet*).

These disparities notwithstanding, real-life applications, backed by research and national or local healthcare guidelines, show more consistency. Lithium's most recognised and accepted uses include:

- acute treatment of mania, hypomania, and mixed episodes
- maintenance (prophylactic) treatment of bipolar disorder
- acute treatment of bipolar depressive episodes
- acute treatment of therapy-resistant depression (TRD) and maintenance treatment of recurrent TRD

The first condition for which lithium was shown to be effective was the acute treatment of mania. Since Cade's discovery in the late 1940s, its effectiveness has been revalidated by subsequent studies (T. W. Hsu et al., 2022; McKnight et al., 2019).

Long-term treatment of bipolar disorder for preventing mood episodes is another major indication of lithium that has sustained the test of time. Older and newer reviews confirm its efficacy (Burgess et al., 2001; Fountoulakis et al., 2022; Geddes et al., 2004; Joas et al., 2017; Miura et al., 2014). National guidelines worldwide generally recommend lithium as the first-line medication for the maintenance treatment of bipolar disorder (Adler et al., 2014; Bschor et al., 2020; Hirschfeld et al., 2002; NICE, 2014; Yatham et al., 2018), making it arguably the most significant contemporary use of lithium.

Compared to its antimanic properties, the effect of lithium in the acute treatment of bipolar depression is less compelling. Recent systematic reviews (Fountoulakis et al., 2022; Rakofsky et al., 2022; Riedinger et al., 2023) have concluded that the available evidence does not support lithium as first-line treatment for this indication. However, the limitations of the existing studies make it impossible to draw definitive conclusions. Such limitations include the recruitment of mainly patients with bipolar II disorder, inadequate s-Li monitoring, or s-Li levels too low, with mean values around 0.6 mmol/l, while certain guidelines recommend a target s-Li of 0.8-1.2 mmol/l for the acute treatment of bipolar depression (Yatham et al., 2018).

In the treatment of major depressive disorder (sometimes referred to as unipolar depression, to clearly differentiate it from depression episodes that are part of bipolar disorder), lithium has a well-defined role, as third-line therapy,

with documented efficacy for TRD (Bauer & Dopfmer, 1999; Vázquez et al., 2021) and recurrent depression (Baethge et al., 2003; Bauer et al., 2000). Furthermore, a recent large registry-based study showed that lithium reduces hospitalisation in patients with severe unipolar depression (Tiihonen et al., 2017).

Although not an indication in itself, lithium's anti-suicidal effect has been recognised early on and has been confirmed by subsequent research (Chen et al., 2023; Cipriani et al., 2013; Smith & Cipriani, 2017; Song et al., 2017; Wilkinson et al., 2022), providing a compelling rationale for its use in maintenance therapy for patients with mood disorders and increased risk of suicidal behaviour.

Since the turn of the century, newer second-generation antipsychotics (SGAs) have increasingly substituted lithium in its core indications. However, direct comparative studies between lithium and SGAs are scarce and usually sponsored by original SGAs manufacturers, raising concerns about potential bias (Bauer et al., 2013; Bowden et al., 2005; Niufan et al., 2008; Weisler et al., 2011). Additionally, some SGAs studies employed 'enriched designs', selectively including patients more likely to respond to the medication (Nolen, 2015; Rakofsky et al., 2023), a strategy not commonly used in lithium studies. Consequently, drawing unequivocal conclusions about the comparative efficacy of lithium and SGAs is challenging, which may contribute to the variability in practice guidelines and recommendations across different countries (Adler et al., 2014; Bschor et al., 2020; Hirschfeld et al., 2002; Malhi et al., 2020; NICE, 2014; Yatham et al., 2018).

NATURAL EXPOSURE TO LITHIUM

Our exposure to lithium occurs naturally through its presence in drinking water, albeit in much smaller quantities than those consumed in medicinal preparations. Lithium concentrations in natural waters vary widely, and are in the range of micromoles per litre (µmol/l). In contrast, the daily dosage of lithium medication ranges from less than 10 to up to 40-50 millimoles (mmol) per day, which is hundreds to thousands of times greater than the amount consumed through drinking water.

More recently, studies on lithium's environmental impact have gained scientific grounding. A study from 1990 (Schrauzer & Shrestha, 1990) investigated the potential behavioural effects of higher lithium concentrations in drinking water. Over a ten-year period (1978-1987), Texas counties with

higher lithium levels in drinking water (70-170µg/l) consistently exhibited statistically significant lower annual rates of suicide, homicide, rape, robbery, and total crime, compared to counties with lower levels (0-12µg/l). The eventual impact of socio-economic factors was not accounted for; however, average income was not higher in the counties with high lithium levels.

In the past 15 years, there has been a marked increase in research exploring the association between lithium in drinking water and various behavioural and health outcomes. Most studies have an ecological design and, although findings are not universally consistent, the preponderance of evidence suggests that higher lithium concentrations in drinking water might correlate with:

- lower rates of suicide; this finding has been confirmed by several studies (Kapusta et al., 2011; Memon et al., 2020; Ohgami et al., 2009; Schrauzer & Shrestha, 1990; Shiotsuki et al., 2016), however not by all (Knudsen et al., 2017)
- reduced rates of Alzheimer's disease; no clear-cut conclusions may be drawn, as some studies support this association (Kessing, Gerds, et al., 2017; Muronaga et al., 2022) while others do not (Duthie et al., 2023)
- decreased crime rates (Schrauzer & Shrestha, 1990)
- increased rates of autism (Liew et al., 2023)

While the debate on the benefits and risks of lithium in drinking water continues, the intriguing nature of these findings has prompted authorities and administrations to acknowledge them and inform the public (*Lithium in drinking water*; *Lithium in drinking water*, 2022).

PHARMACOLOGY

PHARMACOKINETICS

The pharmacokinetics of lithium was primarily studied using lithium carbonate administered to healthy volunteers. Lithium is rapidly and almost completely absorbed from the gastrointestinal tract, with a bioavailability of 80-100%, and it distributes evenly in total body water. For standard tablets, the time to reach peak plasma concentration (T_{max}) is 1-2 hours, extending to 4-6 hours for sustained-release formulations. Other key pharmacokinetic parameters include a distribution volume (V_d) of 0.7-1.0 l/kg, clearance of 10-40 ml/min, and an elimination half-life ($T_{1/2}$) of 18-36 hours (Grandjean & Aubry, 2009).

Notable pharmacokinetic interactions of lithium occur with NSAIDs, ACE inhibitors, and thiazide diuretics, all of which may elevate s-Li. Brain lithium

concentration, studied through magnetic resonance spectroscopy, was found to be roughly half that in blood, displaying daily fluctuations that mirror s-Li (Grandjean & Aubry, 2009). Individuals over 50 years of age showed poorer correlation and higher brain to serum concentration ratios (Forester et al., 2009).

Lithium is excreted as a free ion in urine. It freely passes through the glomerular membrane, and about 80% is reabsorbed in the proximal tubules via passive diffusion, with a clearance of 0.6-2.4l/h (Grandjean & Aubry, 2009).

PHARMACODYNAMICS

The precise mechanism of lithium's action, from the cellular level to its clinical mood-stabilising and anti-suicidal effects, remains elusive. It has been suggested that the mood-stabilising effect may be related to neurocognition, which is in turn linked to changes in brain structure, neuroprotection, neurotransmission, and cellular function (Malhi et al., 2013).

Lithium enters cells via sodium channels, accumulating in electrically active cells like neurons and muscle cells. Once inside, it interacts with various second messenger systems, translating external receptor signals into intracellular responses. Two proposed intracellular mechanisms appear as particularly important. One of them involves the phosphatidyl-inositol signalling. The enzyme inositol monophosphatase (IMP) breaks down inositol monophosphate, with inositol as a result. Lithium has been proposed to inhibit IMP, depleting intracellular inositol and increasing inositol monophosphate. Alterations in the phosphatidyl-inositol signalling pathway are thought to reduce metabolism in overactive cells. The second important intracellular mechanism involves glycogen synthase kinase 3 (GSK3), a ubiquitous enzyme and regulator of a number of signalling pathways and cell functions, influencing metabolism and cell-life cycle (with mainly pro-apoptotic action). Lithium is thought to inhibit GSK3 by increasing its phosphorylation, although the complete mechanism remains partially unclear (Szałach et al., 2023).

Lithium is believed to modulate several neurotransmitter systems, particularly important being the inhibition of excitatory pathways (dopamine and glutamate) and enhancement of GABA-mediated inhibitory signals (Malhi et al., 2013). The glutamate-inhibitory effect, through increased glutamate reuptake and the downregulation of NMDA receptors, may contribute to lithium's neuroprotective properties. Serotonergic and cholinergic

neurotransmission appear to be enhanced, possibly linked to reduced depressive behaviour (Szałach et al., 2023).

In addition to mitigating glutamate excitotoxicity, lithium's neuroprotective effects are also attributed to mechanisms like reduced apoptosis and increased production of brain-derived neurotrophic factor (BDNF), a protein involved in neuron survival and synaptic plasticity (Malhi et al., 2013). Furthermore, immunomodulatory effects of lithium have been described, including changes in immune cells and different serum cytokine levels (Szałach et al., 2023). Also linked to neuroprotection, lithium appears to preserve grey matter volume in brain regions involved in emotional regulation, such as the prefrontal cortex, hippocampus, and amygdala. These areas have been identified with structural abnormalities in bipolar disorder. The effect appears to correlate with clinical response to the drug, however, the clinical significance of these findings remains unclear (Malhi et al., 2013).

Studies on lithium's neurocognitive effects present mixed results. Some research (Grandjean & Aubry, 2009) indicated minor negative effects in long-term use, on cognitive functions such as memory, learning, and information processing speed, observed in both healthy volunteers and bipolar patients. Higher brain lithium concentrations have been associated with frontal dysfunction and elevated depression scores in the elderly (Forester et al., 2009). Other studies (Malhi et al., 2013) reported no significant cognitive effects of lithium in healthy individuals. Finally, observations of improved executive functioning in lithium responders (Malhi et al., 2013), and potential pro-cognitive effects in low-dose lithium interventions (Strawbridge et al., 2023) make it difficult to formulate firm conclusions in this matter. Nevertheless, research interest in lithium's possible protective and/or disease modifying effects in Alzheimer's disease (and other age-related cognitive impairment processes) is on-going and the results so far, although not fully consistent, are encouraging (Forlenza et al., 2019; Singulani et al., 2024).

THERAPEUTIC RANGE

Lithium is characterised by a narrow therapeutic window, meaning that therapeutic serum lithium concentration (s-Li) is close to, or directly overlaps with the level at which toxicity occurs. Therapeutic concentrations are in the range of 0.4-1.0 mmol/l (or even up to 1.2 mmol/l for shorter time periods), while concentrations above 1.2-1.5 mmol/l typically result in symptoms of intoxication.

The clinical effectiveness of lithium is well correlated with its serum concentration, however, many of its side effects are also dose-dependent, and sometimes, particularly in chronic administration, the dose regime is chosen based on a compromise between clinical efficacy and tolerability.

For maintenance treatment in adult bipolar disorder, the recommended therapeutic range is generally 0.4-1.0 mmol/l (Nolen et al., 2019), with some variations between different guidelines recommendations. Some evidence suggests greater efficacy (i.e., fewer relapses) at higher concentrations within this range (C. W. Hsu et al., 2022). Target s-Li at the upper end of the therapeutic range, or even up to 1.2 mmol/l, have been utilised in clinical trials for the acute treatment of mania (Fountoulakis et al., 2022). Such levels are also advocated for in the treatment of acute bipolar depression (Yatham et al., 2018).

SAFETY ASPECTS

SIDE EFFECTS OF LITHIUM

Lithium, even when maintained within the therapeutic range, is linked to a spectrum of side effects. Many of them are clinically manifest and may occur at any time during the treatment. These include: tremor, gastrointestinal problems (diarrhoea and nausea), emotional blunting, induction or exacerbation of skin reactions such as acne or psoriasis, weight gain, hypothyroidism, polyuria and polydipsia. Longer-term effects, less frequent but significant, encompass hypercalcaemia and hyperparathyroidism, nephrogenic diabetes insipidus (NDI), and impaired renal function.

A Swedish study (Öhlund et al., 2018) found that more than half of patients started on lithium stop treatment, mostly due to side effects. Diarrhoea, tremor, weight gain, polyuria/polydipsia, and emotional blunting were common reasons for discontinuing lithium treatment during initial therapy. A Turkish study (Yazıcı et al., 2022) reported that side effects (such as tremor, polyuria, polydipsia, and weight gain) were relatively frequent (over 40%) even among patients continuing the treatment. However, in a naturalistic study in adults over 60 years old (Flapper et al., 2021), 36% of the patients stopped lithium within 18 months from treatment start, but only a minority (8.1%) did so solely due to adverse events.

The incidence and prevalence of side effects reported in studies and reviews may vary, sometimes widely. It is not unthinkable that the side effects

panorama may have changed in time, possibly due to the adoption of lower doses. For example, a recent structured review and meta-analysis (Gomes-da-Costa et al., 2022) found no significant differences in lithium patients' weight at baseline and at follow-up (8-52 weeks). These findings are corroborated by a US study (Phelps et al., 2021) which found no difference in weight gain at six months follow-up, between bipolar patients treated with lithium or lamotrigine. However, a previous review of lithium toxicity profile found a significantly higher weight gain in patients treated with lithium versus placebo (McKnight et al., 2012).

Gastrointestinal side effects are relatively common, and their prevalence is reported at 10-20% for nausea and respectively 10% for diarrhoea, possibly higher for the slow-release formulations (M. Gitlin, 2016).

In a recent study (Joseph et al., 2023), up to 32% of patients on long-term lithium therapy developed a thyroid disorder, with 79% being hypothyroidism. The condition is reversible to some extent, up to 40% of patients might be able to stop thyroid substitution therapy after lithium cessation (Lieber et al., 2020).

Skin conditions are also mentioned among lithium's side effects, but there is not much research focused on this aspect. A large systematic review and meta-analysis (McKnight et al., 2012) found no increase in alopecia or skin reactions in lithium-treated patients, while a retrospective study from China (Chan et al., 2000) found a significantly higher prevalence of skin adverse reactions (primarily acne) in a group of lithium versus non-lithium treated patients (45% versus 25%).

In a study from Sweden, the prevalence of lithium-associated hypercalcaemia was estimated at 26%, with an odds ratio (OR) of 13.45 for hypercalcaemia in lithium versus non-lithium treated bipolar patients (Meehan et al., 2018). A study from England (Shine et al., 2015) reported only a moderate risk increase for hypercalcaemia attributed to lithium (HR 1.43).

A recent registry-based study from Finland found that, compared to psychiatric controls not taking lithium, lithium use was associated with a lower risk of cardiovascular diseases (CVD) and cerebrovascular diseases, higher risk for pulmonary embolism, Parkinson's disease and kidney diseases, and equal risk of dementia (Ponzer et al., 2023). The full impact and consequences of these findings remain to be clarified.

Lithium's renal side effects are presented in the section "Renal effects of lithium".

LITHIUM TOXICITY

Lithium has a narrow therapeutic window which entails the risk of involuntary acute intoxication, in which s-Li is closely linked to the severity of intoxication. Mild acute intoxication typically occurs at concentrations between 1.5-2.5 mmol/l, moderate intoxication at 2.5-3.5 mmol/l, and severe intoxication at levels exceeding 3.5 mmol/l (*Lithionit FASS text*). Symptoms of lithium toxicity are consistent with the affected organ system and include gastrointestinal, renal, cardiac, neurological and endocrinological effects (Altschul et al., 2016). Toxic levels may also arise from chronic intake of inappropriately high doses, resulting in gradual buildup in the nervous system and chronic intoxication, with predominantly neurologic manifestations (Kobylianskii et al., 2021). A retrospective study summarising the experience of a neurology clinic (Hlaing et al., 2020) concludes that chronic intoxication occurs often in elderly (over 65 years old) with acute kidney injury (AKI), correlates poorly with s-Li, and medication impairing lithium excretion is regularly co-prescribed. A summary of published case studies from 2012 (Netto & Phutane, 2012) found that reversible lithium toxicity occurs in all age groups and precipitating factors were co-prescription of antipsychotic, brain pathology and acute manic psychotic state. A rare syndrome of irreversible lithium effectuated toxicity (SILENT) has also been described, but little is currently known about its epidemiology and pathophysiology (MacLeod-Glover & Chuang, 2020).

USE OF LITHIUM IN PREGNANCY AND LACTATION

Lithium is known to cross the placenta and enter breast milk (Grandjean & Aubry, 2009), therefore use in pregnancy and lactation should be avoided (*Lithionit FASS text*; *Lithium carbonate prescribing information*; *Priadel package leaflet*). Teratogenic effects, particularly an increased risk of cardiac malformations, have been documented, though recent studies suggest this risk may be lower than initially believed (Fornaro et al., 2020; Hastie et al., 2021). Other potential foetal risks include a higher likelihood of spontaneous abortion and birth of large-for-gestational-age newborns (Hastie et al., 2021).

There is limited clinical data on infant exposure to lithium through breastmilk. Only recently, this aspect has been examined in a retrospective study from Sweden (Heinonen et al., 2022). Forty-three babies were exposed to lithium through breast milk in the Stockholm region between 2006-2015, of which 30

were included in the study. Two infants presented with high s-Li level, of 0.7 and 1.2 mmol/l at 12 and 29 days of age, respectively. All babies who were followed-up stabilised at levels between 0.05-0.2 mmol/l by two months. In about 25% of the babies, the growth was inadequate during the first month of life, however it normalised thereafter. The study concluded that breastfeeding during lithium treatment could be considered safe, provided there is strict monitoring of the infant, especially in the initial weeks of life.

USE OF LITHIUM IN OLDER ADULTS

Compared to young adults, most elderly will need considerably lower daily doses of lithium to achieve the same s-Li, due to a slower lithium elimination. There is some evidence suggesting that lithium may be more effective in TRD in elderly compared to younger adults (Buspavanich et al., 2019). Another study (Dervic et al., 2023) found that bipolar suicide attempters older than 42 years treated with lithium exhibited less suicidal behaviour in the first 2.5 years after commencing lithium compared to those younger than 42 years. At the same time, elderly appear to be more susceptible to lithium toxicity (Hlaing et al., 2020). There is a general consensus that lithium levels within the lower range of the therapeutic interval should be targeted in older adults (Christl et al., 2023; Nolen et al., 2019).

THE SAFETY GUIDELINES FOR LITHIUM TREATMENT MONITORING

Understanding the narrow therapeutic window and side effects of lithium has prompted the development of guidelines for monitoring lithium therapy, which are based more on consensus than on evidence. In Sweden, reports on, and recommendations for, routine laboratory monitoring of lithium-treated patients were already published in 1980 (Amdisen et al., 1980; Pettersson, 1980). Today, regular biochemical and clinical monitoring is an integral part of lithium treatment.

Before initiating lithium treatment, evaluation of renal, thyroid, and cardiac functions, along with weight and BMI assessments, are advised (Adler et al., 2014; *Lithionit FASS text*; NICE, 2014). Lithium is initially prescribed at a low dose and gradually increased, with weekly monitoring of s-Li levels until the target concentration is reached.

For ongoing treatment, recommendations include regular checks of s-Li and serum creatinine concentration (s-creatinine), thyroid hormones, electrolytes and calcium. Continuous clinical monitoring to assess treatment efficacy and

side effects is mandatory. Regular monitoring of weight and BMI (at least yearly) is also recommended (Adler et al., 2014; NICE, 2014). If medication that may affect lithium elimination is initiated, additional s-Li monitoring and eventual lithium dose adjustments are required.

Recommendations for target s-Li concentration in maintenance therapy vary slightly across countries. Some suggest maintaining s-Li strictly between 0.6-0.8 mmol/l (NICE, 2014), whereas others recommend an individually-adjusted level within the range 0.4-1.0 mmol/l (Hirschfeld et al., 2002). The guidelines vary also with respect to recommended monitoring intervals e.g., 3 to 6 months for s-Li (Adler et al., 2014; NICE, 2014) and 3 to 12 months for other biochemical parameters (Adler et al., 2014; NICE, 2014). The primary goal of the safety guidelines is to maintain therapeutic lithium levels and allow for a timely identification and management of its side effects.

LITHIUM SALTS USED IN PHARMACEUTICALS

Lithium, as mood-stabilising medication, is available in the form of salts, of which lithium carbonate, citrate, and sulphate appear to be the most widely used. Early use of lithium acetate and gluconate was also mentioned (Grandjean & Aubry, 2009), however I did not find any evidence for current medicinal use of these salts in tablet formulation. It appears that lithium gluconate may be available for topical administration and may have a beneficial effect in the treatment of seborrheic dermatitis (Ballanger et al., 2008).

Lithium carbonate is the most commonly used lithium salt, available as both standard and extended-release tablets (*Lithium carbonate prescribing information*; *Priadel package leaflet*). Lithium citrate is available as an oral solution, and also in tablet form (*Litarex package leaflet*). Most published clinical, pharmacological and animal studies on lithium have used lithium carbonate. However, in Sweden and Norway, the only registered lithium salt is lithium sulphate (*Lithionit FASS text*), provided as a slow-release tablet. Lithium citrate is available in Sweden as an extempore oral solution. Unlicensed (or compassionate) use of non-licensed lithium carbonate and lithium citrate is not uncommon in Sweden, but must be motivated by the prescribing physician. The therapeutic effects and most side effects of lithium sulphate, carbonate and citrate are thought to be similar at equivalent s-Li levels. An exception is gastrointestinal tolerability, which appears to be poorer with the slow-release formulation of lithium sulphate. Evidence supporting bioequivalence primarily includes studies from the 1970s suggesting that

lithium carbonate and sulphate achieve comparable plasma concentrations (Persson, 1977). Additionally, similar side effects were observed with lithium sulphate compared to lithium carbonate (Edström & Persson, 1977) and respectively citrate (Widerlöv, 1976) over a treatment period of four weeks.

Organic lithium salts, such as lithium orotate, aspartate and ascorbate, are marketed as over-the-counter (prescription-free) health products and dietary supplements. These can be procured online without a prescription (*Lithium Ascorbate*; *Lithium Aspartate*; *Lithium Orotate*) and are promoted for their neuroprotective attributes, but some manufacturers are advising consultation of a physician before use. Recent scientific interest has revived in lithium orotate suggesting therapeutic advantages over the inorganic lithium salts (such as carbonate, citrate and sulphate), that could be explained by different pharmacokinetics (Murbach et al., 2021; Pacholko & Bekar, 2023). It is proposed that lithium orotate dissociates to a lower extent at physiological pH (compared to inorganic lithium salts), thus a larger proportion of lithium would exist in serum in molecular form (as opposed to ionised form). Lithium orotate molecules use a nucleotide transporter to pass through the cell membrane and cross the blood brain barrier with better efficiency, achieving an increased intracellular accumulation in the nerve cells (Pacholko & Bekar, 2021, 2023). As a consequence, smaller doses of elemental lithium delivered as lithium orotate would produce the same therapeutic effects in the brain, but with reduced toxicity compared to lithium delivered as inorganic salts (Pacholko & Bekar, 2023).

CHRONIC KIDNEY DISEASE (CKD)

ELEMENTS OF ANATOMY AND PHYSIOLOGY OF THE KIDNEYS

The kidneys, together with the ureters and urethra, form the urinary system, with main function to eliminate metabolic waste, toxins, and excess ions, while conserving essential substances like water, glucose, and proteins. The kidneys are small, bean-shaped organs, each about 10-12x5-7 cm in size, located on the lower posterior part of the abdominal wall (Soriano et al., 2023).

The nephron is the basic functional unit of the kidney. A healthy adult kidney contains approximately 2 million nephrons. Each nephron consists of a glomerulus (a capillary loop encased in Bowman's capsule), and a tubule,

which extends from the capsule. The main components of the nephron, including the different parts of the tubule are depicted in Figure 2. Urine production involves glomerular filtration, in which water and solutes are filtered from the blood to form the primary urine, followed by reabsorption and secretion in the tubules, culminating in the final urine composition. Nutrients and water are reabsorbed through the tubular walls back into surrounding capillaries, while waste and hydrogen ions are secreted into the tubules (Ogobuiro & Tuma, 2023).

The glomerular filtration rate (GFR) is a critical measure of kidney function, indicating the volume of blood filtered by the glomeruli per unit time. Direct measurement of GFR, involving the infusion of a substance like Iohexol or Cr-EDTA and subsequent calculation of its clearance from blood and urine samples, is accurate but impractical for routine use, due to its complexity and time requirements. In day-to-day practice, estimated GFR (eGFR) rather than measured GFR is used. eGFR is calculated with the help of equations using s-creatinine, s-cystatin, or both, along with individual characteristics such as sex, age, and possibly weight and ethnicity. Creatinine and cystatin are naturally present in the human body and are relatively good indicators of renal function.

Examples of GFR estimation equations are: the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the Modification of Diet in Renal Disease (MDRD), the Berlin Initiative Equation (BIS), the European Kidney Function Consortium (EKFC), and the revised Lund-Malmö (RLM) equation.

The normal GFR for a healthy young male adult at age 20 is about 100-110 ml/min/1.73 m² (Glassock & Rule, 2016). This rate typically declines after 35-40 years of age, decreasing by about 6-7 ml/min/1.73 m² per decade, due to progressive nephron loss, caused by a process of focal and global glomerulosclerosis (Glassock et al., 2020). An intact glomerular membrane is vital for a healthy renal function. Damage to this membrane is marked by the leakage of plasma proteins, especially albumins, into the urine, a condition known as albuminuria.

The different segments of the tubules (proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct) have distinct absorptive properties through which nutrients and water are reabsorbed and retained in the body. Reabsorption of water occurs through osmosis at different levels of the tubules and collecting duct, facilitated by aquaporins (AQPs), membrane proteins acting as water channels and allowing the passage of water across the

cell membrane. Particularly important are AQP1, abundant in the proximal tubule and descending Henle loop, and AQP2, abundant in the collecting duct (Nielsen et al., 1999).

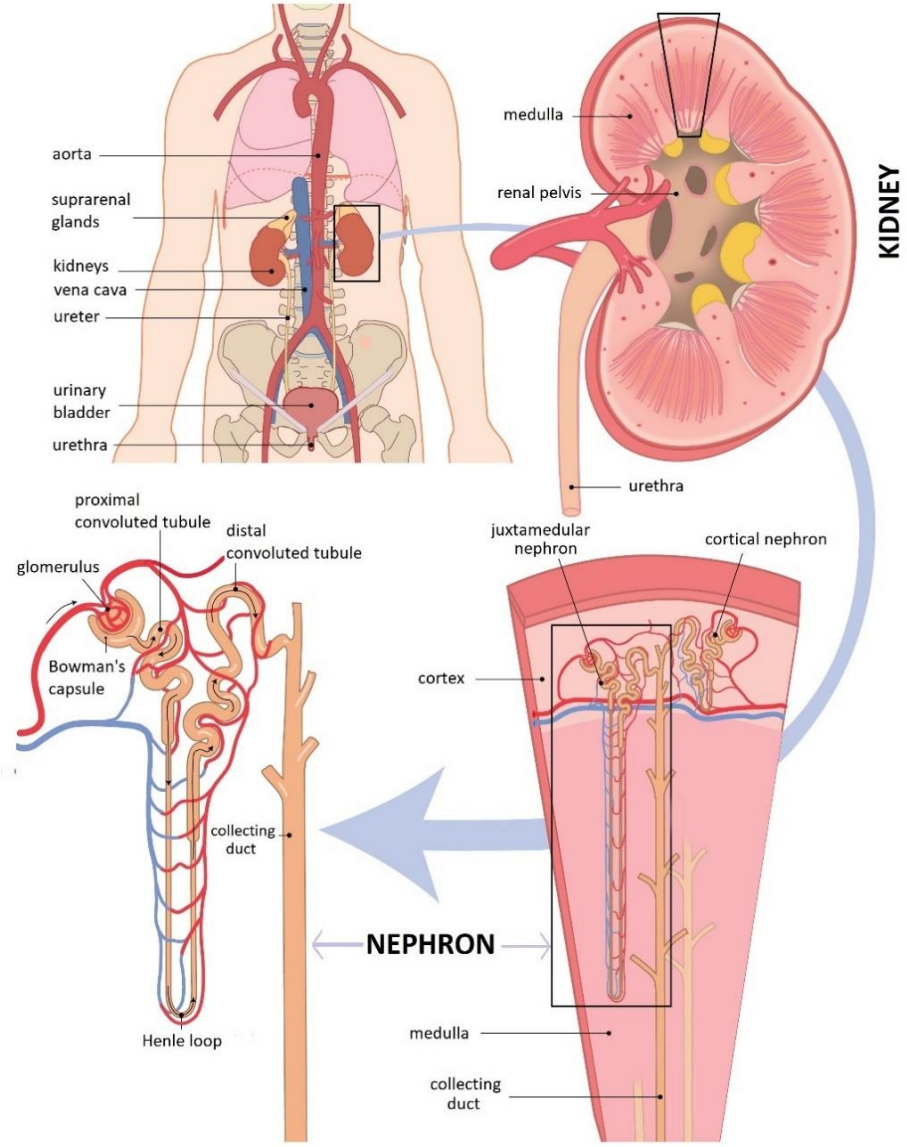

Figure 2 Anatomy of the urinary system. Downloaded 2023-10-24 from Anatomy Tool https://anatomytool.org/content/slagter-drawing-kidney-macroscopic-and-microscopic-anatomy-dutch-labels. The Dutch labels have been replaced with English labels. Used under Creative Commons licence https://creativecommons.org/licenses/by/4.0

In a sagittal section of the kidney (Figure 2), the glomeruli and convoluted parts of the tubules are located in the outer region, known as the cortex. In contrast, the Henle's loop and collecting ducts are situated in the central part, or medulla. The space around the tubules, glomeruli and blood vessels is the renal interstitium, comprising extracellular matrix, interstitial fluid, and cells.

CKD-DEFINITIONS AND TERMINOLOGY

The term 'chronic kidney disease' (CKD) has evolved from earlier terms like 'chronic renal failure' or 'chronic renal insufficiency'. It was adopted in the medical literature and guidelines after the publication, in 2002, of the first "Clinical Practice Guidelines for Chronic Kidney Disease" by The National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (NKF, 2002). These guidelines have established the following CKD definition: kidney damage, defined by structural or functional abnormalities of the kidney persisting for more than three months. This definition marked a significant shift in the approach to kidney disease, emphasising early detection and classification based on the level of kidney function. The use of the standardised term CKD was a key component in the guidelines, helping to establish a common language for clinicians and researchers in the field of nephrology.

In 2012, NKF has updated its guidelines for evaluation and management of CKD (NKF, 2013). The current guidelines recommend a tripartite CKD classification system encompassing the cause of the disease, the GFR category, and the albuminuria category. In the context of lithium-associated CKD, the GFR classification is the most relevant aspect, and includes six levels, as presented in Table 1.

Table 1 GFR categories in CKD, according to NKF (2013)

GFR category	GFR (ml/min/1.73 m^2)	CKD (previous terminology)	Terms
G1**	≥90	CKD 1**	Normal or high
G2**	60-89	CKD 2 **	Mildly decreased*
G3a	45-59	CKD 3a	Mildly to moderately decreased
G3b	30-44	CKD 3b	Moderately to severely decreased
G4	15-29	CKD 4	Severely decreased
G5	<15	CKD 5	Renal failure

* relative to young adult level; ** in absence of evidence of kidney damage, G1 and G2 do not fulfil criteria for CKD

Albuminuria is classified into three categories (NKF, 2013):

- A1: normal to mildly increased (<30 mg/24 hours)

- A2: moderately increased (30-300 mg/24 hours)
- A3: severely increased (>300 mg/24 hours)

While the current age-independent, fix-threshold definition of CKD has the advantage of simplicity, it has been criticised for not discriminating between kidney ageing and kidney disease, potentially medicalising normal ageing, leading to overdiagnosis among the elderly, and possibly delaying a timely identification of younger adults with CKD (Delanaye et al., 2019; Glassock et al., 2020; Glassock & Rule, 2016; Kovesdy, 2022).

End-stage renal disease (ESRD) represents the terminal phase of CKD, where the kidneys can no longer perform their essential tasks of filtering blood and removing waste products from the body. At this stage, renal replacement therapy (RRT), such as dialysis or renal transplantation, becomes necessary. It appears that some ambiguity of terms still persists as the term ESRD (or ESKD – end-stage kidney disease) is sometimes used interchangeably with RRT.

CKD-AETIOLOGY, CLINICAL MANIFESTATIONS, MANAGEMENT AND PROGNOSIS

AETIOLOGY

CKD may be caused by systemic conditions affecting the kidneys and renal conditions such as: intrinsic kidney diseases (glomerular and tubulointerstitial), renal vascular diseases, pre-renal, and post-renal diseases. In the general population of high- and middle-income countries, diabetes mellitus (DM) and hypertension (HT) are the leading causes of CKD (Webster et al., 2017), contributing to up to 70-90% of cases. These are followed by glomerulonephritis, chronic tubulointerstitial nephritis, cystic kidney diseases, and other kidney conditions. Factors such as smoking, obesity, dyslipidaemia, and hyperuricemia may further aggravate CKD (Vaidya & Aeddula, 2022).

EPIDEMIOLOGY

The early stages of CKD are asymptomatic, making it difficult to assess its true incidence and prevalence. Prevalence estimates for CKD vary based on factors such as geographical area, population demographics, but also disease definition and application (or not) of the chronicity criteria. Aggregated results from large epidemiological studies worldwide suggest that the prevalence of CKD in the general adult population is around 10%, being higher in racial minorities. Gender differences have also been observed, with women showing a higher prevalence of CKD, but men having a greater incidence of kidney

failure (advanced CKD stages) due to faster progress of the disease. The most important differential factor is age, with individuals over 70 exhibiting a prevalence 3-8 times higher than young adults. It has been argued that, as GFR declines naturally with age, the high proportion of elderly with GFR<60 ml/min/1.73 m^2 may merely reflect the ageing process (Hill et al., 2016; Kovesdy, 2022).

SYMPTOMS AND LABORATORY SIGNS

The kidneys have significant functional reserves, which is why early CKD stages often go unnoticed, and symptoms may not appear until stage 3b-5. Common symptoms include tiredness, swollen feet and hands, itchy skin, polyuria, disrupted sleep, muscle cramps, and, in advanced stages, nausea, reduced appetite, cold intolerance, chest pain or shortness of breath (Vaidya & Aeddula, 2022). Elevated s-creatinine with reduced eGFR is the hallmark of CKD. Albuminuria is also a common marker and indicator of kidney damage. Its presence in CKD is usually associated with higher risk of progression. Laboratory abnormalities occurring with later stages are: elevated serum concentration of urea (a waste product from protein breakdown) resulting in uraemia, anaemia (low red blood cells count or low haemoglobin), electrolyte imbalance (hyperkalaemia, hyperphosphatemia, hyponatraemia, hypocalcaemia), low bicarbonate (metabolic acidosis), haematuria (blood in urine), secondary hyperparathyroidism, and dyslipidaemia with elevated triglycerides (Webster et al., 2017).

PROGRESSION, PROGNOSIS AND MANAGEMENT

The progression of CKD varies widely among individuals. While it may partially or fully reverse if its underlying cause is treatable, most cases follow a chronic, lifelong course, although the (e)GFR decline is not necessarily linear (Caravaca-Fontán et al., 2018; Tsai et al., 2017; Xie et al., 2016).

Most CKD patients do not advance to stage 4 and even fewer to ESRD. Out of 1,607 patients with CKD 3 referred to a tertiary nephrology centre in Ontario, Canada, 21% progressed to CKD 4 over a seven-year follow-up period, 3% developed ESRD, and 12% died (Sud et al., 2016). In a large meta-analysis including over 185,000 patients with CKD 4 followed up over periods ranging from 2 to 14 years only 12% progressed to ESRD, while 44.3% died, with or without ESRD (Evans et al., 2018).

While the prevalence of CKD increases in the older population, its prognosis has an inverse relation with age. For CKD 3 and higher, the life-years loss

(LYL) is inversely related to age at diagnosis, with the younger patients facing the greatest reduction in life expectancy (Turin et al., 2012).

Basic aspects of CKD management encompass treating reversible causes, promoting lifestyle changes like quitting smoking and regular exercise, managing blood pressure and blood sugar. In early stages, focus is on slowing disease progression. In more advanced stages, additional strategies include optimising diet, managing complications (such as anaemia, fluid and electrolyte imbalance, bone disease), and adjusting medication doses.

Patients reaching ESRD must opt for either RRT, which is meant to prolong life, or so-called conservative management (NICE, 2018; Schell et al., 2013). ESRD usually corresponds with a GFR level below 10 (usually between 5-7) ml/min/1.73 m^2, however it is not defined by a fix threshold, but by the severity of symptoms produced by uraemia and other imbalances, and their impact on the daily life. Renal transplantation, one of the RRT alternatives, is the treatment option offering best quality of life (QoL) for patients with ESRD (Mazzuchi et al., 2000), however it has limited applicability because it requires a suitable donor. The most frequently used RRT is dialysis, which may be administered as haemodialysis (performed in a hospital, several times per week) or peritoneal dialysis (conducted at home, using various daily regimens). In haemodialysis, the blood is drawn from the body, filtered through a machine and returned to the body, while in peritoneal dialysis a cleansing fluid (dialysate) is infused in the peritoneal cavity through a catheter and replaced after a period of time (called dwell time). Waste products will have then passed through the peritoneum into the dialysate, thus being removed from the body.

Conservative management focuses on maintaining quality of life by managing symptoms and complications associated with ESRD, though it provides limited support for kidney function itself. While it can delay the initiation of RRT, conservative management also serves as an alternative to dialysis akin to palliative care, for patients such as elderly with multiple comorbidities, those with limited life expectancy, slow progress or who decline dialysis.

RENAL EFFECTS OF LITHIUM

Lithium's effects on the kidneys include both functional and morphological alterations, with reports of its nephrotoxicity emerging since the 1970s (Forrest et al., 1974; Hestbech et al., 1977; Hällgren et al., 1979).

FUNCTIONAL CHANGES

A common renal effect of lithium therapy is impairment of kidneys' ability to concentrate urine (renal concentration ability, RCA), leading to polyuria and polydipsia. A study on healthy volunteers showed that impairment of RCA is laboratory detectable already after the first weeks of lithium treatment (Walker et al., 2005). While often reversible, RCA may progress to nephrogenic diabetes insipidus (NDI), characterised by persistent symptoms and biochemical changes.

Polyuria and polydipsia are common among lithium users. The reported frequency of nephrogenic diabetes insipidus (NDI) is lower; however, different studies use various outcome measures, and there appears to be a lack of clear definition of terms and consensus on terminology. Thus, the following are reported: reduced RCA 51% (Doornebal et al., 2019), polyuria and polydipsia 48 and 49% respectively (Yazıcı et al., 2022), prevalence of decreased urine osmolality (Uosm) 12.5-17.9% (Rej et al., 2014), prevalence of NDI 3-19% (Doornebal et al., 2019; Rej et al., 2014).

The more debated aspect of lithium-induced renal toxicity is the gradual reduction in glomerular filtration. This typically develops over years of treatment and may lead to advanced stages of CKD or even ESRD (see section "CKD in lithium-treated patients"). The term 'creeping creatinine' mentioned in lithium literature, signifies a gradual increase in s-creatinine in a proportion of lithium-treated patients. The phenomenon is described in a study from Israel (Lepkifker et al., 2004), where 21% of lithium-treated patients presented a slow increase in s-creatinine, in most cases after more than 15 years of treatment. The affected group had a higher s-creatinine at treatment start, more somatic comorbidities (mostly DM and HT) and nephrotoxic medications, and more lithium intoxications compared to the unaffected majority. Rapid deterioration has also been described (Aiff et al., 2019): of patients progressing to eGFR<30 ml/min/1.73 m^2, approximately 30% had an eGFR loss of >50% in less than six months, but in these cases, the eGFR decline was attributed to somatic conditions or toxic factors unrelated to lithium treatment.

Some studies (Dineen et al., 2017; Lepkifker et al., 2004) have found an association between lithium intoxications and an increased risk of CKD. The association is supported by evidence that a single s-Li exceeding 1 mmol/l can impact eGFR for at least three months (Kirkham et al., 2014). However, other investigations did not find a correlation between lithium intoxications and the risk of CKD (Fransson et al., 2022; Hayes et al., 2021). The temporal sequence

of events and the causality might well be inverse, namely patients with impaired renal function are more prone to develop acute kidney injury (AKI), which may lead to toxic s-Li levels.

MORPHOLOGICAL CHANGES

Specific kidney lesions have been identified in biopsies of lithium-treated patients with NDI (Hestbech et al., 1977), and/or with impaired glomerular function (Aurell et al., 1981; Markowitz et al., 2000), with or without albuminuria. The changes included primarily tubular and interstitial lesions such as: focal interstitial fibrosis, tubular atrophy, and dilatation of the distal tubules with medullary and cortical microcysts, with the latter being particularly indicative of lithium nephropathy. While the tubulointerstitial changes dominate the biopsy image, focal-segmental glomerulosclerosis (FSGS) and global glomerulosclerosis was also reported to various degrees (Aurell et al., 1981; Hestbech et al., 1977; Markowitz et al., 2000).

Electron microscopy studies showed varying degrees of glomerular alterations, ranging from minimal, reversible changes of the podocytes (cells integral to the glomerular filtration barrier) to FSGS, which involves scarring in the glomeruli (Markowitz et al., 2000). Renal magnetic resonance imaging (MRI) studies revealed that microcysts may be detected as early as after one year of lithium treatment and suggested that their number (from cut-off five per kidney) can be predictive of low (<45 ml/min/1.73 m^2) measured GFR (Tabibzadeh et al., 2021). Earlier research suggested that interstitial fibrosis is the morphological aspect mostly related to GFR decline, while both interstitial fibrosis, as well as tubular dilatations and cysts were related to the length of lithium treatment (Presne et al., 2003).

It has been suggested that long-term lithium treatment might be associated with a higher incidence of renal tumours, particularly of malignant nature (Zaidan 2014). Subsequent larger population-based studies did not corroborate this finding (Kessing et al., 2015a; Pottegård et al., 2016) and concluded that lithium treatment is not associated with higher risk of renal tumours.

PATHOPHYSIOLOGY

The pathophysiology behind lithium's tubular effects is relatively well-understood. Lithium is freely filtered through the glomeruli and reabsorbed in the tubular epithelial cells, using the same channels as sodium ions. Among the various mechanisms identified, a notable one involves aquaporin-2

(AQP2): lithium accumulates in the collecting duct's principal cells and disrupts intracellular signalling pathways, directly inhibiting AQP2 and thus impairing water reabsorption in the collecting ducts (Davis et al., 2018).

It was shown in animal models that the antidiuretic amiloride blocks the epithelial sodium channels, preventing the intracellular transfer of lithium and the AQP2 inhibition (Kortenoeven et al., 2009). In clinical praxis, amiloride is prescribed off-label to alleviate polyuria experienced by some lithium-treated patients. It is not determined whether the use of amiloride prevents the development of NDI, however, one clinical study reported a significant increase of the maximal urine osmolality in lithium-treated patients after six weeks of treatment with amiloride (Bedford et al., 2008) and in animal studies amiloride was shown to reduce lithium-induced interstitial fibrosis (Kalita-De Croft et al., 2018; Mehta et al., 2022).

The mechanisms underlying lithium's effect on GFR are less clear. Various hypotheses have been proposed, some of which focus on glycogen synthase kinase 3 (GSK3). In the long term, lithium leads to a cellular reorganisation of the collecting duct, with a reduced ratio between principal (cells involved in water and electrolyte reabsorption) versus intercalated cells (involved in the acid-base balance). GSK3, involved in the cell proliferation, may play a role in this process, as well as in the microcysts formation, which likely precedes an increase in s-creatinine (Davis et al., 2018; Nielsen et al., 2008).

Animal studies revealed that four weeks of treatment with high lithium doses caused an increase in oxidative stress, mitochondrial alterations and cellular energy crisis (Ommati et al., 2021). Interestingly, low lithium doses appear to have a reno-protective effect against various aggression factors such as oxidative stress, inflammation or nephrotoxic compounds, enhancing kidneys' ability to recover from AKI, as it has been seen in animal studies (Alsady et al., 2016). Higher dietary lithium intake correlated with reduced risk of graft failure in individuals with kidney transplant (Post et al., 2023). It has been suggested that the molecular mechanism underpinning the reno-protective effect of lithium is also linked to GSK3-inhibition (Alsady et al., 2016). The clinical significance and implications of these findings have yet to be fully understood.

CKD IN LITHIUM-TREATED PATIENTS

While not all reports fully converged (Clos et al., 2015; Hullin et al., 1979), a consensus has been reached within the psychiatric community that lithium

treatment may affect glomerular function in a subset of patients. A key issue has been determining the extent to which this may lead to clinically significant renal function impairment. Furthermore, defining what constitutes 'clinically significant' renal dysfunction remains a challenge. Over the past couple of decades, several studies have examined a range of renal outcomes, from CKD stage 3 to 5 and RRT, to CKD progression (defined variably), and decline in eGFR (either as a fixed threshold or as an annual decline). It appears that no consensus was reached on which renal outcome is the most relevant in this context.

Table 2 summarises newer studies (published during the last ten years), aiming to: explore the association between lithium use and renal function impairment (as defined in each study), identify predictors for renal function impairment, and/or investigate how lithium discontinuation may influence eGFR. Although not exhaustive, this summary gives a perspective on the current state of knowledge in the field. Most studies are observational; therefore, the validity of their results is limited. Furthermore, it is important to acknowledge that differences in design, demographics, outcome measures, definition of disease, eGFR formula used, follow-up time and other possible aspects preclude direct comparisons between their results.

Some newer studies found that the risk for CKD, CKD progression, and RRT does not differ between bipolar patients treated with lithium and those treated with mood-stabilising antiepileptics (MSAs), suggesting that the increased risk of renal function impairment might be associated with the diagnosis (bipolar) rather than with lithium treatment per se (Bosi, Clase, et al., 2023; Kessing et al., 2015b). It was also suggested that a more frequent diagnosis of CKD in lithium-treated patients may reflect detection bias, as renal function is more rigorously monitored in this patient group compared to those on other types of medication (Kessing et al., 2015b; Wiuff et al., 2023). However, other studies found that a higher risk of CKD was associated with lithium treatment compared to MSAs (Højlund et al., 2022) or other treatments for bipolar disorder (Close et al., 2014). The weight of evidence favours the hypothesis that, compared to lithium-naïve individuals, those taking long-term lithium treatment had elevated risk of CKD 3 (Close et al., 2014; Højlund et al., 2022; Shine et al., 2015), CKD 4 (Close et al., 2014) and RRT (Aiff et al., 2014). Few studies do not support these findings (Wiuff et al., 2023).

A number of predictors for CKD or steeper eGFR decline in lithium-treated populations have been proposed, of which the most frequently studied are:

- Advanced age; association supported by Bocchetta et al. (2015), Clos et al. (2015), Castro et al. (2016), Fransson et al. (2022), Boivin et al. (2023).
- Lower pretreatment eGFR; association supported by Clos et al. (2015), Hayes et al. (2021), Van Alphen et al. (2021).
- Longer lithium exposure; association supported by Van Alphen et al. (2021), Fransson et al. (2022), Højlund et al. (2022), Yazıcı et al. (2022); not supported by Hayes et al. (2021), Pahwa et al. (2021).
- Higher mean s-Li; association supported by Castro et al. (2016), Rej et al. (2020), Yazıcı et al. (2022); not supported by Clos et al. (2015), Van Alphen et al. (2021).
- History of lithium intoxications: association supported by Clos et al. (2015), not supported by Fransson et al. (2022), Hayes et al. (2021).
- History of DM: association supported by Close et al. (2014), Rej et al. (2014), Pahwa et al. (2021), Aiff et al. (2019); not supported by Castro et al. (2016), Shine et al. (2015).
- History of HT or CVD: association supported by Castro et al. (2016), Aiff et al. (2019); not supported by Close et al. (2014), Pahwa et al. (2021).
- Female sex; association supported by Bocchetta et al. (2015), Castro et al. (2016), Hayes et al. (2021), Shine et al. (2015); not supported by Close et al. (2014), Aiff et al. (2015), Pahwa et al. (2021).

Lithium discontinuation, in particular rapid withdrawal, was found to be associated with a high risk of relapse of mood episodes and suicidal behaviour (Baldessarini et al., 1999). Furthermore, it was hypothesised that the renal benefits for patients with impaired renal function are questionable. For lithium-treated patients experiencing the 'creeping creatinine', it has been proposed that a 'point of no return' for GFR may exist, beyond which lithium withdrawal would not be followed by an improvement in renal function. This eGFR threshold has been suggested somewhere around 30-45 ml/min/1.73 m^2 (Bocchetta et al., 2013; Bocchetta et al., 2015; Presne et al., 2003). However, the research findings are mixed: a Dutch study suggests that lithium discontinuation may be followed by renal function improvement or a slower pace of deterioration in a large proportion of patients (Hoekstra et al., 2022), while others found no significant difference in eGFR development between patients continuing and those discontinuing lithium (Bocchetta et al., 2015; Kumar et al., 2023).

Table 2 Renal function in lithium treated patients: overview of studies (original research) published during the last 10 years (see the legend below the table for a list of abbreviations used in the table).

(Author yr.) Design	Renal outcome(s) (eGFR formula used)	Length of follow-up	Nr. subjects (psych. dg.)	Main findings
(Wiuff et al., 2023), Matched cohort *	eGFR decline; CKD def. by a) one value eGFR<60 or b) dg.codes (CKD-EPI)	Li: 19[a] mths. non-Li: 41[a] mths.	Li: 1646; non-Li: 5013 (BD)	eGFR started to decline after ca 4 yrs. on Li Li-use assoc. with low absolute number of renal outcomes. No SSD in rate of CKD in Li- vs non-Li cohort. More intense monitoring in Li- vs non-Li cohort.
(Bosi, Clase, et al., 2023), Cohort *	CKD progress: (30% eGFR decline, RRT); AKI, albuminuria, eGFR decline (CKD-EPI)	4.5[a] yrs.	Li: 5308: non-Li: 5638 (BD)	Li- vs Valpro cohort: no SSD in CKD progression, eGFR slope and new albuminuria. Higher cum. dose of Li, but not Valpro, was modestly assoc. with risk of CKD progression. s-Li >0.8 assoc with higher risk of AKI.
(Boivin et al., 2023), Cross-s. *	eGFR (CKD-EPI)	NA	Li: 248; non-Li: 0 (mixed, BD 71%)	Time on Li and cum. Li-dose was assoc. with eGFR decline. Pats. with s-Li > 0.8 had lower eGFR compared to those with s-Li < 0.8. Age and time on Li (but not DM or HT) were risk factors for low eGFR.
(Kumar et al., 2023), Discont. *	S-crea and eGFR changes 2 yrs. post- vs 2 yrs. pre-Li discont. (CKD-EPI)	2+2 yrs.	Li: 38; non-Li: 0 (BD)	Continuers vs discontinuers: no SSD in change of s-crea or eGFR pre- vs post-CKD dg. Discontinuers - more likely to have mood episodes first 2 yrs. after Li discont.
(Yazıcı et al., 2022), Cross-s. *	S-crea; CKD def. by one value eGFR<60; proteinuria; urine density (CKD-EPI)	NA	Li: 375; non-Li: 0 (mixed, BD 77%)	Pats. with time on Li ≥8 yrs. had: higher s-crea, higher s-urea, higher % with proteinuria, higher % with CKD 2-3, lower urine density and lower eGFR. Predictors of CKD were: s-Li, time on Li, cum. Li-dose, age at illness onset, and caffeine consumption.
(Højlund et al., 2022), Case-c. *	CKD def. according to KDIGO guidelines (CKD-EPI)	NR	Li: 738; CKD: 21,432; ctrls: 85,532; (NR)	Li use (ever/current) assoc. with risk of incident CKD. Risk of CKD assoc. with cum. Li-dose and time on Li > 10 yrs. Risk of CKD not assoc. with duration of trt. with MSAs.
(Fransson et al., 2022), Cross-s. *	Age-assoc. annual eGFR decline (RLM)	NA	LiSIE: 785; MONICA: 1549 (mixed)	Steeper eGFR decline in BD or schizoaff. may be attributed to Li. Time on Li >10 yrs. assoc. with steeper eGFR decline vs all groups. Hist. of Li intox. not assoc. with CKD

(Author yr.) Design	Renal outcome(s) (eGFR formula used)	Length of follow-up	Nr. subjects (psych. dg.)	Main findings
(Hoekstra et al., 2022), Discont. *	eGFR progress after Li discont. (CKD-EPI)	6-16 yrs. after discont:	Li: 43; non-Li: 0 (mixed, BD 42%)	43 pats: 29 (67%) improved eGFR, 8 (19%) cont. decline but at lower rate, and 6 (14%) cont. decline at similar rate. 13 pats. had eGFR <60 at cessation: of these, 7 improved, 5 cont. decline at lower rate.
(Hayes et al., 2021), Pred. model, Cohort *	CKD def. by eGFR<60, no information on time criterion (CKD-EPI)	7.10[a] yrs.	Li: 1609+934; non-Li: 0 (BD)	Pats. at high risk for CKD 3+ more likely: women, younger at Li start, obese, hyperlipidaemia, lower baseline eGFR, migraine. Time on Li and Li intox. (s-Li>1.5) not assoc. with high risk. A simple model including age, sex and eGFR at Li onset performed as well as a model with 44 variables.
(Tabibzadeh et al., 2021), Cross-s. *	mGFR; MRI lesions (NR)	NA	Li: 217; non-Li: 0 (NR)	52% of pats had CKD 2. Determinants for mGFR: time on Li, age, albuminuria, HT, hypothyroidism. S-Li - not assoc. MRI: microcysts in 51% pf pats; number of microcysts (cut-off: 5) – assoc. with mGRF<45. Time on Li and mGFR - strongly assoc. only in pat with microcysts.
(Van Alphen et al., 2021), Cohort *	CKD 3+ (2 eGFR<60, min 30 days apart); eGFR decline (CKD-EPI)	NR. Exposure: 9.2[b] yrs.	Li: 1012; non-Li: 0 (NR)	eGFR at Li onset - significantly lower in pats. reaching CKD 3+. Mean s-Li did not differ between pats. reaching CKD and those who didn't. Age at Li start and time on Li was assoc. with eGFR decline.
(Pahwa et al., 2021), Cohort *	CKD 3+ def. by dg.codes or KDIGO guidelines but time criterion uncertain (MDRD)	7.9[b] yrs.	Li: 154; non-Li: 0 (BD)	Pats. who developed CKD vs those who didn't: higher s-crea at baseline and older at the end of the study. After adjusting for baseline age: type 2 DM and BZD use – predictors for CKD; sex, s-crea at baseline, time on Li, HT- not assoc. with CKD.
(Rej et al., 2020), Matched cohort **	eGFR decline≥30%; s-crea increase ≥2 times; RRT (CKD-EPI)	Li: 3.0[a] yrs. Valpro: 3.1[a] yrs.	Li: 3113; Valpro: 3113 (mixed, BD 60-70%)	Li assoc. with risk of eGFR decline vs Valpro. S-Li > 0.7 mmol/l assoc. with risk of eGFR decline vs Valpro; s-Li ≤ 0.7 mmol/l not assoc. No steeper decline for pats with eGFR < 60 at baseline. No SSD between Li- and Valpro-cohorts with respect to RRT and s-crea doubling.
(Nestsiarovich et al., 2019), Cohort *	Severe KDs (RRT, CKD 4+); all KDs def. by dg.codes. (NA)	289[a] days	Total: 591,052; Li monotherapy: 57,547 (BD)	'No drug' – lowest risk of KD. Polypharmacy - consistently higher HRs. MAOIs and FGAs monotherapy – higher risk of severe KD than Li monotherapy. Highest risk of severe KD - regimes containing 'Li + MSA + SGA', MAOIs alone and 'tri-/tetracyclic AD + SGA'.

(Author yr.) Design	Renal outcome(s) (eGFR formula used)	Length of follow-up	Nr. subjects (psych. dg.)	Main findings
(Aiff et al., 2019), Case-c. *	CKD 4+ def. by last eGFR in the study period (RLM)	NR	Li: 109+109; non-Li: 0 (NR)	Somatic co-morbidity, in particular CVD, DM and urological conditions – significantly more prevalent in the cases (i.e. pats with CKD 4+).
(Kessing, Feldt-Rasmussen, et al., 2017), Cohort *	ESRD (used as synonym with RRT); ESRD (RRT) or death (NA)	5.94[a] yrs. (CKD+Li) vs 4.48[a] yrs. (CKD +Li+BD)	5757 with CKD of which Li: 754 (mixed)	All pats: cont. of Li and respectively MSAs - assoc. with lower rate of RRT vs respective drug cessation. BD pats: cont. of Li, but not MSA - assoc. with lower rate of RRT (vs respective drug cessation). Cum. incidence of ESRD over 10 yrs., considering the competing risk of death, was about 20% in all cohorts.
(Rej et al., 2017), Case-c. **	Five-yr. risk of incident CKD def. by dg.codes, for Li vs Valpro vs neither (NA)	NR	Cases: 21,741; ctrls.: 86,930; Li: 529; (NR)	Li-only use and co-medication Li + Valpro assoc. with increased risk of CKD compared to non-use of neither Li nor Valpro. Valpro-only use was not assoc. with increased risk of CKD.
(Dineen et al., 2017), Cohort *	CKD def. by eGFR <60, no information on time criterion (MDRD)	9[a] yrs.	Li: 580; non-Li: 0 (NR)	70 pats. (12.1%) had at least 1 toxic s-Li (>1.2 mmol/l). 94 pats. (16.2%) had at least 1 s-Na > 145 mmol/l. 161 pats. (27.8%) developed CKD 3+. CKD 3+ was more frequent among pats. with toxic s-Li (51.4%) and hypernatremia (44.2%) vs the rest (24.5%).
(Castro et al., 2016), Pred. model, Case-c. *	Renal insufficiency (RI) = CKD 3+ def. by dg.codes (ICD9) or eGFR<60 and 'not improving' (MDRD)	NR Exposure: 158[a] days (cases) vs 180[a] (ctrls)	Li: 3850 + 1901, of which: 991+454 with CKD 3+ (NR)	Assoc. with increased risk of CKD: age, female, smoking, HT, somatic co-morbidity, lifetime dg. schizophrenia/schizoaff., mean s-Li > 0.6, Li more than once daily, co-trt with FGAs. Not assoc. with CKD risk: time on Li and DM. Assoc with lower CKD risk: once-daily dosing and co-trt with newer AD.
(Shine et al., 2015), Cohort *	CKD 3 def. by one value eGFR<60 (MDRD)	NR	In renal study: Li: 2487: non-Li: 501,675 (NR)	After adjustment for age (cut-off 60 yrs.) sex, and DM, Li-use was assoc. with risk of CKD 3. Young women without DM had largest effect size. Median s-Li higher than the overall median - assoc. with eGFR decline. In Li-users - no association between the development of outcome and DM (*Note: low prevalence of DM in sample*).

(Author yr.) Design	Renal outcome(s) (eGFR formula used)	Length of follow-up	Nr. subjects (psych. dg.)	Main findings
(Kessing et al., 2015b), Cohort *	Definite CKD (by discharge dg.codes); ESRD/RRT; possible CKD (by discharge dg.codes), used for sensitivity analysis (NA)	NR	Overall (cohort 1): 1,800,591 of which Li users: 26,731 (NR)	In Cohort 1 (all pats.), rates of CKD increased with nr. of Li prescriptions, not MSAs, APs or ADs; rates of RRT- no increase. In Cohort 2 (dg. BD/mania), CKD risk increased with nr. of Li- and MSAs-prescriptions, similar effect sizes. RRT risk increased with nr. MSAs- but not Li-prescriptions. Assoc. between medication and CKD risk may be partly attributed to bias.
(Clos et al., 2015), Cohort ***	Annual eGFR decline; (2) Exploration of predictors. (CKD-EPI)	NR	Li: 305; non-Li: 815 (mixed)	Li- vs non-Li cohort: no SSD in mean annual eGFR decline, adjusted for age, sex, and baseline eGFR (1.3 vs 0.9 mL/min/1.73 m²). Predictors for eGFR decline: age, baseline eGFR, comorbidities, nephrotoxic drugs, episodes of Li toxicity (s-Li>0.8). Time on Li and mean s-Li: not significant predictors.
(Bocchetta et al., 2015), Cross-s., cohort, discont. *	eGFR (MDRD)	NR	Li: 953; non-Li: 0 (NR)	eGFR lower in: women, elderly, pats. with longer time on Li. Results of Cox regression: i) HR for CKD 3a increased with age; ii) men - lower risk of CKD 3b vs women. After discont, up to 4-yr. follow-up: no difference in eGFR/eGFR decline between CKD 3b pat. who a) continued with s-Li 0.5-1.0 vs b) discontinued Li or continued at s-Li<0.5.
(Aiff et al., 2015), Cohort *	eGFR (RLM)	NR	Li: 630 (at least 10 yrs.) (NR)	Median s-crea increased from the first yr. on Li trt. After at least 10 yrs. follow-up: 45.2 % of pats. had a s-crea increase of at least 30%; 32% of pats. had eGFR<60; almost 5% of pats. developed CKD 4+, no SSD between women and men.
(Roxanas et al., 2014), Cohort *	Incident RRT (MDRD)	NA	LiN-RRT: 187 RRT other causes: 38,316 (NR)	No LiN-RRT before 1991. 1991-2011, 187 RRT pats. with LiN (38,316 pats. with RRT of other causes). LiN rate increased over time: 1992-1996: 0.14 cases/million population/yr. (0.19% of all RRT), 2007-2011: 0.78 cases/million population/yr. (0.7% of all RRT). Pats. with LiN-RRT were more likely: women, white, smoke, have a higher BMI; age was similar with pats. with RRT of other causes.
(Aprahamian et al., 2014), RCT **	S-crea and eGFR (aMDRD and CKD-EPI)	4 yrs.	61 of which Li: 32 (MCI)	At baseline, pats. in Li-group were slightly younger vs placebo group (mean age = 71.6 vs 74.8 yrs). No other SSD in socio-demographics, comorbidities or medications. At 4 yrs. follow-up, no SSD between Li and placebo with respect to mean s-crea or eGFR. Target s-Li: 0.25-0.5.

(Author yr.) Design	Renal outcome(s) (eGFR formula used)	Length of follow-up	Nr. subjects (psych. dg.)	Main findings
(Close et al., 2014), Cohort *	RI and RF def. by dg.codes for CKD 3, resp. CKD 4+, ESRD and RRT (NA)	5.4[a] yrs. Range: 3 mths. - 18 yrs.	Li: 2496; non-Li: 3864 (BD)	Adjusted for age and gender, ever-use of Li - assoc. with increased risk of RF and RI. In fully adjusted models: Li use, diuretic use and DM were assoc. with RF. HT, gender, smoking, alcohol use, and NSAID use were not assoc. with RF. Number needed to harm (NNH) :44
(Aiff et al., 2014), Cross-s. *	ESRD (used as synonym with RRT) (NA)	NA	Li hist: 30 non-Li hist: 2614 (NR)	Prevalence of RRT (at 31 dec 2010): 15.0‰ among Li-users, 1.9‰ among non-Li users. Relative risk of RRT in Li user-population compared to Li non-users was 7.8.
(Rej et al., 2014), Cross-s. **	CKD; AKI; NDI def. by dg.codes (NA)	NA	Li: 2480; non-Li: 0 (NR)	1-yr. prevalence rates of CKD, NDI, AKI were 6.3%, 1.0%, and negligible. 6-yr. prevalence rates of CKD, NDI and AKI were 13.9%, 3.0% and 1.3%, respectively. Li use > 2 years, HT, DM, IHD, NDI, AKI, hydrochlorothiazide, loop diuretics, and SGAs were independently assoc. with CKD.

*=included adult patients; **=included elderly; ***=included patients 18-65 years; [a]=median; [b]=mean

Following abbreviations have been used in Table 2 (besides the ones listed in the Abbreviations List): Li (lithium); Cohort (cohort design); Case-c. (case-control design); Cross-s. (cross-sectional design); pred. model (prediction model); assoc. (associated/associates/association); cum. (cumulative); cont. (continuation/continued); ctrls. (controls); def. (definition/defined); dg. (diagnosis); dg.codes (diagnostic codes); discont. (discontinuation/discontinued); hist. (history); mGFR (measured GFR); mths. (months); nr. (number); pat./pats. (patient/patients); psych. dg. (psychiatric diagnoses); s-crea (s-creatinine); time on Li (cumulative lithium treatment duration); trt. (treatment); yr./yrs. (year/years); vs (versus); NA (not applicable); NR (not reported); BD (bipolar disorder); IHD (ischaemic heart disease); KD (kidney disease); Li intox. (lithium intoxication); LiN (lithium nephropathy); LiN-RRT (RRT due to LiN); MCI (mild cognitive impairment); RF (renal failure); RI (renal insufficiency); schizoaff. (schizoaffective disorder); SSD (statistically significant difference); AD (antidepressant); AP (antipsychotic); BZD (benzodiazepines); MAOI (monoamine oxidase inhibitor); FGA (first generation antipsychotic); Valpro (valproate); aMDRD (abbreviated MDRD). The abbreviation MSAs (mood stabilising antiepileptic) is used to designate all anticonvulsants; eGFR is expressed in ml/min/1.73 m^2; s-Li is expressed in mmol/l.

AIMS

The thesis examines epidemiological aspects of severe CKD in a lithium treated population. The specific objectives are outlined in four papers:

PAPER I

This study aimed to evaluate compliance with the Swedish guidelines for long-term lithium treatment between 1981 and 2010. It assessed the real-life practice' conformity with biochemical monitoring and recommended s-Li therapeutic range, and explored potential gender differences.

PAPER II

The aim was to examine the progression of renal impairment in patients who exhibited elevated s-creatinine levels, indicating impaired renal function, at the onset of lithium treatment.

PAPER III

This paper investigated whether the risk of severe renal impairment, defined as chronic kidney disease stage 4 or higher (CKD 4+), has decreased over time in long-term lithium-treated patients.

PAPER IV

The aim was to estimate the age-specific cumulative incidence and / or lifetime risk of severe renal impairment (defined as CKD 4+) in a cohort of long-term lithium-treated patients, observed for up to 37 years. Additionally, the study explored the relationship between the duration of lithium exposure and the risk of developing CKD 4+.

PATIENTS AND METHODS

PATIENTS

Study participants have been selected from the laboratory database of the Department of Clinical Chemistry at Sahlgrenska University Hospital (Gothenburg, Sweden). Patient data were collected from the laboratory database and from additional data sources outlined in this section.

DATA SOURCES

LABORATORY DATABASE

Established in the 1970s, the laboratory database encompasses data from all public hospitals and outpatient clinics in the greater Gothenburg area, serving approximately 650,000 inhabitants. It comprises sex, birth date, and laboratory tests (results and dates) of the included patients, identified by the unique Swedish personal identification number.

SWEDISH RENAL REGISTRY (SVENSK NJURREGISTER, SNR)

Managed by the Swedish Nephrology Association (Svensk Njurmedicinsk Förening) and the Swedish Transplant Association (Svensk Transplantationsförening), this web-based registry tracks patients with chronic renal failure, dialysis, and renal transplantation, and it aims to ensure adherence to care and treatment guidelines (*Svenskt Njurregister (SNR)*, 2023). SNR has been used to identify patients that have received RRT.

SWEDISH DEATH REGISTRY (SVERIGES DÖDBOK)

A computerised database maintained by the Swedish Genealogist Association (Sveriges Släktforskarförbund), it records information on Swedish residents who died in Sweden since 1860. Version 7 includes data up to 2017. The registry claims near-complete coverage, thanks to the Swedish personal identification number system, although the coverage for individuals who died abroad is less certain ("Sveriges Dödbok," 2018).

MEDICAL RECORDS

For Papers II and IV, structured reviews of medical records of selected study participants were conducted. This involved identifying somatic comorbid conditions, psychiatric diagnoses, and, for Paper II, prior lithium exposure

(pre-1980). Data were extracted from electronic medical records and the Patient Archive of Sahlgrenska University Hospital.

PROJECT DATABASE

The project database was established by identifying all individuals with at least one s-Li measurement recorded between January 1, 1980, and December 31, 2010, in the laboratory database. The data, including birth date, sex, and all s-Li and s-creatinine during this period, were compiled into a unified database for use across all papers.

In 2018, following an ethical board extension, the project database was further expanded with additional laboratory test results (s-Li and s-creatinine) up to December 31, 2017, for the included patients.

Participants in each study were selected from the project database, based on specific inclusion and exclusion criteria tailored to each paper. While some criteria were consistent across multiple studies (e.g., adult at first s-Li), others varied to align with the specific aims of each study.

Selected participants were cross-referenced with the Swedish Renal Registry (Svenskt Njurregister, SNR) and the Swedish Death Registry (Sveriges Dödbok), as required by the study protocols. This allowed for the integration of additional information on RRT and mortality into the study-specific databases.

METHODS

MEASUREMENTS AND ESTIMATES

LABORATORY METHODS

Serum lithium (s-Li) concentrations were determined using flame photometry. For serum creatinine (s-creatinine) levels, the picrate method was used until June 1, 2004, after which an enzymatic method was adopted. The enzymatic method offers greater specificity, and as a result, s-creatinine values obtained before this transition were adjusted (diminished by 25 μmol/l) for comparability (Aiff et al., 2015). The standard reference intervals for s-creatinine were 45-90 μmol/l for women and 60-105 μmol/l for men.

EGFR FORMULA

Each s-creatinine measurement was paired with the corresponding eGFR, calculated with the help of the revised Lund-Malmö (RLM) formula. Endorsed by the Swedish Council on Health Technology Assessment, the RLM formula incorporates factors such as s-creatinine, sex, and age, and has been shown to produce accurate GFR estimates in the Swedish population (Björk et al., 2011; Nyman et al., 2014).

DATA VALIDATION

Blocks of missing data were identified and verified in the database. In total, 12 months of data were missing (2.7-3.3% of the total time covered by the studies), distributed over three years between 1980 and 1985. The missing data was not considered to significantly impact the results of the studies.

Obvious erroneous laboratory values (negative or equal to zero) were excluded. Pretreatment s-creatinine values below 50 μmol/l were manually checked and obvious erroneous values were ignored in favour of the next consecutive value.

OPERATIONAL PARAMETERS

For each study, a set of operational parameters were defined. There was a certain degree of overlap, with a few parameters being common across several papers. Some parameters were similar but not identical, while others were unique to individual papers. These parameters are detailed in Table 3. The individual study database of each paper was compiled by calculating and adding the relevant parameters defined by means of operationalisation.

Table 3 Definitions of operational parameters

Operational parameter	Definition			
	Paper I	**Paper II**	**Paper III**	**Paper IV**
calendar decades			1980-1989; 1990-1999; 2000-2009	
first S-Li	first s-Li in the database			
last S-Li	last s-Li in the database up and including 2010	last s-Li in the database up and including 2017		
treatment duration	interval between *first s-Li* and *last s-Li*			
discontinuation period	period of more than 365 days without a s-Li value			
treatment restart	s-Li preceded by a discontinuation period			
treatment-year	defined by one (or more) s-Li in a given calendar year for a given patient			
continuous treatment period	period with maximum 365 days between consecutive s-Li values			
index treatment			first continuous treatment period with a duration of at least one year	
index start			first s-Li in *index treatment*	
age at start of Li treatment		age at *first s-Li*		
age at index start / start age			age at *index start*	

Operational parameter	Definition			
	Paper I	**Paper II**	**Paper III**	**Paper IV**
initial s-creatinine		s-creatinine closest to and within six months from *first s-Li*		
s-creatinine at index start / start creatinine			s-creatinine closest before, on the same day as, or closest after, and within one year from *index start*	
last creatinine		last s-creatinine in the study database (up and including 2017)		
(incident) CKD 4+ / CKD 4-5 (diagnosis)		first eGFR in the study database <30 ml/min/1.73 m^2	eGFR values consistently below 30 ml/min/1.73 m^2 for at least three months	
CKD 4+ patient		patient assigned *incident CKD 4+ / CKD 4-5 diagnosis* during the *follow-up time*, according to definitions in this table		
follow-up time	from *first s-Li* to *last s-Li*	starts at *first s-Li*; ends at *CKD 4+ diagnosis* (for *CKD 4+ patients*), respectively at *last creatinine* (for all others)	starts at *index start;* ends at *CKD 4+ diagnosis* (for *CKD 4+ patients*) resp. at *last creatinine* (for all others); or ten years after end of *index treatment,* whichever comes first	Cohort study: starts at *first s-Li*; ends at *CKD 4+ diagnosis* (for *CKD 4+ patients*) resp. at *last creatinine* (for all others). Case-control study: starts at *first s-Li;* ends at *CKD 4+ diagnosis* (for *CKD 4+ patients*) resp. at last s-creatinine in *matching year* (for all others)
time on Li		sum of the *continuous treatment periods* within *follow-up time*		
AUC		area under the *s-Li* vs time-curve		
average / mean s-Li	calculated per patient, for each *treatment-year*	calculated per patient, for the whole follow-up time, as *AUC* divided by t*ime on Li*		
Li intoxication		episode of s-Li of 1.5 mmol/l and higher		

Operational parameter	Definition			
	Paper I	**Paper II**	**Paper III**	**Paper IV**
compliance	defined binary, per patient, for each *treatment-year*; a *treatment-year* is *compliant* if s-Li and s-creatinine are measured at least every six months and/or s-creatinine not older than six months is available before *first s-Li* or *treatment restart*		defined per patient, over the whole *follow-up time*, as proportion of *time on Li* with s-Li and s-creatinine measured at least every six months	
exposed cohort		patients with *initial s-creatinine* over reference interval		
reference cohort		matched patients with *initial s-creatinine* within/below reference interval		
progressors		*CKD 4+ patients* in the *exposed cohort*		
non-progressors		patients in the *exposed cohort* not progressing to CKD 4+		
matching year				calendar year for *CKD 4+ diagnosis* (matching variable)
matched age (group)				age (group) at *matching year* (matching variable)

PARTICIPANT SELECTION

For each paper, participants were recruited from the project database, based on a specific set of inclusion and exclusion criteria. These criteria are detailed in Table 4.

Table 4 Selection criteria

Paper	Inclusion	Exclusion
Paper I	- *first s-Li*: 1981-2010 - adult patients	- no s-creatinine - *treatment duration* < 1 year
Paper II- Step 1 (Exposed Cohort)	- *first s-Li*: 1981-2010 - adult patients - *initial s-creatinine* – present - *initial s-creatinine* above upper limit of the reference interval (women: >90, men: >105 µmol/l)	- < 2 s-creatinine values - *treatment duration* < 1 year - patients in dialysis at first s-Li
Step 2 (Reference Cohort)	- 1:1 matching - same sex, *age at start of Li treatment,* and *treatment duration,* as patients in *exposed cohort* - *initial s-creatinine* – present - *initial s-creatinine* below upper limit of the reference interval	
Paper III	- *first s-Li*: 1980-2009 - adult patients - *index treatment* - present - *index start* in the same calendar decade as *first s-Li* - *s-creatinine at index start* – present - *last creatinine* – not earlier than six months before last s-Li	- *s-creatinine at index start* above upper limit of the reference interval (women: >90, men: >105 µmol/l) - *follow-up time* <1 year
Paper IV – Step 1 (Cohort Study)	- adult patients - *index treatment* – present - *index start*: 1980-2009 - *start creatinine* – present	- *start creatinine* above upper limit of the reference interval (women: >90, men: >105 µmol/l) - *follow-up time* <1 year - inconsequent data
Step 2 (Cases)	- *incident CKD 4+*	
Step 3 (Controls)	- 4:1 matching - same sex and *matched age group* at *matching year*, as cases - no CKD 4+ by *matching year*	

STATISTICAL METHODS

STATISTICAL SIGNIFICANCE TESTS

For means comparison, the independent samples t-test was employed for variables with normal distribution and the Mann-Whitney U test for those with non-normal distribution. Categorical variables were analysed using the Pearson Chi-square test. The Log Rank (Mantel-Cox) test was used to test the equality of survival times in survival analyses. In all analyses, a two-sided p-value of less than 0.05 was considered indicative of statistical significance.

SURVIVAL ANALYSIS

Survival analysis, or time-to-event analysis, is a statistical approach used to analyse survival time or the time until a particular event occurs in a cohort, over a specified period. This technique is versatile, applicable not only to studying mortality (time to death) but also other events such as healing, remission, disease progression, ischemic events, etc.

Key applications of survival analysis include:

- investigating the time to a defined event
- examining how potential predictive variables influence the time-to-event
- estimating the proportion of individuals that are event-free at the end of follow-up
- building predictive models for survival

In survival analysis, individuals are tracked from a defined starting point, such as the onset of exposure, until the study's conclusion or until they are lost to follow-up. Those experiencing the event are followed until its occurrence, while the others are followed until their last observation up to the study end. Individuals who do not experience the event are considered censored.

A notable advantage of this method is the incorporation of all patient time (or follow-up time), including that of censored individuals (Figure 3). The survival function infers that the probability of remaining event-free is the same for the censored individuals as for those who continue to be followed up, based on the assumption that the censoring is non-informative (or random).

The Kaplan-Meier curve is the graphical representation of the survival function over time, with the time plotted on the horizontal axis and the percentage of subjects free from outcome plotted on the vertical axis (Figure 4).

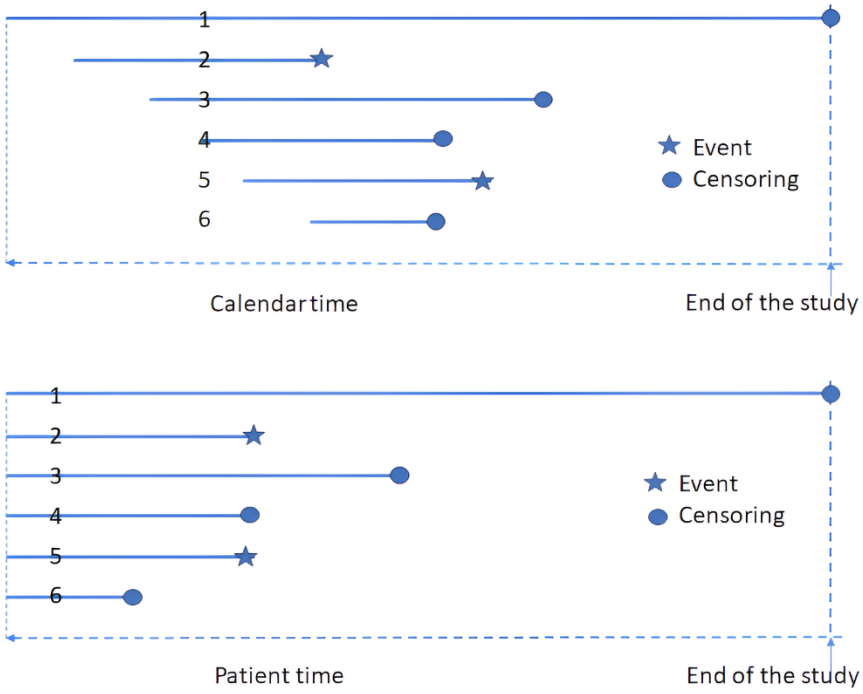

Figure 3. Calendar time (upper) versus patient time in the study (lower).

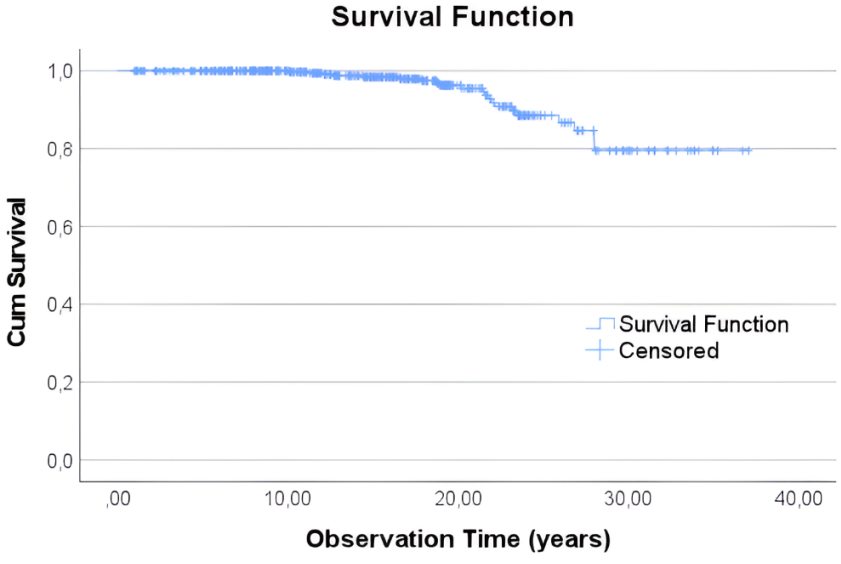

Figure 4 Example of Kaplan Meier curve (cumulative survival over time)

The Cox proportional hazards model, a multivariable regression method accommodating both categorical and continuous variables, is used to explore how presumed predictive variables affect the time-to-event. The outputs of the Cox model are Hazard Ratios (HR) - the ratios of the hazards between groups defined by different levels of the explanatory variables. Hazard, or hazard rate is defined as the instantaneous rate of occurrence of the event, given the subject has been event-free up to that time (Walters et al., 2021).

Survival analysis was employed in Papers II and III.

CUMULATIVE INCIDENCE ACCOUNTING FOR COMPETING RISKS

In survival analysis, the cumulative incidence of an event of interest over the follow-up period is typically calculated as '1 minus the survival function', and graphically depicted as the inverse of the Kaplan-Meier curve. This approach is good enough if there is no significant competing risk, i.e., an alternative outcome that precludes the event of interest, such as death from other causes. However, if a significant proportion of the censored population encounters a competing risk '1 minus the survival function' will overestimate the real cumulative incidence.

To address this limitation, the Cumulative Incidence Function (CIF) was constructed. It may be seen as a further development of survival analysis which effectively incorporates competing risks, thus providing more accurate estimates (Jeon & Lee, 2020). Alongside CIF, the subdistribution hazards model (Fine & Gray, 1999) may be utilised to assess the influence of covariates. This model, akin to the Cox proportional hazards model, accommodates both continuous and categorical variables, yielding Hazard Ratios (HR) as its output.

Lifetime risk corresponds to the cumulative incidence of the investigated event for the remaining life span of an individual or a studied patient group. When lifetime risk is determined for a group, it is therefore important that the group is reasonably age-homogeneous, and it typically spans 5-10 years of age intervals.

The use of CIF, accounting for the competing risk of death, was necessary in Paper IV, because a large proportion of the censored observations (approximately 30%) died before the end of the study.

CIF was used in Paper IV.

LOGISTIC REGRESSION

Logistic regression is a statistical method used to model the relationship between a binary outcome and one or more predictor variables, which may be either continuous or categorical. This technique applies the logit (or logistic) transformation to the outcome data and is suitable for analysing both randomised controlled trials (RCTs) and observational studies. It is particularly useful in case-control studies (Walters et al., 2021).

Logistic regression produces Odds Ratios (OR) as its measure of effect. Odds represent the likelihood of an event occurring relative to it not occurring. Although odds may not be inherently intuitive, they are a fundamental aspect of logistic regression, accepted for their utility in the absence of a more direct measure. In medical research, odds are useful to the extent that they can estimate risk. Provided the incidence of the outcome in the studied population does not exceed 10-20%, OR can serve as a reasonable approximation of the relative risk or risk ratio (Chen et al., 2010; Davies et al., 1998).

Logistic regression was employed in Paper IV.

ETHICAL APPROVAL

This project was approved by the Regional Ethical Review Board in Gothenburg on August 15th, 2015 (Dnr: 594-15) with an amendment approved on May 8th, 2018 (T378-18). Patient consent was not deemed necessary. The research adhered to the principles of the Declaration of Helsinki as revised in 1989.

SOFTWARE

Throughout the preparation of the thesis and the included papers, various software tools were employed for data processing, statistical analysis, and text enhancement:

- data processing: Microsoft Excel (versions 2007, 2010, and 2019), MatLab 2019a, and Python 2.7.
- statistical analysis: R version 4.3.1 with the cmprsk package version 2.2-11; Python 3.7.9, supplemented by numpy version 1.25.0, pandas version 2.0.1, and matplotlib 3.7.0; SPSS Statistics versions 23 and 28.0.1.0.
- text enhancement: ChatGPT-4 for improving the grammar, style, and clarity of the text.

DESIGN, RESULTS AND DISCUSSION

PAPER I

STUDY DESIGN

In Paper I, a cohort study design was employed. Patients were selected according to inclusion and exclusion criteria presented in Table 4, and operational parameters were calculated according to definitions presented in Table 3. The study focused on the following outcomes:

- yearly average compliance: calculated across the whole patient population for each calendar year, this metric represents the ratio between sum of individual compliant treatment-years to the total treatment-years.
- yearly average s-Li: calculated for the whole cohort from the pool of individual s-Li averages, for each calendar year.
- distribution of s-Li samples: analysed on a yearly basis, categorised by their value range.

These outcomes were analysed to understand their temporal evolution and implications. Gender disparities were also investigated.

RESULTS

The study encompassed 2,841 patients (1,700 women), accumulating 25,300 treatment-years and 92,786 s-Li measurements. The number of treatment-years per calendar year rose from 215 in 1981 to 1,202 in 1998, stabilising thereafter.

Yearly compliance with lithium monitoring guidelines increased from 36% in 1981 to 68% in 2010. This trend was consistent across genders, with women showing an approximately 2% higher compliance rate than men. A higher compliance rate (reaching 76% in 2010) was obtained when the threshold for compliant-status was increased to seven-month interval between two consecutive measurements of the same parameter (instead of six).

The yearly *average s-Li* decreased from 0.70 mmol/l to 0.58 mmol/l. Women consistently had slightly lower yearly *average s-Li* (0-0.04 mmol/l lower than men).

Most s-Li samples (87-94%) remained, throughout the study, within the therapeutic range of 0.3-0.9 mmol/l, as per Swedish recommendations from

2004 (Bendz & Aurell, 2004). Samples exceeding 0.9 mmol/l dropped from 11% in 1981 to 4% in 2010. A small proportion of samples (1-5%) were below 0.3 mmol/l. When the lower end of the therapeutic range was changed to 0.4 mmol/l to reflect the current standard, the percentage of subtherapeutic samples would become 4% in 1981, rising over time and stabilising at 13%.

DISCUSSION

The development of safety guidelines for lithium treatment monitoring was primarily based on accumulated clinical experience and knowledge. The guidelines have evolved over time and given the historical context of the study, it was important to identify and select the guidelines that were relevant in Sweden during the period under investigation.

In 2004, the first formalised Swedish safety guidelines for lithium treatment monitoring were published in the Swedish medical journal "Läkartidningen" (Bendz & Aurell, 2004). They advised monitoring s-Li and s-creatinine every 4-6 months, and the thyroid hormones, calcium and glucose blood concentrations, blood pressure, weight and daily fluid intake or urine osmolality - annually. Desmopressin tests (measuring RCA) and direct renal function measurements were recommended at least every five years. For maintenance therapy, the lowest effective s-Li level within the range 0.3-0.9 mmol/l was advised. This article was a crystallisation of the accumulated clinical experience and existing consensus for targeting lower lithium levels compared to those used before 1980, and was chosen as a benchmark for Paper I. The current guidelines of the Swedish Psychiatric Association recommend a s-Li range of 0.5-0.9 mmol/l (Adler et al., 2014), while some regional recommendations allow 0.4-1.0 mmol/l (Aiff & Aiff, 2016; "Regional Medicink Riktlinje - Läkemedel. Bipolär sjukdom," 2023).

Operationally, compliant status required a maximum six-month interval between two consecutive, identical measurements (i.e., s-Li or s-creatinine). Yearly average compliance allowing a seven-month interval between measurements was also calculated, as in real-life clinical practice, a few days' (or even weeks') delay of the scheduled blood tests in such cases would be generally inconsequential.

The development over time of the safety guidelines was also taken into consideration: the distribution of s-Li samples was recalculated using a 0.4 mmol/l cutoff for the lower therapeutic concentration limit, aligning with contemporary standards.

The primary findings of the study were an increase in yearly average compliance, reflecting an improvement in guidelines implementation, and a decrease in yearly average s-Li over the 30-year analysis period. The minor differences in compliance and average s-Li between women and men, although statistically significant, are likely clinically irrelevant. The declining proportion of supratherapeutic s-Li samples, coupled with the increasing proportion of subtherapeutic ones may be due to changes in recommendations, heightened awareness of lithium's long-term effects or attempts to minimise side effects.

Other studies investigating the adherence to lithium monitoring guidelines used different outcome measures, making the results difficult to compare. A 2008 French study (Bassilios et al., 2008) analysing eight years of data on 1,179 lithium-treated outpatients found that 41% had no s-creatinine measurements during the analysed period. The mean s-Li, however, did not differ significantly between patients with and without s-creatinine control.

In the UK, lithium monitoring patterns were examined before and after the implementation of a quality initiative. The compliance with biochemical monitoring improved after the three-year Quality Improvement Programme (Paton et al., 2013), but still fell short of national standards.

A recent Swedish study (Bosi, Ceriani, et al., 2023) found that 21% of 4,428 bipolar patients who started lithium treatment in 2007 did not undergo pretreatment s-creatinine testing. Additionally, the proportion of patients with annual s-Li and s-creatinine measurements declined from 79% in 2008 to 63% in 2018. This trend suggests that compliance with monitoring guidelines decreased as the duration of lithium treatment extended. In older patients, a renal function decline is expected with ageing, and adjustments of lithium doses may become necessary. Thus, the need for adequate monitoring becomes even more critical with passing of time in this patient group, making the findings of this study particularly concerning.

The inherent limitations of the operational definitions could have influenced the findings of Paper I. For instance, what was defined as *discontinuation periods* could have in reality been instances of extremely poor compliance, leading to an overestimation of *compliance*. Another consideration is the impact of missing data, which could have led to either an over- or underestimation of *compliance*, particularly in the earlier part of the study period.

PAPER II

STUDY DESIGN

A matched cohort study design was used in Paper II. The patient selection process involved two steps:

- defining the exposed cohort: patients with elevated pretreatment creatinine (women: >90µmol/l, men >105µmol/l) were selected based on criteria outlined in Table 4.
- formation of the reference cohort: patients in the exposed cohort were matched 1:1 with individuals who had normal creatinine levels at the start of lithium treatment. Matching criteria included sex, *age at start of Li treatment*, and *treatment duration*.

The primary exposure was defined as elevated *initial s-creatinine*, with the outcome of interest being *CKD 4+ diagnosis*. Survival analysis, employing Kaplan-Meier curves, were used to plot the survival curves (proportions surviving without CKD 4+) in the two cohorts, over the defined *follow-up time*. Cox proportional hazards model, adjusted for sex and *age at start of Li treatment*, was used to compare the risk of CKD 4+ between the two cohorts.

In the secondary phase of analysis, characteristics and background factors of patients in the *exposed cohort* were examined, focusing on differences between those who progressed to CKD 4+ and those who did not. Variables such as *age at start of Li treatment*, sex, somatic comorbidities, previous lithium use, and *Li intoxications* were compared and discussed.

RESULTS

In Paper II, 83 patients met the criteria for inclusion in the *exposed cohort*, leading to a total of 166 patients (83 in each of the cohorts). In the *exposed cohort*, 40 patients progressed to CKD 4+, compared to eight in the *reference cohort*. After adjusting for matching parameters (sex, *age at start of Li treatment*, and *treatment duration*), the hazard ratio for *incident CKD 4+* was HR = 6.7 (95% CI 3.1-14.3, $p < 0.001$) in the *exposed cohort* compared to the *reference cohort*.

There were no significant differences between the cohorts in terms of matching variables, *time on Li*, *AUC*, or instances of *Li intoxication*. The *reference cohort* exhibited a higher *mean s-Li* than the *exposed cohort* (0.58 mmol/l versus 0.54 mmol/l). Eleven patients in the *exposed cohort* progressed to RRT,

while none did in the *reference cohort*. During the *follow-up time*, 58 deaths occurred in the *exposed cohort* and 51 in the *reference cohort*; however, these differences were not statistically significant, nor was the average age at death (79.5 years in the *exposed* versus 76.1 years in the *reference cohort*).

Comparing the *progressors* (n=40) and *non-progressors* (n=43) within the *exposed cohort*, the *progressors* were older at *first s-Li* (67.4 versus 55.5 years), had a higher burden of somatic comorbidities, and included a larger proportion of women. They were also more likely to have used lithium prior to the study period, as per medical records (43% of *progressors* versus 7% of *non-progressors*). *Initial s-creatinine* levels were similar between the groups, but *progressors* experienced a more rapid decline in kidney function during the study (eGFR decline of -2.7 versus -0.3 ml/min/1.73 m²/year).

DISCUSSION

The *exposed* patients exhibited an almost sevenfold increased risk of developing CKD 4+ compared to the *reference cohort*. Furthermore, 13% of the *exposed cohort* (11 out of 83 patients) progressed to RRT, while none in the *reference cohort* did. On the other hand, over 50% of the *exposed* patients, despite their pre-existing renal impairment and extended follow-up time, did not develop CKD 4+. It is in the eye of the beholder to decide if the bottle is half full or half empty, when evaluating the risk size and the proportion of *exposed* patients reaching (or not) CKD 4+.

The progression to CKD 4+ in both cohorts occurred steadily over two decades. The total lithium exposure, measured as *AUC*, was similar between the *exposed* and *reference cohorts*. The elevated risk of CKD 4+ in the *exposed cohort* is thus most likely attributable to pre-existing health conditions rather than lithium treatment itself. However, the specific impact of lithium treatment on renal outcomes in the presence of other renal risks factors or conditions remains uncertain. It is not clear whether lithium acts synergistically, additively, or independent of these factors.

The studied population was older than those reported in other studies. The average *age at start of Li treatment* in Paper II was 61.2 years in the *exposed cohort* and 60.9 years in the *reference cohort*. In contrast, the average (or median) age at initiation of lithium treatment reported in other studies typically ranges between 40 and 50 years (Bosi, Clase, et al., 2023; Close et al., 2014), with some studies reporting average ages even below 40 (Højlund et al., 2022).

It is likely that the benefits of lithium treatment were assumed to outweigh the increased renal risk for patients in the *exposed cohort*. This perspective becomes particularly relevant when psychiatric symptoms are severe, and patients might consider the risk of CKD 4 or even ESRD as an acceptable trade-off for a substantially improved quality of life. An illustrative example is provided by an English case study (Belgamwar et al., 2010), describing a 73-year-old woman who discontinued lithium after 20 years of treatment due to severe kidney disease (eGFR 28 ml/min/1.73 m²). However, she chose to resume it two years later due to frequent and severe mood episodes and hospitalisations, as well as a serious deterioration of her quality of life, despite having tried other mood stabilising agents and ECT.

A notable limitation of Paper II is the definition of CKD 4+, based on a single eGFR, which could have led to an overestimation of CKD 4+ incidence. Additionally, previous lithium treatment outside the observation period, (identified through review of the medical records), may have introduced a selection bias.

PAPER III

STUDY DESIGN

A cohort study design was used in Paper III, with patient recruitment based on criteria listed in Table 4. Patients were organised into three time-based cohorts according to the calendar decade of their *index start*: Cohort 1 (1980-1989), Cohort 2 (1990-1999), and Cohort 3 (2000-2009). Patients were followed up ten years after *index treatment*.

The primary outcome of the study was *incident CKD 4+*, with cohort affiliation serving as the main exposure variable. Survival analysis with Kaplan-Meier curves and Time to event analysis were employed to plot the cumulative incidence of CKD 4+ and to estimate survival times. The equality of survival times across cohorts was assessed using the Log Rank (Mantel-Cox) test. Furthermore, a Cox proportional hazards model, adjusted for baseline covariates such as sex, *age at index start*, and *s-creatinine at index start*, was utilised to investigate the association between the decade of *index start* and the risk of *incident CKD 4+*.

The null hypothesis stated that there would be no significant difference in Survival times across the three cohorts.

RESULTS

The study comprised 2,169 patients: 623 (398 women) in Cohort 1, 874 (512 women) in Cohort 2, and 672 (406 women) in Cohort 3.

There was a notable improvement in mean *compliance* across cohorts (from 75% in Cohort 1 to 89% and 93% in Cohorts 2 and 3, respectively), while *mean s-Li* decreased progressively (0.64, 0.60, and 0.58 mmol/l in Cohorts 1, 2, and 3, respectively), with differences being statistically significant.

During the follow-up, 22 CKD 4+ events were recorded: seven in Cohort 1, ten in Cohort 2, and five in Cohort 3. Survival Time did not differ significantly among the cohorts. Cox proportional hazards model, adjusted for sex, categorised *age at index start*, and categorised *s-creatinine at index start*, indicated no significant risk difference for CKD 4+ across the cohorts. *Age* and *s-creatinine at index start*, but not sex, were strong predictors for CKD 4+.

DISCUSSION

It was hypothesised that a difference in the risk of CKD 4+ among the three chronologically defined cohorts would be detected. More specifically, it was expected that the newest cohort would exhibit the lowest risk. As the study did not differentiate between the causes of CKD 4+ in the identified cases, two assumptions underpinned this hypothesis:

- the first assumption was that enhanced management of lithium treatment, characterised by stricter monitoring and lower average s-Li levels (as noted in Paper I), might have contributed to a decreased risk of lithium-induced CKD progression in the studied population.
- the second assumption was that the incidence of CKD 4+ due to other causes (primarily HT and DM) has either decreased or at least not increased during the study period in the target demographic.

The first assumption was based on the results of Paper I, which were reconfirmed here: improved *compliance* and lower *mean s-Li* levels over time were observed across the cohorts; however, no significant difference in the median survival times (or hazard rates for CKD 4+) between the three cohorts was observed.

The latter assumption may require clarification. DM and HT are primary risk factors and leading cause for CKD 4+ in the general population (Webster et al., 2017). It was assumed that the control of these conditions has substantially

improved over recent decades due to availability of more effective treatments and enhanced management guidelines. For instance, significant advancements in DM care, including the development of long-term and medium-term insulin products, user-friendly insulin pumps and monitoring devices have occurred since the 1980s (Deeb, 2008). The blood pressure control has improved, particularly in the elderly (Törmä et al., 2015), while the management of hyperlipidaemia has evolved with the introduction of statins, a highly effective class of lipid-lowering drugs not available in the 1980s. Lifestyle factors (smoking, exercise, eating habits impacting body weight) may play a role as well, but their impact is more challenging to quantify.

However, despite better disease control, the prevalence of DM has risen (Ringborg et al., 2008), potentially affecting CKD incidence in the opposite direction. Population ageing is another critical factor, likely increasing the incidence of CKD 4+ as more individuals live long enough to develop the condition. Quantifying these trends' net effect is not trivial, however, it appears that the incidence of CKD in the general population has actually increased worldwide over the last three decades (Ying et al., 2024). Furthermore, a recent Swedish study indicates that renal function in the general population in Northern Sweden deteriorated between 1986 and 2014 (de Man Lapidoth et al., 2023), and there are no reasons to believe the trend would have been different in Western Sweden.

Thus, contrary to the initial second assumption, it is reasonable to consider that the incidence of stage 4 CKD due to causes other than lithium may have actually increased in the study population over the observation period. This could offset potential reductions in lithium-related CKD 4+ cases, providing a plausible explanation for the findings. Another possible explanation could be that the improved monitoring and decreasing s-Li levels, in the range observed in the study, did not significantly impact the incidence of CKD 4+ during the follow-up period. Additionally, the small number of events (22 cases of *incident CKD 4+*) might have been too low to detect any significant differences. These possible explanations are not mutually exclusive, and the absence of observable differences over 10 years does not preclude the possibility of differences emerging over an extended follow-up.

The study has several limitations. Selection bias due to lithium treatment prior to the observation period cannot be ruled out. The low outcome count (22) may cause the regression model to be overfit and indicates a risk that the failure to reject the null hypothesis could stem from insufficient power of the study.

Furthermore, the Cox regression model was not adjusted for variables like comorbidities, concurrent medications, and socio-economic status.

PAPER IV

STUDY DESIGN

Paper IV comprised two studies: a cohort study and a case-control study.

COHORT STUDY DESIGN

This study estimated the age-specific lifetime risk and cumulative incidence of CKD 4+, accounting for the risk of competing deaths, in a cohort of patients constructed according to the criteria outlined in Table 4. Participants were categorised into six *start age* groups: 0 (18-34), 1 (35-44), 2 (45-54), 3 (55-64), 4 (65-74), and 5 (≥75 years). For all *start age* groups, age-specific cumulative incidence was determined at 5-year intervals for up to 35 years of follow-up. For groups aged ≥55 years, age-specific lifetime risk (for a life expectancy of 90 years) was also determined. The impact of baseline covariates (sex, *start age* group, *start creatinine*) was analysed using the Fine-Gray subdistribution hazards model. *Start creatinine* was divided into three categories based on the reference interval's thirds.

CASE-CONTROL STUDY DESIGN

The second part of Paper IV employed a 1:4 retrospective case-control design. All CKD 4+ patients were included as cases. Matching was based on sex, *matching year* (calendar year of CKD 4+ diagnosis) and *matched age* (age at *incident CKD 4+*), categorised into four groups: 0 (40-59 years), 1 (60-69 years), 2 (70-79 years), and 3 (≥80 years). A pool of eligible controls without *incident CKD 4+* by *matching year* was constructed for each case and four controls were subsequently randomly selected from each pool.

The primary exposure was *time on Li*, with *incident CKD 4+* as the outcome of interest. Logistic regression, adjusted for matching variables (sex, *matching year*, *matched age group*) and categorised *start creatinine*, was used to assess the association between *time on Li* and *incident CKD 4+*. *Time on Li* was evaluated as both a continuous variable and in various categorical patterns.

RESULTS

The cohort study encompassed 2,381 patients, including 1,450 (60.9%) women. The mean follow-up duration was 14.9 years with an average *time on*

Li of 9.7 years. The number of *incident CKD 4+* cases and RRT cases identified during 35,453 observation years covering 23,120 years of lithium exposure were 103 and 15, respectively.

No *incident CKD 4+* occurred in patients below 40 years of age, 8.7% occurred in patients aged 40-59 years and 63.1% occurred in patients over 70 years.

The *CKD 4+ patients* exhibited a high prevalence of somatic comorbidities, with 84 of 100 patients for whom medical records were available, having at least one such comorbidity.

The age-specific cumulative incidence of CKD 4+, taking into account the competing risk of death, for patients < 55 years and for the whole cohort, are presented in Table 5.

Table 5 Age-specific cumulative incidence of CKD 4+, taking into account the competing risk of death, for start age groups <55 years

	Estimate (%)						
Start Age Group	**Follow-up time (years)**						
(years)	**5**	**10**	**15**	**20**	**25**	**30**	**35**
18-34	0	0	0	0.6	0.6	4.2	9.6
35-44	0	0.7	0.9	3.2	6.5	11.3	13.3
45-54	0	0	1.5	3.2	8.8	14.3	14.3
All patients (18- ≥75)	**0.2**	**1.1**	**2.4**	**4.5**	**7.2**	**10.9**	**13.2**

Lifetime risk estimates of CKD 4+, considering a life horizon of 90 years, in patients starting lithium after 55 years were: 13.9% for *start age* 55-64, 18.6% for *start age* 65-74 and 5.4% for *start age* ≥75 years.

The Fine-Gray subdistribution hazards model revealed that *start age* and *start creatinine* (categorised) were significant predictors of risk of CKD 4+, while sex was not.

The 1:4 matched case-control study included 515 patients, comprising 103 cases and 412 controls. There was no significant difference between cases and controls in terms of matching variables, *start age*, and *mean s-Li* levels. However, *start creatinine* levels showed a significant difference, with a higher proportion of cases having *start creatinine* in the upper third of the reference interval, and fewer in the lower third.

The logistic regression model, adjusted for matching variables and *start creatinine*, indicated a significant association between lithium exposure (*time on Li*) and *incident CKD 4+*. This association held across all categorisation patterns and when treating *time on Li* as a continuous variable. Individuals with *time on Li* 5-20 years had an OR for developing CKD 4+ of 2.29 compared to those with *time on Li* 1-5 years. Individuals with *time on Li* over 20 years had an OR for progressing to CKD 4+ of 5.85 (compared to the same reference category *time on Li* 1-5 years).

DISCUSSION

In patients who commenced lithium treatment after the age of 55, the highest lifetime risk of CKD 4+ was observed in the 65-74 age group. Conversely, individuals initiating lithium therapy at 75 years or older exhibited a much lower lifetime risk. This difference was striking, raising the question of whether it resulted from estimation errors due to a small sample size, or if it reflects a genuine difference, possibly because many older individuals do not survive long enough to experience an advanced-stage CKD.

Estimating lifetime risk for individuals who began lithium treatment before the age of 55 was not feasible, due to insufficient follow-up time. Instead, only the cumulative incidence, expressed in 5-year intervals, was estimated for these younger *start age* groups. No cases of CKD 4+ were observed in these patients during the first 5 years after starting lithium, with the cumulative incidence remaining low during the initial 10-15 years.

Lifetime risk estimates for CKD 4+ of up to 18.6% may seem high, but it is important to interpret these figures within a broader context. Ideally, they should be compared with estimates for same-age bipolar patients treated with different mood stabilisers. However, such comparative data are currently unavailable, and lifetime risk estimates for the general population are also limited. European data from a study in Iceland (Inker et al., 2015) exist, but the lifetime horizon considered in that study was shorter, thus rendering the results not directly comparable with those in Paper IV. A US study estimated the risk of CKD stage 4 or higher in the general population, assuming an expected lifetime of 90 years, to be around 9.9-10.5% for white men and 11.1-11.8% for white women aged 50-80 years. Higher rates were observed in the Black population (Grams et al., 2013). While not suggesting a direct comparison to the results presented in Paper IV, these data offer some perspective.

Compared to the general population, a higher lifetime risk of CKD is expected in lithium-treated individuals, partly due to lithium exposure and partly to the increased burden of somatic comorbidities recognised in patients with mood disorders (Arnaud et al., 2022; Goldstein et al., 2009; van Winkel et al., 2008).

In the general population, the incidence rate and prevalence of advanced CKD stages escalate with age (Kovesdy, 2022; van Blijderveen et al., 2014). Although Paper IV did not specifically focus on these epidemiological measures, a similar age-related pattern was observed in this lithium-treated cohort: *incident CKD 4+* occurred mostly in older individuals, with over 60% of cases occurring in those aged 70 and above.

The results of the case-control study demonstrated a clear association between longer lithium exposure (*time on Li*) and increased risk of CKD 4+, particularly pronounced for exposures exceeding 20 years. This is consistent with the results of other studies (Fransson et al., 2022; Højlund et al., 2022).

The strength of the study lies in its extensive duration, necessary for detecting outcomes such as CKD 4+. Additionally, it provides risk estimates in an easily understandable format.

Several factors might have biased the results. Selection bias due to previous lithium treatment outside the follow-up period cannot be dismissed. Moreover, censoring may not have been entirely non-informative. In Sweden, routine annual examinations for individuals without any somatic health issues are not standard practice. Subjects who discontinued lithium treatment, and had normal renal function at lithium cessation, were probably not monitored further and were therefore censored in the analysis. On the contrary, individuals who ceased lithium treatment and continued to contribute s-creatinine test results were likely to have had renal function impairment or other health concerns. In other words, patients who were censored early on (and remained alive) were more likely to have had adequate renal function and, therefore, a lower risk of CKD 4+ compared to those remained under follow-up a longer time. Thus, potential non-random censoring, coupled with a large number of deaths treated as censorings, could have inflated the estimated cumulative incidence figures.

Additionally, the formula used to calculate eGFR may have impacted the results. Paper IV employed the RLM formula for GFR estimations, which tends to identify more CKD 4+ cases in older individuals compared to other

eGFR formulas, more frequently used internationally, such as CKD-EPI and MDRD (Malmgren et al., 2015)

It is worth noting that while the cumulative incidence estimates for the entire study population seems reasonably precise, the estimates for each *start age* group are characterised by relatively large standard deviations (SDs), indicating a lower precision. Furthermore, the logistic regression model was not adjusted for factors such as comorbidities, co-medication, and socio-economic status, which could have influenced the strength of the observed association (OR).

GENERAL DISCUSSION

CHOICE OF OUTCOME AND ESTIMATION METHOD

CHOICE OF OUTCOME

Most studies exploring the association between lithium and CKD have focused either on 'softer' endpoints (such as CKD 3 or decline in estimated GFR), or, alternatively, on the most critical outcome: end-stage renal disease (ESRD) requiring RRT. The former are mainly indicators or markers of disease process, but most often would not prompt a decision to stop lithium.

Lithium stands out as the most efficacious treatment in preventing mood episodes in individuals with bipolar disorder. Termination of lithium treatment, even when replaced with other mood stabilisers, is often associated with increased risk of relapse and associated fallouts (Baldessarini et al., 2019; Belgamwar et al., 2010; Kumar et al., 2023). The objective here was to select a renal outcome with significant implications for health, quality of life, and life expectancy—consequences serious enough to consider discontinuing lithium therapy or even to refrain from prescribing it in the first place.

In order to identify the most pertinent renal outcome, first, the repercussions of inadequately controlled bipolar disorder were reviewed. Next, the effects of various levels of renal function impairment were assessed. Finally, the level of renal impairment that aligns most closely with the consequences of uncontrolled bipolar disorder was selected.

Mood disorders, when poorly controlled, may profoundly affect an individual's life, being linked to: impaired functioning, lower educational

attainment, substance abuse, negative impact on family life, unemployment, economic hardships, hospitalisations, suicide attempts, and completed suicides (Fajutrao et al., 2009; Hakulinen et al., 2019; Lundberg et al., 2022; Plans et al., 2019). Patients with severe mood disorders, have been consistently found to have a high burden of psychiatric and somatic comorbidities, and a roughly 10 to 13 years shorter life expectancy compared to the general population (Chan et al., 2023; Momen et al., 2022; Pan et al., 2020).

The onset of bipolar disorder typically occurs in late adolescence to early adulthood, affecting individuals during their most productive life period. In contrast, CKD primarily affects older individuals (Kovesdy, 2022; van Blijderveen et al., 2014). A study from Canada (Liu et al., 2021) found that in a large cohort of patients diagnosed with CKD, 75% were aged 65 years or older and had eGFRs between 45-59 ml/min/1.73 m², with normal or mild albuminuria. Their 5-year risk of kidney failure and death was comparable to individuals without CKD, suggesting that many elderly patients diagnosed with CKD 3 may not experience a significant decline in quality of life (QoL) or life-years loss (LYL).

As the severity of CKD increases, its impact on quality of life becomes more pronounced. Patients with CKD 4 exhibit lower energy, vitality, physical and social functioning than both healthy individuals and patients with CKD 2-3, while patients with CKD 5 present a further deterioration (Pagels et al., 2012). However, only a minority of CKD patients will reach ESRD (Evans et al., 2018). A US study that estimated the lifetime incidence of CKD at various stages (Grams et al., 2013), indicated that for young and middle aged individuals, the lifetime risk of ESRD is only a fraction of their lifetime risk of reaching CKD 4: 16-36% for white individuals and 37-54% for the Black population.

All things considered, stage 4 CKD was deemed the most relevant outcome because it best matches, qualitatively and quantitatively, the consequences of poorly controlled mood disorder. It is also the level of renal function loss at which, regardless of the cause of CKD or the patient's age, a nephrologist must be involved, if this hasn't been done already. Nonetheless, a possible decision to continue or discontinue lithium should ideally be made by the patient in collaboration with their psychiatrist, with the nephrologist having a consultative role.

It is important to acknowledge that CKD 4 is an adequate choice of outcome for a large majority of patients; however, it is not suitable for all. In younger patients, even lower stages of CKD may result in a diminished QoL (Pagels et al., 2012) and, notably, a poor prognosis regarding life expectancy (Turin et al., 2012). This highlights a limitation inherently linked to the deficiencies of the current CKD-definition system, which fails to account for age differences.

CHOICE OF METHOD FOR GFR ESTIMATION

Among the various GFR estimation equations, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and The Modification of Diet in Renal Disease (MDRD) are most widely used, particularly in research settings. The Berlin Initiative Study-1 Equation (BIS) and European Kidney Function Consortium (EKFC) are newer models developed to address limitations of older equations and enhance accuracy of estimates in the elderly.

The revised Lund-Malmö (RLM) equation was developed in Sweden and is commonly used in clinical settings here, being incorporated into the most widely used electronic medical records systems. The RLM equation demonstrated good accuracy across various age and BMI intervals within the Swedish population, outperforming the internationally more established CKD-EPI and MDRD formulas (Björk et al., 2011; Nyman et al., 2014).

The RLM equation was selected for GFR estimation in this project, on the basis of its superior performance within the target demographic. When comparing the results of different studies, it is important to bear in mind that different estimation equations might yield different outcomes. The RLM formula, which incorporates variables such as sex, age, and s-creatinine, is readily accessible as an online calculator (Grubb, 2023).

ETHICAL CONSIDERATIONS

SECONDARY USE OF (ANONYMISED) HEALTH DATA FOR RESEARCH PURPOSES WITHOUT INFORMED CONSENT

The papers included in this thesis utilised patient data from the laboratory database of Sahlgrenska University Hospital, supplemented by data from medical records. Collected primarily for individual healthcare needs, the health data served a secondary purpose in this research, which has been granted ethical approval without the need for patient consent.

The use of anonymised health data without specific patient consent is a topic on which opinions may vary. On one side, there is the argument that patients should have the right to control how their personal health information is used. Practical concerns also exist, particularly regarding the risk of de-anonymisation during data handling, which could compromise patient privacy. Nevertheless, anonymised patient data represent a vital resource for research, offering insights and knowledge that might be otherwise unattainable. In many instances, obtaining individual patient consent is not practical, especially in studies involving deceased patients or large datasets.

Sweden has a long tradition of maintaining comprehensive population-based registries. Several authorities hold registries with mandatory participation, with no provision for individual opt-out. Notably, there has been little, or indeed no public debate concerning the ethical implications of this compulsory participation. Other repositories of health data are national quality registries (where participation is voluntary) and healthcare providers (which maintain health databases necessary for their primary activity).

Health data may not be released without approval from the Ethical Research Board, which is a prerequisite in order to conduct research in Sweden. For large-scale studies utilising registry data, patient consent is typically not required. This practice is based on an assumed general willingness of Swedish people to contribute their data to research endeavours (Ludvigsson et al., 2015), confirmed by a recent study showing a high level (80%) of trust in the institutions' dealing with health data (Belfrage et al., 2022). Despite these positive public attitudes in Sweden, legal and bureaucratic barriers have so far restricted the use of health data for research purposes. This has been increasingly viewed as a significant obstacle to healthcare system improvements. Recently, a governmental investigation concluded, proposing measures to simplify the secondary use of health data (Regeringen, 2023).

In the UK, patients have the right to opt-out from the use of their health data for research and planning purposes, however a recent study indicated that more than 75% of the public did not know about their opt-out right. The use of patient data without consent was considered acceptable by the UK public as well, provided it benefited patients and public, but the need for transparency was emphasised (Atkin et al., 2021).

In summary, evidence suggests that in Sweden and the UK, the public largely supports the secondary unconsented use of health data for research purposes,

if the data usage directly contributes to patients' welfare and that there is transparency in its application.

TOO MUCH FOCUS ON LITHIUM'S RENAL SIDE EFFECTS – DO WE RISK THROWING AWAY THE BABY WITH THE BATHWATER?

The relationship between lithium use and the risk of CKD has been explored and debated extensively over the last two decades. This has enriched our understanding of the issue, yet, focus on negative effects might fuel the negative perceptions about lithium, potentially aggravating its underutilisation and depriving patients of a treatment that could be life-saving.

Repeatedly, experts have highlighted lithium's underuse, despite its recognised efficacy (Gomes et al., 2022; Kessing, 2024; Malhi et al., 2023; Post, 2018; Zivanovic, 2017). An international online survey (Hidalgo-Mazzei et al., 2023) involving 886 respondents, predominantly psychiatrists, found that 74% considered lithium their first-choice maintenance treatment for bipolar disorder, yet, 55% of those favoring lithium harboured concerns about lithium's long-term renal effects. Clinicians who did not favour lithium cited negative beliefs and perceptions among patients as the main reason for their stance. Based on the answers received, the authors concluded that lithium is prescribed in more than 50% of patients with bipolar disorder.

However, actual prescription patterns tell a different story. A cross-sectional analysis including 10,351 bipolar patients enrolled in clinical studies in 11 research centres between 1998 and 2020 (Singh et al., 2023) revealed that only 29% were on lithium at the time of enrolment. North American sites had the lowest lithium prescription rates (27% for bipolar I and 16% for bipolar II), with Australian sites slightly higher (35% and 25%, respectively). European sites reported the highest prescription levels (44% for bipolar I and 29% for bipolar II). The prescription pattern is likely to vary widely even among European countries. According to data from the Swedish bipolar registry (*BipoläR (Swedish National Quality Register for bipolar disorder)*, 2023), 58% of Swedish patients with bipolar I disorder were prescribed lithium in 2023, while in Germany, 30.8% of bipolar patients (type not specified) were prescribed lithium in 2021 (Kriner et al., 2023).

The relatively low prescription rates worldwide suggest a need to reevaluate the balance between acknowledging lithium's renal risks and leveraging its therapeutic potential. While lithium's renal side effects raise legitimate concerns, it is essential to recognise that alternative mood-stabilising

psychopharmaceuticals also carry a risk of significant adverse effects. In fact, most medication used in bipolar disorder appear to increase the risk of CKD (Højlund et al., 2020; Kessing et al., 2015b; Nestsiarovich et al., 2019), with polypharmacy having the highest risk compared to 'no medication' (Nestsiarovich et al., 2019). Additionally, valproate is known for its liver toxicity and teratogenic effects, antipsychotics appear to increase the risk of stroke (Wang et al., 2012), while widely-used SGAs like olanzapine and quetiapine are frequently linked to weight gain, hyperlipidaemia and DM (Vancampfort et al., 2016). Akathisia, a distressing feeling of inner restlessness (Poyurovsky, 2010) that not seldom is reason for terminating the treatment, is a frequent side effect of the newer SGA such as aripiprazole and cariprazine.

The fact that all mood stabilisers, including lithium, are associated with various short- and long-term side effects is not controversial. However, the research focus has disproportionately emphasised the lithium-associated side effects, possibly contributing to its underutilisation. This skewed perspective raises ethical questions about the societal benefits of research. Curtailing research on lithium is certainly not a viable solution, however, there is a need for a more balanced approach that accurately reflects the clinical reality of all mood stabilisers.

PROVIDING RELEVANT INFORMATION TO PATIENTS

Patients expect to receive accurate and balanced information that helps them understand the different choices, especially when selecting chronic medications. However, effectively implementing this in practice presents several challenges. Key among these are respecting patient priorities, remaining objective without letting personal beliefs influence the information presented, and explaining alternative risks in a comprehensible manner.

A Dutch study (Kerckhoffs et al., 2018) exploring the experiences of ten patients with lithium-associated ESRD highlighted significant gaps in this process. The majority of these patients, who had been on lithium for an average of 25 years, perceived their treatment, monitoring, and information processes as inadequate. They felt deprived of appropriate information and choices, describing the decision-making as paternalistic rather than patient-centred. This study, published in 2018, possibly reflects practices from an era dominated by an authoritative approach in healthcare, preceding the current patient-centred and collaborative model. It is also important to consider potential biases such as: the influence of high emotional states at the time of decision-making, recall bias, evolving patient preferences, and psychodynamic

defence mechanisms, all of which could have led to inaccuracies in patients' recollections and descriptions of their experiences.

However, one key concern emerged as most compelling among all patients, namely the need for more information. Patients emphasised the importance of receiving detailed information at the initial decision-making stage, but also the need for regular repetition. Some suggested that providing handouts and allowing more time for decision-making would be beneficial, while others mentioned the preference to have a friend or relative present when treatment decisions are made (Kerckhoffs et al., 2018).

To complicate matters further, effective communication requires time, a resource that is notably limited. Recently, serious concerns have been raised about the feasibility of strictly adhering to all relevant clinical guidelines, due to physicians' time constraints (Johansson et al., 2023). The concept "time needed to treat" has been coined to emphasise that every act of healthcare consumes a portion of the physician's finite working day. Utilising written materials, standardised for clarity and readability, as a supplement to verbal communication, may be an effective strategy. To ensure the delivery of unbiased information, clear information sheets should ideally be made available for all mood stabilisers, to prevent lithium from being unjustly singled out as the 'dangerous' treatment option.

CLINICAL SIGNIFICANCE OF FINDINGS

The findings and their clinical utility should be considered alongside existing knowledge and results from other studies. A key takeaway is the importance of adhering to the guidelines for lithium treatment monitoring. Paper I indicated improved compliance over the period 1980 to 2010 in the Gothenburg area. However, the more recent study from Stockholm (Bosi, Ceriani, et al., 2023) revealed a concerning decline in compliance after 2008, in other parts of Sweden. This shift warrants attention and action to reinforce diligent monitoring practices among both clinicians and patients. The observation in Paper III that improved compliance did not necessarily translate into better renal outcomes during the first ten years after lithium start should not undermine the compliance-goal, but should rather highlight the importance of managing all potential renal risk factors. Besides, a longer follow-up period may reveal a different picture.

Paper IV showed that the lifetime risk of CKD 4+ in lithium-treated patients (arguably most of them with bipolar disorder), appears higher than in the

general population. A clearly increased risk of CKD 4+ with prolonged lithium use was also found, thus supporting the proposition that lithium per se is a risk factor for severe renal disease. Compared to the general population, the increase in lifetime risk could be regarded as moderate, but one should bear in mind that some of the risk is inherently linked to the extra burden of somatic comorbidities in this patient group.

In younger adults with normal pretreatment s-creatinine, lithium treatment managed according to modern guidelines was not associated with any notable risk of severe renal impairment in the short and medium term (up to 5-10 years).

However, elevated pre-lithium creatinine, as shown in Paper II, was associated with a considerably increased risk of CKD 4+. While not an absolute contraindication for lithium use, elevated baseline creatinine signals the need for a thorough risk-benefit analysis in this patient group. Cooperation with somatic specialists for optimal management of the associated comorbid conditions should definitely be considered.

The nature of lithium's potential renal impact, whether additive, synergistic with, or independent of, other risk factors, remains unclear. A ‘safety first’ approach should be advised, involving assertive control of all risk factors for CKD, including DM, HT, blood lipid levels, and optimisation of medication, along with regular monitoring of lithium levels and renal function. Aiming for the lowest effective lithium concentration without compromising its efficacy should also be considered.

GENERAL STRENGTHS AND LIMITATIONS

STRENGTHS

Large sample size and extended follow-up: The project database encompasses over 2000 participants with follow-up periods of up to 37 years. This extensive follow-up is mandatory for identifying patterns and associations of severe renal outcomes that develop slowly.

Accurate diagnosis: The diagnosis of CKD 4+ was based on actual creatinine values rather than medical records, in which a diagnosis may sometimes be delayed or missing. This ensures greater accuracy of the findings.

Clinical applicability: The results are easy to grasp, with potential application in individual risk assessment and patient communication.

LIMITATIONS

Inherent observational design challenges: As with any observational study, there are inherent limitations. These include potential data gaps, such as periods from the beginning to the mid-1980s with missing data or selection bias due to lithium treatment outside the study period. Additionally, the operational definitions might not perfectly align with reality, leading to potential information bias in exposure and covariate calculations. For example, active treatment periods (time on lithium) were defined based on presence of s-Li, and not on dispensed medication.

Limited data on important covariates: Data on comorbidities and psychiatric diagnoses were incomplete, and there was no information on variables such as co-medication, smoking, obesity, and socio-economic status. These factors are important covariates and some of them are known risk factors for CKD.

Limited generalisability: The findings and conclusions are primarily applicable to settings with similar lithium treatment protocols. This includes recommendations for target s-Li concentrations, biochemical and clinical monitoring, and general management practices.

SUMMARY AND CONCLUSIONS

SUMMARY

Paper I: From 1980 to 2010, compliance with lithium monitoring guidelines in Sweden improved, and the average s-Li level decreased. The reduction in average s-Li levels over time might be explained by changes in the target levels recommended by guidelines for monitoring lithium treatment.

Paper II: Individuals with impaired renal function, reflected in elevated pretreatment s-creatinine, who started lithium treatment faced an almost sevenfold increased risk of developing CKD 4+ compared to age- and sex-matched peers with normal creatinine levels at lithium initiation. Elevated pretreatment creatinine was also linked to a higher risk of RRT. Since current lithium exposure was similar in both groups, the risk disparity is likely attributable to factors other than lithium, such as pre-existent somatic comorbidity.

Paper III: The ten-year cumulative incidence of CKD 4+ remained steady at about 1% in a population treated with lithium between 1980 and 2017. Despite improved adherence to the lithium safety guidelines and advances in the management of somatic comorbidities, the risk of CKD 4+ was unchanged over the studied period. A possible explanation is increased incidence of CKD, of causes not related to lithium, in the general population. Pretreatment creatinine and age were predictors for CKD 4+.

Paper IV: The cumulative incidence for CKD 4+ in patients with normal pretreatment creatinine is age-specific, with marked differences between age groups. In younger patients (below 55 years at the start of treatment), the 5-year cumulative incidence for CKD 4+ was zero, and it remained negligible at 10 years. The lifetime risk (estimated for the older age groups) was higher than in the general population. More than 63% of the incident CKD 4+ cases occurred in patients 70 years and older. Patients who developed CKD 4+ had a significant burden of somatic comorbidities. A clear association was observed between longer lithium exposure (over five years) and increased risk of CKD 4+, especially for treatment lasting 20 years or more. Pretreatment creatinine level, even when within the reference range, was a significant predictor for CKD 4+.

CONCLUSIONS

Lithium as a risk factor: The findings corroborate the notion that lithium treatment per se poses a risk of severe renal function impairment.

Moderate excess risk with normal pretreatment creatinine: In patients with normal pretreatment creatinine, the excess risk of severe renal impairment among lithium users, compared to the general population, appears to be moderate. Lithium treatment should not be withheld in individuals with normal pretreatment creatinine levels out of excessive fears of renal side effects.

Considerable risk with elevated pretreatment creatinine: While elevated s-creatinine is not an absolute contraindication for lithium use, it requires a detailed risk-benefit analysis in each case due to a substantial increased risk of severe renal impairment in this patient group.

Age, pretreatment creatinine, and length of lithium exposure - important predictors: Age at lithium start correlated with both short- and medium-term risk, as well as with lifetime risk of severe renal impairment. Pretreatment creatinine had predictive value, even in follow-up as long as 35+ years. Prolonged lithium exposure, particularly beyond 20 years, was associated with an increased risk, while sex was not a predictor.

FUTURE PERSPECTIVES

The field of research, the research around lithium not the least, is fascinating. Each inquiry uncovers new intriguing aspects, stimulating curiosity and an appetite to delve deeper. However, given that research is time-intensive and costly, it is essential to remain pragmatic and focus on achievable objectives.

As a practitioner, my primary goals are to provide patients with comprehensive, accurate information to aid in treatment decisions, recommend options based on objective risk-benefit analysis, and employ strategies to minimise risks. As a researcher, I aspire to uncover facts that underpin these clinical decisions.

A precise quantification of lithium's contribution to the burden of severe CKD in patients treated with lithium is challenging without biopsy verification (an unrealistic option due to the invasive nature of the procedure). A recent review and meta-analysis investigating the CKD risk associated with lithium use suggested that this risk might be twofold compared to non-lithium treated patients, yet it also highlighted substantial heterogeneity among the studies (Schoretsanitis et al., 2022). Identifying effective strategies for mitigating long-term renal risks in individuals treated with lithium remains imperative. Several avenues in this direction appear to be underexplored.

The association between NDI and the development of severe renal function impairment warrants further investigation. A definite link between the two is not clearly established, however Canadian studies (Rej et al., 2013; Rej et al., 2014) suggested hypernatraemic events and respectively NDI are predictors for CKD in older lithium users. Amiloride, an antidiuretic that alleviates lithium-induced polyuria (Kortenoeven et al., 2009), was also found to reduce renal interstitial fibrosis in animal models (Kalita-De Croft et al., 2018). The available evidence so far provides a sound rationale for the use of amiloride in lithium-treated patients who experience troublesome polyuria and polydipsia. If a definitive link is established between amiloride use, diminished interstitial fibrosis and reduced rate of GFR loss, then perhaps a more proactive approach in treating polyuria and polydipsia, through earlier and wider use of amiloride, may have a GFR-preserving effect in lithium-treated patients.

Administering lithium in single daily doses as a strategy to mitigate its renal effects was proposed early on (Plenge & Mellerup, 1986) and has been reiterated over time (Singh et al., 2011). A review of studies investigating

potential effects of once-daily dosing suggested that, although the findings are not entirely consistent, once-daily dosing regimen may have the potential to reduce polyuria, enable a reduction in lithium dosage while maintaining efficacy, and potentially lessen the structural changes associated with lithium treatment (Carter et al., 2013). Prospective studies investigating this approach evaluated primarily its effect on polyuria; however, in a larger retrospective investigation, once-daily administration has been associated with a reduced risk of CKD (Castro et al., 2016). While a French study reported that 86% of lithium-treated patients were on once-daily dosing (Boivin et al., 2023), in Sweden, this practice has not been widely adopted or discussed at the level of clinical guidelines. A notable difference is that in Sweden the approved lithium medication contains lithium sulphate, and not carbonate, as in most other countries. However, lithium sulphate is available as a slow-release formulation, so further exploration of this dosing strategy could be worthwhile.

Efforts to develop risk prediction models for CKD (of various stages) have already been initiated, both in general population (Kshirsagar et al., 2008; Schroeder et al., 2017), as well as in lithium-treated population (Castro et al., 2016; Hayes et al., 2021), and other special patient groups, such as diabetes patients (Østergaard et al., 2022). With advancements in data processing and the availability of large clinical and laboratory databases, the goal should be to create an easily accessible web-based tool for risk estimation in lithium treated patients, based on available clinical parameters.

Searching the relevant literature in preparation for this thesis, I encountered intriguing details about various lithium salts. Recent animal studies (Murbach et al., 2021; Pacholko & Bekar, 2023) suggest lithium orotate may require lower doses of elemental lithium to produce the desired clinical effects. It has been hypothesised that, compared to lithium carbonate, lithium orotate has a different pharmacokinetics and it may be a less nephrotoxic alternative. If these results are confirmed by other research groups, further exploring the use of lithium orotate in mood disorders could be worthwhile.

Last but perhaps not least, the investigations of the potential benefits of low-dose lithium interventions are promising. These include both neuroprotective/pro-cognitive effects (Dell'Osso et al., 2016; Forlenza et al., 2011; Gerhard et al., 2015; Strawbridge et al., 2023) and reno-protective effects (Alsady et al., 2016; Post et al., 2023). This area of research may potentially extend the medical applications of the lightest metal on Earth.

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REFERENCES

Adler, M., Häggström, L., Jarbin, H., Mikael, L., Liberg, B., Mathe, A., Ryden, E., & Svanborg, C. (Eds.). (2014). Bipolär sjukdom – kliniska riktlinjer för utredning och behandling. Gothia Fortbildning AB. https://www.svenskpsykiatri.se/wp-content/uploads/2017/02/SPF-kliniska-riktlinjer-om-Bipol%C3%A4r-sjukdom.pdf.

Aiff, D., & Aiff, H. (2016). Bipolär sjukdom, vårdriktlinjer Retrieved Feb 18, 2024 from https://registercentrum.blob.core.windows.net/bipolar/r/Region-Halland-V-rdriktlinjer-bipol-r-sjukdom-Bkrtd7X6-.pdf

Aiff, H., Attman, P. O., Aurell, M., Bendz, H., Ramsauer, B., Schön, S., & Svedlund, J. (2015). Effects of 10 to 30 years of lithium treatment on kidney function. J Psychopharmacol, 29(5), 608-614. https://doi.org/10.1177/0269881115573808

Aiff, H., Attman, P. O., Aurell, M., Bendz, H., Schön, S., & Svedlund, J. (2014). End-stage renal disease associated with prophylactic lithium treatment. Eur Neuropsychopharmacol, 24(4), 540-544. https://doi.org/10.1016/j.euroneuro.2014.01.002

Aiff, H., Attman, P. O., Ramsauer, B., Schön, S., & Svedlund, J. (2019). Cardiovascular comorbidity increases the risk for renal failure during prophylactic lithium treatment. J Affect Disord, 243, 416-420. https://doi.org/10.1016/j.jad.2018.09.044

Alsady, M., Baumgarten, R., Deen, P. M., & de Groot, T. (2016). Lithium in the Kidney: Friend and Foe? J Am Soc Nephrol, 27(6), 1587-1595. https://doi.org/10.1681/asn.2015080907

Altschul, E., Grossman, C., Dougherty, R., Gaikwad, R., Nguyen, V., Schwimmer, J., Merker, E., & Mandel, S. (2016). Lithium Toxicity: A Review of Pathophysiology, Treatment, and Prognosis. Practical Neurology, Marxch.

Amdisen, A., Bucht, H., Dencker, S. J., Hansen, H. E., Helgason, T., Lindstedt, G., Nagy, A., Nilsson, G., Rapp, W., Robak, O., & Sjöström, R. (1980). [Are you planning long-term treatment with lithium?]. Lakartidningen, 77(1-2), 35-38. (Tänker du långtidsbehandla med litium?)

Aprahamian, I., Santos, F. S., dos Santos, B., Talib, L., Diniz, B. S., Radanovic, M., Gattaz, W. F., & Forlenza, O. V. (2014). Long-term, low-dose lithium treatment does not impair renal function in the elderly: a 2-year randomized, placebo-controlled trial followed by single-blind extension. J Clin Psychiatry, 75(7), e672-678. https://doi.org/10.4088/JCP.13m08741

Arias-de la Torre, J., Vilagut, G., Ronaldson, A., Serrano-Blanco, A., Martín, V., Peters, M., Valderas, J. M., Dregan, A., & Alonso, J. (2021). Prevalence and variability of current depressive disorder in 27 European countries: a population-based study. Lancet Public Health, 6(10), e729-e738. https://doi.org/10.1016/s2468-2667(21)00047-5

Arnaud, A. M., Brister, T. S., Duckworth, K., Foxworth, P., Fulwider, T., Suthoff, E. D., Werneburg, B., Aleksanderek, I., & Reinhart, M. L. (2022). Impact of Major Depressive Disorder on Comorbidities: A Systematic Literature Review. J Clin Psychiatry, 83(6). https://doi.org/10.4088/JCP.21r14328

Atkin, C., Crosby, B., Dunn, K., Price, G., Marston, E., Crawford, C., O'Hara, M., Morgan, C., Levermore, M., Gallier, S., Modhwadia, S., Attwood, J., Perks, S., Denniston, A. K., Gkoutos, G., Dormer, R., Rosser, A., Ignatowicz, A., Fanning, H., . . . On behalf of the, P. D. H. (2021). Perceptions of anonymised data use and awareness of the NHS data opt-out amongst patients, carers and healthcare staff. Research Involvement and Engagement, 7(1), 40. https://doi.org/10.1186/s40900-021-00281-2

Aurell, M., Svalander, C., Wallin, L., & Alling, C. (1981). Renal function and biopsy findings in patients on long-term lithium treatment. Kidney Int, 20(5), 663-670. https://doi.org/10.1038/ki.1981.191

Baethge, C., Gruschka, P., Smolka, M. N., Berghöfer, A., Bschor, T., Müller-Oerlinghausen, B., & Bauer, M. (2003). Effectiveness and outcome predictors of long-term lithium prophylaxis in unipolar major depressive disorder. J Psychiatry Neurosci, 28(5), 355-361.

Baldessarini, R. J., Tondo, L., & Vázquez, G. H. (2019). Pharmacological treatment of adult bipolar disorder. Mol Psychiatry, 24(2), 198-217. https://doi.org/10.1038/s41380-018-0044-2

Baldessarini, R. J., Tondo, L., & Viguera, A. C. (1999). Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. Bipolar Disord, 1(1), 17-24. https://doi.org/10.1034/j.1399-5618.1999.10106.x

Baldessarini, R. J., Vázquez, G. H., & Tondo, L. (2020). Bipolar depression: a major unsolved challenge. Int J Bipolar Disord, 8(1), 1. https://doi.org/10.1186/s40345-019-0160-1

Ballanger, F., Tenaud, I., Volteau, C., Khammari, A., & Dréno, B. (2008). Anti-inflammatory effects of lithium gluconate on keratinocytes: a possible explanation for efficiency in seborrhoeic dermatitis. Arch Dermatol Res, 300(5), 215-223. https://doi.org/10.1007/s00403-007-0824-z

Bassilios, N., Martel, P., Godard, V., Froissart, M., Grünfeld, J. P., & Stengel, B. (2008). Monitoring of glomerular filtration rate in lithium-treated outpatients--an ambulatory laboratory database surveillance. Nephrol Dial Transplant, 23(2), 562-565. https://doi.org/10.1093/ndt/gfm567

Bauer, M., Bschor, T., Kunz, D., Berghöfer, A., Ströhle, A., & Müller-Oerlinghausen, B. (2000). Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry, 157(9), 1429-1435. https://doi.org/10.1176/appi.ajp.157.9.1429

Bauer, M., Dell'osso, L., Kasper, S., Pitchot, W., Dencker Vansvik, E., Köhler, J., Jørgensen, L., & Montgomery, S. A. (2013). Extended-release quetiapine fumarate (quetiapine XR) monotherapy and quetiapine XR or lithium as add-on

to antidepressants in patients with treatment-resistant major depressive disorder. J Affect Disord, 151(1), 209-219. https://doi.org/10.1016/j.jad.2013.05.079

Bauer, M., & Dopfmer, S. (1999). Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol, 19(5), 427-434. https://doi.org/10.1097/00004714-199910000-00006

Bedford, J. J., Weggery, S., Ellis, G., McDonald, F. J., Joyce, P. R., Leader, J. P., & Walker, R. J. (2008). Lithium-induced nephrogenic diabetes insipidus: renal effects of amiloride. Clin J Am Soc Nephrol, 3(5), 1324-1331. https://doi.org/10.2215/cjn.01640408

Belfrage, S., Helgesson, G., & Lynøe, N. (2022). Trust and digital privacy in healthcare: a cross-sectional descriptive study of trust and attitudes towards uses of electronic health data among the general public in Sweden. BMC Medical Ethics, 23(1), 19. https://doi.org/10.1186/s12910-022-00758-z

Belgamwar, R. B., Ebrahim, F., & Campbell, C. (2010). Lithium in chronic renal failure: a case report. Gen Hosp Psychiatry, 32(3), 341.e343-345. https://doi.org/10.1016/j.genhosppsych.2009.03.008

Bendz, H., & Aurell, M. (2004). Litiumbehandlingens biverkningar och säkerhetsrutiner. Lakartidningen, 101(21-22), 1902-1908. https://lakartidningen.se/wp-content/uploads/OldPdfFiles/2004/28660.pdf

BipoläR (Swedish National Quality Register for bipolar disorder). (2023). https://bipolar.registercentrum.se/

Björk, J., Grubb, A., Sterner, G., & Nyman, U. (2011). Revised equations for estimating glomerular filtration rate based on the Lund-Malmö Study cohort. Scand J Clin Lab Invest, 71(3), 232-239. https://doi.org/10.3109/00365513.2011.557086

Bocchetta, A., Ardau, R., Carta, P., Ligas, F., Sardu, C., Pani, A., & Del Zompo, M. (2013). Duration of lithium treatment is a risk factor for reduced glomerular function: a cross-sectional study. BMC Med, 11, 33. https://doi.org/10.1186/1741-7015-11-33

Bocchetta, A., Ardau, R., Fanni, T., Sardu, C., Piras, D., Pani, A., & Del Zompo, M. (2015). Renal function during long-term lithium treatment: a cross-sectional and longitudinal study. BMC Med, 13, 12. https://doi.org/10.1186/s12916-014-0249-4

Boivin, E., Le Daré, B., Bellay, R., Vigneau, C., Mercerolle, M., & Bacle, A. (2023). Long-term lithium therapy and risk of chronic kidney disease, hyperparathyroidism and hypercalcemia: a cohort study. Int J Bipolar Disord, 11(1), 4. https://doi.org/10.1186/s40345-023-00286-8

Bosi, A., Ceriani, L., Elinder, C. G., Bellocco, R., Clase, C. M., Landen, M., Carrero, J. J., & Runesson, B. (2023). Quality of laboratory biomarker monitoring during treatment with lithium in patients with bipolar disorder. Bipolar Disord, 25(6), 499-506. https://doi.org/10.1111/bdi.13302

Bosi, A., Clase, C. M., Ceriani, L., Sjölander, A., Fu, E. L., Runesson, B., Chang, Z., Landén, M., Bellocco, R., Elinder, C. G., & Carrero, J. J. (2023). Absolute and Relative Risks of Kidney Outcomes Associated With Lithium vs Valproate Use in Sweden. JAMA Netw Open, 6(7), e2322056. https://doi.org/10.1001/jamanetworkopen.2023.22056

Bowden, C. L., Grunze, H., Mullen, J., Brecher, M., Paulsson, B., Jones, M., Vågerö, M., & Svensson, K. (2005). A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry, 66(1), 111-121. https://doi.org/10.4088/jcp.v66n0116

Brown, W. A. (2019). Lithium. A Doctor, a Drug and a Breakthrough (First ed.). Liveright Publishing Corporation.

Bschor, T., Baethge, C., Grunze, H., Lewitzka, U., Scherk, H., Severus, E., & Bauer, M. (2020). [German S3 guidelines on bipolar disorders-first update 2019 : What is new in pharmacotherapy?]. Nervenarzt, 91(3), 216-221. https://doi.org/10.1007/s00115-019-00852-5 (S3-Leitlinie Bipolare Störungen – 1. Update 2019 : Was ist neu in der Pharmakotherapie?)

Burgess, S., Geddes, J., Hawton, K., Townsend, E., Jamison, K., & Goodwin, G. (2001). Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev(2), Cd003013. https://doi.org/10.1002/14651858.Cd003013

Buspavanich, P., Behr, J., Stamm, T., Schlattmann, P., Bschor, T., Richter, C., Hellweg, R., Heinz, A., Berger, M., Hindinger, C., Rentzsch, J., de Millas, W., Jockers-Scherübl, M. C., Bräunig, P., Adli, M., & Ricken, R. (2019). Treatment response of lithium augmentation in geriatric compared to non-geriatric patients with treatment-resistant depression. J Affect Disord, 251, 136-140. https://doi.org/10.1016/j.jad.2019.03.057

Cade, J. F. (1949). Lithium salts in the treatment of psychotic excitement. Med J Aust, 2(10), 349-352. https://doi.org/10.1080/j.1440-1614.1999.06241.x

Caravaca-Fontán, F., Azevedo, L., Luna, E., & Caravaca, F. (2018). Patterns of progression of chronic kidney disease at later stages. Clin Kidney J, 11(2), 246-253. https://doi.org/10.1093/ckj/sfx083

Carter, L., Zolezzi, M., & Lewczyk, A. (2013). An updated review of the optimal lithium dosage regimen for renal protection. Can J Psychiatry, 58(10), 595-600. https://doi.org/10.1177/070674371305801009

Castro, V. M., Roberson, A. M., McCoy, T. H., Wiste, A., Cagan, A., Smoller, J. W., Rosenbaum, J. F., Ostacher, M., & Perlis, R. H. (2016). Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study. Neuropsychopharmacology, 41(4), 1138-1143. https://doi.org/10.1038/npp.2015.254

Chan, H. H., Wing, Y., Su, R., Van Krevel, C., & Lee, S. (2000). A control study of the cutaneous side effects of chronic lithium therapy. J Affect Disord, 57(1-3), 107-113. https://doi.org/10.1016/s0165-0327(99)00064-6

Chan, J. K. N., Correll, C. U., Wong, C. S. M., Chu, R. S. T., Fung, V. S. C., Wong, G. H. S., Lei, J. H. C., Chang, W. C., & less, S. (2023). Life expectancy and years of potential life lost in people with mental disorders: a systematic review and meta-analysis. Lancet. https://doi.org/https://doi.org/10.1016/j.eclinm.2023.102294

Chen, H., Cohen, P., & Chen, S. (2010). How Big is a Big Odds Ratio? Interpreting the Magnitudes of Odds Ratios in Epidemiological Studies. Communications in Statistics - Simulation and Computation, 39(4), 860-864. https://doi.org/10.1080/03610911003650383

Chen, P. H., Tsai, S. Y., Chen, P. Y., Pan, C. H., Su, S. S., Chen, C. C., & Kuo, C. J. (2023). Mood stabilizers and risk of all-cause, natural, and suicide mortality in bipolar disorder: A nationwide cohort study. Acta Psychiatr Scand, 147(3), 234-247. https://doi.org/10.1111/acps.13519

Christl, J., Müller-Oerlinghausen, B., Bauer, M., Kamp, D., Fußer, F., Benninghoff, J., Fehrenbach, R. A., Lange-Asschenfeldt, C., Rapp, M., Ibach, B., Schaub, R., Wollmer, A., Strotmann-Tack, T., Hüll, M., Biermann, S., Roscher, K., Meissnest, B., Menges, A., Weigel, B., . . . Supprian, T. (2023). Lithium Therapy in Old Age: Recommendations from a Delphi Survey. Pharmacopsychiatry, 56(5), 188-196. https://doi.org/10.1055/a-2117-5200

Cipriani, A., Hawton, K., Stockton, S., & Geddes, J. R. (2013). Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. Bmj, 346, f3646. https://doi.org/10.1136/bmj.f3646

Clos, S., Rauchhaus, P., Severn, A., Cochrane, L., & Donnan, P. T. (2015). Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study. Lancet Psychiatry, 2(12), 1075-1083. https://doi.org/10.1016/s2215-0366(15)00316-8

Close, H., Reilly, J., Mason, J. M., Kripalani, M., Wilson, D., Main, J., & Hungin, A. P. (2014). Renal failure in lithium-treated bipolar disorder: a retrospective cohort study. PLoS One, 9(3), e90169. https://doi.org/10.1371/journal.pone.0090169

Davies, H. T., Crombie, I. K., & Tavakoli, M. (1998). When can odds ratios mislead? Bmj, 316(7136), 989-991. https://doi.org/10.1136/bmj.316.7136.989

Davis, J., Desmond, M., & Berk, M. (2018). Lithium and nephrotoxicity: Unravelling the complex pathophysiological threads of the lightest metal. Nephrology (Carlton), 23(10), 897-903. https://doi.org/10.1111/nep.13263

de Man Lapidoth, J., Hultdin, J., Jonsson, P. A., Eriksson Svensson, M., Wennberg, M., Zeller, T., & Söderberg, S. (2023). Trends in renal function in Northern Sweden 1986-2014: data from the seven cross-sectional surveys within the Northern Sweden MONICA study. BMJ Open, 13(8), e072664. https://doi.org/10.1136/bmjopen-2023-072664

Deeb, L. C. (2008). Diabetes Technology During the Past 30 Years: A Lot of Changes and Mostly for the Better. Diabetes Spectrum, 21(2), 78-83. https://doi.org/10.2337/diaspect.21.2.78

Delanaye, P., Jager, K. J., Bökenkamp, A., Christensson, A., Dubourg, L., Eriksen, B. O., Gaillard, F., Gambaro, G., van der Giet, M., Glassock, R. J., Indridason, O. S., van Londen, M., Mariat, C., Melsom, T., Moranne, O., Nordin, G., Palsson, R., Pottel, H., Rule, A. D., . . . van den Brand, J. (2019). CKD: A Call for an Age-Adapted Definition. J Am Soc Nephrol, 30(10), 1785-1805. https://doi.org/10.1681/asn.2019030238

Dell'Osso, L., Del Grande, C., Gesi, C., Carmassi, C., & Musetti, L. (2016). A new look at an old drug: neuroprotective effects and therapeutic potentials of lithium salts. Neuropsychiatr Dis Treat, 12, 1687-1703. https://doi.org/10.2147/ndt.S106479

Dervic, K., Sher, L., Galfalvy, H. C., Grunebaum, M., Burke, A. K., Sullivan, G., Sublette, M. E., Mann, J. J., & Oquendo, M. A. (2023). Antisuicidal effect of lithum in bipolar disorder: is there an age-specific effect? J Affect Disord, 341, 8-11. https://doi.org/10.1016/j.jad.2023.08.107

Dineen, R., Bogdanet, D., Thompson, D., Thompson, C. J., Behan, L. A., McKay, A. P., Boran, G., Wall, C., Gibney, J., O'Keane, V., & Sherlock, M. (2017). Endocrinopathies and renal outcomes in lithium therapy: impact of lithium toxicity. Qjm, 110(12), 821-827. https://doi.org/10.1093/qjmed/hcx171

Doornebal, J., Diepenbroek, A., van de Luijtgaarden, M. W. M., Hartong, E., Grootens, K. P., Kupka, R. W., Klumpers, U. M. H., Deen, P. M. T., Gaillard, C. A., & Wetzels, J. F. M. (2019). Renal concentrating ability and glomerular filtration rate in lithium-treated patients. Neth J Med, 77(4), 139-149.

Duthie, A. C., Hannah, J., Batty, G. D., Deary, I. J., Starr, J. M., Smith, D. J., & Russ, T. C. (2023). Low-level lithium in drinking water and subsequent risk of dementia: Cohort study. Int J Geriatr Psychiatry, 38(3), e5890. https://doi.org/10.1002/gps.5890

Edström, A., & Persson, G. (1977). Comparison of side effects with coated lithium carbonate tablets and lithium sulphate preparations giving medium-slow and slow-release. Acta Psychiatr Scand, 55(2), 153-158. https://doi.org/10.1111/j.1600-0447.1977.tb00152.x

Evans, M., Grams, M. E., Sang, Y., Astor, B. C., Blankestijn, P. J., Brunskill, N. J., Collins, J. F., Kalra, P. A., Kovesdy, C. P., Levin, A., Mark, P. B., Moranne, O., Rao, P., Rios, P. G., Schneider, M. P., Shalev, V., Zhang, H., Chang, A. R., Gansevoort, R. T., . . . Wheeler, D. C. (2018). Risk Factors for Prognosis in Patients With Severely Decreased GFR. Kidney Int Rep, 3(3), 625-637. https://doi.org/10.1016/j.ekir.2018.01.002

Fajutrao, L., Locklear, J., Priaulx, J., & Heyes, A. (2009). A systematic review of the evidence of the burden of bipolar disorder in Europe. Clin Pract Epidemiol Ment Health, 5, 3. https://doi.org/10.1186/1745-0179-5-3

Fine, J. P., & Gray, R. J. (1999). A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association, 94(446), 496-509. https://doi.org/10.1080/01621459.1999.10474144

Flapper, M., van Melick, E., van Campen, J., Schutter, N., & Kok, R. (2021). Tolerability of lithium: A naturalistic discontinuation study in older inpatients (≥60 years). Int J Geriatr Psychiatry, 36(8), 1231-1240. https://doi.org/10.1002/gps.5517

Forester, B. P., Streeter, C. C., Berlow, Y. A., Tian, H., Wardrop, M., Finn, C. T., Harper, D., Renshaw, P. F., & Moore, C. M. (2009). Brain lithium levels and effects on cognition and mood in geriatric bipolar disorder: a lithium-7 magnetic resonance spectroscopy study. Am J Geriatr Psychiatry, 17(1), 13-23. https://doi.org/10.1097/JGP.0b013e318172b3d0

Forlenza, O. V., Diniz, B. S., Radanovic, M., Santos, F. S., Talib, L. L., & Gattaz, W. F. (2011). Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry, 198(5), 351-356. https://doi.org/10.1192/bjp.bp.110.080044

Forlenza, O. V., Radanovic, M., Talib, L. L., & Gattaz, W. F. (2019). Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial. Br J Psychiatry, 215(5), 668-674. https://doi.org/10.1192/bjp.2019.76

Fornaro, M., Maritan, E., Ferranti, R., Zaninotto, L., Miola, A., Anastasia, A., Murru, A., Solé, E., Stubbs, B., Carvalho, A. F., Serretti, A., Vieta, E., Fusar-Poli, P., McGuire, P., Young, A. H., Dazzan, P., Vigod, S. N., Correll, C. U., & Solmi, M. (2020). Lithium Exposure During Pregnancy and the Postpartum Period: A Systematic Review and Meta-Analysis of Safety and Efficacy Outcomes. Am J Psychiatry, 177(1), 76-92. https://doi.org/10.1176/appi.ajp.2019.19030228

Forrest, J. N., Jr., Cohen, A. D., Torretti, J., Himmelhoch, J. M., & Epstein, F. H. (1974). On the mechanism of lithium-induced diabetes insipidus in man and the rat. J Clin Invest, 53(4), 1115-1123. https://doi.org/10.1172/jci107649

Fountoulakis, K. N., Tohen, M., & Zarate, C. A., Jr. (2022). Lithium treatment of Bipolar disorder in adults: A systematic review of randomized trials and meta-analyses. Eur Neuropsychopharmacol, 54, 100-115. https://doi.org/10.1016/j.euroneuro.2021.10.003

Fransson, F., Werneke, U., Harju, V., Öhlund, L., de Man Lapidoth, J., Jonsson, P. A., Stegmayr, B., Renberg, E. S., & Ott, M. (2022). Kidney function in patients with bipolar disorder with and without lithium treatment compared with the general population in northern Sweden: results from the LiSIE and MONICA cohorts. Lancet Psychiatry, 9(10), 804-814. https://doi.org/10.1016/s2215-0366(22)00265-6

Geddes, J. R., Burgess, S., Hawton, K., Jamison, K., & Goodwin, G. M. (2004). Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry, 161(2), 217-222. https://doi.org/10.1176/appi.ajp.161.2.217

Gerhard, T., Devanand, D. P., Huang, C., Crystal, S., & Olfson, M. (2015). Lithium treatment and risk for dementia in adults with bipolar disorder:

population-based cohort study. Br J Psychiatry, 207(1), 46-51. https://doi.org/10.1192/bjp.bp.114.154047

Gitlin, M. (2016). Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord, 4(1), 27. https://doi.org/10.1186/s40345-016-0068-y

Gitlin, M. (2016). Why is not Lithium Prescribed More Often? Here are the Reasons [Review]. The Journal of Psychiatry and Neurological Sciences, 29, 293-297 G. https://doi.org/10.5350/DAJPN20162904001

Glassock, R. J., Delanaye, P., & Rule, A. D. (2020). Should the definition of CKD be changed to include age-adapted GFR criteria? YES. Kidney Int, 97(1), 34-37. https://doi.org/10.1016/j.kint.2019.08.033

Glassock, R. J., & Rule, A. D. (2016). Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease. Nephron, 134(1), 25-29. https://doi.org/10.1159/000445450

Goldstein, B. I., Fagiolini, A., Houck, P., & Kupfer, D. J. (2009). Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord, 11(6), 657-662. https://doi.org/10.1111/j.1399-5618.2009.00735.x

Gomes-da-Costa, S., Marx, W., Corponi, F., Anmella, G., Murru, A., Pons-Cabrera, M. T., Giménez-Palomo, A., Gutiérrez-Arango, F., Llach, C. D., Fico, G., Kotzalidis, G. D., Verdolini, N., Valentí, M., Berk, M., Vieta, E., & Pacchiarotti, I. (2022). Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev, 134, 104266. https://doi.org/10.1016/j.neubiorev.2021.07.011

Gomes, F. A., Brietzke, E., Bauer, M., & Post, R. M. (2022). A call for improving lithium literacy among clinicians and patients. Int J Bipolar Disord, 10(1), 5. https://doi.org/10.1186/s40345-022-00250-y

Grams, M. E., Chow, E. K., Segev, D. L., & Coresh, J. (2013). Lifetime incidence of CKD stages 3-5 in the United States. Am J Kidney Dis, 62(2), 245-252. https://doi.org/10.1053/j.ajkd.2013.03.009

Grandjean, E. M., & Aubry, J. M. (2009). Lithium: updated human knowledge using an evidence-based approach. Part II: Clinical pharmacology and therapeutic monitoring. CNS Drugs, 23(4), 331-349. https://doi.org/10.2165/00023210-200923040-00005

Grubb, A. D., Alexander. (2023). Beräkning av eGFR med Lund-Malmö-modellen (LMR18). Retrieved Feb 18, 2024 from https://www.egfr.se/

Hakulinen, C., Musliner, K. L., & Agerbo, E. (2019). Bipolar disorder and depression in early adulthood and long-term employment, income, and educational attainment: A nationwide cohort study of 2,390,127 individuals. Depress Anxiety, 36(11), 1080-1088. https://doi.org/10.1002/da.22956

Hastie, R., Tong, S., Hiscock, R., Lindquist, A., Lindström, L., Wikström, A. K., & Sundström-Poromaa, I. (2021). Maternal lithium use and the risk of adverse

pregnancy and neonatal outcomes: a Swedish population-based cohort study. BMC Med, 19(1), 291. https://doi.org/10.1186/s12916-021-02170-7

Hayes, J. F., Osborn, D. P. J., Francis, E., Ambler, G., Tomlinson, L. A., Boman, M., Wong, I. C. K., Geddes, J. R., Dalman, C., & Lewis, G. (2021). Prediction of individuals at high risk of chronic kidney disease during treatment with lithium for bipolar disorder. BMC Med, 19(1), 99. https://doi.org/10.1186/s12916-021-01964-z

Heinonen, E., Tötterman, K., Bäck, K., Sarman, I., Svedenkrans, J., & Forsberg, L. (2022). Lithium use during breastfeeding was safe in healthy full-term infants under strict monitoring. Acta Paediatr, 111(10), 1891-1898. https://doi.org/10.1111/apa.16444

Hestbech, J., Hansen, H. E., Amdisen, A., & Olsen, S. (1977). Chronic renal lesions following long-term treatment with lithium. Kidney Int, 12(3), 205-213. https://doi.org/10.1038/ki.1977.102

Hidalgo-Mazzei, D., Mantingh, T., Pérez de Mendiola, X., Samalin, L., Undurraga, J., Strejilevich, S., Severus, E., Bauer, M., González-Pinto, A., Nolen, W. A., Young, A. H., & Vieta, E. (2023). Clinicians' preferences and attitudes towards the use of lithium in the maintenance treatment of bipolar disorders around the world: a survey from the ISBD Lithium task force. Int J Bipolar Disord, 11(1), 20. https://doi.org/10.1186/s40345-023-00301-y

Hill, N. R., Fatoba, S. T., Oke, J. L., Hirst, J. A., O'Callaghan, C. A., Lasserson, D. S., & Hobbs, F. D. (2016). Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One, 11(7), e0158765. https://doi.org/10.1371/journal.pone.0158765

Hirschfeld, R. M. A., Bowden, C. L., Gitlin, M. J., Keck, P. E., Suppes, T., Thase, M. E., & Perlis, R. H. (2002). Practice guideline for the treatment of patients with bipolar disorder, second edition. In N. C. Numerous Contributors (Ed.),. Retrieved Feb 18, 2024 from https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf

Hlaing, P. M., Isoardi, K. Z., Page, C. B., & Pillans, P. (2020). Neurotoxicity in chronic lithium poisoning. Intern Med J, 50(4), 427-432. https://doi.org/10.1111/imj.14402

Hoekstra, R., Lekkerkerker, M. N., Kuijper, T. M., Bosch, T. M., & van Alphen, A. M. (2022). Renal function after withdrawal of lithium. Bipolar Disord, 24(6), 667-670. https://doi.org/10.1111/bdi.13178

Hsu, C. W., Tsai, S. Y., Tseng, P. T., Liang, C. S., Vieta, E., Carvalho, A. F., Stubbs, B., Kao, H. Y., Tu, Y. K., & Lin, P. Y. (2022). Differences in the prophylactic effect of serum lithium levels on depression and mania in bipolar disorder: A dose-response meta-analysis. Eur Neuropsychopharmacol, 58, 20-29. https://doi.org/10.1016/j.euroneuro.2022.01.112

Hsu, T. W., Thompson, T., Solmi, M., Vieta, E., Yang, F. C., Tseng, P. T., Hsu, C. W., Tu, Y. K., Yu, C. L., Tsai, C. K., Liang, C. S., & Carvalho, A. F. (2022). Variability and efficacy in treatment effects on manic symptoms with lithium,

anticonvulsants, and antipsychotics in acute bipolar mania: A systematic review and meta-analysis. EClinicalMedicine, 54, 101690. https://doi.org/10.1016/j.eclinm.2022.101690

Hullin, R. P., Coley, V. P., Birch, N. J., Thomas, T. H., & Morgan, D. B. (1979). Renal function after long-term treatment with lithium. Br Med J, 1(6176), 1457-1459. https://doi.org/10.1136/bmj.1.6176.1457

Hällgren, R., Alm, P. O., & Hellsing, K. (1979). Renal function in patients on lithium treatment. Br J Psychiatry, 135, 22-27. https://doi.org/10.1192/bjp.135.1.22

Højlund, M., Lund, L. C., Herping, J. L. E., Haastrup, M. B., Damkier, P., & Henriksen, D. P. (2020). Second-generation antipsychotics and the risk of chronic kidney disease: a population-based case-control study. BMJ Open, 10(8), e038247. https://doi.org/10.1136/bmjopen-2020-038247

Højlund, M., Winkel, J. S., Nybo, M., Hallas, J., Henriksen, D. P., & Damkier, P. (2022). Lithium and the risk of chronic kidney disease: A population-based case-control study. Basic Clin Pharmacol Toxicol, 131(2), 129-137. https://doi.org/10.1111/bcpt.13758

Inker, L. A., Tighiouart, H., Aspelund, T., Gudnason, V., Harris, T., Indridason, O. S., Palsson, R., Shastri, S., Levey, A. S., & Sarnak, M. J. (2015). Lifetime Risk of Stage 3-5 CKD in a Community-Based Sample in Iceland. Clin J Am Soc Nephrol, 10(9), 1575-1584. https://doi.org/10.2215/cjn.00180115

Jeon, Y., & Lee, W. K. (2020). Competing Risk Model in Survival Analysis. Cardiovasc Prev Pharmacother., 2, 77-84.

Joas, E., Karanti, A., Song, J., Goodwin, G. M., Lichtenstein, P., & Landén, M. (2017). Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. Br J Psychiatry, 210(3), 197-202. https://doi.org/10.1192/bjp.bp.116.187989

Johansson, M., Guyatt, G., & Montori, V. (2023). Guidelines should consider clinicians' time needed to treat. Bmj, 380, e072953. https://doi.org/10.1136/bmj-2022-072953

Joseph, B., Nunez, N. A., Pazdernik, V., Kumar, R., Pahwa, M., Ercis, M., Ozerdem, A., Cuellar-Barboza, A. B., Romo-Nava, F., McElroy, S. L., Coombes, B. J., Biernacka, J. M., Stan, M. N., Frye, M. A., & Singh, B. (2023). Long-Term Lithium Therapy and Thyroid Disorders in Bipolar Disorder: A Historical Cohort Study. Brain Sci, 13(1). https://doi.org/10.3390/brainsci13010133

Kalita-De Croft, P., Bedford, J. J., Leader, J. P., & Walker, R. J. (2018). Amiloride modifies the progression of lithium-induced renal interstitial fibrosis. Nephrology, 23(1), 20-30. https://doi.org/https://doi.org/10.1111/nep.12929

Kapusta, N. D., Mossaheb, N., Etzersdorfer, E., Hlavin, G., Thau, K., Willeit, M., Praschak-Rieder, N., Sonneck, G., & Leithner-Dziubas, K. (2011). Lithium in drinking water and suicide mortality. The British Journal of Psychiatry, 198(5), 346-350. https://doi.org/10.1192/bjp.bp.110.091041

Karanti, A., Kardell, M., Lundberg, U., & Landén, M. (2016). Changes in mood stabilizer prescription patterns in bipolar disorder. J Affect Disord, 195, 50-56. https://doi.org/10.1016/j.jad.2016.01.043

Kerckhoffs, A. P. M., Hartong, E., & Grootens, K. P. (2018). The perspectives of patients with lithium-induced end-stage renal disease. Int J Bipolar Disord, 6(1), 13. https://doi.org/10.1186/s40345-018-0121-0

Kessing, L. V. (2024). Why is lithium [not] the drug of choice for bipolar disorder? a controversy between science and clinical practice. Int J Bipolar Disord, 12(1), 3. https://doi.org/10.1186/s40345-023-00322-7

Kessing, L. V., Feldt-Rasmussen, B., Andersen, P. K., Gerds, T. A., & Licht, R. W. (2017). Continuation of lithium after a diagnosis of chronic kidney disease. Acta Psychiatr Scand, 136(6), 615-622. https://doi.org/10.1111/acps.12820

Kessing, L. V., Gerds, T. A., Feldt-Rasmussen, B., Andersen, P. K., & Licht, R. W. (2015a). Lithium and renal and upper urinary tract tumors - results from a nationwide population-based study. Bipolar Disord, 17(8), 805-813. https://doi.org/10.1111/bdi.12344

Kessing, L. V., Gerds, T. A., Feldt-Rasmussen, B., Andersen, P. K., & Licht, R. W. (2015b). Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study. JAMA Psychiatry, 72(12), 1182-1191. https://doi.org/10.1001/jamapsychiatry.2015.1834

Kessing, L. V., Gerds, T. A., Knudsen, N. N., Jørgensen, L. F., Kristiansen, S. M., Voutchkova, D., Ernstsen, V., Schullehner, J., Hansen, B., Andersen, P. K., & Ersbøll, A. K. (2017). Association of Lithium in Drinking Water With the Incidence of Dementia. JAMA Psychiatry, 74(10), 1005-1010. https://doi.org/10.1001/jamapsychiatry.2017.2362

Kirkham, E., Skinner, J., Anderson, T., Bazire, S., Twigg, M. J., & Desborough, J. A. (2014). One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database. BMJ Open, 4(11), e006020. https://doi.org/10.1136/bmjopen-2014-006020

Knudsen, N. N., Schullehner, J., Hansen, B., Jørgensen, L. F., Kristiansen, S. M., Voutchkova, D. D., Gerds, T. A., Andersen, P. K., Bihrmann, K., Grønbæk, M., Kessing, L. V., & Ersbøll, A. K. (2017). Lithium in Drinking Water and Incidence of Suicide: A Nationwide Individual-Level Cohort Study with 22 Years of Follow-Up. Int J Environ Res Public Health, 14(6). https://doi.org/10.3390/ijerph14060627

Kobylianskii, J., Austin, E., Gold, W. L., & Wu, P. E. (2021). A 54-year-old woman with chronic lithium toxicity. Cmaj, 193(34), E1345-e1348. https://doi.org/10.1503/cmaj.210725

Kortenoeven, M. L., Li, Y., Shaw, S., Gaeggeler, H. P., Rossier, B. C., Wetzels, J. F., & Deen, P. M. (2009). Amiloride blocks lithium entry through the sodium channel thereby attenuating the resultant nephrogenic diabetes insipidus. Kidney Int, 76(1), 44-53. https://doi.org/10.1038/ki.2009.91

Kovesdy, C. P. (2022). Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011), 12(1), 7-11. https://doi.org/10.1016/j.kisu.2021.11.003

Kriner, P., Severus, E., Korbmacher, J., Mußmann, L., & Seemueller, F. (2023). Lithium prescription trends in psychiatric inpatient care 2014 to 2021: data from a Bavarian drug surveillance project. International Journal of Bipolar Disorders, 11(1), 40. https://doi.org/10.1186/s40345-023-00323-6

Kshirsagar, A. V., Bang, H., Bomback, A. S., Vupputuri, S., Shoham, D. A., Kern, L. M., Klemmer, P. J., Mazumdar, M., & August, P. A. (2008). A simple algorithm to predict incident kidney disease. Arch Intern Med, 168(22), 2466-2473. https://doi.org/10.1001/archinte.168.22.2466

Kumar, R., Joseph, B., Pazdernik, V. M., Geske, J., Nuñez, N. A., Pahwa, M., Kashani, K. B., Veldic, M., Betcher, H. K., Moore, K. M., Croarkin, P. E., Ozerdem, A., Cuellar-Barboza, A. B., McElroy, S. L., Biernacka, J. M., Frye, M. A., & Singh, B. (2023). Real-World Clinical Practice Among Patients With Bipolar Disorder and Chronic Kidney Disease on Long-term Lithium Therapy. J Clin Psychopharmacol, 43(1), 6-11. https://doi.org/10.1097/jcp.0000000000001632

Larcher, D., & Tarascon, J.-M. (2017). The Lithium Ion. In G. Malhi (Ed.), The Science and Practice of Lithium Therapy (pp. 3-23). Springer International Publishing. https://doi.org/DOI 10.1007/978-3-319-45923-3_1

Lepkifker, E., Sverdlik, A., Iancu, I., Ziv, R., Segev, S., & Kotler, M. (2004). Renal insufficiency in long-term lithium treatment. J Clin Psychiatry, 65(6), 850-856. https://doi.org/10.4088/jcp.v65n0618

Lieber, I., Ott, M., Öhlund, L., Lundqvist, R., Eliasson, M., Sandlund, M., & Werneke, U. (2020). Lithium-associated hypothyroidism and potential for reversibility after lithium discontinuation: Findings from the LiSIE retrospective cohort study. J Psychopharmacol, 34(3), 293-303. https://doi.org/10.1177/0269881119882858

Liew, Z., Meng, Q., Yan, Q., Schullehner, J., Hansen, B., Kristiansen, S. M., Voutchkova, D. D., Olsen, J., Ersbøll, A. K., Ketzel, M., Raaschou-Nielsen, O., & Ritz, B. R. (2023). Association Between Estimated Geocoded Residential Maternal Exposure to Lithium in Drinking Water and Risk for Autism Spectrum Disorder in Offspring in Denmark. JAMA Pediatr, 177(6), 617-624. https://doi.org/10.1001/jamapediatrics.2023.0346

Lim, G. Y., Tam, W. W., Lu, Y., Ho, C. S., Zhang, M. W., & Ho, R. C. (2018). Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. Scientific Reports, 8(1), 2861. https://doi.org/10.1038/s41598-018-21243-x

Lin, Y., Mojtabai, R., Goes, F. S., & Zandi, P. P. (2020). Trends in prescriptions of lithium and other medications for patients with bipolar disorder in office-based practices in the United States: 1996-2015. J Affect Disord, 276, 883-889. https://doi.org/10.1016/j.jad.2020.07.063

Litarex package leaflet. Medicin.dk. Retrieved Feb 18, 2024 from https://pro.medicin.dk/Medicin/Praeparater/768

Lithionit FASS text. (Jan 2024). Karo Healthcare. Retrieved Feb 18, 2024 from https://www.fass.se/LIF/product?userType=0&nplId=19971114000058&docType=3&scrollPosition=586.4000244140625

Lithium Ascorbate. Retrieved Jan 26, 2024 from https://www.amazon.com/Depression-Supplement-Cognitive-Ascorbate-Normopharm/dp/B08VWHWJS8

Lithium Aspartate. Retrieved Jan 24, 2024 from https://www.amazon.com/Solaray-Lithium-Aspartate-Supplement-Count/dp/B00028NUY8

Lithium carbonate prescribing information. (Sept 2011). Roxane Laboratories Inc. Retrieved Feb 18, 2024 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017812s028,018421s027lbl.pdf

Lithium facts. Government of Canada. Retrieved Jan 24, 2024 from https://natural-resources.canada.ca/our-natural-resources/minerals-mining/mining-data-statistics-and-analysis/minerals-metals-facts/lithium-facts/24009

Lithium in drinking water. Connecticut state - Department of Public Health. Retrieved Feb 18, 2024 from https://portal.ct.gov/DPH/Drinking-Water/DWS/Lithium-in-Drinking-Water-.

Lithium in drinking water. (2022). American Water Works Association. Retrieved Feb 18, 2024 from https://www.awwa.org/Portals/0/AWWA/ETS/Research/2022_Lithium%20Health%20Effects%20Review.pdf?ver=2022-12-01-104741-013

Lithium Orotate. Retrieved Jan 24, 2024 from https://www.amazon.com/s?k=lithium+orotate&crid=2U3XY8FQAL08O&sprefix=lithium+orotate%2Caps%2C199&ref=nb_sb_noss_1

Liu, P., Quinn, R. R., Lam, N. N., Elliott, M. J., Xu, Y., James, M. T., Manns, B., & Ravani, P. (2021). Accounting for Age in the Definition of Chronic Kidney Disease. JAMA Intern Med, 181(10), 1359-1366. https://doi.org/10.1001/jamainternmed.2021.4813

Ludvigsson, J., Håberg, S., Knudsen, G., Lafolie, P., Zoega, H., Sarkkola, C., von Kraemer, S., Weiderpass, E., & Nørgaard, M. (2015). Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. , 7, 491-508. https://doi.org/https://doi.org/10.2147/CLEP.S90589

Lundberg, J., Cars, T., Löövi, S., Söderling, J., Sundström, J., Tiihonen, J., Leval, A., Gannedahl, A., Björkholm, C., Själin, M., & Hellner, C. (2023). Association of Treatment-Resistant Depression With Patient Outcomes and Health Care Resource Utilization in a Population-Wide Study. JAMA Psychiatry, 80(2), 167-175. https://doi.org/10.1001/jamapsychiatry.2022.3860

Lundberg, J., Cars, T., Löövi, S., Söderling, J., Tiihonen, J., Leval, A., Gannedahl, A., Björkholm, C., Själin, M., & Hellner, C. (2022). Clinical and societal burden of incident major depressive disorder: A population-wide cohort

study in Stockholm. Acta Psychiatr Scand, 146(1), 51-63. https://doi.org/10.1111/acps.13414

MacLeod-Glover, N., & Chuang, R. (2020). Chronic lithium toxicity: Considerations and systems analysis. Can Fam Physician, 66(4), 258-261.

Malhi, G. S., Bell, E., Boyce, P., Bassett, D., Berk, M., Bryant, R., Gitlin, M., Hamilton, A., Hazell, P., Hopwood, M., Lyndon, B., McIntyre, R. S., Morris, G., Mulder, R., Porter, R., Singh, A. B., Yatham, L. N., Young, A., & Murray, G. (2020). The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary. Bipolar Disord, 22(8), 805-821. https://doi.org/10.1111/bdi.13036

Malhi, G. S., Bell, E., Jadidi, M., Gitlin, M., & Bauer, M. (2023). Countering the declining use of lithium therapy: a call to arms. Int J Bipolar Disord, 11(1), 30. https://doi.org/10.1186/s40345-023-00310-x

Malhi, G. S., Tanious, M., Das, P., Coulston, C. M., & Berk, M. (2013). Potential mechanisms of action of lithium in bipolar disorder. Current understanding. CNS Drugs, 27(2), 135-153. https://doi.org/10.1007/s40263-013-0039-0

Malmgren, L., McGuigan, F. E., Berglundh, S., Westman, K., Christensson, A., & Åkesson, K. (2015). Declining Estimated Glomerular Filtration Rate and Its Association with Mortality and Comorbidity Over 10 Years in Elderly Women. Nephron, 130(4), 245-255. https://doi.org/10.1159/000435790

Markowitz, G. S., Radhakrishnan, J., Kambham, N., Valeri, A. M., Hines, W. H., & D'Agati, V. D. (2000). Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol, 11(8), 1439-1448. https://doi.org/10.1681/asn.V1181439

Mazzuchi, N., Fernandez-Cean, J. M., & Carbonell, E. (2000). Criteria for selection of ESRD treatment modalities. Kidney International, 57, 136-143.

McKnight, R. F., Adida, M., Budge, K., Stockton, S., Goodwin, G. M., & Geddes, J. R. (2012). Lithium toxicity profile: a systematic review and meta-analysis. Lancet, 379(9817), 721-728. https://doi.org/10.1016/s0140-6736(11)61516-x

McKnight, R. F., de La Motte de Broöns de Vauvert, S., Chesney, E., Amit, B. H., Geddes, J., & Cipriani, A. (2019). Lithium for acute mania. Cochrane Database Syst Rev, 6(6), Cd004048. https://doi.org/10.1002/14651858.CD004048.pub4

Meehan, A. D., Udumyan, R., Kardell, M., Landén, M., Järhult, J., & Wallin, G. (2018). Lithium-Associated Hypercalcemia: Pathophysiology, Prevalence, Management. World J Surg, 42(2), 415-424. https://doi.org/10.1007/s00268-017-4328-5

Mehta, P. M., Gimenez, G., Walker, R. J., & Slatter, T. L. (2022). Reduction of lithium induced interstitial fibrosis on co-administration with amiloride. Sci Rep, 12(1), 14598. https://doi.org/10.1038/s41598-022-18825-1

Memon, A., Rogers, I., Fitzsimmons, S., Carter, B., Strawbridge, R., Hidalgo-Mazzei, D., & Young, A. H. (2020). Association between naturally occurring lithium in drinking water and suicide rates: systematic review and meta-analysis

of ecological studies. Br J Psychiatry, 217(6), 667-678. https://doi.org/10.1192/bjp.2020.128

Merikangas, K. R., Jin, R., He, J. P., Kessler, R. C., Lee, S., Sampson, N. A., Viana, M. C., Andrade, L. H., Hu, C., Karam, E. G., Ladea, M., Medina-Mora, M. E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J. E., & Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry, 68(3), 241-251. https://doi.org/10.1001/archgenpsychiatry.2011.12

Miura, T., Noma, H., Furukawa, T. A., Mitsuyasu, H., Tanaka, S., Stockton, S., Salanti, G., Motomura, K., Shimano-Katsuki, S., Leucht, S., Cipriani, A., Geddes, J. R., & Kanba, S. (2014). Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry, 1(5), 351-359. https://doi.org/10.1016/s2215-0366(14)70314-1

Momen, N. C., Plana-Ripoll, O., Agerbo, E., Christensen, M. K., Iburg, K. M., Laursen, T. M., Mortensen, P. B., Pedersen, C. B., Prior, A., Weye, N., & McGrath, J. J. (2022). Mortality Associated With Mental Disorders and Comorbid General Medical Conditions. JAMA Psychiatry, 79(5), 444-453. https://doi.org/10.1001/jamapsychiatry.2022.0347

Moreno-Agostino, D., Wu, Y. T., Daskalopoulou, C., Hasan, M. T., Huisman, M., & Prina, M. (2021). Global trends in the prevalence and incidence of depression:a systematic review and meta-analysis. J Affect Disord, 281, 235-243. https://doi.org/10.1016/j.jad.2020.12.035

Murbach, T. S., Glávits, R., Endres, J. R., Hirka, G., Vértesi, A., Béres, E., & Szakonyiné, I. P. (2021). A toxicological evaluation of lithium orotate. Regul Toxicol Pharmacol, 124, 104973. https://doi.org/10.1016/j.yrtph.2021.104973

Muronaga, M., Terao, T., Kohno, K., Hirakawa, H., Izumi, T., & Etoh, M. (2022). Lithium in drinking water and Alzheimer's dementia: Epidemiological Findings from National Data Base of Japan. Bipolar Disord, 24(8), 788-794. https://doi.org/10.1111/bdi.13257

Nestsiarovich, A., Kerner, B., Mazurie, A. J., Cannon, D. C., Hurwitz, N. G., Zhu, Y., Nelson, S. J., Oprea, T. I., Unruh, M. L., Crisanti, A. S., Tohen, M., Perkins, D. J., & Lambert, C. G. (2019). Comparison of 71 bipolar disorder pharmacotherapies for kidney disorder risk: The potential hazards of polypharmacy. J Affect Disord, 252, 201-211. https://doi.org/10.1016/j.jad.2019.04.009

Netto, I., & Phutane, V. H. (2012). Reversible lithium neurotoxicity: review of the literatur. Prim Care Companion CNS Disord, 14(1). https://doi.org/10.4088/PCC.11r01197

NICE. (2014, December 2023). Bipolar disorder: assessment and management. NICE. Retrieved January 2024 from https://www.nice.org.uk/guidance/cg185

NICE. (2018). Renal replacement therapy and conservative management. Retrieved Feb 24, 2024 from https://www.nice.org.uk/guidance/ng107

Nielsen, J., Kwon, T. H., Christensen, B. M., Frøkiaer, J., & Nielsen, S. (2008). Dysregulation of renal aquaporins and epithelial sodium channel in lithium-induced nephrogenic diabetes insipidus. Semin Nephrol, 28(3), 227-244. https://doi.org/10.1016/j.semnephrol.2008.03.002

Nielsen, S., Kwon, T. H., Christensen, B. M., Promeneur, D., Frøkiaer, J., & Marples, D. (1999). Physiology and pathophysiology of renal aquaporins. J Am Soc Nephrol, 10(3), 647-663. https://doi.org/10.1681/asn.V103647

Niufan, G., Tohen, M., Qiuqing, A., Fude, Y., Pope, E., McElroy, H., Ming, L., Gaohua, W., Xinbao, Z., Huichun, L., & Liang, S. (2008). Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. J Affect Disord, 105(1-3), 101-108. https://doi.org/10.1016/j.jad.2007.04.020

NKF. (2002). KDOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis, 39(2 Suppl 1), S1-266.

NKF. (2013). KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. . Kidney Int Suppl, 3(1), 1–150.

Nolen, W. A. (2015). More robust evidence for the efficacy of lithium in the long-term treatment of bipolar disorder: should lithium (again) be recommended as the single preferred first-line treatment? Int J Bipolar Disord, 3, 1. https://doi.org/10.1186/s40345-014-0017-6

Nolen, W. A., Licht, R. W., Young, A. H., Malhi, G. S., Tohen, M., Vieta, E., Kupka, R. W., Zarate, C., Nielsen, R. E., Baldessarini, R. J., & Severus, E. (2019). What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Bipolar Disord, 21(5), 394-409. https://doi.org/10.1111/bdi.12805

Nyman, U., Grubb, A., Larsson, A., Hansson, L. O., Flodin, M., Nordin, G., Lindström, V., & Björk, J. (2014). The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med, 52(6), 815-824. https://doi.org/10.1515/cclm-2013-0741

Ogobuiro, I., & Tuma, F. (2023). Physiology, Renal. [Updated 2023 Jul 24]. In StatPearls. StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK538339/

Ohgami, H. I., Nobuyoshi, Iwata, N., Shiotsuki, I., & Terao, T. (2009). Lithium levels in drinking water and risk of suicide. British Journal of Psychiatry, 194(5), 464-465. https://doi.org/10.1192/bjp.bp.108.055798

Ommati, M. M., Niknahad, H., Farshad, O., Azarpira, N., & Heidari, R. (2021). In Vitro and In Vivo Evidence on the Role of Mitochondrial Impairment as a Mechanism of Lithium-Induced Nephrotoxicity. Biol Trace Elem Res, 199(5), 1908-1918. https://doi.org/10.1007/s12011-020-02302-9

Pacholko, A. G., & Bekar, L. K. (2021). Lithium orotate: A superior option for lithium therapy? Brain Behav, 11(8), e2262. https://doi.org/10.1002/brb3.2262

Pacholko, A. G., & Bekar, L. K. (2023). Different pharmacokinetics of lithium orotate inform why it is more potent, effective, and less toxic than lithium carbonate in a mouse model of mania. J Psychiatr Res, 164, 192-201. https://doi.org/10.1016/j.jpsychires.2023.06.012

Pagels, A. A., Söderkvist, B. K., Medin, C., Hylander, B., & Heiwe, S. (2012). Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. Health and Quality of Life Outcomes, 10(1), 71. https://doi.org/10.1186/1477-7525-10-71

Pahwa, M., Joseph, B., Nunez, N. A., Jenkins, G. D., Colby, C. L., Kashani, K. B., Marin, V., Moore, K. M., Betcher, H. K., Ozerdem, A., Cuellar-Barboza, A. B., McElroy, S. L., Biernacka, J. M., Frye, M. A., & Singh, B. (2021). Long-term lithium therapy and risk of chronic kidney disease in bipolar disorder: A historical cohort study. Bipolar Disord, 23(7), 715-723. https://doi.org/10.1111/bdi.13052

Pan, Y. J., Yeh, L. L., Chan, H. Y., & Chang, C. K. (2020). Excess mortality and shortened life expectancy in people with major mental illnesses in Taiwan. Epidemiol Psychiatr Sci, 29, e156. https://doi.org/10.1017/s2045796020000694

Paton, C., Adroer, R., & Barnes, T. R. (2013). Monitoring lithium therapy: the impact of a quality improvement programme in the UK. Bipolar Disord, 15(8), 865-875. https://doi.org/10.1111/bdi.12128

Persson, G. (1977). Comparison of plasma lithium levels and their interindividual variations with coated lithium carbonate tablets and a medium-slow-release lithium sulphate preparation (Lithionit Duretter). Acta Psychiatr Scand, 55(2), 147-152. https://doi.org/10.1111/j.1600-0447.1977.tb00151.x

Pettersson, U. (1980). Experience from a lithium clinic (Erfarenheter från en litium dispensär). Lakartidningen, 77(19), 1845-1847.

Phelps, J. R., Pipitone, O. R., Squires, K., & Bale, J. D. (2021). Lamotrigine and lithium in primary care psychiatric consultation: adoption and adverse effects. Fam Pract, 38(4), 381-386. https://doi.org/10.1093/fampra/cmaa131

Plans, L., Barrot, C., Nieto, E., Rios, J., Schulze, T. G., Papiol, S., Mitjans, M., Vieta, E., & Benabarre, A. (2019). Association between completed suicide and bipolar disorder: A systematic review of the literature. J Affect Disord, 242, 111-122. https://doi.org/10.1016/j.jad.2018.08.054

Plenge, P., & Mellerup, E. T. (1986). Lithium and the kidney: Is one daily dose better than two? Comprehensive Psychiatry, 27(4), 336-342. https://doi.org/https://doi.org/10.1016/0010-440X(86)90009-X

Ponzer, K., Millischer, V., Schalling, M., Gissler, M., Lavebratt, C., & Backlund, L. (2023). Lithium and risk of cardiovascular disease, dementia and venous thromboembolism. Bipolar Disord, 25(5), 391-401. https://doi.org/10.1111/bdi.13300

Post, A., Kremer, D., Groothof, D., Seidel, U., Huebbe, P., Franssen, C. F. M., Kema, I. P., Lüersen, K., Rimbach, G., & Bakker, S. J. L. (2023). Dietary lithium intake, graft failure and mortality in kidney transplant recipients. Nephrol Dial Transplant, 38(8), 1867-1879. https://doi.org/10.1093/ndt/gfac340

Post, R. M. (2018). The New News about Lithium: An Underutilized Treatment in the United States. Neuropsychopharmacology, 43(5), 1174-1179. https://doi.org/10.1038/npp.2017.238

Pottegård, A., Hallas, J., Jensen, B. L., Madsen, K., & Friis, S. (2016). Long-Term Lithium Use and Risk of Renal and Upper Urinary Tract Cancers. J Am Soc Nephrol, 27(1), 249-255. https://doi.org/10.1681/asn.2015010061

Poyurovsky, M. (2010). Acute antipsychotic-induced akathisia revisited. Br J Psychiatry, 196(2), 89-91. https://doi.org/10.1192/bjp.bp.109.070540

Presne, C., Fakhouri, F., Noël, L. H., Stengel, B., Even, C., Kreis, H., Mignon, F., & Grünfeld, J. P. (2003). Lithium-induced nephropathy: Rate of progression and prognostic factors. Kidney Int, 64(2), 585-592. https://doi.org/10.1046/j.1523-1755.2003.00096.x

Priadel package leaflet. Essential Pharma Ltd. Retrieved Feb 18, 2024 from https://www.medicines.org.uk/emc/product/13163/smpc/print#INDICATIONS

Rakofsky, J. J., Lucido, M. J., & Dunlop, B. W. (2022). Lithium in the treatment of acute bipolar depression: A systematic review and meta-analysis. J Affect Disord, 308, 268-280. https://doi.org/10.1016/j.jad.2022.04.058

Rakofsky, J. J., Lucido, M. J., & Dunlop, B. W. (2023). All studies are not created equal: A systematic narrative review of bipolar depression clinical trial inclusion/exclusion rules and baseline severity scores. J Affect Disord, 333, 130-139. https://doi.org/10.1016/j.jad.2023.04.035

Regeringen. (2023). Vidareanvändning av hälsodata för vård och klinisk forskning. Swedish Government. Retrieved Feb 26, 2024 from https://www.regeringen.se/rattsliga-dokument/statens-offentliga-utredningar/2023/11/sou-202376/

Regional Medicink Riktlinje - Läkemedel. Bipolär sjukdom. (2023). In V. G. Region (Ed.), Västra Götaland Region. Västra Götaland Region: Västra Götaland Region.

Rej, S., Herrmann, N., Gruneir, A., McArthur, E., Jeyakumar, N., Muanda, F. T., Harel, Z., Dixon, S., & Garg, A. X. (2020). Association of Lithium Use and a Higher Serum Concentration of Lithium With the Risk of Declining Renal Function in Older Adults: A Population-Based Cohort Study. J Clin Psychiatry, 81(5). https://doi.org/10.4088/JCP.19m13045

Rej, S., Herrmann, N., Shulman, K., Fischer, H. D., Fung, K., Harel, Z., & Gruneir, A. (2017). Lithium Use, but Not Valproate Use, Is Associated With a Higher Risk of Chronic Kidney Disease in Older Adults With Mental Illness. J Clin Psychiatry, 78(8), e980-e985. https://doi.org/10.4088/JCP.16m11125

Rej, S., Senouci, S. I., Looper, K., & Segal, M. (2013). Using hypernatraemic events to predict reduced renal function in elderly lithium patients: a brief

report. Psychogeriatrics, 13(1), 25-28. https://doi.org/10.1111/j.1479-8301.2012.00433.x

Rej, S., Shulman, K., Herrmann, N., Harel, Z., Fischer, H. D., Fung, K., & Gruneir, A. (2014). Prevalence and correlates of renal disease in older lithium users: a population-based study. Am J Geriatr Psychiatry, 22(11), 1075-1082. https://doi.org/10.1016/j.jagp.2014.01.015

Riedinger, M. A., van der Wee, N. J. A., Giltay, E. J., & de Leeuw, M. (2023). Lithium in bipolar depression: A review of the evidence. Hum Psychopharmacol, 38(5), e2881. https://doi.org/10.1002/hup.2881

Ringborg, A., Lindgren, P., Martinell, M., Yin, D. D., Schön, S., & Stålhammar, J. (2008). Prevalence and incidence of Type 2 diabetes and its complications 1996-2003--estimates from a Swedish population-based study. Diabet Med, 25(10), 1178-1186. https://doi.org/10.1111/j.1464-5491.2008.02541.x

Roxanas, M., Grace, B. S., & George, C. R. (2014). Renal replacement therapy associated with lithium nephrotoxicity in Australia. Med J Aust, 200(4), 226-228. https://doi.org/10.5694/mja13.10435

Schell, J. O., Da Silva-Gane, M., & Germain, M. J. (2013). Recent insights into life expectancy with and without dialysis. Curr Opin Nephrol Hypertens, 22(2), 185-192. https://doi.org/10.1097/MNH.0b013e32835ddb69

Schoretsanitis, G., de Filippis, R., Brady, B. M., Homan, P., Suppes, T., & Kane, J. M. (2022). Prevalence of impaired kidney function in patients with long-term lithium treatment: A systematic review and meta-analysis. Bipolar Disord, 24(3), 264-274. https://doi.org/10.1111/bdi.13154

Schou, M., Juel-Nielsen, N., Stromgren, E., & Voldby, H. (1954). The treatment of manic psychoses by the administration of lithium salts. J Neurol Neurosurg Psychiatry, 17(4), 250-260. https://doi.org/10.1136/jnnp.17.4.250

Schrauzer, G. N., & Shrestha, K. P. (1990). Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol Trace Elem Res, 25(2), 105-113. https://doi.org/10.1007/bf02990271

Schroeder, E. B., Yang, X., Thorp, M. L., Arnold, B. M., Tabano, D. C., Petrik, A. F., Smith, D. H., Platt, R. W., & Johnson, E. S. (2017). Predicting 5-Year Risk of RRT in Stage 3 or 4 CKD: Development and External Validation. Clin J Am Soc Nephrol, 12(1), 87-94. https://doi.org/10.2215/cjn.01290216

Shine, B., McKnight, R. F., Leaver, L., & Geddes, J. R. (2015). Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. Lancet, 386(9992), 461-468. https://doi.org/10.1016/s0140-6736(14)61842-0

Shiotsuki, I., Terao, T., Ishii, N., Takeuchi, S., Kuroda, Y., Kohno, K., Mizokami, Y., Hatano, K., Tanabe, S., Kanehisa, M., Iwata, N., & Matusda, S. (2016). Trace lithium is inversely associated with male suicide after adjustment of climatic factors. J Affect Disord, 189, 282-286. https://doi.org/10.1016/j.jad.2015.09.070

Shorter, E. (2009). The history of lithium therapy. Bipolar Disord, 11 Suppl 2(Suppl 2), 4-9. https://doi.org/10.1111/j.1399-5618.2009.00706.x

Singh, B., Yocum, A. K., Strawbridge, R., Burdick, K. E., Millett, C. E., Peters, A. T., Sperry, S. H., Fico, G., Vieta, E., Verdolini, N., Godin, O., Leboyer, M., Etain, B., Tso, I. F., Coombes, B. J., McInnis, M. G., Nierenberg, A. A., Young, A. H., Ashton, M. M., . . . Frye, M. A. (2023). Patterns of pharmacotherapy for bipolar disorder: A GBC survey. Bipolar Disord. https://doi.org/10.1111/bdi.13366

Singh, L. K., Nizamie, S. H., Akhtar, S., & Praharaj, S. K. (2011). Improving tolerability of lithium with a once-daily dosing schedule. Am J Ther, 18(4), 288-291. https://doi.org/10.1097/MJT.0b013e3181d070c3

Singulani, M. P., Ferreira, A. F. F., Figueroa, P. S., Cuyul-Vásquez, I., Talib, L. L., Britto, L. R., & Forlenza, O. V. (2024). Lithium and Disease Modification: A Systematic Review and Meta-analysis in Alzheimer's and Parkinson's Disease. Ageing Res Rev, 102231. https://doi.org/10.1016/j.arr.2024.102231

Smith, K. A., & Cipriani, A. (2017). Lithium and suicide in mood disorders: Updated meta-review of the scientific literature. Bipolar Disord, 19(7), 575-586. https://doi.org/10.1111/bdi.12543

Song, J., Sjölander, A., Joas, E., Bergen, S. E., Runeson, B., Larsson, H., Landén, M., & Lichtenstein, P. (2017). Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50,000 Patients With Bipolar Disorder. Am J Psychiatry, 174(8), 795-802. https://doi.org/10.1176/appi.ajp.2017.16050542

Soriano, R., Penfold, D., & Leslie, S. (2023). Anatomy, Abdomen and Pelvis: Kidneys. [Updated 2023 Jul 24]. In StatPearls. StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK482385/

Strawbridge, R., Kerr-Gaffney, J., Bessa, G., Loschi, G., Freitas, H. L. O., Pires, H., Cousins, D. A., Juruena, M. F., & Young, A. H. (2023). Identifying the neuropsychiatric health effects of low-dose lithium interventions: A systematic review. Neurosci Biobehav Rev, 144, 104975. https://doi.org/10.1016/j.neubiorev.2022.104975

Strobusch, A. D., & Jefferson, J. W. (1980). The checkered history of lithium in medicine. Pharm Hist, 22(2), 72-76.

Sud, M., Tangri, N., Pintilie, M., Levey, A. S., & Naimark, D. M. (2016). Progression to Stage 4 chronic kidney disease and death, acute kidney injury and hospitalization risk: a retrospective cohort study. Nephrol Dial Transplant, 31(7), 1122-1130. https://doi.org/10.1093/ndt/gfv389

Svenskt Njurregister (SNR). (2023). https://www.medscinet.net/snr/page.aspx?id=1

Sveriges Dödbok. (2018). In. Sweden: Sveriges Släktforskarförbund.

Szałach, Ł. P., Lisowska, K. A., Cubała, W. J., Barbuti, M., & Perugi, G. (2023). The immunomodulatory effect of lithium as a mechanism of action in bipolar disorder. Front Neurosci, 17, 1213766. https://doi.org/10.3389/fnins.2023.1213766

Tabibzadeh, N., Faucon, A. L., Vidal-Petiot, E., Serrano, F., Males, L., Fernandez, P., Khalil, A., Rouzet, F., Tardivon, C., Mazer, N., Dubertret, C., Delavest, M., Marlinge, E., Etain, B., Bellivier, F., Vrtovsnik, F., & Flamant, M. (2021). Determinants of Kidney Function and Accuracy of Kidney Microcysts Detection in Patients Treated With Lithium Salts for Bipolar Disorder. Front Pharmacol, 12, 784298. https://doi.org/10.3389/fphar.2021.784298

Tiihonen, J., Tanskanen, A., Hoti, F., Vattulainen, P., Taipale, H., Mehtälä, J., & Lähteenvuo, M. (2017). Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study. Lancet Psychiatry, 4(7), 547-553. https://doi.org/10.1016/s2215-0366(17)30134-7

Tsai, C. W., Ting, I. W., Yeh, H. C., & Kuo, C. C. (2017). Longitudinal change in estimated GFR among CKD patients: A 10-year follow-up study of an integrated kidney disease care program in Taiwan. PLoS One, 12(4), e0173843. https://doi.org/10.1371/journal.pone.0173843

Turin, T. C., Tonelli, M., Manns, B. J., Ravani, P., Ahmed, S. B., & Hemmelgarn, B. R. (2012). Chronic kidney disease and life expectancy. Nephrol Dial Transplant, 27(8), 3182-3186. https://doi.org/10.1093/ndt/gfs052

Törmä, E., Carlberg, B., Eriksson, M., Jansson, J. H., & Eliasson, M. (2015). Long term trends in control of hypertension in the Northern Sweden MONICA study 1986-2009. BMC Public Health, 15, 957. https://doi.org/10.1186/s12889-015-2280-6

Vaidya, S., & Aeddula, N. (2022). Chronic Kidney Disease. StatPearls [Internet]. Retrieved Jan 2024, from https://www.ncbi.nlm.nih.gov/books/NBK535404/

Van Alphen, A. M., Bosch, T. M., Kupka, R. W., & Hoekstra, R. (2021). Chronic kidney disease in lithium-treated patients, incidence and rate of decline. Int J Bipolar Disord, 9(1), 1. https://doi.org/10.1186/s40345-020-00204-2

van Blijderveen, J. C., Straus, S. M., Zietse, R., Stricker, B. H., Sturkenboom, M. C., & Verhamme, K. M. (2014). A population-based study on the prevalence and incidence of chronic kidney disease in the Netherlands. Int Urol Nephrol, 46(3), 583-592. https://doi.org/10.1007/s11255-013-0563-3

van Winkel, R., De Hert, M., Van Eyck, D., Hanssens, L., Wampers, M., Scheen, A., & Peuskens, J. (2008). Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder. Bipolar Disord, 10(2), 342-348. https://doi.org/10.1111/j.1399-5618.2007.00520.x

Vancampfort, D., Correll, C. U., Galling, B., Probst, M., De Hert, M., Ward, P. B., Rosenbaum, S., Gaughran, F., Lally, J., & Stubbs, B. (2016). Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry, 15(2), 166-174. https://doi.org/10.1002/wps.20309

Vázquez, G. H., Bahji, A., Undurraga, J., Tondo, L., & Baldessarini, R. J. (2021). Efficacy and Tolerability of Combination Treatments for Major Depression: Antidepressants plus Second-Generation Antipsychotics vs.

Esketamine vs. Lithium. J Psychopharmacol, 35(8), 890-900. https://doi.org/10.1177/02698811211013579

Walker, R. J., Weggery, S., Bedford, J. J., McDonald, F. J., Ellis, G., & Leader, J. P. (2005). Lithium-induced reduction in urinary concentrating ability and urinary aquaporin 2 (AQP2) excretion in healthy volunteers. Kidney Int, 67(1), 291-294. https://doi.org/10.1111/j.1523-1755.2005.00081.x

Walters, S. J., Campbell, M. J., & Machin, D. (2021). Medical Statistics: A Textbook for the Health Scientists. Wiley-Blackwell, .

Wang, S., Linkletter, C., Dore, D., Mor, V., Buka, S., & Maclure, M. (2012). Age, antipsychotics, and the risk of ischemic stroke in the Veterans Health Administration. Stroke, 43(1), 28-31. https://doi.org/10.1161/strokeaha.111.617191

Webster, A. C., Nagler, E. V., Morton, R. L., & Masson, P. (2017). Chronic Kidney Disease. Lancet, 389(10075), 1238-1252. https://doi.org/10.1016/s0140-6736(16)32064-5

Weisler, R. H., Nolen, W. A., Neijber, A., Hellqvist, A., & Paulsson, B. (2011). Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). J Clin Psychiatry, 72(11), 1452-1464. https://doi.org/10.4088/JCP.11m06878

Widerlöv, E. (1976). A comparative double-blind study of the side effects of Litarex and Lithionit Durettes. Acta Psychiatr Scand, 54(4), 294-302. https://doi.org/10.1111/j.1600-0447.1976.tb00123.x

Wilkinson, S. T., Trujillo Diaz, D., Rupp, Z. W., Kidambi, A., Ramirez, K. L., Flores, J. M., Avila-Quintero, V. J., Rhee, T. G., Olfson, M., & Bloch, M. H. (2022). Pharmacological and somatic treatment effects on suicide in adults: A systematic review and meta-analysis. Depress Anxiety, 39(2), 100-112. https://doi.org/10.1002/da.23222

Wiuff, A. C., Rohde, C., Jensen, B. D., Nierenberg, A. A., Østergaard, S. D., & Köhler-Forsberg, O. (2023). Association between lithium treatment and renal, thyroid and parathyroid function: A cohort study of 6659 patients with bipolar disorder. Bipolar Disord. https://doi.org/10.1111/bdi.13356

Xie, Y., Bowe, B., Xian, H., Balasubramanian, S., & Al-Aly, Z. (2016). Estimated GFR Trajectories of People Entering CKD Stage 4 and Subsequent Kidney Disease Outcomes and Mortality. Am J Kidney Dis, 68(2), 219-228. https://doi.org/10.1053/j.ajkd.2016.02.039

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., Sharma, V., Goldstein, B. I., Rej, S., Beaulieu, S., Alda, M., MacQueen, G., Milev, R. V., Ravindran, A., O'Donovan, C., McIntosh, D., Lam, R. W., Vazquez, G., Kapczinski, F., . . . Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord, 20(2), 97-170. https://doi.org/10.1111/bdi.12609

Yazıcı, M. K., Özçelik Eroğlu, E., Ertuğrul, A., Anıl Yağcıoğlu, A. E., Ağaoğlu, E., Karahan, S., Eni, N., Sağlam Aykut, D., Kavak, Ö., & Erdem, Y. (2022). Renal effects of long-term lithium therapy, revisited. Hum Psychopharmacol, 37(2), e2812. https://doi.org/10.1002/hup.2812

Ying, M., Shao, X., Qin, H., Yin, P., Lin, Y., Wu, J., Ren, J., & Zheng, Y. (2024). Disease Burden and Epidemiological Trends of Chronic Kidney Disease at the Global, Regional, National Levels from 1990 to 2019. Nephron, 148(2), 113-123. https://doi.org/10.1159/000534071

Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., & Sheehan, J. J. (2021). The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. J Clin Psychiatry, 82(2). https://doi.org/10.4088/JCP.20m13699

Zivanovic, O. (2017). Lithium: A classic drug-Frequently discussed, but, sadly, seldom prescribed! Aust N Z J Psychiatry, 51(9), 886-896. https://doi.org/10.1177/0004867417695889

Öhlund, L., Ott, M., Oja, S., Bergqvist, M., Lundqvist, R., Sandlund, M., Salander Renberg, E., & Werneke, U. (2018). Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. BMC Psychiatry, 18(1), 37. https://doi.org/10.1186/s12888-018-1622-1

Østergaard, H. B., Read, S. H., Sattar, N., Franzén, S., Halbesma, N., Dorresteijn, J. A. N., Westerink, J., Visseren, F. L. J., Wild, S. H., Eliasson, B., & van der Leeuw, J. (2022). Development and Validation of a Lifetime Risk Model for Kidney Failure and Treatment Benefit in Type 2 Diabetes: 10-Year and Lifetime Risk Prediction Models. Clin J Am Soc Nephrol, 17(12), 1783-1791. https://doi.org/10.2215/cjn.05020422