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Lithium effects on renal functioning: an expert opinion and management algorithm

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Abstract

Objective This expert opinion paper addresses the critical balance between lithium's therapeutic efficacy in recurrent mood disorders and its potential renal side effects. The objective is to provide evidence-based guidelines to enhance clinical decision-making, prevent emergence of, and mitigate risks associated with lithium-induced renal impairment.

Methods An extensive review of epidemiological, observational, and experimental studies on lithium-induced renal impairment, focusing on its pathophysiology, clinical manifestations, and risk factors was conducted. Expert consensus and recent data were integrated to develop a management algorithm for renal monitoring and intervention.

Results Lithium remains the gold standard for mood stabilization in bipolar disorders, with robust evidence supporting its role in recurrence prevention and suicide risk reduction. While mild to moderate renal impairment is recognized as a risk factor, newer studies show a lower incidence of severe outcomes, such as end-stage kidney disease, necessitating dialysis treatment and renal transplantation, especially with appropriate monitoring, as compared to older studies. This paper addresses pathophysiological mechanisms, including arginine vasopressin resistance and chronic interstitial nephritis, alongside risk factors like rapid initial decline in glomerular filtration rate, early age at treatment initiation, cumulative dosage, mean serum levels of lithium and episodes of lithium

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intoxication. Effective management strategies, including judicious dosing, routine monitoring, and early nephrology referral, can significantly improve outcomes.

Conclusions Lithium remains an invaluable treatment for recurrent mood disorders, and its benefits often outweigh the risks when managed appropriately. This paper provides a practical framework for clinicians to address renal concerns, emphasizing the importance of systematic monitoring and individualized care. The paper underscores the need for continued research and education of clinicians and patients to optimize lithium use while safeguarding patient health.

Keywords Lithium, Bipolar disorder, Chronic kidney disease, Renal impairment, Nephrotoxicity, Arginine vasopressin resistance

Background

Lithium has long been regarded as the benchmark for preventing recurrences in patients diagnosed with bipolar disorders, with most guidelines advocating for its use as the primary treatment option (Gitlin and Bauer 2024; Malhi and Bauer 2023). The efficacy of lithium has been demonstrated under real-world conditions, enhancing the applicability of study findings to patients without a documented acute response to lithium prior to maintenance therapy, unlike most other mood stabilizers (Nielsen and Licht 2023; Ulrichsen et al. 2023). Therefore, evidence supports that clinicians should consider lithium maintenance treatment even in the absence of prior knowledge regarding its effectiveness during acute mood episodes (Malhi et al. 2023; Nielsen and Licht 2023; Ulrichsen et al. 2023).

Beyond its role in decreasing the likelihood of recurrences in patients with bipolar disorder, there is accumulating evidence suggesting lithium's potential in reducing suicide-related mortality (Smith and Cipriani 2017; Tondo and Baldessarini 2024). Moreover, its therapeutic utility extends beyond individuals with bipolar disorders, encompassing both acute and preventive interventions for individuals with unipolar major depressive disorder, although mainly used in patients to augment a partial response in those with difficult to treat depression (Abou-Saleh et al. 2017; Ercis et al. 2023). There is evidence that lithium prevents cognitive and structural change in bipolar disorder and perhaps also in dementia and lithium is potentially a disease modifying drug that should be used more often and early in the course of bipolar illness (Aron et al. 2025; De-Paula et al. 2025; Post et al. 2025).

A significant barrier to broader lithium adoption is the apprehension and prescriber's fear regarding its side effects. As with any pharmacological treatment, lithium carries inherent risks, and concerns regarding adverse reactions have fostered hesitancy among both patients and healthcare providers, with concerns regarding renal impairment being prominent (Gitlin and Bauer 2023; Nielsen et al. 2018). Several observational studies have explored the link between lithium treatment and decreased glomerular filtration rates (GFR). Bendz et al. conducted a large epidemiological study in 2010 including one-third of the Swedish population, examining 2,202 individuals with end stage kidney disease (ESKD) (Bendz et al. 2010). They found a prevalence of 0.53% of lithium-induced ESKD, six times higher than in the general population. A similar study by Aiff et al. in 2014 found a prevalence of 1.5% in patients exposed to lithium as compared to a prevalence of 0.19% in the general population (Aiff et al. 2014). However, limitations like recall bias and study design complexities warrant cautious interpretation as described in the review by Nielsen et al. (Nielsen et al. 2018). In the study by Close et al. (2014), the authors investigated chronic kidney disease (CKD) stage 4 or 5 in patients with bipolar disorder using the UK General Practice Research Database and found a more than doubled rate of CKD in those exposed to lithium (Close et al. 2014). Shine et al. assessed renal function in those exposed to lithium in the UK population showing an increased hazard rate ratio (HR) of 1.93, 95%CI (1.76–2.12) for CKD stage 3, however they were unable to adjust for surveillance bias (Shine et al. 2015). In 2015, Kessing et al. conducted a nationwide registry-based study in Denmark finding no significant increase in ESKD with more lithium prescriptions (Kessing et al. 2015). Similarly, Hayes et al. (2016), in a propensity-score matched study design, found no association between lithium exposure and CKD 4 and 5, when comparing patients exposed to lithium to others with bipolar disorder treated with other drugs (Hayes et al. 2016). Similarly, in 2023, Bosi et al. utilized Swedish registry data to track 10,946 adults who newly started lithium (n = 5,308) or valproate (n = 5,638) from 2007–2018, with a median follow-up of 4.5 years. Propensity-weighted models showed lithium did not increase the risk of CKD progression (HR 1.11, 95% CI 0.86–1.45) or acute kidney injury (AKI) (HR 0.88, 0.70–1.10) versus valproate, and 10-year absolute risk of CKD was virtually identical (8.4% vs 8.2%). Annual eGFR decline and incident albuminuria were likewise comparable. Risk of CKD rose, however, with exposure intensity: every extra 500 defined-daily-dose equivalents of lithium carried a 30% higher hazard of CKD progression,

and median serum levels > 1.0 mmol/L tripled both CKD and AKI risk, even though high levels comprised only 3% of > 35 000 tests (Bosi et al. 2023). Using linked national registries, Gislason et al. constructed an Iceland-wide retrospective cohort and followed 2,695 adults treated with lithium and 1,615 mood-disorder controls from 2008 to 2017, each with ≥ 2 P-creatinine measurements. After exclusions, 3,198 individuals (mean age 46 years) were analyzed. CKD Stage 3–5 developed in 10.4% of lithium users versus 3.0% of controls, yielding an adjusted HR 1.90 (95% CI 1.32–2.75). Risk rose sharply with higher mean serum lithium: specifically, HR 2.93, 95%CI:(1.97–4.36) for 0.60–0.79 mmol/L and HR 4.31, 95%CI:(2.66–6.99) for 0.80–0.99 mmol/L, while levels 0.30–0.59 mmol/L were not associated with excess CKD. Older age, lower baseline eGFR, diabetes, and prior acute kidney injury independently amplified risk of CKD (Gislason et al. 2024).

Recently, Chan et al., did a territory-wide cohort in Hong Kong (Chan et al., 2024) including 7,029 people with bipolar disorder followed for a mean of 8.4 years and compared lithium users with those receiving valproate or second-generation antipsychotics. Lithium was linked to a 35% higher risk of CKD stage 3 + (adjusted HR 1.35, 95%CI:(1.15–1.60)), but not to ESKD. Risk increased in a dose–response manner: with levels > 0.59 mmol/L and each episode with lithium levels > 1.0 mmol/L independently predicting CKD stage 3 + (Chan et al. 2025a). In a second publication on the same dataset, the team investigated predictors of CKD and showed that older age at diagnosis of bipolar disorder, male sex, physical comorbidities, higher mean lithium serum-level, fewer antipsychotic and mood-stabilizing anticonvulsant use, and greater antidepressant exposure were independent risk factors of CKD progression (Chan et al. 2025b).

Overall, while studies associate lithium treatment with less severe renal impairment, the evidence regarding ESKD is more mixed, with surveillance biases and study limitations complicating interpretation. However, newer, larger, and more well-designed studies have not found evidence of an increased risk of ESKD, suggesting that improved monitoring and treatment practices have resulted in better outcomes (Nielsen et al. 2018).

To improve clinical interpretability, we provide a harmonized overview of major cohort and registry studies (Table 1), explicitly separating intermediate renal outcomes (CKD stage 3 or eGFR < 60 mL/min/1.73 m^2) from advanced endpoints (CKD stage 4–5 and ESKD). The table contextualizes relative and absolute risks and highlights the consistent dissociation between increased detection of mild CKD and the absence of a clear excess risk of ESKD in contemporary comparator-controlled studies.

To facilitate the use of lithium and to address clinician uncertainty regarding its management, there is a pressing need for pragmatic and evidence-informed clinical guidelines delineating treatment protocols. In this paper, we present an overview of the pathophysiological mechanisms underlying lithium-induced renal impairment and propose a systematic algorithm to aid clinicians in the initial management of renal side effects in patients undergoing lithium treatment, as well as guidelines for appropriate referral to nephrology specialists when necessary.

Approach to evidence and scope

This paper represents an expert consensus narrative review and clinical management framework. No formal systematic database search, predefined inclusion or exclusion criteria, or structured quality scoring procedures were applied. Evidence was selected based on clinical relevance, methodological robustness, and contemporary applicability, with particular emphasis on large population-based cohort studies, nationwide registry analyses with appropriate comparator groups, and international guideline documents. When findings were heterogeneous or conflicting, uncertainties are explicitly acknowledged and interpreted in the context of known limitations, including confounding by indication and surveillance intensity in lithium-treated populations. This approach reflects the intent to synthesize clinically actionable knowledge rather than to provide an exhaustive systematic review.

Table 1 Renal outcomes associated with lithium treatment: harmonized summary of major cohort and registry studies (CKD = chronic kidney disease; ESKD = end-stage kidney disease; HR = hazard ratio; PS = propensity-score; NS = non-significant)

Study	Comparator	Outcome	Relative risk	Absolute risk/key finding	Interpretation
Bendz 2010	General population	ESKD	↑ (prevalence)	Rare outcome	Historical signal; not comparator-adjusted
Aiff 2014	General population	ESKD	↑ (prevalence)	Rare outcome	Likely influenced by ascertainment
Close 2014	Bipolar, non-lithium	CKD 4–5	↑	Low absolute numbers	Severe CKD uncommon
Shine 2015	General population	CKD 3	HR 1.93	Detection of mild CKD	Surveillance bias likely
Kessing 2015	Bipolar, registry	ESKD	No increase	No dose–response	Severe endpoints neutral
Hayes 2016	Bipolar, PS-matched	CKD 4–5	No increase	Neutral vs comparators	Comparator-controlled
Bosi 2023	Valproate	CKD progression	HR 1.11 (NS)	10-yr risk: 8.4% vs 8.2%	Level & dose dependent
Gislason 2024	Mood disorder controls	CKD 3–5	HR 1.90	No ESKD signal	Strong level-response
Chan 2025	Valproate / SGA	CKD 3 +	HR 1.35	No ESKD association	Confirms CKD–ESKD dissociation

Pathophysiology of lithium-induced nephrotoxicity

Renal complications of long-term lithium treatment are primarily arginine vasopressin resistance (AVP-R) (formerly known as nephrogenic diabetes insipidus) and chronic interstitial nephropathy eventually progressing to CKD. Less common are renal tubular acidosis and nephrotic syndrome (commonly due to minimal change disease or focal segmental glomerulosclerosis) (Bosquet et al. 1997).

While the mechanism behind the development of chronic interstitial nephritis is incompletely understood, the mechanism involved in AVP-R is more clearly established. Lithium is taken up by the principal cells in the collecting ducts through the epithelial sodium channel (ENaC). It accumulates in the cells and disrupts the insertion of the protein aquaporin-2 (AQP2) water channels in the cell membrane by decreasing the levels of cyclic adenosine monophosphatase (cAMP) and the activity of protein kinase A. This causes a resistance to vasopressin (also named anti-diuretic hormone (ADH)) (Christensen et al. 2011; Davis et al. 2018a). Lithium may also impair the action of vasopressin through other mechanisms. Studies have shown an elevated level of urinary prostaglandin E2, suggesting an increased activity of cyclooxygenase 2 (COX-2) enzymes interfering with the action of vasopressin, and selective experimental COX-2 blockade has a mitigating effect in lithium-induced AVP-R (Kim et al. 2008). Inhibition of the enzyme glycogen synthase kinase 3 (GSK3) may also be involved as this enzyme regulates AQP2 water channels (Rao 2012).

Commonly, an increase in plasma osmolarity (or a decrease in blood pressure) causes an increase in the release of vasopressin which acts in the distal tubules and the collecting ducts by increasing the number of AQP2 water channels in the luminal membrane of the principal cells thereby increasing the water reabsorption and the urine concentration. When vasopressin resistance is present, polyuria (defined as > 3L urine output per 24 h) arises (Davis et al. 2018b).

The pathophysiology behind the development of chronic interstitial nephritis is incompletely understood. In rodent models, prolonged lithium exposure induces collecting-duct–predominant injury with interstitial inflammation, fibrosis/sclerosis, and cystic remodeling, leading to progressive concentrating defects and renal functional decline. Mechanistically, lithium enters principal cells chiefly via the epithelial sodium channel (ENaC). Pharmacologic ENaC blockade limits intracellular lithium uptake, attenuates AVP resistance, and has been shown to slow progression of lithium-induced interstitial fibrosis (Kalita-De Croft et al. 2018; Mehta et al. 2022). The pathogenesis of chronic interstitial nephritis seems to involve the inhibition of GSK3 (Kjaersgaard et al. 2012) a core mechanism of action of lithium involved in the regulation of cell cycle progression and cell survival, and inhibition results in an increased expression of different proteins in the cell like the regulator gene c-myc, cyclin D1, and hypoxia-inducible factor 1 disrupting normal cell cycle progression (De Groot et al. 2014). GSK3 also regulates the microtubules being part of the cilium in the collecting ducts, and the dysfunction caused by lithium is likely due to the development of microcysts in the tubules (Davis et al. 2018c). Lithium also interferes with cell division of the principal cells in the collecting ducts and modulates the inositol monophosphate pathway, which interferes with the normal cell cycle in the nephrons. Furthermore, upregulation of profibrotic transforming growth factor beta 1 and overexpression of beta-catenin may lead to fibrosis (Davis et al. 2018c). Kidney biopsies of lithium-induced chronic interstitial nephritis exhibit interstitial fibrosis, atrophy of the tubules and microcysts, in the distal tubules. The affection of glomeruli with glomerulosclerosis is a late event (Aurell et al. 1981; Hestbech et al. 1977; Markowitz et al. 2000).

The main pathophysiological events are summarized in Table 2.

Lithium is almost entirely excreted by the kidneys, being freely filtered by the glomeruli and some of it is reabsorbed in the nephron in a manner similar to sodium, with which it shares many properties. Several

Table 2 Main pathophysiological events occurring in lithium exposed individuals

Phase (approximate time-scale)	Cellular/molecular event	Functional consequence in the nephron	Clinical footprint
1. Immediate (minutes–hours after exposure)	• Li + enters principal cells through apical ENaC channels	—	—
2. Early intracellular (hours–days)	• Cytosolic Li + accumulates • ↓ adenylyl-cyclase → ↓ cAMP / ↓ PKA activity • GSK-3 inhibition • ↑ COX-2 expression → ↑ prostaglandin E2	Signalling pathways that normally traffic aquaporin-2 are down-regulated	—
3. Sub-acute (days–weeks)	• Reduced phosphorylation & apical insertion of AQP-2 water channels	Collecting duct loses water permeability despite vasopressin	Falling urine osmolality
4. Functional (weeks)	• Tubule becomes vasopressin-resistant	Inability to concentrate urine even with ADH	Polyuria / nocturia begin
5. Chronic structural (months–years)	• Persistent signalling deficits + GSK-3 blockade contribute to micro-cysts & interstitial change	Fixed concentrating defect; may progress to chronic interstitial nephritis	Stable high urine volumes; risk of dehydration / hypernatraemia

proteins that normally transport sodium also transport lithium, including the Na/K/2CL cotransporter 2 in the thick ascending leg of the loop of Henle and the ENaC channel in the collecting ducts (Alsady et al. 2016). This not only means that decreasing kidney function will cause increasing serum levels of lithium but also that conditions in which there is sodium retention (such as congestive heart failure, cirrhosis or simply dehydration) will lead to a decreased excretion rate of lithium.

Taken together, these mechanisms provide a nephrology-oriented framework for understanding the clinical course of lithium-associated renal disease. Clinically, lithium-related renal effects often evolve along a continuum, where early functional tubular disturbances, most notably AVP with impaired urinary concentrating capacity, may precede, and in a subset of patients coexist with, slowly progressive structural tubulointerstitial nephropathy characterized by fibrosis, tubular atrophy, and microcystic remodeling (Alsady et al. 2016; Davis et al. 2018a, 2018c; Tabibzadeh et al. 2022). The natural history of renal function decline during lithium exposure is typically gradual and heterogeneous, frequently observed as a slow reduction in eGFR over years rather than abrupt loss of function; importantly, progression to advanced CKD is uncommon in most cohorts, although it clearly occurs in a clinically relevant minority and appears related to cumulative exposure, serum lithium levels, and episodes of intoxication (Shine et al. 2015; Bendz et al. 2010; Close et al. 2014; Hayes et al. 2016; Gitlin and Bauer 2023).

From a diagnostic perspective, distinguishing lithium-associated CKD from coincidental, age-related, or comorbidity-driven CKD is a key clinical challenge, particularly because lithium-treated patients undergo regular biochemical monitoring that facilitates earlier detection of even minor eGFR reductions than in comparator populations (Shine et al. 2015; Castro et al. 2016). Therefore, attribution should rely on longitudinal assessment of renal trajectories (e.g., sustained eGFR slope), exposure intensity, and the presence of compatible tubular features (such as a history of polyuria or concentrating defects), while carefully evaluating competing causes including diabetes, hypertension, and vascular disease (Davis et al. 2018b; Schoot et al. 2020; KDIGO, 2024). Risk-prediction approaches using routinely available clinical data further underscore that risk is not uniform across lithium-treated individuals and may be stratified, supporting individualized monitoring and shared decision-making (Castro et al. 2016; Chan et al. 2025b).

These considerations translate directly into evidence-informed decision-making regarding lithium continuation or withdrawal in patients with CKD stages 2–4 as discussed later, see Table 3. Importantly, contemporary nationwide data suggest that while lithium is associated with increased detection of CKD, the absolute risk of ESKD is low and, in recent large cohort comparisons, not clearly higher than in patients treated with alternative mood stabilizers, reinforcing that decisions should be individualized and trajectory-based rather than reflexive (Bosi et al. 2023; Gislason et al. 2024; Chan et al. 2025a).

Table 3 Chronic kidney disease (CKD) staging according to KDIGO and clinical implications for lithium treatment

CKD stage	eGFR (mL/min/1.73 m^2)	KDIGO definition	Typical clinical implications	Implications for lithium management
G1	≥ 90	Normal or high kidney function	Usually asymptomatic; CKD only if other markers (e.g. albuminuria) present	Lithium can be initiated and continued with standard monitoring
G2	60–89	Mildly decreased kidney function	Often age-related; limited clinical impact	Lithium generally safe; monitor eGFR trajectory and risk factors
G3a	45–59	Mild to moderate CKD	Early CKD; increased cardiovascular and renal risk	Increased monitoring frequency; consider nephrology input
G3b	30–44	Moderate to severe CKD	Clinically relevant CKD; higher risk of progression	Nephrology referral recommended; dose reduction and close monitoring
G4	15–29	Severe CKD	High risk of complications; limited reversibility	Mandatory nephrology co-management; careful risk–benefit evaluation
G5	< 15	Kidney failure (ESKD)	Dialysis or transplantation required	Lithium usually discontinued; may be used selectively during dialysis with specialist oversight

Clinical manifestations of renal impairment

A proportion of patients treated with lithium experience polyuria, increased thirst, and polydipsia, along with nocturia. The gold standard for diagnosis of polyuria is a water restriction test, however usually not necessary nor feasible to perform. Typically, polyuria is defined as total urine output of more than 40mL/kg/day (approximately 3 L per 24 h). Even if the diagnostic criteria are not fully met, people treated with lithium often experience polyuria to various extents. AVP-R occurs in 3–17% of patients while some degree of polyuria afflicts 20–87%

of patients exposed (Damba et al. 2022; Rej et al. 2014). While CKD, if it develops, most often manifests itself after many years of treatment, AVP-R can develop as early as 2–4 months after treatment initiation (Damba et al. 2022). In general, AVP-R carries a good prognosis and does not necessarily cause a significant risk to overall health, if the patient maintains sufficient hydration. However, it may affect quality of life, especially due to disrupted sleep and reduced occupational ability. Additionally, AVP-R increases the risk of fluid and electrolyte disturbances, primarily hypovolemia and hypernatremia (Damba et al. 2022).

Chronic interstitial nephritis is often asymptomatic until kidney function is impaired significantly (stage CKD-4 or CKD-5). As such, regular screening is necessary as CKD progression otherwise may go unnoticed for years (McKnight et al. 2012). Proteinuria in various degrees may be present along with microscopic hematuria and leukocyturia, yet these are not consistent findings. Various manifestations of tubular dysfunction such as renal tubular acidosis may also occur (Stevens et al. 2024). The risk of renal anemia, hyperkalemia, and secondary hyperparathyroidism due to CKD usually appear when GFR falls below 30 ml/min, although in lithium-induced interstitial nephritis renal anemia may be apparent earlier. Symptoms of overt uremia such as itching, fatigue, loss of appetite, and nausea are late symptoms in CKD progression (Markowitz et al. 2000; Stevens et al. 2024).

Dosing and monitoring of lithium treatment

Before initiating lithium treatment, and once or twice yearly thereafter, we recommend assessment of renal function by measuring serum creatinine and estimating eGFR, alongside serum urea nitrogen (BUN), sodium, potassium, and calcium. In addition, thyroid and parathyroid function should be evaluated, and an electrocardiogram obtained, as these parameters may be affected by lithium treatment. Monitoring frequency should be increased in older patients, in those with reduced baseline eGFR, rapid decline in renal function, relevant medical comorbidities, or following episodes of lithium intoxication.(Tondo et al. 2019). The standard prescription typically involves regular once-daily intake of lithium, most likely associated with reduced kidney damage owing to lower trough concentrations and fewer peaks as compared to twice-daily intake (Bowen et al. 1991; Castrogiovanni 2002; P et al. 1982; Schoot et al. 2020; Tondo et al. 2019).

Dosing optimization is guided by clinical response and measurement of blood lithium levels, with serum assays typically initiated one-week post-treatment commencement, albeit longer in elderly and individuals with a low eGFR, to ensure that steady state has been reached. Dose requirements vary between patients according to efficacy and adverse effects. Some can be maintained at lower serum levels while others require higher levels to remain stable. Levels of lithium are typically followed by monthly to three-monthly assessments after initial dose adjustments based on individual factors such as age, health status, clinical response, medication interactions, and stability of blood levels (Nolen et al. 2019). Consistent blood sampling timing, ideally 12 h post-dose, is recommended, with a 5–7-day interval after dose changes to attain steady-state tissue distribution, a time-period which should be extended if there is a reduced renal clearance resulting in a longer time to reach steady state (Nolen et al. 2019). As CKD risk increased with increasing serum lithium concentration, even 0.6 mmol/L may be excessive in some patients. For older adults, recommended maintenance targets are 0.4–0.8 mmol/L for ages 60–79 and 0.4–0.7 mmol/L for those ≥ 80 years (Shulman et al. 2019).

Management of renal side-effects

Management of AVP-R

Early detection and treatment of AVP-R is important to improve quality of life and prevent electrolyte disturbances. Therefore, we suggest screening at each visit by routinely asking about symptoms of polyuria (including nocturia), polydipsia, and thirst (also nocturnal). If symptoms are pronounced, confirmation of AVP-R can be obtained with a 24 h urine collection to assess urine volume and osmolarity along with serum osmolarity. Also, patients with hypernatremia without symptoms may require examination.

If AVP-R is suspected, ensuring lithium is used at the lowest effective therapeutic range may attenuate the symptoms. Some studies have shown that higher lithium levels are associated with more impaired urine concentration ability, albeit others fail to show similar results. Once-daily dosing of lithium may also improve urine concentration ability compared to multiple daily doses (Bowen et al. 1991; Plenge et al. 1982; Schoot et al. 2020; Tabibzadeh et al. 2022).

Potassium-sparing diuretics

Treatment of AVP-R may be possible. The potassium-sparing diuretic amiloride has been shown to reduce urine volume and increase urine osmolarity (Batlle et al. 1985; Bedford et al. 2008; Finch et al. 2003; Kosten and Forrest 1986) and inhibit lithium uptake in the principal cells by blocking ENaC channels (Kortenoeven et al. 2009). As a result, we recommend this off-label treatment if once-daily dosage and dose reduction are unsuccessful or not feasible for the individual patient, starting with a dose of 5 mg amiloride once to twice daily for 2 weeks followed by a maintenance dose of 10 mg once to twice

daily onwards (Schoot et al. 2020), as shown in Fig. 1. Another potassium-sparing diuretic spironolactone has been studied showing no beneficial effect on AVP-R (Nielsen et al. 2006; Strawbridge et al. 2025).

If concomitant treatment with spironolactone is initiated, it warrants particular caution in patients receiving lithium. Spironolactone may increase serum lithium concentrations by altering renal sodium and water handling, thereby increasing the risk of lithium accumulation and toxicity. When spironolactone is initiated, discontinued, or dose-adjusted in patients treated with lithium, we recommend closer monitoring of serum lithium concentrations and renal function, with dose adjustment as clinically indicated (Strawbridge et al. 2025).

Thiazides

Thiazide diuretics, such as hydrochlorothiazide, are another option for mitigating polyuria by blocking the sodium/chloride-cotransporter in distal tubule thereby introducing a mild volume depletion (Janjua et al. 2001; Sinke et al. 2014). The water preserving effect of thiazides is unlikely to be a direct effect hereof, and it has been hypothesized that the effect is secondary to increased sodium excretion. If a low sodium diet can be introduced simultaneously, the effect of thiazide treatment seems promising. However, data of their effects in humans are sparce (Miller et al. 1985). Off-label treatment, with hydrochlorothiazide of 25 mg once or twice daily has been suggested. Treatment with thiazide diuretics may cause mild electrolyte disturbances such as hypokalemia and metabolic alkalosis, warranting close monitoring, although combining hydrochlorothiazide and amiloride may reduce the risk of such side effects. However, the risk of acute lithium intoxication may be increased when volume depletion is introduced. Close monitoring of s-lithium levels is recommended at initiation and change of lithium dosage.

Other medications

Other treatments have been studied without convincing results. NSAIDs, particularly indomethacin, can alleviate symptoms of AVP-R but the use is limited by the nephrotoxic effects. Aspirin, statins, aliskiren, prasugrel, and sildenafil have been studied in animals but to our knowledge not in humans and cannot as such be recommended (Kjaersgaard et al. 2014; Lin et al. 2017; Sanches et al. 2012; Zhang et al. 2017).

When managing lithium-induced AVP-R, we recommend regularly assessing symptoms such as polydipsia, polyuria, nocturia, and nocturnal thirst.

Management of renal impairment in patients treated with lithium

As chronic lithium-induced interstitial nephritis evolves silently, regular serum creatinine (and eGFR) surveillance is the only reliable early-warning system, as most patients remain asymptomatic until the GFR has slipped below ≈ 30 mL/min/1.73 m^2. Typically, the decline is gradual, a "creatinine creep" over years, and only a minority of patients develop overt proteinuria. The threshold beyond

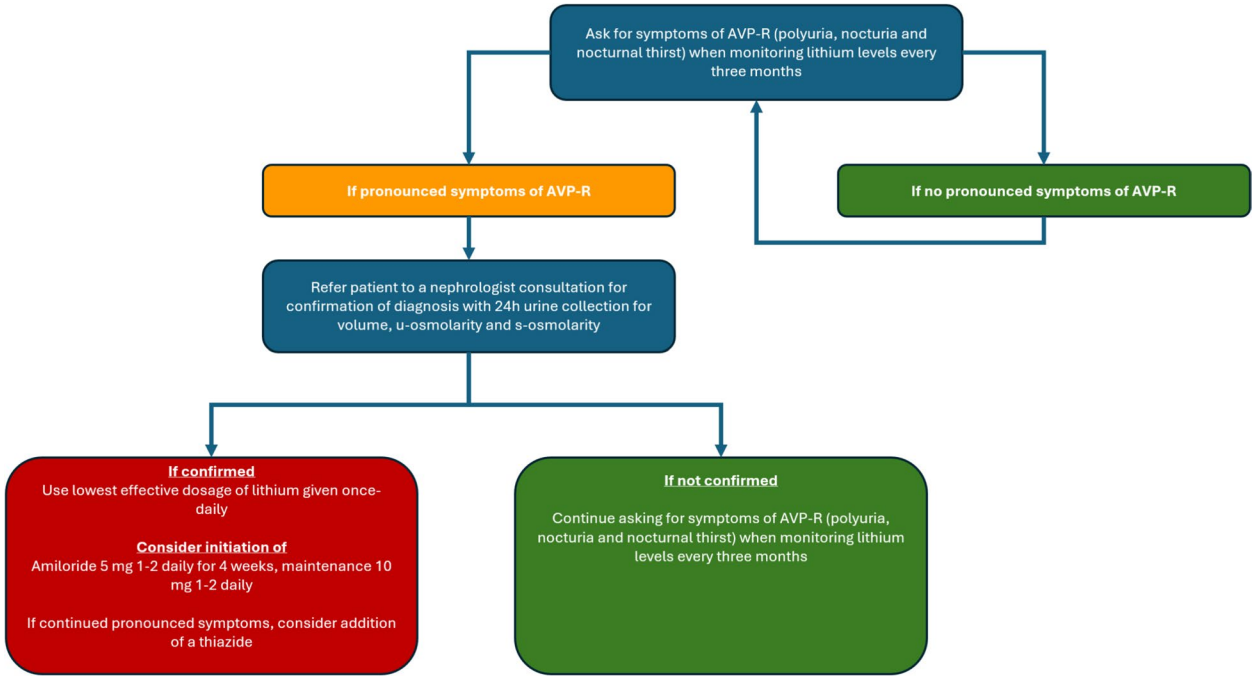

Fig. 1 Arginine vasopressin resistance (AVP-R) diagnosis and management

which damage becomes irreversible is uncertain, yet several case series suggest that once eGFR falls below 30–40 mL/min improvement after lithium withdrawal is less likely (Van Alphen et al. 2021; Bocchetta et al. 2017; Close et al. 2014; Fransson et al. 2025; Hoekstra et al. 2022). As clearance decreases, lithium dose must be reduced to prevent rising serum levels and ultimately intoxication. If treatment is to be continued, ensuring the use of the lowest effective dose administered once-daily, mirroring the strategy used for AVP-R, is recommended.

Renal biopsy is reserved for diagnostic doubt, but would show characteristic bilateral corticomedullary micro-cysts, which can also be visualized by ultrasound or MRI, albeit these have not entered routine management algorithms. No intervention has convincingly halted progression, except discontinuation of lithium treatment early (Van Alphen et al. 2021; Bocchetta et al. 2017; Close et al. 2014; Fransson et al. 2025; Hoekstra et al. 2022). Amiloride is theoretically attractive, as it limits tubular lithium entry and could potentially diminish interstitial injury, but evidence for long-term renoprotection is lacking (Kalita-De Croft et al. 2018).

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), originally developed for type 2 diabetes, reduce renal glucose reabsorption and provide renoprotective effects in CKD, potentially by mitigating tubular injury and fibrosis (Chao 2014; 2023). Dapagliflozin, canagliflozin, and empagliflozin are FDA-approved for CKD, but no randomized trial data exists in patients with mood disorders. Recent observational evidence suggests SGLT2i may improve eGFR trajectories in patients who had received lithium therapy, highlighting a potential later role in mitigating lithium-associated kidney dysfunction (Ercis et al. 2025). SGLT2i can be continued as long as GFR is ≥ 20. There is a potential, hypothetical pharmacokinetic interaction between SGLT2i and lithium, where SGLT2i could reduce lithium levels, highlighting the need for careful lithium level monitoring (Powers et al. 2025).

Accordingly, management centers on careful consideration of discontinuing lithium therapy, as well as an ongoing focus on optimizing treatment if continued. Efforts should focus on avoiding acute intoxication by progressively reducing the lithium dose as eGFR declines. Furthermore, the lowest effective lithium dosage should be employed, with preference given to a once-daily dosing schedule. Detailed guidance for monitoring lithium functioning before and during treatment is elucidated in Fig. 2.

We recommend consulting a nephrologist if eGFR < 60 ml/min. Competing disorders such as diabetes

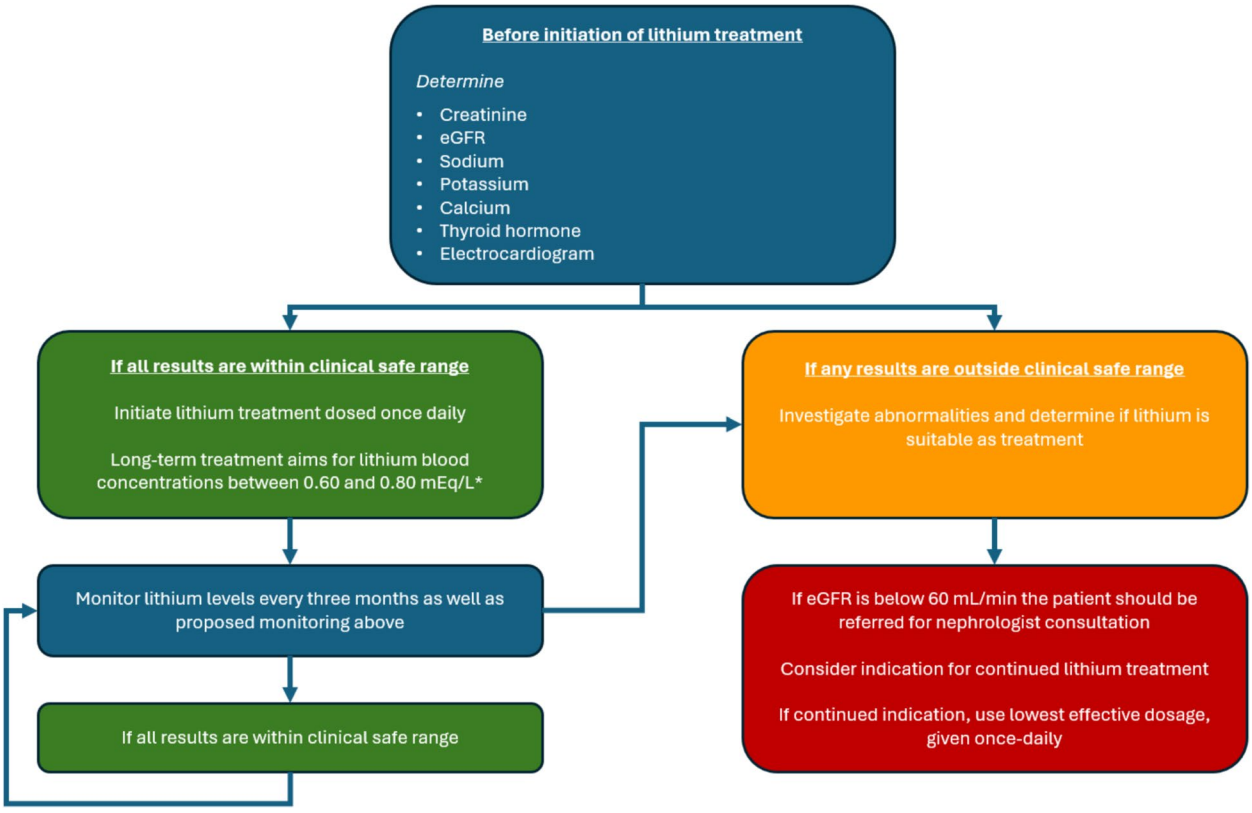

Fig. 2 Monitoring before and during lithium treatment (note: target serum lithium concentrations are individualized; while maintenance commonly aims for 0.6–0.8 mmol/L, higher or lower targets may be appropriate based on clinical efficacy and tolerability)

mellitus, hypertension, and cardiovascular disorders may coexist and may also influence renal function. Also, postrenal obstruction is a common problem particularly in elderly patients.

If eGFR is reduced below 30 ml/min, it is critical to collaborate closely with a nephrology outpatient clinic as the risk of complications of CKD such as renal anemia, electrolyte disturbances, and secondary hyperparathyroidism is markedly increased, as well as to ensure diagnosis of other causes of reduced renal functioning (Brady and Suppes 2024).

Risk factors for accelerated decline of GFR

A growing body of cohort and registry-based research shows specific variables associated with an increased risk of CKD during lithium therapy. The strongest single predictor of CKD stage 4 and 5 is an early, steep fall in eGFR or a low baseline eGFR < 60 mL/min/1.73 m^2 at initiation of lithium treatment, as patients who start with fewer functioning nephrons lose renal clearance more quickly once lithium is introduced (Castro et al. 2016; Shine et al. 2015). Treatment-related exposures compound this risk: each additional decade of therapy or several-hundred–millimole increase in cumulative dose raises the hazard of CKD by roughly 20–40%, and even one episode of high lithium levels (serum-lithium > 1.0 mmol/L) can double the hazard, with successive episodes accelerating decline further (Chan et al. 2025a; Hayes et al. 2016). Large national datasets confirm a clear concentration–response gradient: mean levels 0.60–0.79 mmol/L nearly triple, and 0.80–0.99 mmol/L quadruple the risk of CKD stage 4 and 5 compared with < 0.60 mmol/L (Gislason et al. 2024). Similarly, every additional 500 defined-daily-dose equivalents increases relative risk approximately 30%(Bosi et al. 2023).

Patient factors such as age and sex are relevant also. Women display a higher adjusted incidence of lithium-associated CKD than men, possibly owing to smaller renal mass and greater susceptibility to vasopressin resistance, and those who begin treatment at a younger age simply accumulate longer lifetime exposure (Bosi et al. 2023; Shine et al. 2015). Comorbid disease amplifies renal loss: hypertension, diabetes, prior acute kidney injury, baseline albuminuria, and chronic use of other nephrotoxic agents (NSAIDs, ACE-inhibitors/ARBs, loop or thiazide diuretics) independently increase eGFR decline; several of these drugs also raise serum lithium, creating a feedback loop between potential toxicity and loss of clearance.

Data supports that improvement in GFR can occur when lithium is discontinued, but evidence also suggests a point-of-no-return once eGFR falls to 30–40 mL/min/1.73 m^2, and hereafter renal function often continues to deteriorate despite lithium discontinuation, highlighting the need for early dose optimization, strict serum-level monitoring, avoidance of other nephrotoxic drugs and substances and early collaboration with a nephrologist (Bocchetta et al. 2017; Fransson et al. 2025; Hoekstra et al. 2022).

Risk factors for decreased renal functioning are summarized in Tables 4 and 5.

Table 4 Patient-related risk factors

Domain	Specific variable(s)	Approximate quantitative signal*
Baseline kidney reserve	• eGFR < 60 mL min^{-1} 1.73 m^{-2} at start • Early fall > 5 mL min^{-1} in first 12–18 mo	Doubles later stage ≥ 3 CKD risk; early drop adds a further ~ twofold risk
Demography	• Female sex • Younger age at initiation	HR ≈ 1.2–1.4 vs men; longer lifetime exposure window
Medical comorbidity	Hypertension, diabetes, baseline albuminuria, prior AKI	Independent 1.3–1.8-fold risk multipliers
Nephrotoxic co-medication	Chronic NSAIDs, ACE-i/ARBs, loop/thiazide diuretics	Additive eGFR decline; many agents also raise serum lithium

Table 5 Lithium-treatment related risk factors

Domain	Specific variable(s)	Approximate quantitative signal*
Treatment duration/cumulative dose	Each decade of therapy or comparable cumulative dose increment	~ 20–40% relative-risk increase per decade / dose step
Average serum concentration	0.60–0.79 mmol L^{-1} 0.80–0.99 mmol L^{-1}	2.9-fold ↑ CKD3 4.3-fold ↑ CKD3
Toxicity episodes	Any level > 1.0 mmol L^{-1} Multiple episodes	≈ twofold hazard for first episode; additive risk with each recurrence
Exposure intensity	Every extra 500 defined-daily-dose equivalents (≈ 18 mo at 1 DDD day^{-1})	~ 30% ↑ CKD risk

Lithium during maintenance dialysis

Once glomerular filtration is negligible and a patient transitions to chronic hemodialysis, lithium can still be employed as a mood stabilizer, provided its unique pharmacokinetics are respected. Case-series and single-patient reports show that giving the whole dose *after* each dialysis session prevents both under-treatment and large interdialytic rebounds (Gruner et al. 1991). Grüner and colleagues maintained stable pre-dialysis levels of 0.50–0.77 mmol/L for 19 months with 10.8 mmol administered thrice weekly, illustrating that a simple "post-run only" regimen can keep serum concentrations within an effective dose window (Gruner et al. 1991). More recent experience confirms feasibility: Chang & Ho achieved symptom control by titrating to < 0.6 mmol/L and initially sampling lithium daily, then three-times-a-week

once levels stabilized (Chang and Ho 2020). An American Journal of Psychiatry report cautions that toxicity can still occur if inter-current illness delays dialysis, if normal administration of lithium is continued, underlining the need for close liaison with the renal team and rapid drug holds during missed sessions (Knebel et al. 2010). A newly published systematic review in 18 hemodialysis patients found that most required only 300–900 mg lithium carbonate per dialysis day, with acceptable stabilizing outcomes in regard to mood and no excess neurotoxicity when treatment target were held below 0.6 mmol/L (McGrane et al. 2022).

High-flux membranes remove lithium faster than conventional dialyzers and minimize the post-dialysis rebound that may follow shorter, low-clearance runs (Peces and Pobes 2001). Acute intoxication episodes remain an important threat, but prompt high-efficiency dialysis combined with an extended (8–12 h) continuous hemofiltration "tail" effectively blunts the rebound and improves neurological recovery (Peces and Pobes 2001). Observational data suggest that mood deterioration is common if lithium is withheld after dialysis is initiated; one literature review documents mania emerging within the first two weeks of discontinuation in one-third of cases, an effect reversed once lithium was re-started at a reduced thrice-weekly dose (Gruner et al. 1991; McGrane et al. 2022). Consequently, most authors advocate aiming for pre-dialysis troughs of 0.4–0.6 mmol/L, measuring levels at least weekly until stable and thereafter every 4–6 weeks, with extra checks whenever dialysis prescriptions change. Finally, shared decision-making is paramount: psychiatrists, nephrologists, and dialysis nurses should pre-agree hold parameters (e.g., pre-dialysis level > 1 mmol/L or two missed sessions) and ensure rapid access to mental-health follow-up should suspension be necessary (Kuiper et al. 2024; McGrane et al. 2022).

Continuation or discontinuation of lithium treatment

When routine monitoring reveals a decline in renal function, the decision to discontinue lithium should be guided by an individualized evaluation of potential gains and losses from continued treatment. In patients who have remained clinically stable on lithium, who have not experienced other severe adverse effects and for whom alternative mood-stabilizing treatments have proved ineffective or poorly tolerated, continuation of lithium treatment is often straightforward. Age, comorbid physical disease and the rate of renal decline must also be weighed, because in an older or medically fragile population the competing risks of death from other causes may exceed the likelihood of progression to end-stage renal disease. Again, in such cases, continuation of lithium may still represent the most reasonable option. Conversely, if an individual has not tried other maintenance treatments, has achieved only a partial response to lithium, or is experiencing additional side-effects, the balance may favor discontinuation. Suicide risk deserves explicit weighting. Meta-analyses and large naturalistic cohorts show that lithium reduces suicidal acts and deaths by approximately 60% compared with placebo or other mood stabilizers, an effect that appears partly independent of its mood-stabilizing properties(Fitzgerald et al. 2022; Smith and Cipriani 2017). Moreover, discontinuation is followed by a transient rebound in suicidal behavior (Tondo et al. 2001; Tondo et al. 1998). Accordingly, any plan to taper lithium in patients with a history of suicide attempts, persistent ideation, or other high-risk features should be undertaken with heightened vigilance, contingency arrangements for rapid re-initiation, and parallel optimization of psychosocial support.

If discontinuation is the chosen way of treatment, and when renal impairment advances slowly, lithium can usually be tapered gradually over several months to reduce the risk of discontinuation-induced mood episodes, while an alternative mood stabilizer is introduced and titrated.

Throughout this process, shared decision-making that involves the patient, psychiatrist and nephrologist is essential so that prognostic information on renal function, potential psychiatric consequences and plans for intensified follow-up are fully understood (Brady and Suppes 2024). Should substantial mood deterioration occur after cessation, a cautious re-trial of lithium remains an option. The possibility of permanent treatment refractoriness to lithium after withdrawal has been raised, but contemporary data does not provide convincing support for this concern (Kupka et al. 2024).

Decision related factors are summarized in Table 6.

Changes in renal functioning after lithium discontinuation

Emerging withdrawal-specific cohorts suggest that stopping lithium slows, but seldom reverses, renal decline. A six-year follow-up in elderly people showed only transient 5–10 mL/min improvements in eGFR in 8% of patients before age-expected decline resumed (Bocchetta et al. 2017). More encouraging results come from two recent dedicated studies: a Dutch withdrawal series found that 70% of patients with CKD stage 4 or 5 either improved or at least halved their pre-discontinuation slope, while further deterioration was confined to those whose eGFR was already ~ 30 mL/min/1.73m^2 at cessation (Hoekstra et al. 2022); and a Swedish mirror-image analysis reported a shift in mean annual eGFR change from −1.6 to essentially 0 mL/min after stopping, persisting for five years and reverting to −1.7 mL/min when lithium was restarted (Fransson et al. 2025). Across datasets, meaningful recovery is observed almost exclusively when baseline eGFR exceeds 30–40 mL/min/1.73m^2,

Table 6 Decision related factors in determining if lithium should be continued or discontinued

Decision factor	Signals that favour continuing lithium	Signals that favour discontinuing/ tapering	Practical notes & references
Current mood stability	Full remission for ≥ 12 mo; history of robust relapse prevention	Only partial response; frequent breakthrough episodes	Consider trial of alternative mood stabiliser **before** stopping if efficacy uncertain
Availability / tolerability of alternatives	Other mood stabilisers previously ineffective or poorly tolerated	Patient has not yet tried valproate, lamotrigine, SGAs, etc	Shared decision-making about alternative options
Renal trajectory	Slow "creatinine creep"; eGFR > 40 mL min^{-1} and falling < 3 mL min^{-1} yr^{-1}	Rapid fall (> 5 mL min^{-1} yr^{-1}) or eGFR ~ 30–40 mL min^{-1}; rising lithium troughs	Dose-reduce / once-daily while monitoring; nephrology input if eGFR < 60
Age / competing medical risk	Older or frail patient where ESRD unlikely before competing mortality	Younger patient with long life expectancy	In older patients, risk of relapse or suicide may outweigh ESRD risk
Other adverse effects	No troublesome thyroid, weight, cognitive or tremor problems	Multiple side-effects or poor quality-of-life on lithium	Side-effect burden tips scales toward cessation
Suicide risk	Recurrent attempts or persistent ideation → argues for **continuation** (60% suicide-risk reduction vs comparators)	Low suicidal risk profile	Suicide rebound peaks in first 6–12 mo post-lithium (Smith & Cipriani 2017; Fitzgerald 2022; Tondo 1998/2001)
Patient preference	Strong wish to remain on lithium	Patient anxious about kidneys / wishes to stop	Provide balanced data on risks/benefits
Plan if stopping	—	Taper slowly over ≥ 3 mo; start alternative mood stabiliser in parallel; schedule close follow-up; relapse action plan	Re-trial of lithium remains viable; no solid evidence of permanent refractoriness (de Vries 2013)

Table 7 Effects of discontinuation of lithium

Study (year, country)	Sample/baseline kidney status	Mean eGFR slope on lithium (mL min^{-1} yr^{-1})	Mean eGFR slope after stop	Who benefits? "Point-of-no-return" threshold	Notes
Close 2014 (UK primary-care registry)	130 discontinuers analysed; mixed CKD	-1.9	-1.5 (ns); large variance	Improvement "sporadic & modest"	Registry follow-up ≈ 2 y; no stage-stratified data
Bocchetta 2017 (Italy, elderly cohort)	110 pts, mean age 70 y, mean eGFR 47	-1.4	42% gained 5–10 mL in 12 mo, but only 8% regained pre-Li level	Little rebound if stop-eGFR < 30	Age may blunt recovery
van Alphen 2021 (Netherlands)	148 pts, mean eGFR 57	-2.3	-0.8 ($p < 0.01$)	Slope stabilised only if stop-eGFR ≥ 40	Prospective ≥ 3 y slopes
Hoekstra 2022 (Dutch withdrawal series)	161 pts, CKD ≥ stage 3	-2.0	Median -0.6; 70% at least halved decline	Continued fall almost only when stop-eGFR ≈ 30	Highlights 30–40 "no-return" zone
Fransson 2025 (Sweden, LiSIE)	168 pts, mixed CKD	-1.6	+0.1 (flat) for 5 y; slope resumed (-1.7) when Li re-started	Reversal confined to baseline eGFR > 35	Mirror-image strengthens causality

supporting the concept of a renal "point-of-no-return" and underscoring the importance of early dose optimization and nephrology partnership rather than late discontinuation (Brady and Suppes 2024).

Data regarding effects of lithium discontinuation are summarized in Table 7.

Reversibility and the concept of a renal "point of no return"

From a clinical perspective, it is essential to distinguish reversible functional tubular alterations from irreversible structural kidney disease in patients treated with lithium. Functional tubular disturbances, most notably AVP-R with impaired urinary concentrating capacity, may improve partially or fully after dose reduction or lithium discontinuation and do not, in themselves, predict progression to advanced CKD. In contrast, chronic lithium-associated tubulointerstitial nephropathy represents a structural process characterized by fibrosis, tubular atrophy, and microcystic remodeling, for which reversibility appears limited.

Across observational withdrawal studies, improvement or stabilization of renal function is most consistently observed when lithium is discontinued at earlier stages of CKD. Conversely, once eGFR has declined to approximately 30–40 mL/min/1.73 m^2, further deterioration frequently continues despite lithium cessation, suggesting a pragmatic renal "point of no return" (Bocchetta et al. 2017; Hoekstra et al. 2022; Fransson et al. 2025). Importantly, this concept does not imply abrupt irreversibility at a fixed threshold but rather reflects a transition

zone beyond which structural damage predominates and late discontinuation is unlikely to yield meaningful renal recovery. This distinction has direct implications for clinical decision-making and underscores the importance of early risk stratification and timely nephrology collaboration.

Conclusion

Lithium remains a cornerstone in the long-term treatment of bipolar disorders, with robust evidence supporting its unique efficacy in preventing mood episode recurrence and reducing suicide risk. Concerns regarding renal side effects have, however, contributed to declining use in clinical practice. While mild to moderate reductions in kidney function are a recognized risk during long-term lithium treatment, contemporary large-scale cohort and registry studies suggest that progression to ESKD is uncommon when lithium is used judiciously and monitored appropriately.

By integrating current evidence on pathophysiology, clinical manifestations, and risk factors, this expert consensus provides a practical framework to support informed clinical decision-making. Central to this approach is systematic monitoring of renal function, optimization of lithium dosing, and timely collaboration between psychiatry and nephrology. In clinical practice, nephrology referral should be considered when eGFR declines below 60 mL/min/1.73 m^2, with close co-management warranted once eGFR approaches 30 mL/min/1.73 m^2, particularly in the presence of rapid decline, recurrent intoxication, or significant somatic comorbidity. At the same time, there are clinical scenarios in which nephrological risk may outweigh psychiatric benefit, including advanced CKD, rapid and sustained eGFR decline, or substantial competing renal comorbidity. Kidney biopsy has a limited role and should be reserved for selected cases with diagnostic uncertainty.

Taken together, these principles underscore that lithium treatment should neither be withheld nor continued reflexively solely on the basis of renal concerns. Instead, individualized, trajectory-based assessment and shared decision-making allow clinicians to balance lithium's substantial therapeutic benefits against renal risk, preserving its role as a first-line treatment while safeguarding long-term patient health.

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Declarations

Ethics approval and consent to participate

The study does not include individual patient data, and as such has no ethical approval or consent to participate.

Consent for publication

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Competing interests

The authors declare no competing interests.

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References

Abou-Saleh MT, Müller-Oerlinghausen B, Coppen AJ. Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. Int J Bipolar Disord. 2017 Dec 8 [cited 2017 Sep 26];5(1):11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28247268

Aiff H, Attman PO, Aurell M, Bendz H, Schön S, Svedlund J. End-stage renal disease associated with prophylactic lithium treatment. Eur Neuropsychopharmacol. 2014 Apr [cited 2017 Sep 28];24(4):540–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24503277

Van Alphen AM, Bosch TM, Kupka RW, Hoekstra R. Chronic kidney disease in lithium-treated patients, incidence and rate of decline. Int J Bipolar Disord. Springer Science and Business Media Deutschland GmbH; 2021 Dec 1 [cited 2025 Jun 30];9(1):1–5. Available from: https://journalbipolardisorders.springeropen.com/articles/https://doi.org/10.1186/s40345-020-00204-2

Alsady M, Baumgarten R, Deen PMT, De Groot T. Lithium in the kidney: Friend and foe? Journal of the American Society of Nephrology. American Society of Nephrology; 2016 Jun 1 [cited 2025 Aug 27];27(6):1587–95. Available from: https://pubmed.ncbi.nlm.nih.gov/26577775/

Aron L, Ngian ZK, Qiu C, Choi J, Liang M, Drake DM, et al. Lithium deficiency and the onset of Alzheimer's disease. Nature. Nature; 2025 Sep 18 [cited 2025 Oct 5];645(8081):712–21. Available from: https://pubmed.ncbi.nlm.nih.gov/40770094/

Aurell M, Svalander C, Wallin L, Alling C. Renal function and biopsy findings in patients on long-term lithium treatment. Kidney Int. 1981 Nov [cited 2017 Sep 26];20(5):663–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7343714

Batlle DC, von Riotte AB, Gaviria M, Grupp M. Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med. N Engl J Med; 1985 Feb 14 [cited 2025 Jun 29];312(7):408–14. Available from: https://pubmed.ncbi.nlm.nih.gov/3969096/

Bedford JJ, Weggery S, Ellis G, McDonald FJ, Joyce PR, Leader JP, et al. Lithium-induced nephrogenic diabetes insipidus: renal effects of amiloride. Clin J Am Soc Nephrol. Clin J Am Soc Nephrol; 2008 Sep [cited 2025 Jun 29];3(5):1324–31. Available from: https://pubmed.ncbi.nlm.nih.gov/18596116/

Bendz H, Schön S, Attman PO, Aurell M. Renal failure occurs in chronic lithium treatment but is uncommon. Kidney Int. 2010 Feb [cited 2017 Sep 28];77(3):219–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19940841

Bocchetta A, Cabras F, Pinna M, Poddighe A, Sardu C, Ardau R, et al. An observational study of 110 elderly lithium-treated patients followed up for 6 years with particular reference to renal function. Int J Bipolar Disord. SpringerOpen; 2017 Dec 1 [cited 2025 Jun 29];5(1):1–7. Available from: https://journalbipolardisorders.springeropen.com/articles/https://doi.org/10.1186/s40345-017-0089-1

Bosi A, Clase CM, Ceriani L, Sjölander A, Fu EL, Runesson B, et al. Absolute and Relative Risks of Kidney Outcomes Associated With Lithium vs Valproate Use in Sweden. JAMA Netw Open. JAMA Netw Open; 2023 Jul 7 [cited 2025 Jun 29];6(7):E2322056. Available from: https://pubmed.ncbi.nlm.nih.gov/37418264/

Bosquet S, Descombes E, Gauthier T, Fellay G, Regamey C. Nephrotic syndrome during lithium therapy. Nephrology Dialysis Transplantation. Oxford University Press; 1997 [cited 2025 Aug 27];12(12):2728–31. Available from: https://pubmed.ncbi.nlm.nih.gov/9430882/

Bowen RC, Grof P, Grof E. Less frequent lithium administration and lower urine volume. Am J Psychiatry. Am J Psychiatry; 1991 [cited 2025 Jun 29];148(2):189–92. Available from: https://pubmed.ncbi.nlm.nih.gov/1987816/

Brady B, Suppes T. Psychiatry and nephrology partnering to improve quality of care. Lancet Psychiatry. Lancet Psychiatry; 2024 Dec 1 [cited 2025 Oct 6];11(12):948–9. Available from: https://pubmed.ncbi.nlm.nih.gov/39572108/

Castro VM, Roberson AM, McCoy TH, Wiste A, Cagan A, Smoller JW, et al. Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study. Neuropsychopharmacology. Neuropsychopharmacology; 2016 Mar 1 [cited 2025 Jun 29];41(4):1138–43. Available from: https://pubmed.ncbi.nlm.nih.gov/26294109/

Castrogiovanni P. A novel slow-release formulation of lithium carbonate (carbolithium Once-a-day®) vs. standard Carbolithium®: A comparative pharmacokinetic study. Clinica Terapeutica. 2002;153(2):107–15.

Chan JKN, Solmi M, Correll CU, Man Wong CS, Lo HKY, Lai FTT, et al. Lithium for Bipolar Disorder and Risk of Thyroid Dysfunction and Chronic Kidney Disease. JAMA Netw Open. JAMA Netw Open; 2025a Feb 11 [cited 2025 Jun 29];8(2):e2458608. Available from: https://pubmed.ncbi.nlm.nih.gov/39932712/

Chan JKN, Solmi M, Correll CU, Wong CSM, Lo HKY, Lai FTT, et al. Predicting 10-year risk of chronic kidney disease in lithium-treated patients with bipolar disorder: A risk model development and internal cross-validation study. Eur

Neuropsychopharmacol. Eur Neuropsychopharmacol; 2025b Jun 1 [cited 2025 Jun 29];95:24–30. Available from: https://pubmed.ncbi.nlm.nih.gov/40220570/

Chang CWL, Ho CSH. Lithium use in a patient with bipolar disorder and end-stage kidney disease on hemodialysis: a case report. Front Psychiatry. Frontiers Media S.A.; 2020 Feb 3 [cited 2025 Jun 29];11:6. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7008228/

Chao EC. SGLT-2 inhibitors: a new mechanism for glycemic control. Clin Diabetes. Clin Diabetes; 2014 Jan [cited 2025 Oct 6];32(1):4–11. Available from: https://pubmed.ncbi.nlm.nih.gov/26246672/

Christensen BM, Zuber AM, Loffing J, Stehle JC, Deen PMT, Rossier BC, et al. αENaC-mediated lithium absorption promotes nephrogenic diabetes insipidus. J Am Soc Nephrol. 2011 [cited 2025 Aug 27];22(2):253–61. Available from: https://pubmed.ncbi.nlm.nih.gov/21051735/

Close H, Reilly J, Mason JM, Kripalani M, Wilson D, Main J, et al. Renal failure in lithium-treated bipolar disorder: a retrospective cohort study. van Os J, editor. PLoS One. 2014 Mar 26 [cited 2017 Jan 5];9(3):e90169. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24670976

Damba JJ, Bodenstein K, Lavin P, Drury J, Sekhon H, Renoux C, et al. Psychotropic drugs and adverse kidney effects: a systematic review of the past decade of research. CNS Drugs. Adis; 2022 Oct 1 [cited 2025 Aug 27];36(10):1049–77. Available from: https://pubmed.ncbi.nlm.nih.gov/36161425/

Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: unravelling the complex pathophysiological threads of the lightest metal. Nephrology. Blackwell Publishing; 2018a Oct 1 [cited 2025 Aug 27];23(10):897–903. Available from: https://pubmed.ncbi.nlm.nih.gov/29607573/

Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. BMC Nephrol. BioMed Central Ltd.; 2018b Nov 3 [cited 2025 Aug 27];19(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30390660/

Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: unravelling the complex pathophysiological threads of the lightest metal. Nephrology. Blackwell Publishing; 2018c Oct 1 [cited 2025 Aug 27];23(10):897–903. Available from: https://pubmed.ncbi.nlm.nih.gov/29607573/

De-Paula V de JR, Radanovic M, Forlenza OV. Lithium and neuroprotection: a review of molecular targets and biological effects at subtherapeutic concentrations in preclinical models of Alzheimer's disease. Int J Bipolar Disord. Springer Science and Business Media Deutschland GmbH; 2025 Dec 1 [cited 2025 Oct 6];13(1):1–8. Available from: https://journalbipolardisorders.springeropen.com/articles/https://doi.org/10.1186/s40345-025-00386-7

Ercis M, Ozerdem A, Singh B. When and how to use lithium augmentation for treating major depressive disorder. J Clin Psychiatry; 2023 [cited 2025 Oct 6];84(2). Available from: https://pubmed.ncbi.nlm.nih.gov/36883886/

Ercis M, Tarikogullari I, Pazdernik VK, Gonzalez-Suarez ML, Baweja R, Miola A, et al. Sodium-glucose cotransporter 2 inhibitors for lithium-associated kidney dysfunction in mood disorders: a real-world historical cohort study. medRxiv; 2025 Sep 3 [cited 2025 Oct 6]; Available from: https://pubmed.ncbi.nlm.nih.gov/40950471/

Finch CK, Kelley KW, Williams RB. Treatment of lithium-induced diabetes insipidus with amiloride. Pharmacotherapy; 2003 Apr 1 [cited 2025 Jun 29];23(4):546–50. Available from: https://pubmed.ncbi.nlm.nih.gov/12680486/

Fitzgerald C, Christensen RHB, Simons J, Andersen PK, Benros ME, Nordentoft M, et al. Effectiveness of medical treatment for bipolar disorder regarding suicide, self-harm and psychiatric hospital admission: between- and within-individual study on Danish national data. Br J Psychiatry. 2022 Nov 13 [cited 2025 Jun 29];221(5):692–700. Available from: https://pubmed.ncbi.nlm.nih.gov/35450547/

Fransson F, Werneke U, Öhlund L, Jonsson PA, Ott M. Kidney function decline improves after lithium discontinuation. J Intern Med. 2025 Mar 1 [cited 2025 Jun 29];297(3). Available from: https://pubmed.ncbi.nlm.nih.gov/39829336/

Gislason G, Indridason OS, Sigurdsson E, Palsson R. Risk of chronic kidney disease in individuals on lithium therapy in Iceland: a nationwide retrospective cohort study. Lancet Psychiatry. 2024 Dec 1 [cited 2025 Jun 29];11(12):1002–11. Available from: https://pubmed.ncbi.nlm.nih.gov/39572104/

Gitlin M, Bauer M. Key questions on the long term renal effects of lithium: a review of pertinent data. Int J Bipolar Disord. 2023 Dec 1 [cited 2025 Oct 6];11(1). Available from: https://pubmed.ncbi.nlm.nih.gov/37971552/

Gitlin M, Bauer M. Lithium: current state of the art and future directions. Int J Bipolar Disord. Springer Science and Business Media Deutschland GmbH; 2024 Dec 1 [cited 2025 Jun 29];12(1):40. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11604892/

De Groot T, Alsady M, Jaklofsky M, Otte-Höller I, Baumgarten R, Giles RH, et al. Lithium causes G2 arrest of renal principal cells. J Am Soc Nephrol. 2014 [cited 2025 Aug 27];25(3):501–10. Available from: https://pubmed.ncbi.nlm.nih.gov/24408872/

Gruner JF, Dennert J, Schafer G. Lithium treatment in maintenance dialysis. Review of the literature and report of a new case on hemodialysis. Pharmacopsychiatry; 1991 [cited 2025 Jun 29];24(1):13–6. Available from: https://pubmed.ncbi.nlm.nih.gov/2011616/

Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DPJ. Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based cohort study. Tsai AC, editor. PLoS Med. 2016 Aug 2 [cited 2017 Sep 28];13(8):e1002058. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27483368

Hestbech J, Hansen HE, Amdisen A, Olsen S. Chronic renal lesions following long-term treatment with lithium. Kidney Int. 1977 Sep [cited 2017 Sep 26];12(3):205–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/926612

Hoekstra R, Lekkerkerker MN, Kuijper TM, Bosch TM, van Alphen AM. Renal function after withdrawal of lithium. Bipolar Disord; 2022 Sep 1 [cited 2025 Jun 29];24(6):667–70. Available from: https://pubmed.ncbi.nlm.nih.gov/35075735/

Janjua NR, Jonassen TEN, Langhoff S, Thomsen K, Christensen S. Role of sodium depletion in acute antidiuretic effect of bendroflumethiazide in rats with nephrogenic diabetes insipidus. Journal of Pharmacology and Experimental Therapeutics. American Society for Pharmacology and Experimental Therapy; 2001 Oct 1 [cited 2025 Aug 27];299(1):307–13. Available from: https://jpet.aspetjournals.org/action/showFullText?pii=S0022356524293319

Kalita-De Croft P, Bedford JJ, Leader JP, Walker RJ. Amiloride modifies the progression of lithium-induced renal interstitial fibrosis. Nephrology. Blackwell Publishing; 2018 Jan 1 [cited 2025 Aug 27];23(1):20–30. Available from: https://pubmed.ncbi.nlm.nih.gov/27682266/

Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. JAMA Psychiatry. American Medical Association; 2015 Dec 1 [cited 2025 Oct 20];72(12):1182–91. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2467821

Kim GH, Nak WC, Jung JY, Song JH, Chang HL, Chong MK, et al. Treating lithium-induced nephrogenic diabetes insipidus with a COX-2 inhibitor improves polyuria via upregulation of AQP2 and NKCC2. Am J Physiol Renal Physiol. American Physiological Society; 2008 [cited 2025 Aug 27];294(4):702–9. Available from: https://journals.physiology.org/doi/pdf/https://doi.org/10.1152/ajprenal.00366.2007

Kjaersgaard G, Madsen K, Marcussen N, Christensen S, Walter S, Jensen BL. Tissue injury after lithium treatment in human and rat postnatal kidney involves glycogen synthase kinase-3β-positive epithelium. Am J Physiol Renal Physiol. American Physiological Society; 2012 [cited 2025 Aug 27];302(4). Available from: https://pubmed.ncbi.nlm.nih.gov/22088436/

Kjaersgaard G, Madsen K, Marcussen N, Jensen BL. Lithium induces microcysts and polyuria in adolescent rat kidney independent of cyclooxygenase-2. Physiol Rep. American Physiological Society; 2014 Jan 1 [cited 2025 Aug 27];2(1). Available from: https://pubmed.ncbi.nlm.nih.gov/24744881/

Knebel RJ, Rosenlicht N, Colllins L. Lithium carbonate maintenance therapy in a hemodialysis patient with end-stage renal disease. Am J Psychiatry. Am J Psychiatry; 2010 Nov [cited 2025 Jun 29];167(11):1409–10. Available from: https://pubmed.ncbi.nlm.nih.gov/21041259/

Kortenoeven MLA, Li Y, Shaw S, Gaeggeler HP, Rossier BC, Wetzels JFM, et al. Amiloride blocks lithium entry through the sodium channel thereby attenuating the resultant nephrogenic diabetes insipidus. Kidney Int. Kidney Int; 2009 Jul [cited 2025 Jun 29];76(1):44–53. Available from: https://pubmed.ncbi.nlm.nih.gov/19367330/

Kosten TR, Forrest JN. Treatment of severe lithium-induced polyuria with amiloride. Am J Psychiatry. Am J Psychiatry; 1986 [cited 2025 Jun 29];143(12):1563–8. Available from: https://pubmed.ncbi.nlm.nih.gov/3538913/

Kuiper WJ, Grootens KP, Kerckhoffs APM. Concurrent lithium and haemodialysis treatment: Clinical recommendations based on the literature and a multicentre survey. Bipolar Disord. Bipolar Disord; 2024 Jun 1 [cited 2025 Oct 6];26(4):335–47. Available from: https://pubmed.ncbi.nlm.nih.gov/37968245/

Kupka R, Regeer E, van Bergen A, Tondo L, Bauer M. Lithium-discontinuation-induced treatment refractoriness revisited. Int J Bipolar Disord. Int J Bipolar Disord; 2024 Dec 1 [cited 2025 Oct 5];12(1). Available from: https://pubmed.ncbi.nlm.nih.gov/38750382/

Lin Y, Zhang T, Feng P, Qiu M, Liu Q, Li S, et al. Aliskiren increases aquaporin-2 expression and attenuates lithium-induced nephrogenic diabetes insipidus. Am J Physiol Renal Physiol. American Physiological Society; 2017 Oct 1 [cited 2025 Aug 27];313(4):F914–25. Available from: https://journals.physiology.org/doi/pdf/https://doi.org/10.1152/ajprenal.00553.2016

Malhi GS, Bauer M. Lithium first: Not merely first line. Bipolar Disord. Bipolar Disord; 2023 Feb 1 [cited 2023 Nov 13];25(1):7–8. Available from: https://pubmed.ncbi.nlm.nih.gov/36808784/

Malhi GS, Bell E, Jadidi M, Gitlin M, Bauer M. Countering the declining use of lithium therapy: a call to arms. Int J Bipolar Disord; 2023 Dec 1 [cited 2025 Jun 29];11(1). Available from: https://pubmed.ncbi.nlm.nih.gov/37633877/

Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'agati VD. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol; 2000 Aug [cited 2025 Aug 27];11(8):1439–48. Available from: https://pubmed.ncbi.nlm.nih.gov/10906157/

McGrane IR, Omar FA, Morgan NF, Shuman MD. Lithium therapy in patients on dialysis: a systematic review. Int J Psychiatry Med. Int J Psychiatry Med; 2022 May 1 [cited 2025 Jun 29];57(3):187–201. Available from: https://pubmed.ncbi.nlm.nih.gov/34176305/

McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012 Feb 25 [cited 2017 Jan 5];379(9817):721–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S014067361161516X

Mehta PM, Gimenez G, Walker RJ, Slatter TL. Reduction of lithium induced interstitial fibrosis on co-administration with amiloride. Scientific Reports 2022 12:1. Nature Publishing Group; 2022 Aug 26 [cited 2025 Oct 6];12(1):1–15. Available from: https://www.nature.com/articles/s41598-022-18825-1

Miller AL, Bowden CL, Plewes J. Lithium and impairment of renal concentrating ability. J Affect Disord; 1985 [cited 2025 Aug 27];9(2):115–9. Available from: https://pubmed.ncbi.nlm.nih.gov/2932483/

Nielsen J, Kwon TH, Frøkiær J, Knepper MA, Nielsen S. Lithium-induced NDI in rats is associated with loss of α-ENaC regulation by aldosterone in CCD. Am J Physiol Renal Physiol. American Physiological Society; 2006 [cited 2025 Aug 27];290(5):1222–33. Available from: https://journals.physiology.org/doi/pdf/https://doi.org/10.1152/ajprenal.00321.2005

Nielsen RE, Kessing LV, Nolen WA, Licht RW. Lithium and renal impairment: a review on a still hot topic. Pharmacopsychiatry. 2018. https://doi.org/10.1055/s-0043-125393. (Georg Thieme Verlag;).

Nielsen RE, Licht RW. The true effect of lithium is hard to determine. BJPsych Open; 2023 Nov 12 [cited 2023 Nov 13];9(6):e187. Available from: https://pubmed.ncbi.nlm.nih.gov/37822221/

Nolen WA, Licht RW, Young AH, Malhi GS, Tohen M, Vieta E, et al. 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. Blackwell Publishing Inc.; 2019. p. 394–409.

Plenge P, Mellerup ET, Bolwig TG, Brun C, Hetmar O, Ladefoged J, et al. Lithium treatment: does the kidney prefer one daily dose instead of two? Acta Psychiatr Scand; 1982 [cited 2025 Jun 29];66(2):121–8. Available from: https://pubmed.ncbi.nlm.nih.gov/6814197/

Peces R, Pobes A. Effectiveness of haemodialysis with high-flux membranes in the extracorporeal therapy of life-threatening acute lithium intoxication. Nephrol Dial Transplant; 2001 [cited 2025 Jun 29];16(6):1301–3. Available from: https://pubmed.ncbi.nlm.nih.gov/11390745/

Post RM, Li VW, Berk M, Yatham LN. Lithium as a disease-modifying drug for bipolar disorder. Lancet Psychiatry; 2025 [cited 2025 Oct 5]; Available from: https://pubmed.ncbi.nlm.nih.gov/40505671/

Powers J, Singh B, Stonerock LR, Leung JG. Exploratory case series assessing the potential interaction between lithium and sodium-glucose cotransporter-2 inhibitors. J Clin Psychopharmacol; 2025 Sep 30 [cited 2025 Oct 6]; Available from: https://pubmed.ncbi.nlm.nih.gov/41025541/

Rao R. Glycogen synthase kinase-3 regulation of urinary concentrating ability. Curr Opin Nephrol Hypertens; 2012 Sep [cited 2025 Aug 27];21(5):541–6. Available from: https://pubmed.ncbi.nlm.nih.gov/22691876/

Rej S, Shulman K, Herrmann N, Harel Z, Fischer HD, Fung K, et al. Prevalence and correlates of renal disease in older lithium users: a population-based study. American Journal of Geriatric Psychiatry. Elsevier B.V.; 2014 Nov 1 [cited 2025 Aug 27];22(11):1075–82. Available from: https://pubmed.ncbi.nlm.nih.gov/24566239/

Sanches TR, Volpini RA, Massola Shimizu MH, de Bragança AC, Oshiro-Monreal F, Seguro AC, et al. Sildenafil reduces polyuria in rats with lithium-induced NDI. Am J Physiol Renal Physiol. American Physiological Society; 2012 [cited 2025 Aug 27];302(1):216–25. Available from: https://journals.physiology.org/doi/pdf/https://doi.org/10.1152/ajprenal.00439.2010

Schoot TS, Molmans THJ, Grootens KP, Kerckhoffs APM. Systematic review and practical guideline for the prevention and management of the renal side effects of lithium therapy. Eur Neuropsychopharmacol; 2020 Feb 1 [cited 2025 Jun 29];31:16–32. Available from: https://pubmed.ncbi.nlm.nih.gov/31837914/

Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. The Lancet. 2015 Aug 1 [cited 2017 Jan 5];386(9992):461–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26003379

Shulman KI, Almeida OP, Herrmann N, Schaffer A, Strejilevich SA, Paternoster C, et al. Delphi survey of maintenance lithium treatment in older adults with bipolar disorder: An ISBD task force report. Bipolar Disord; 2019 Mar 1 [cited 2025 Oct 6];21(2):117–23. Available from: https://pubmed.ncbi.nlm.nih.gov/30375703/

Sinke AP, Kortenoeven MLA, de Groot T, Baumgarten R, Devuyst O, Wetzels JFM, et al. Hydrochlorothiazide attenuates lithium-induced nephrogenic diabetes insipidus independently of the sodium-chloride cotransporter. Am J Physiol Renal Physiol [Internet]. American Physiological Society; 2014 Mar 1 [cited 2025 Aug 27];306(5):525–33. Available from: https://journals.physiology.org/doi/pdf/https://doi.org/10.1152/ajprenal.00617.2013

Smith KA, Cipriani A. Lithium and suicide in mood disorders: updated meta-review of the scientific literature. Bipolar Disord. 2017 Sep 12 [cited 2017 Sep 26]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/28895269

Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. Elsevier B.V.; 2024 Apr 1 [cited 2025 Aug 27];105(4):S117–314. Available from: https://pubmed.ncbi.nlm.nih.gov/38490803/

Strawbridge R, Ott M, Werneke U, Abbott MG, Prabhu A, Young AH, et al. ENaC inhibitors for the management of lithium related polyuria: a systematic review. J Affect Disord. Elsevier; 2025 Nov 1;388:119542.

Tabibzadeh N, Vidal-Petiot E, Cheddani L, Haymann JP, Lefevre G, Etain B, et al. Chronic lithium therapy and urine-concentrating ability in individuals with bipolar disorder: association between daily dose and resistance to vasopressin and polyuria. Kidney Int Rep; 2022 Jul 1 [cited 2025 Jun 29];7(7):1557–64. Available from: https://pubmed.ncbi.nlm.nih.gov/35812274/

Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, et al. Clinical use of lithium salts: guide for users and prescribers. Int J Bipolar Disord. SpringerOpen. 2019.

Tondo L, Baldessarini RJ. Prevention of suicidal behavior with lithium treatment in patients with recurrent mood disorders. Int J Bipolar Disord; 2024 Dec 1 [cited 2025 Oct 6];12(1). Available from: https://pubmed.ncbi.nlm.nih.gov/38460088/

Tondo L, Baldessarini RJ, Hennen J, Floris G, Silvetti F, Tohen M. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. Journal of Clinical Psychiatry. Physicians Postgraduate Press Inc.; 1998;59(8):405–14.

Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness:
a meta-analysis. Acta Psychiatr Scand. John Wiley & Sons, Ltd; 2001 Sep 1 [cited 2022 Jul 22];104(3):163–72. Available from: http://doi.wiley.com/https://doi.org/10.1034/j.1600-0447.2001.00464.x

Ulrichsen A, Hampsey E, Taylor RH, Gadelrab R, Strawbridge R, Young AH. Comparing measurements of lithium treatment efficacy in people with bipolar disorder: systematic review and meta-analysis. BJPsych Open. Royal College of Psychiatrists; 2023 May [cited 2025 Jun 29];9(3):e98. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10228238/

Zhang Y, Peti-Peterdi J, Brandes AU, Riquier-Brison A, Carlson NG, Müller CE, et al. Prasugrel suppresses development of lithium-induced nephrogenic diabetes insipidus in mice. Purinergic Signal. Springer Netherlands; 2017 Jun 1 [cited 2025 Aug 27];13(2):239–48. Available from: https://pubmed.ncbi.nlm.nih.gov/28233082/

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