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REVIEW ARTICLE

Chronic Kidney Disease in Lithium-Treated Older Adults: A Review of Epidemiology, Mechanisms, and Implications for the Treatment of Late-Life Mood Disorders

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Abstract Lithium is an important medication in the treatment of mood disorders. However, clinicians are hesitant to use lithium in older adults for fear of its medical effects, particularly kidney disease. This review describes the current understanding of the epidemiology and mechanisms underlying chronic kidney disease (CKD) in older lithium users, with recommendations for using lithium safely in late life. Prevalence estimates of CKD in older lithium users range from 42–50 %, which does not differ greatly from the 37.8 % rates seen in community-dwelling non-lithium using, non-psychiatric populations. Clinical and pre-clinical data suggest a variety of synergistic mechanisms contributing to CKD in older lithium users, including aging, cardiovascular factors, oxidative stress, inflammation, nephrogenic diabetes insipidus, acute kidney injury, and medication interactions. With regards to CKD, lithium can be used safely in many older adults with mood disorders. Compared to patients with pre-existing CKD, those with an estimated glomerular filtration rate >60 mL/min/1.73 m^2 are probably not as susceptible to lithium-associated renal decline. Using lithium concentrations <0.8 mmol/L; monitoring lithium concentrations and renal function every 3–6 months; being vigilant about concurrent medication use (e.g., diuretics, anti-inflammatories); as well as preventing/treating acute kidney injury, nephrogenic diabetes insipidus, diabetes mellitus, hypertension, smoking, and coronary artery disease can all help prevent CKD and further renal decline in older lithium users.

Key Points

Older lithium users commonly have chronic kidney disease (CKD), although these rates may not be very different compared with geriatric controls. CKD in older lithium users can potentially be explained by several synergistic etiologic mechanisms.

Lithium exposure may not necessarily cause renal decline, especially in older adults with normal pre-morbid renal function (estimated glomerular filtration rate >60 mL/min/1.73 m^2).

Strategies to prevent CKD in older lithium users include using lithium levels <0.8 mmol/L; monitoring lithium levels and renal function every 3–6 months; being vigilant about concurrent medication use (e.g., diuretics, anti-inflammatories); as well as preventing/treating acute kidney injury, nephrogenic diabetes insipidus, smoking, diabetes mellitus, hypertension, and coronary artery disease.

The medical risks associated with lithium should be carefully balanced with its important psychiatric benefits in many geriatric mood disorder patients.

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1 Introduction

Lithium remains a gold-standard treatment in bipolar disorder [1] and an important adjunctive therapy in unipolar depression [2]. Although there is some debate [3], lithium appears to be superior to alternative bipolar pharmacotherapies with respect to mood disorder relapse [4] and suicide [5]. An estimated 30–40 % of patients with bipolar disorder respond to lithium but not other agents [6]. In older adults, between 0.27 and 0.77 % of the general population aged >65 years has been reported to use lithium [7, 8]. Despite these facts and the rapidly increasing number of older adults with mental disorders, geriatric lithium prescribing has dropped markedly in the past two decades [9]. This drop in lithium use has been attributed to increasing use of atypical antipsychotics, discontinuation of previous lithium use due to adverse effects/toxicity, and avoidance of lithium prescribing [9, 10] due to its potential medical effects, particularly chronic kidney disease (CKD) [11].

This review aims to provide an overview of the current literature regarding CKD in older lithium users, its epidemiology, and potential underlying etiologic mechanisms. We then provide recommendations for using lithium safely in late-life mood disorders.

MEDLINE was searched for all English-language research articles published before July 2014 that were either clinical studies (e.g., trials, cohort and cross-sectional studies) or case series with five or more cases pertaining to kidney disease in lithium users. The following search strategy was employed:

> (English[lang]) AND ((((“Kidney Failure, Chronic”[MeSH]) OR (“Diabetes Insipidus”[MeSH]) OR (“Renal Insufficiency”[MeSH]) OR (“Lithium Carbonate/toxicity”[MeSH]) OR (“Lithium/toxicity”[MeSH]) OR (“Hypernatremia” [MeSH]) OR (“hypernatremia”) OR (“diabetes” AND “insipidus”) OR (intox*) OR (toxicity OR toxic) OR ((“renal” OR “kidney”) AND (“failure” OR dysfunction*))) AND ((“lithium”) OR ((“Lithium Carbonate”[MeSH]) OR “Lithium”[MeSH]))).

A total of 2,594 abstracts were identified. Of these, 125 papers were deemed to be of particular relevance to CKD in older lithium users.

We first described the definition, prevalence, and reported risk factors for CKD in this population. We then organized the remaining information by potential etiologic pathway (Fig. 1). In Sect. 2.12, a paper that summarized CKD genetics was also included to complement the lithium-specific data. Studies investigating patients aged >65 years were highlighted (Table 1). Data specific to patients >65 years was prefaced with terms such as “geriatric”, “late-life” and “older”, as opposed to “mixed-aged” data from samples including both older and younger adults.

2 Chronic Kidney Disease in Older Lithium Users

2.1 Definition

CKD has been defined by the UK National Institute for Health and Clinical Excellence (NICE) as an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (severe stage IV and V CKD) and <60 mL/min/1.73 m^2 (moderate stage III CKD) on two or more occasions in a ≥3-month interval [12]. Other definitions using serum creatinine exist [13, 14], but they are less reliable to assess renal function in older adults given the muscle mass lost with aging. CKD, especially at eGFR <45 mL/min/1.73 m^2, is concerning because it is associated with high rates of physical and psychiatric co-morbidity (e.g., cardiovascular disease [15] and depression), decline in both functioning and quality of life, as well as mortality [16].

2.2 Epidemiology

The prevalence of laboratory-confirmed CKD in geriatric lithium users (age >65 years, eGFR <60 mL/min/1.73 m^2) is believed to be 42–50 % [17–20], or even as high as 70 % in one small study ($n = 10$) [21]. Of these geriatric lithium users, 12–14 % receive some sort of clinical attention for CKD [18, 22]. These figures are still much higher than the 1.2–17 % laboratory-confirmed CKD seen in mixed-aged samples of lithium users [8, 23], although systematic comparisons between adult and geriatric lithium users are lacking. Given the high 37.8 % general community prevalence of CKD in older adults [24], however, the rates in geriatric lithium users do not seem markedly elevated, especially considering the high rates of cardiovascular risk factors, oxidative stress, and inflammation in mood disorder patients [25–27]. Future research will need to assess whether the prevalence and incidence of CKD is higher in older lithium users than in mood disorder and non-psychiatric controls.

In mixed-aged community samples of long-term lithium users, the prevalence and incidence of severe renal disease is 0.5–2 % [22, 23] and 0.65 cases/million population/year [28], respectively, depending on the definition used [stage IV–V CKD: eGFR <30 mL/min/1.73 m^2, end-stage renal disease (ESRD), or renal replacement therapy (RRT)]. In lithium users older than 55 years, the prevalence of RRT has been estimated to be 1.5 % [29]. RRT rates in lithium

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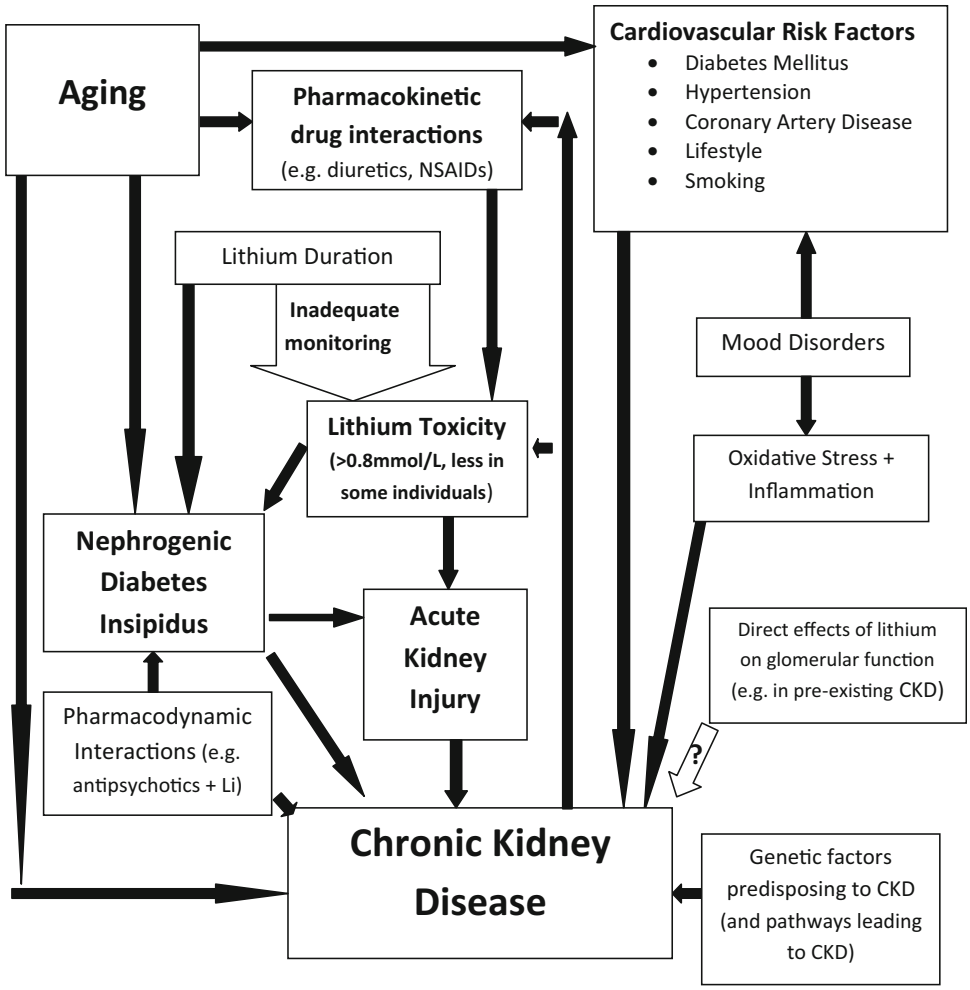

Fig. 1 Potential pathways to chronic kidney disease in older lithium users. *Li* lithium, *CKD* chronic kidney disease

users have been described as 2–8 times higher than in controls [22, 23, 28, 29]; however, these events continue to be uncommon and may be mostly restricted to patients previously exposed to exceedingly high lithium concentrations [30].

A number of potential CKD risk factors have been identified in this patient population [31]: age [32–34], acute lithium intoxication-induced acute kidney injury (AKI) [18, 35–37], nephrogenic diabetes insipidus (NDI) [18, 33, 38], and diabetes mellitus [22]. In geriatric lithium users, the most robust independent predictors of CKD appear to be age [20], hypertension, diabetes, ischemic heart disease, NDI, AKI, and loop diuretic, hydrochlorothiazide, and antipsychotic use [18]. The following sections describe the effects of these and other factors in older lithium users as potential etiologic pathways to CKD (Fig. 1).

2.3 Aging

Aging acts in numerous ways to produce CKD. With age, there are changes in the glomerular basement membrane, a loss of glomeruli in renal cortex, as well as decreases in renal blood flow due to renal vasoconstriction and age-related decreases in cardiac output [39]. As a result, aging is associated with a mean decline in eGFR of 0.8 mL/min/1.73 m^2 every year after age 40 years, although the course of renal decline can vary [39]. Aging is also associated with decreased urine osmolality (UOsm) due to decreased antidiuretic hormone (ADH) production [33, 40, 41], decreased dose requirements to achieve a given lithium concentration [42, 43], interactions with medication such as diuretics and NSAIDs [7], and cardiovascular co-morbidities such as diabetes and hypertension [24], all of which may predispose older lithium users to CKD [18].

2.4 Cardiovascular Risk Factors

In older lithium users, as in other geriatric populations, cardiovascular factors contribute heavily to CKD. Hypertension and diabetes are the most established risk factors for CKD [24]. Hypertension can lead to progressive hyaline accumulation in renal vessels and renin–angiotensin-mediated renal injury resulting in interstitial/glomerular changes [44]. Diabetes promotes the formation of advanced

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Table 1 Studies investigating lithium and chronic kidney disease that reported data on geriatric patients (age >65 years)

Study	Geriatric sample size (lithium users/controls)	Main findings
RCTs (category I)		
Aprahamian et al. [116]	59 (32/27 placebo)	No difference in renal decline (eGFR) between lithium exposed (0.25–0.5 mmol/L) and unexposed MCI patients during 4-year follow-up
Hardy et al. [42]	12 (6 continuers/6 placebo discontinuers)	Renal function worse in lithium continuers after 2-year RCT in unipolar depressed patients: creatinine 89.0 vs. 77.6 μmol/L; net change +6.5 vs. −6.8 μmol/L
Cohort studies (category II)		
Rej et al. [17]	27 (17 continuers, 10 discontinuers)	CKD prevalence 48 %. Amongst lithium users with CKD ($n = 27$), lithium continuation associated with large eGFR declines (>10 mL/min/1.73 m^2) in 5-year follow-up
Rej et al. [115]	282 (19/263 geriatric psychiatry and primary care controls)	Lithium use associated with important declines in eGFR (>10 mL/min/1.73 m^2) in 4-year follow-up only when CKD (eGFR <60) present at baseline. When eGFR >60, negligible renal decline in lithium-exposed patients
Cross-sectional studies (category III)		
Bendz et al. [23]	911/474,470 general population controls	Prevalence of end-stage renal disease low (0.5 %); however, represents an RR = 6 amongst geriatric patients
Head and Dening [37]	141	Previous lithium toxicity a risk factor for "abnormal renal function" (OR = 8.02)
Rej et al. [18]	2,480	CKD prevalence 42 %, independent predictors of CKD (ORs >1.5): NDI, AKI, hypertension, diabetes mellitus, coronary artery disease, hydrochlorothiazide, loop diuretic, and atypical antipsychotic use
Tredget et al. [21]	21 (10/11 mood disorder controls)	CKD prevalence 70 % ($n = 10$) vs. 36.4 %. However, lithium duration not associated with CKD
Van Melick et al. [20]	48	CKD prevalence 50 %; 4 % had eGFR <30 mL/min/1.73 m^2. Lithium duration not associated with CKD

AKI acute kidney injury, *CKD* chronic kidney disease (eGFR <60 mL/min/1.73 m^2), *eGFR* estimated glomerular filtration rate, *MCI* mild cognitive impairment, *NDI* nephrogenic diabetes insipidus, *OR* odds ratio, *RCT* randomized control trial, *RR* relative risk

glycation end-products, which can induce inflammatory and oxidative stress in renal capillaries and glomerular basement membranes, leading to glomerular and tubulointerstitial injury [45].

In older lithium users, diabetes [22], hypertension [20], and ischemic heart disease are all independently associated with CKD (odds ratio [OR] 1.7–2.0) [22]. Especially in bipolar disorder, but also in unipolar depression, lifestyle factors such as decreased physical activity, unhealthy diet, and substance use (e.g., smoking) can contribute to cardiovascular risk, thereby indirectly increasing CKD risk [26]. Although smoking and body mass index may correlate with CKD in lithium users [28], there is conflicting evidence [22].

2.5 Oxidative Stress and Inflammation

Although there are not yet data specifically linking oxidative stress with renal disease in lithium users [31, 46], mood disorders and their metabolic/cardiovascular comorbidities have been associated with both inflammation [47, 48] and oxidative stress pathways [27, 49]. Considering that inflammation and oxidative stress are important contributors to renal interstitial fibrosis, thereby precipitating CKD [50, 51], these may be areas worth examining in older lithium users.

2.6 Nephrogenic Diabetes Insipidus

NDI refers to a decrease in the urinary concentrating ability that results from resistance to the action of ADH. NDI is characterized by excessive thirst (polydipsia) due to increased production of dilute urine (polyuria). NDI occurs commonly in older lithium users: 12–19 % have decreased UOsm (defined as UOsm <300 mOsm/Kg) [20, 52], while 33 % have polyuria (defined as >3 L/day) [20]. Several NDI risk factors have been identified: age [33, 38, 41], non-responsiveness of mood disorder to lithium [53, 54], concurrent use of antipsychotics [55–59] or other psychiatric medications [60] (although there are conflicting data

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regarding antidepressants [61, 62]), slow-release lithium formulation [38, 63], twice-daily lithium dosing [54, 64–66], increased lithium concentration [41, 58, 63], and longer duration of lithium use [20, 33, 38, 67–70]. Of these, age, lithium duration, and lithium concentration are most robustly associated with NDI in older patients [20, 52]. In terms of the treatment of lithium-associated NDI, the only medication with evidence from randomized clinical trials is amiloride 5–20 mg/day [71, 72]. However, as a potassium-sparing diuretic, amiloride needs to be used cautiously to prevent lithium concentration elevations [7]. The symptoms of NDI are bothersome, but even more concerning is that NDI increases the risk of hypernatremia [62], lithium intoxication [73], and CKD [18, 33, 38, 74].

In NDI, lithium is believed to interact with the inositol monophosphate [75] and protein kinase C [76] pathways, thereby affecting calcium-related intracellular signaling, cyclic adenosine monophosphate (cAMP), and inhibition of glycogen synthase kinase-3 beta (GSK3Beta) [77]. Recently, phosphodiesterases (which hydrolyze cAMP) [78] and the mitogen-activated protein kinases [extracellular signal-regulated protein kinases (ERK) 1/2, p38] have also been implicated [79]. These changes in NDI lower the kidney's sensitivity to centrally produced ADH (vasopressin), thereby decreasing expression of aquaporin 2 (AQP2) in renal collecting duct principal cells and possibly lowering the number of principal cells [80]. Lowering the amount of water reabsorbed by renal AQP2 creates polyuria and dilute urine (decreased UOsm), abnormalities that increase the probability of CKD occurring [18, 33, 38, 74].

Clinically, almost all mixed-aged [31, 33, 38] and geriatric studies have found an independent association between NDI and CKD [18, 74]. It had long been thought that most lithium users would develop renal tubular changes and NDI, eventually becoming at high risk for interstitial fibrosis and CKD [81]. This concept has been revised: although 50 % of long-term lithium users have at least mild decreases in UOsm [81] and 12–33 % meet UOsm or urine volume definitions for NDI [20, 52], classical severe lithium nephropathy is relatively rare [23, 82]. Furthermore, tubular dysfunction on biopsy (generally in the form of tubular dilatation and renal micro-cysts) does not appear to predict decline in eGFR over 10- to 20-year follow-up [68, 83]. Similar results have been found in recent cross-sectional imaging studies [84], but in mixed-aged or adult samples. Given these data, whether NDI is (1) a cause of or (2) a co-occurring predictor of CKD has yet to be clarified, particularly in older adults. Nonetheless, since its presence predicts a threefold increase in CKD risk amongst older lithium users [18], treating NDI and addressing NDI's risk factors may potentially be helpful in the prevention of CKD.

2.7 Acute Kidney Injury

AKI occurs in 1.3–7 % of older lithium users over 5-year follow-up [7, 18, 85]. AKI has been formally defined as an acute reduction in eGFR by 50 % from baseline (severe) or by smaller acute eGFR increments (mild) [86]. However, the lithium literature had previously defined AKI as any decrease in renal function accompanying an acute lithium concentration of >1.5 mmol/L (or lower in many geriatric patients) [31], only more recently using administrative health data [7, 18, 85]. Risk factors for AKI in older lithium users include advanced age [73, 87, 88], previous lithium concentration elevations or intoxication [73, 87, 89], NDI [73], as well as concurrent use of ACE inhibitors, loop diuretics [7, 93], NSAIDs [90, 91], cyclo-oxygenase 2 (COX2) inhibitors [92], and diuretics [93]. Mild cases of AKI can be treated with saline, while severe cases may benefit from hemodialysis [94], as well as sodium polystyrene sulfonate, which can shorten the half-life of lithium during dialysis [95].

Little is known about the pathophysiology of AKI in lithium users and how this may lead to CKD. One hypothesis is that acute lithium toxicity causes acute NDI [73, 96], which then causes pre-renal volume depletion and concomitant AKI, although this has yet to be validated [31]. Nevertheless, AKI is associated with CKD and may increase the risk of CKD in older lithium users by up to tenfold [18].

2.8 Lithium Monitoring

Lithium monitoring often falls short of the usually recommended measurement of serum lithium concentrations and eGFR every 3–6 months [97], after even 1 year of use [98]. This is concerning since the grand majority of older lithium users have used the medication for >5 years [18]. Also, since lithium is eliminated by the kidneys, the lithium dose required to achieve a given serum concentration can drop by 33–50 % or more as patients age beyond 65 years [42, 43, 99]. In the context of poor monitoring, accidental/chronic lithium intoxication increases the risk of NDI and AKI [73, 96], thereby increasing CKD risk [18]. With proper monitoring, however, there is little variability in geriatric serum lithium concentrations [19, 100] and improved renal outcomes [101].

2.9 Lithium Concentrations

In the context of regular lithium monitoring and the use of levels <0.8 mEq/L, serum lithium concentrations do not appear to be directly associated with CKD in older lithium users [19, 20]. This echoes findings from mixed-aged samples [23, 36]. However, certain patients may have NDI

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or acute declines in eGFR, especially with concentrations >0.8 mEq/L, but potentially with lower concentrations as well [20, 52, 73]. As a result, even though lithium concentrations may not directly influence eGFR, higher concentrations may increase the risk of NDI or AKI, thereby indirectly increasing CKD risk.

2.10 Lithium Duration

Meanwhile, the effect of lithium duration is more controversial [8, 64, 67, 102–107], with most mixed-aged studies suggesting low CKD risk in the grand majority of adult patients [31, 33, 40, 41, 46, 69, 108–111], especially after properly controlling for the effect of simple aging [112]. Along similar lines, lithium discontinuation may not lead to improvement in eGFR [59, 113].

On the other hand, studies investigating older patients with pre-morbid CKD (eGFR <60 mL/min/1.73 m^2) [17, 114, 115], even when lithium concentrations were <0.8 mmol/L, found an association with clinically important declines of eGFR >10 mL/min/1.73 m^2 over 4- to 5-year follow-up [17, 115]. In geriatric analyses using administrative databases, longer lithium duration was associated with higher rates of severe CKD and ESRD (OR 1.8–2.7) [18, 22], although patients with 2–5 years versus >5 years of lithium exposure did not differ [18]. In contrast, older patients with normal pre-morbid renal function (eGFR >60 mL/min/1.73 m^2) do not appear to have this type of renal decline at baseline [20] or over longitudinal follow-up [19, 115]. An exciting recent 4-year randomized controlled trial (RCT) in 59 older adults (mean baseline eGFR 79.3 mL/min/1.73 m^2) found that lithium targeted at 0.25–0.5 mmol/L was not associated with decline in eGFR [116]. Taken together, lithium duration appears to be most robustly associated with renal decline/severe CKD when eGFR is <60 mL/min/1.73 m^2.

In geriatric patients with an eGFR <60 mL/min/1.73 m^2, there are a number of hypothetical mechanisms that could explain how lithium may directly affect renal glomerular function. The transforming growth factor-β and similar inflammatory cytokine signaling pathways can induce epithelial 'micro-injuries' that can lead to G2 cell-cycle arrest [117], apoptosis, and the formation of fibrogenic foci [118]. It is believed that the focal fibrosis, tubular atrophy, and glomerulosclerosis contribute to renal tubulo-interstitial disease, which leads to further collagen deposition and inflammation [82]. Although this has been most well-documented in rats exposed to 6 months of relatively high-dose lithium (0.8–1.3 mmol/L) [82], there is some human evidence that higher-grade interstitial fibrosis predicts poor 20-year decline in renal function when baseline eGFR is approximately 60 mL/min/1.73 m^2 [68], but not when pre-morbid renal function is normal [83]. Along similar lines, lithium-associated GSK3Beta inhibition is believed to be important in NDI [75], may activate the same Wnt/β-catenin signaling pathways affected in cystic kidney diseases [82], and may lead to dysregulated proliferation of tubular cells [80] and even renal cancer in rare cases [119]. However, a direct association has not yet been found between GSK3Beta promoter polymorphisms and decreased eGFR in lithium patients [120].

There are also many explanations, however, for how lithium duration may indirectly affect eGFR (Fig. 1). Many of the positive studies in this field did not control for aging [112] or the hypertension/diabetes that often accompany aging [31]. Longer lithium duration is associated with less frequent monitoring [98] and more possibilities for AKI [73]. Since NDI has been repeatedly associated with longer lithium duration [24], it is possible that lithium duration acts through NDI, thereby contributing to CKD (see Sect. 2.6).

2.11 Drug Interactions

Pharmacokinetic drug interactions with lithium also contribute to CKD. NSAIDs [90, 91], COX2 inhibitors [92], and hydrochlorothiazide [93] can cause serum lithium concentrations to increase by 15–49 %, thereby potentially precipitating AKI [73]. Of these, loop diuretics and ACE inhibitors have been most robustly associated with acute lithium toxicity and AKI in older adults [7]. However, in a recent analysis, loop diuretics and hydrochlorothiazide were the only medications associated with CKD after controlling for age, lithium duration, and cardiovascular risk factors [18].

Although less studied, pharmacodynamic interactions can also affect CKD. Both typical and atypical antipsychotics appear to increase the frequency and severity of lithium-associated NDI [55–59], thereby indirectly increasing CKD risk. Atypical antipsychotics are also associated with CKD in older adults independent of NDI, diabetes, hypertension, and other factors [18], although whether antipsychotics directly affect eGFR will need to be verified.

2.12 Genetic Factors

Genetic contributions for CKD have not yet been extensively studied in older lithium users. The inositol monophosphate pathway, which involves calcium, cAMP, and GSK3Beta signaling, is believed to be involved in lithium's mechanisms in the CNS and in NDI [75]. A mixed-aged analysis found that the C/C promoter polymorphism of the *GSK3Beta* gene correlated with decreased urine-specific gravity (a potential marker of NDI), but not with CKD [120].

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- Monitor lithium concentrations and renal function (eGFR) monitoring every 3–6 months;
- Appropriate monitoring can prevent lithium toxicity, since the lithium dose required to achieve a given serum concentration can drop by 33–50 % or more as patients age beyond 65 years;
- Monitoring is especially important in geriatric patients with pre-morbid CKD (eGFR <60 mL/min/1.73 m^2)
- Consult nephrology if: (1) eGFR <30 mL/min/1.73 m^2, or (2) decline in eGFR is faster than 5 mL/min/1.73 m^2 in 1 year or 10 mL/min/1.73 m^2 in 5 years;
- Use serum lithium concentrations <0.8 mmol/L, if clinically possible;
- Avoid slow-release lithium formulations;
- Use once-daily lithium dosing (as opposed to ≥2 times/day);
- Prevent and treat cardiovascular and metabolic risk factors, especially hypertension, diabetes mellitus, and ischemic coronary disease, but also smoking, dyslipidemia, and obesity;
- Use concurrent medication cautiously, particularly those associated with lithium concentration elevations: loop diuretics, hydrochlorothiazide and other diuretics, ACE inhibitors/ARBs, NSAIDs;
- Prevent and treat other non-CKD renal disorders (AKI, NDI), which can otherwise increase the risk of CKD;
- Carefully weigh psychiatric benefits and renal risks before lithium discontinuation in this population: the risk of affective relapse is high, even in unipolar depression.

Fig. 2 Recommendations for clinicians: how to use lithium safely in older adults from a chronic kidney disease perspective. *AKI* acute kidney injury, *ARB* angiontensin-2 receptor blocker (antagonist), *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *NDI* nephrogenic diabetes insipidus

There are a broad range of possible genetic pathways that have not yet been examined (Fig. 1). Since poor lithium response in bipolar disorder has been associated with higher rates of NDI [53, 54], the effect of lithium-response [121] and bipolar genes [120] on CKD may be worth investigating. Calcium [120], glutamate [122], bicarbonate [123], and glutathione/oxidative stress [49] pathways appear promising, although genome-wide association study results in this field remain difficult to replicate [124]. The pharmacogenetics of lithium's interactions with diuretics, anti-inflammatories, ACE inhibitors, and other medications [125] may also be of interest. Otherwise, genetic and epigenetic mechanisms thus far identified in CKD (in general) include those affecting the renin–angiotensin–aldosterone, diabetes, and inflammatory pathways, amongst others [122].

3 Recommendations for the Use of Lithium in Older Adults

Does lithium cause renal disease in older adults? For the majority of older adults with appropriate dosing and monitoring, lithium exposure does not appear to be associated with an increased risk of CKD or renal decline [18–20, 46, 115, 116]. Common risk factors may be more important in these patients: hypertension, diabetes, coronary artery disease, and normal aging [18]. However, a small minority of long-term lithium users require hemodialysis or RRT during their lives: 0.5–2 %, a 2–8 times increased risk [22, 23, 28, 29]. Even with appropriate dosing and monitoring, continued lithium use in elders with a baseline eGFR <60 mL/min/1.73 m^2 may accelerate renal decline [17, 114, 115]. In other sub-populations, lithium may indirectly increase the risk of CKD or renal decline [18]: those with (1) NDI due to lithium use; or (2) AKI as a result of acute lithium toxicity, which can occur with inadequate monitoring or medication interactions [73]. We offer the following suggestions to help lower the risk of CKD in older lithium users.

Lithium remains one of the most effective interventions to treat bipolar disorder, reduce suicide risk, and augment antidepressant therapy for unipolar depression [1]. Clinicians may be reluctant to prescribe lithium due to safety concerns [9, 11]; however, the following recommendations may help minimize renal risks in older patients with mood disorders (Fig. 2).

Monitoring of lithium concentrations and renal function (eGFR) every 3–6 months is suggested by the International Society for Bipolar Disorder (ISBD) [97], with similar guidance from NICE [98]. Appropriate monitoring of serum lithium concentrations and eGFR can help prevent lithium toxicity [98, 101] and renal dysfunction [8, 19, 30], particularly since the lithium dose required to achieve a given serum concentration may decrease by 33–50 % (or more) as patients age beyond 65 years [99]. Lithium monitoring is especially crucial in the presence of pre-morbid CKD (eGFR <60 mL/min/1.73 m^2) to minimize renal harm [17, 115], particularly in bipolar disorder as lithium exposure can often be more long-term than in unipolar depression. Clinicians should not hesitate to ask for a nephrology referral when a patient's eGFR declines below 30 mL/min/1.73 m^2, decreases by more than 5 mL/min/1.73 m^2 in 1 year, or by more than 10 mL/min/1.73 m^2 in 5 years [12].

Lithium prescribing can be optimized to reduce renal risk. Clinicians should aim for a lithium concentration <0.8 mmol/L to prevent renal dysfunction [19]. Lower

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concentrations are encouraged if clinically feasible, since individual patients may have vulnerabilities to other renal effects (e.g., AKI and NDI, which are both associated with higher lithium concentrations), as well as other medical effects. For example, neurological or cognitive toxicity may occur even at concentrations 0.8 mmol/L or lower in some individuals (CNS lithium concentrations may differ from serum concentrations) [127]. Avoiding slow-release lithium formulations [38] and using once-daily lithium dosing schedules (as opposed to two or more times per day) [66] can also be beneficial in preventing renal toxicity, including NDI.

Managing medical co-morbidity and concurrent medication use is also important. Cardiovascular and metabolic risk factors, such as hypertension, diabetes, smoking, and ischemic coronary disease, should be addressed early to prevent renal decline [12, 18]. Medications known to cause pharmacokinetic drug interactions with lithium should be used with caution, especially hydrochlorothiazide, loop diuretics, NSAIDs, and ACE inhibitors [7, 18]. Since these drugs can increase serum concentrations by 50 % (or more), lithium concentrations should be monitored closely when initiating them. Antipsychotics may independently increase CKD risk in older lithium users (OR 1.7) [18], although this needs further investigation. AKI and NDI may greatly increase the risk of CKD (OR up to 3–10) [18], so preventing and treating them can indirectly reduce CKD risk. Saline and hemodialysis/sodium polystyrene sulfonate can be helpful for treating mild and severe AKI [94, 95], respectively. Although data are limited, two RCTs suggest that amiloride (5–20 mg/day) may be helpful in treating NDI [71, 72].

Weighing the psychiatric benefits and renal risks in long-term lithium users, decisional analyses of the literature suggest that lithium continuation may be recommended in most cases where patients experience renal dysfunction [128]. Why? There are disastrous 33–50 % rates of geriatric unipolar depression relapse with lithium discontinuation, albeit when using a relatively short <12-week discontinuation period [129]. There is no such data in lithium responders with bipolar disorder, where it would be unethical to test lithium discontinuation in a clinical trial. It is worth noting that older bipolar patients may require similar 0.6–1.0 mmol/L lithium concentrations as adults for psychiatric stability [130]. There are even instances in which lithium has been used in ESRD, including in renal transplant and dialysis patients [131], although maintaining stable lithium concentrations can be challenging in patients undergoing dialysis. Especially given the unclear renal benefits of discontinuation [59, 113, 116], the medical risks of lithium need to be closely balanced with the psychiatric risks of dose reduction or discontinuation on a patient-by-patient basis.

4 Limitations and Future Directions for Research

Although the field has come a long way thanks to pioneers such as Drs. Schou [94, 132] and Bendz [23, 133], and recent efforts, there remain some limitations to the literature. The literature had previously primarily consisted mostly of small ($n < 100$, often $n < 50$), cross-sectional studies with very little geriatric data [31]. In recent years, geriatric data examining lithium and CKD has expanded, with one new RCT [116], a number of population-based studies ($n > 1{,}000$ each) [8, 18, 22, 28, 30], and several other geriatric papers [17, 19, 52, 62, 74, 100, 115]. Still, many reports do not account for covariates such as age, cardiovascular risk factors, and NDI, and most of the population-based/clinical database studies do not use laboratory-defined measures of renal function.

Further large-scale administrative data studies, prospective clinical registries, and RCTs (including treatment with lithium concentrations 0.5–0.8 mmol/L [116]), all with laboratory confirmation of eGFR, will be needed to confirm CKD prevalence and incidence and eGFR decline estimates in older lithium users. Ideally, such studies will include both psychiatric and non-psychiatric controls and control for the effects of age, cardiovascular risk factors, NDI, and other variables to help us answer the primordial questions: "does lithium cause/worsen CKD in older adults?" and "which subpopulations are at highest risk of renal decline?" Investigating new areas such as genetics, inflammation, and oxidative stress and their effects, may shed additional light on the molecular mechanisms contributing to renal disease in older lithium users.

5 Conclusions

Based on our review and in agreement with fellow authors, "advanced age should not be considered as a contraindication to initiate or pursue lithium therapy" [100]. Close monitoring, careful prescribing of lithium (Fig. 2), and appropriate specialist consultation when necessary can help prevent CKD and renal decline in older mood disorders patients.

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