# Pharmacologic Renal Protective Strategies in Lithium Use: A Case for Prophylaxis?


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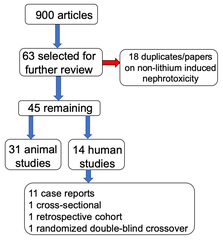
## Background

- Lithium (Li) is the mood stabilizer of choice for treatment of bipolar disorder, but it has well known renal side effects
- Majority of Li users develop urine concentrating deficits
- About 20% develop lithium-induced nephrogenic diabetes insipidus (Li-NDI), in which impaired response to vasopressin (AVP) leads to clinically significant polydipsia and polyuria
- Chronic Li-induced renal damage can lead to chronic kidney disease (CKD) and, rarely, end-stage renal disease (ESRD)
- Li-NDI and kidney damage do not typically reverse with cessation of Li, yet Li is often discontinued when renal function begins to decline
- Discontinuing Li carries a high risk of relapse, suicide and diminished response if the medication is restarted later
- Most literature on Li-NDI focuses on treatment of established disease, with limited information on prevention
- Similarly, there is a lack of research on prevention of chronic Li-induced renal damage, such as interstitial fibrosis
- This lack of evidence may stem in part from the difficulties inherent in conducting long-term prospective human studies
- The aim of this project is to examine the literature on pharmacologic agents shown to have renal protective properties in Li use and assess their potential for prophylaxis of Li-induced kidney disease based on their mechanisms, efficacy and tolerability

## Methods

- PubMed search for articles published in English 1/1/1990–8/17/2020
- Search strings:
  - "(lithium) AND (renal protective)"
  - "(lithium) AND (prevent OR treat) AND (renal failure OR nephrotoxicity OR nephrogenic diabetes insipidus OR kidney disease OR renal disease OR renal insufficiency OR nephropathy OR polyuria OR nephrotic syndrome OR nephritis)"
- Articles with animal or human evidence for pharmacologic prevention or management of Li-induced kidney disease were reviewed




## Results

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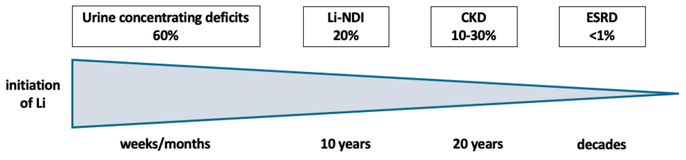
| **DIURETICS** | |
| **Potassium-sparing diuretics** – Amiloride, triamterene<br>*2 case reports, 1 randomized crossover study, 3 animal studies* | **Inhibits ENaC in renal collecting duct**<br>• May limit development of Li-NDI and prevent Li-induced fibrosis<br>• Partly restores urine concentrating mechanism and upregulates AQP2<br>• Unlikely to increase serum Li levels or worsen hypokalemia |
| **Carbonic anhydrase inhibitors** – Acetazolamide *3 animal studies, 1 human pilot study, 2 case reports* | **Inhibits carbonic anhydrase (CA), thereby decreasing NHE3 activity**<br>• Attenuates Li-induced AQP2 reduction<br>• As effective as amiloride + thiazide for Li-NDI in animal studies<br>• Human use limited by side effects, reduced GFR and metabolic acidosis |
| **Thiazides** – Hydrochlorothiazide, Bendroflumethiazide<br>*4 animal studies* | **Blocks NCC in distal convoluted tubule**<br>• Appears to upregulate AQP2, NCC and ENaC; may also inhibit CA<br>• Chronic use may increase serum Li levels by decreasing Li clearance |
| **HORMONES** | |
| **Desmopressin**<br>*3 case reports* | **Vasopressin receptor 2 (V2) agonist**<br>• At high doses, can overcome partial vasopressin resistance from Li-NDI |
| **NSAIDs** | |
| **COX inhibitors** – Indomethacin, ketorolac<br>*1 animal study, 3 case reports* | **Inhibits production of PGE2, which is upregulated in Li-NDI**<br>• Reduces polyuria and increases urine osmolality (UOsm)<br>• Increases NKCC2 and AQP2 expression<br>• Rapid resolution of severe NDI and acute hypernatremia |
| **ANTIPLATELETS** | |
| **P2Y12 inhibitors**<br>Clopidogrel, prasugrel<br>*3 animal studies* | **Enhances renal sensitivity to the effects of vasopressin**<br>• Increases AQP2, NKCC2, NCC and ENaC; serum Li levels unaffected<br>• Decreases urinary markers of oxidative stress |
| **MISCELLANEOUS AGENTS** | |
| **Antiepileptics** – Carbamazepine<br>*1 animal study* | **V2 agonist; also increases water absorption and AQP2 expression**<br>• Sodium loss and diuresis offset hypernatremia and polyuria in Li-NDI<br>• Can also be used to treat bipolar disorder |
| **Antidepressants** – SSRIs<br>*1 retrospective cohort study* | **SIADH-related hyponatremia may offset Li-induced hypernatremia**<br>• However, hypernatremia in this study was not necessarily related to Li-NDI |
| **Sildenafil**<br>*1 animal study* | **Phosphodiesterase-5 inhibitor; upregulates AQP2 and UT-A1**<br>• Restores nitric oxide synthase (NOS) reduced by lithium, normalizing renal vascular resistance; may slow renal damage and increase GFR |
| **Tamoxifen**<br>*2 animal studies* | **Selective estrogen receptor modulator (SERM)**<br>• Attenuates Li-induced decrease in AQP2 and NHE3, but reduces serum Li |
| **Antimalarials** – Chloroquine<br>*1 animal study* | **Inhibits autophagy; attenuates downregulation of AQP2 and NKCC2**<br>• Also protects against CD cell proliferation (Li-induced autophagy thought to induce proliferation leading to microcysts and long-term renal damage) |
| **Antihypertensives** – Aliskiren<br>*1 animal study* | **Direct renin inhibitor**<br>• Activates cAMP-PKA pathway that mediates AVP-induced AQP2 trafficking |
| **Statins**<br>*1 cross-sectional study* | **HMG-CoA reductase inhibitors**<br>• Statin users on Li maintained urine UOsm >300 mmol/kg |

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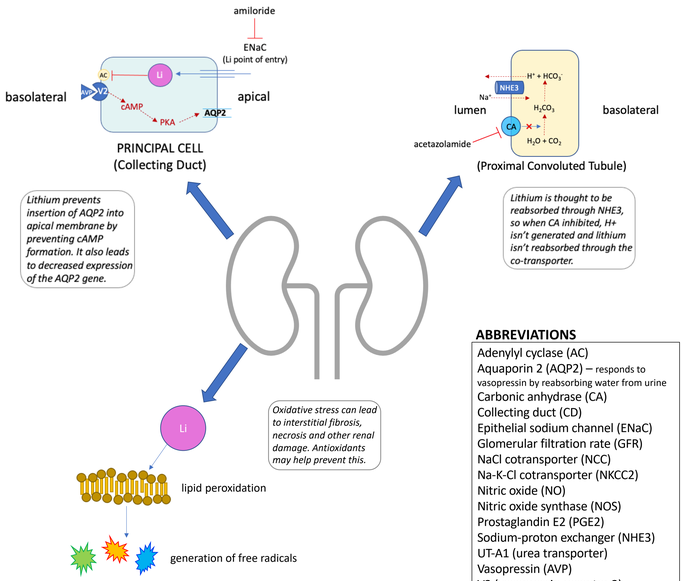
| **SUPPLEMENTS** | |
| **N-acetylcysteine (NAC)**<br>*1 animal study* | **Antioxidant that decreases oxidative stress, likely via nitric oxide (NO) vasodilation**<br>• Concurrent use with Li preserves GFR and attenuates rise in BUN/creatinine<br>• Significantly reduces Li-induced renal tubular damage |
| **Cactus extract**<br>*1 animal study* | **Plant extract with antioxidant and anti-inflammatory properties**<br>• Upregulates antioxidants, reduces oxidative stress & attenuates rise in creatinine<br>• Reduces Li-induced tubular and glomerular damage |
| **Malva sylvestris extract**<br>*1 animal study* | **Herb with anti-inflammatory and antioxidant properties**<br>• Attenuates reduction in antioxidants and increase in lipid peroxidation that occur in response to Li-generated reactive oxygen species (ROS) |
| **Ginsenoside-Rb1**<br>*1 animal study* | **Active component of ginseng with adaptogenic and anti-inflammatory properties**<br>• Reverses structural/functional renal impairments, likely by reducing NO products<br>• Lowers serum Li levels and decreases Li distribution in the brain |
| **Caffeic acid**<br>*1 animal study* | **Antioxidant compound found in honeybee propolis**<br>• Reduces urine markers of tubular injury and lipid peroxidation in Li use<br>• Attenuates Li-induced reduction in renal antioxidant activity |
| **4-phenylbutyric acid**<br>*1 animal study* | **Fatty acid used in treatment of urea cycle disorders**<br>• Promotes proper folding/maturation/secretion of proteins (e.g., AQP2), reducing endoplasmic reticulum stress & possibly preventing glomerular/tubular disorders |
| **Selenium**<br>*2 animal studies* | **Antioxidant with possible antidepressant properties**<br>• Reduces lithium levels in animal kidneys; protective effects unclear |
| **Potassium**<br>*Review of human and animal studies* | **Electrolyte affected variably by lithium use**<br>• May reduce polyuria/polydipsia<br>• Correcting chronic hypokalemia may reduce renal scarring & insufficiency |




**ABBREVIATIONS**

Adenylyl cyclase (AC)
Aquaporin 2 (AQP2) – responds to vasopressin by reabsorbing water from urine
Carbonic anhydrase (CA)
Collecting duct (CD)
Epithelial sodium channel (ENaC)
Glomerular filtration rate (GFR)
NaCl cotransporter (NCC)
Na-K-Cl cotransporter (NKCC2)
Nitric oxide (NO)
Nitric oxide synthase (NOS)
Prostaglandin E2 (PGE2)
Sodium-proton exchanger (NHE3)
UT-A1 (urea transporter)
Vasopressin (AVP)
V2 (vasopressin receptor 2)

## Conclusions

- Evidence for pharmacologic renal protective strategies in Li use is limited and largely comprised of animal studies
- Most agents used in Li-NDI work at least in part by upregulating AQP2
- Most agents with potential to prevent long-term renal damage have antioxidant and/or anti-inflammatory properties
- Agents to consider for prophylactic use:
  - Amiloride: Most studied. Has evidence for preventing both Li-NDI and fibrosis. However, may wish to avoid long-term diuretic use in patients for whom it is not otherwise indicated.
  - N-acetylcysteine: Shows promise for preserving renal structure and function. Is also relatively benign and some evidence suggests it has benefit in treatment of primary psychiatric disorders.
  - Malva sylvestris & cactus extract, caffeic acid, 4-PBA: Appear to have similar benefits to NAC, but less evidence and availability.
  - Antiplatelets, statins, sildenafil: Consider using in Li patients who have comorbidities for which these medications are indicated.
  - Potassium: Li patients might benefit from more aggressive repletion of chronic subthreshold or mild hypokalemia.
- Chloroquine has a novel mechanism with potential to prevent cysts and even renal cancers, but its use is limited by adverse effects
- Of note, there are multiple non-pharmacological renal protective strategies for Li use beyond the scope of this project
- Finally, I implore clinicians and researchers to invest in prevention of Li-induced kidney disease, not only to preserve patients' renal health, but to preserve lithium as a long-term treatment option in those whose lives it has changed for the better.

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