

# Drug-Induced Lithium Toxicity in the Elderly: A Population-Based Study

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**OBJECTIVES:** To study the association between hospital admission for lithium toxicity and the use of diuretics, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal antiinflammatory drugs (NSAIDs) in the elderly.

**DESIGN:** Population-based nested case-control study.

**SETTING:** Ontario, Canada.

**PARTICIPANTS:** Ontario residents aged 66 and older treated with lithium.

**MEASUREMENTS:** Estimated relative risk of hospital admission for lithium toxicity.

**RESULTS:** From January 1992 to December 2001, 10,615 elderly patients continuously receiving lithium were identified, of whom 413 (3.9%) were admitted to the hospital at least once for lithium toxicity. After adjustment for potential confounders, a dramatically increased risk of lithium toxicity was seen within a month of initiating treatment with a loop diuretic (relative risk (RR) = 5.5, 95% confidence interval (CI) = 1.9–16.1) or an ACE inhibitor (RR = 7.6, 95% CI = 2.6–22.0). Conversely, neither thiazide diuretics nor NSAIDs were independently associated with a significantly increased risk of hospitalization for lithium toxicity.

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**CONCLUSION:** The use of loop diuretics or ACE inhibitors significantly increases the risk of hospitalization for lithium toxicity, particularly in naïve recipients. *J Am Geriatr Soc* 52:794–798, 2004.

**Key words:** drug interactions; aged; lithium; diuretics; nonsteroidal anti-inflammatory agents; ACE inhibitors; toxicity; pharmacoepidemiology; nested case-control studies

Lithium is commonly used for the treatment of unipolar and bipolar affective disorder, but a low therapeutic index and significant toxicity limit its clinical utility.<sup>1,2</sup> The most dramatic manifestations of lithium toxicity involve the central nervous system and kidneys, and some of these effects may be permanent.<sup>2–8</sup> Elderly patients are at a particularly high risk of lithium toxicity because of altered pharmacokinetics, polypharmacy, renal impairment, and proneness to medication confusion.<sup>4,9–11</sup> Three major drug classes have been identified as potential precipitants of lithium toxicity.<sup>1,12</sup> Both diuretics, which promote renal sodium wasting, and angiotensin-converting enzyme (ACE) inhibitors, which reduce glomerular perfusion pressure, can enhance the tubular reabsorption of lithium.<sup>13–20</sup> Nonsteroidal antiinflammatory drugs (NSAIDs) have also been associated with lithium toxicity through a mechanism that is presumed to involve interruption of renal prostaglandin synthesis.<sup>4,21–24</sup> Reports of pharmacokinetic interactions between lithium and other medications are uncommon.

Lithium toxicity can be life threatening, and the medications that may precipitate lithium toxicity are among the most widely used medications in the elderly.<sup>25</sup> No studies have quantified the risks of lithium toxicity after the use of these medications. Accordingly, this study sought to explore the risk of hospitalization for lithium toxicity after receipt of a prescription for a diuretic, ACE inhibitor, or NSAID in a large population-based study of older adults receiving lithium.

## METHODS

### Setting and Design

The study was a nested case-control analysis of multiple linked healthcare databases over 10 years (January 1, 1992, to December 31, 2001) in Ontario, Canada. Ontario is Canada's most populous province, with a registered population of 11,669,344 at the midpoint of the study interval of whom 1,377,530 were aged 66 years and older. Ontario's elderly residents have universal access to hospital care, physician services, and prescription drug coverage. The ethics review board of Sunnybrook and Women's College Health Sciences Center approved this research.

### Data Sources

Prescriptions for lithium were identified from the Ontario Drug Benefit Program, which records prescription medications dispensed to Ontario residents aged 65 and older. Admissions for lithium toxicity were identified from the Canadian Institute for Health Information Discharge Abstract Database, which contains a detailed record of all hospital admissions in Ontario. The Ontario Health Insurance Plan provided physician claims information for inpatient and outpatient services, and the Ontario Registered Persons Database contained basic demographic information for each Ontario resident. All analyses were conducted anonymously using an encrypted version of the individual health card number.

### Observation Period

Elderly patients whose prescription records allowed for the definition of a period of uninterrupted lithium use were studied. This observation period began with the first prescription for lithium after patient's 66th birthday and ended with patient's hospital admission for lithium toxicity, the end of the study period, the patient's death, or discontinuation of lithium, whichever occurred first. Subjects were deemed to discontinue lithium if more than 180 days elapsed between prescriptions for the drug; in such cases, the observation period was extended to 60 days after the last lithium prescription so that admissions for lithium toxicity that may have prompted cessation of therapy would not be omitted. Patients were not studied during their first year of eligibility for prescription drug coverage (age 65) to avoid incomplete medication records.

### Case Patients

Case patients were defined as those admitted to the hospital during the study period with a diagnosis of lithium toxicity, represented by *International Classification of Diseases, Ninth Revision (ICD-9)* codes 969.8 (psychotropic agents not elsewhere classified) and 985.9 (toxic effects of metals not otherwise specified). Because these codes have not been validated, only admissions for these diagnoses of patients actively receiving lithium therapy were considered. The toxic effects of most other psychotropic agents and metals are denoted by different ICD-9 codes.<sup>26</sup> The date of admission served as the index date for all analyses, and only the first admission was considered for patients hospitalized more than once for lithium toxicity.

### Controls

Four controls were selected for each case, matching for age, sex, and continuous use of lithium on the index date. When multiple potential controls existed for a case, four were randomly selected for analysis. In the one instance in which only three controls were available, only those controls were analyzed, and the matching process was not altered.

### Exposure to Interacting Medications

Prescriptions for any diuretic (alone or in combination with another agent), any ACE inhibitor, or any prescription NSAID (including selective cyclooxygenase-2 inhibitors) before the index date were examined. Thiazide-type (such as chlorthalidone) and loop diuretics (such as furosemide) were also examined independently. Combination products containing an ACE inhibitor plus a diuretic or a NSAID plus misoprostol were excluded. As a test of specificity, prescriptions for topical corticosteroids preparations were also examined to establish that no association was observed where none was expected.

Because these interactions are most likely to be clinically relevant at the outset of treatment, two separate analyses were conducted. The first considered any exposure to a potential interacting drug within 28 days before admission for lithium toxicity. In the second, only new exposures to these agents, defined as no other prescriptions from the same drug class in the preceding 365 days, were considered.

Additional drug interactions involving lithium have also been described with calcium antagonists<sup>4,27-30</sup> and neuroleptics,<sup>4,31-34</sup> but these were not considered in the analysis because these interactions are primarily pharmacodynamic in nature and may be more prone to misdiagnosis and miscoding. Finally, although a few reports exist of lithium toxicity during concomitant use of an angiotensin-receptor antagonist, these drugs were excluded from analysis because they were not in widespread use during most of the study period.<sup>31</sup>

### Statistical Analysis

The primary analysis considered prescriptions in the 28 days before admission for lithium toxicity, and a secondary analysis considered prescriptions within 14 days. In each analysis, the odds ratio obtained from conditional logistic regression was used to estimate the relative risk and 95% confidence interval for the association between medication use and hospital admission for lithium toxicity. To estimate the proportion of admissions that might be averted by avoiding each interaction, attributable fractions were calculated for new users of these medications using standard methods for case-control studies.<sup>35</sup>

A multivariate conditional logistic regression model was used to adjust for potential confounders. Renal insufficiency was adjusted for by examining inpatient and outpatient records (physician claims, inpatient diagnostic codes, and hemodialysis records) in the year before the index date for any evidence of renal impairment. Because patients with a previous history of lithium toxicity may have more subtle reasons to experience a recurrence, any previous hospitalizations for lithium toxicity in the year before cohort entry were adjusted for. The use of diuretics,

ACE inhibitors, and NSAIDs within 90 days of the index date when they were not the primary exposure of interest were also adjusted for. Finally, for each patient, the number of different drugs prescribed in the year before the index date, a recently validated measure of comorbidity, was adjusted for.<sup>36</sup>

### Sensitivity Analyses

The analyses were repeated with a variety of modifications to assess the robustness of the findings. For patients who appeared to discontinue lithium because of a lapse between refills of more than 180 days, this period was reduced to 100 days. The 60-day extension to the observation period after the final prescription was also altered to 30 days and then 90 days. Finally, the multivariate analysis was repeated, adjusting for exposure to other interacting medications within 2 weeks, 4 weeks, 6 weeks, and 8 weeks of the index date.

### RESULTS

Ten thousand six hundred fifteen elderly patients treated continuously with lithium for a total of 26,866 patient-years of therapy were identified. The mean age  $\pm$  standard deviation at entry to the cohort was  $72 \pm 6.3$ ; 62% were women. During the 10-year study period, 413 patients were admitted to the hospital with lithium toxicity. These patients were, on average, about 2 years older than the rest of the cohort and were marginally more likely to be women (66%). Patients admitted with lithium toxicity spent a total of 7,885 days (median 11; interquartile range 6–23 days) in the hospital. Sixty-one (15%) were treated in a critical care unit, 13 (3%) underwent dialysis, and 19 (5%) died before discharge.

Of the 413 elderly patients admitted with lithium toxicity, many had received prescriptions for a potential interacting medication during the preceding month (Table 1). After adjustment for potential confounders, the use of diuretics (particularly loop diuretics) and ACE inhibitors in

the preceding month was associated with a modest increase in the risk of admission for lithium toxicity. In new users of these agents, the risk of toxicity was considerably higher. Patients newly treated with loop diuretics were nearly six times more likely more likely to be hospitalized, and those started on ACE inhibitors were four times more likely to be hospitalized (Table 2). In no analysis was the use of thiazide diuretics or NSAIDs associated with a significantly greater risk of hospitalization for lithium toxicity, even in new users of these agents. As expected, no association was found between topical corticosteroid use and lithium toxicity. Sensitivity analyses employing various definitions of the discontinuation date, individual observation period, and covariate exposure interval yielded uniformly consistent results.

Approximately 2.4% of all hospitalizations for lithium toxicity in this cohort could be ascribed to new use of a loop diuretic in the preceding 28 days, and about 3.0% of such admissions could be ascribed to new use of an ACE inhibitor.

### DISCUSSION

Using population-based healthcare data, it was found that about 4% of elderly patients treated with lithium were admitted to hospital for lithium toxicity. Although many of these admissions occurred shortly after a prescription for a potentially interacting drug, the risk of toxicity appeared to be greatest after the start of treatment with ACE inhibitors or loop diuretics. It is likely that ACE inhibitors provoke lithium toxicity by inhibiting the production of angiotensin II, thereby diminishing glomerular perfusion and reducing renal lithium clearance. In contrast, furosemide actually increases lithium elimination when given to healthy volunteers, and is considered the diuretic of choice for patients receiving lithium.<sup>37–39</sup> The findings of the current study suggest that this practice should be reconsidered. Older patients, particularly those with subtle renal insufficiency, may become sufficiently volume contracted and

**Table 1. Association Between Hospitalization for Lithium Toxicity and Any Use of Other Medications**

Analysis	Cases (n = 413)	Controls (n = 1,651)	Relative Risk (95% Confidence Interval)	
			Univariate	Multivariate*
		n (%)		
Primary (dispensed within 28 days)				
Thiazide diuretics	16 (3.9)	37 (2.2)	1.8 (1.0–3.3)	1.3 (0.7–2.5)
Loop diuretics	54 (13.1)	71 (4.3)	3.4 (2.3–5.0)	1.7 (1.1–2.7)
ACE inhibitors	63 (15.3)	110 (6.7)	2.5 (1.8–3.5)	1.6 (1.1–2.3)
NSAIDs	63 (15.3)	187 (11.3)	1.4 (1.0–1.9)	1.1 (0.8–1.6)
Topical corticosteroids	29 (7.0)	75 (4.5)	1.6 (1.0–2.5)	1.2 (0.7–1.9)
Secondary (dispensed within 14 days)				
Thiazide diuretics	8 (1.9)	21 (1.3)	1.6 (0.7–3.6)	0.9 (0.4–2.2)
Loop diuretics	29 (7.0)	50 (3.0)	2.5 (1.5–4.0)	1.3 (0.7–2.2)
ACE inhibitors	38 (9.2)	60 (3.6)	2.7 (1.5–4.0)	1.3 (0.7–2.2)
NSAIDs	39 (9.4)	108 (6.5)	1.5 (1.0–2.2)	1.2 (0.8–1.8)
Topical corticosteroids	11 (2.7)	43 (2.6)	1.0 (0.5–2.0)	0.8 (0.4–1.6)

\* Multivariate analysis adjusts for other potential interacting medications (diuretics, angiotensin-converting enzyme (ACE) inhibitors, or nonsteroidal antiinflammatory drugs (NSAIDs) when not the primary exposure of interest), previous admissions for lithium toxicity, documented renal disease, and number of different prescription drugs in a preceding year.

**Table 2. Association between Hospitalization for Lithium Toxicity and New Use of Other Medications**

Analysis	Cases (n = 413)	Controls (n = 1,651)	Relative Risk (95% Confidence Interval)	
	n (%)		Univariate	Multivariate*
Primary (dispensed within 28 days)				
Thiazide diuretics	5 (1.2)	6 (0.4)	3.3 (1.0–10.9)	1.3 (0.3–4.7)
Loop diuretics	12 (2.9)	6 (0.4)	8.0 (3.0–21.3)	5.5 (1.9–16.1)
ACE inhibitors	14 (3.4)	5 (0.3)	11.2 (4.0–31.1)	7.6 (2.6–22.0)
NSAIDs	4 (1.0)	17 (1.0)	0.9 (0.3–2.8)	0.6 (0.2–2.1)
Topical corticosteroids	4 (1.0)	15 (0.9)	1.1 (0.4–3.2)	0.7 (0.2–2.3)
Secondary (dispensed within 14 days)				
Thiazide diuretics	3 (0.7)	3 (0.2)	4.0 (0.8–19.8)	1.0 (0.2–6.1)
Loop diuretics	9 (2.2)	4 (0.2)	9.0 (2.8–29.2)	5.5 (1.5–19.8)
ACE inhibitors	8 (1.9)	4 (0.2)	8.0 (2.4–26.6)	6.1 (1.7–21.7)
NSAIDs	3 (0.7)	8 (0.5)	1.5 (0.4–5.7)	0.9 (0.2–3.9)
Topical corticosteroids	2 (0.5)	5 (0.3)	1.6 (0.3–8.3)	1.1 (0.2–6.0)

\* Multivariate analysis adjusts for other potential interacting medications (diuretics, angiotensin-converting enzyme (ACE) inhibitors, or nonsteroidal antiinflammatory drugs (NSAIDs) when not the primary exposure of interest), previous admissions for lithium toxicity, documented renal disease, and number of different prescription drugs in preceding year.

sodium-avid during furosemide therapy that virtually all filtered lithium is reclaimed in the proximal tubule. Without dose adjustments, a progressive reduction in the fractional excretion of lithium would culminate in lithium accumulation and clinical manifestations of toxicity.

Conversely, neither thiazide diuretics nor NSAIDs were significantly associated with hospitalization for lithium toxicity, even when newly prescribed to elderly patients receiving lithium. These findings provide useful information to clinicians contemplating other medical therapies in elderly patients receiving lithium and suggest that the use of thiazide diuretics and NSAIDs may not be as hazardous in this population as was previously thought.<sup>1,2,3</sup> However, clinicians may have been aware of a potential interaction between these agents and lithium and may have adjusted doses or observed patients more closely for toxicity in the outpatient setting. The findings of the current study do not exclude the possibility that these drugs may precipitate lithium toxicity in some patients, particularly those with severe left ventricular dysfunction, renal impairment, or other recognized risk factors for lithium toxicity.

The limitations of this study deserve mention. Only patients with lithium toxicity admitted to a hospital were studied; others may have had the condition recognized and treated as outpatients. Others may also have been misdiagnosed during hospitalization, and miscoding tends to attenuate these observations. The sample size was small, and many estimates were imprecise. Administrative data were used, and therefore there was no direct measure of compliance, lithium levels, or nonprescription drugs (possibly including some NSAIDs). Ontario's elderly have universal prescription coverage for drugs, including all NSAIDs, and use of nonprescription drugs is unlikely to bias the findings. Importantly, the data include no direct measure of renal function. Finally, only patients aged 66 and older were studied, and the findings may not be generalizable to younger patients.

Physicians who care for patients receiving lithium should be aware of the potential hazards of concomitant drug therapies. In particular, lithium intoxication should be anticipated in the weeks after institution of a loop diuretic or an ACE inhibitor. These patients should be watched closely for evidence of toxicity and should be instructed to seek medical attention should they experience increasing tremor, fatigue, or confusion. Greater appreciation of the risk factors for lithium toxicity, particularly the role of commonly prescribed medications, may lessen the burden of lithium toxicity in elderly patients.

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