Renal Toxicity of Long-Term Lithium Treatment for Mild Cognitive Impairment

To the Editor: Having read with great interest the recent *JCP* article by Aprahamian et al[1] that examined nephrotoxicity in lithium-treated patients with mild cognitive impairment, I would like to make some remarks on this important topic.

First, regarding how lithium affects renal function, we know that renal toxicity induced by lithium mainly manifests as nephrogenic diabetes insipidus (NDI)[2] and that risk for its occurrence is influenced by lithium treatment duration, dose, and plasma level.[3] These patients show progressive reduction in urinary concentrating ability that can progress to chronic interstitial nephropathy and permanently impaired renal function.[4] Therefore, it would have been informative if Aprahamian et al had also reported data on urinary concentrating ability; such information might have been useful for monitoring NDI duration and would have been complementary to the clinical data presented in their study.

Second, with respect to the study period required to evaluate lithium renal toxicity, when considering the influence of lithium treatment duration on the risk of developing renal toxicity, current data indicate that patients treated with lithium need an average of 13.6 years to develop chronic interstitial nephropathy and more than 15 years to develop end-stage renal failure.[5] Furthermore, these effects appear to be progressive, at least for the first decade.[6] Accordingly, Aprahamian et al should have used a study period greater than 4 years and close to those of studies previously enumerated.[5,6]

Third, in relation to neurologic side effects of lithium, we know that lithium neurotoxicity causes neurologic sequelae, such as dementia, among others,[7] and that presence of NDI and age > 50 years are 2 of the most important risk factors contributing to the appearance of neurotoxicity.[8] Because of this, data on neurotoxicity during lithium treatment could have been informative, since this side effect has the potential to hide the effectiveness of lithium on mild cognitive impairment.

Fourth and finally, with regard to coadministered drugs, the study by Aprahamian et al[1] was also limited by the fact that the authors did not present data on the use of diuretics (eg, amiloride, thiazides), which can mask renal toxicity (eg, NDI) and/or alter lithium clearance.[9]

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Potential conflicts of interest: None reported.
Funding/support: None reported.
J Clin Psychiatry 2015;76(2):e232 (doi:10.4088/JCP.14lr09429).

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Drs Aprahamian and Forlenza Reply

To the Editor: In his letter commenting on our recent article,[1] Dr Lozano accurately reinforced the risk of renal and neurologic complications secondary to chronic lithium use. These adverse events are well known to most clinicians and have been clearly reported in the medical literature. Nonetheless, the use of lithium salts still represents an important strategy for the treatment of complex neuropsychiatric disorders, namely bipolar disorder, which invariably requires long-term management. Lithium represents a first-line therapeutic strategy or an adjunctive approach in the pharmacotherapy of mood disorders. Good clinical practice dictates that the clinician will perform a rigorous risk-benefit assessment prior to prescribing lithium and that safety and tolerability will be actively monitored throughout the treatment. This recommendation may be critical for the treatment of elderly patients and other individuals with comorbid medical or neurologic conditions that might increase the risk for such complications.

We agree with Dr Lozano's concerns about the safety limits of long-term lithium use. But perhaps his reading of our article[1] missed a few important points. First, rather than as a mood stabilizer, we addressed the potential of lithium as a candidate drug for the treatment of neurocognitive disorders, such as Alzheimer's disease,[2] amyotrophic lateral sclerosis,[3] and multiple system atrophy.[4] For this purpose, the putative disease-modifying effects may rely on serum concentrations of lithium much lower than those required for the treatment of bipolar disorder. In our study, the therapeutic range of lithium carbonate was set to yield concentrations of 0.25 to 0.5 mEq/L. This low-dose regimen is presumably associated with a better tolerability profile and a smaller incidence of adverse events and systemic complications.

Second, the author of the letter was concerned about the duration of the trial, which might have been too short to warrant a definitive conclusion. We partially agree with that, but this limitation of the study design must be balanced by the many advantages of conducting a randomized controlled trial (RCT), particularly with respect to the level of evidence provided. The duration of follow-up is one of the most important methodological constraints in any RCT. Most of the available evidence on lithium safety is derived from observational, naturalistic, and uncontrolled studies; retrospective analyses of patient charts; case reports and small case series; and a few short-duration case-control studies.[5,6] Very little of the information on the topic is derived from RCTs, of which there is considered to be an acute paucity by most authors in this field.[6] The study we conducted was double-blinded in the first 2 years of follow-up and single-blinded in the extension phase of up to 4 years. To the best of our knowledge, this was the longest such trial of lithium ever conducted. We understand that the onset of renal impairment may be far beyond our endpoint; however, it is practically and financially impossible to conduct a controlled trial with a duration of follow-up close to the one suggested by Dr Lozano.

Third, our study was not designed to detect subtle impairments of urinary osmolality reflecting initial impairment of renal tubular function, although we agree that this set of data should be included in future studies with low-dose lithium treatment. In our protocol, safety and tolerability variables were captured by means of a thorough medical examination (physical, neurologic, and psychiatric), in addition to a comprehensive neuropsychological assessment. None of our subjects presented with clinically relevant polyuria or other related symptoms. Signs of severe neurologic impairments were also not detected. In fact, participants

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receiving lithium (as compared to placebo) presented with significant improvements in global cognitive function, memory, and attention.[2]

Finally, diuretic use was an exclusion/withdrawal criterion in our study, as were any other medications with known potential drug interaction with lithium.

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Potential conflicts of interest: None reported.
Funding/support: Funding sources for the study discussed in this letter are listed at the end of the original article [*J Clin Psychiatry* 2014;75(7):e672–e678].
J Clin Psychiatry 2015;76(2):e232–e233 (doi:10.4088/JCP.14lr09429a).

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