

# Long-Term, Low-Dose Lithium Treatment Does Not Impair Renal Function in the Elderly: A 2-Year Randomized, Placebo-Controlled Trial Followed by Single-Blind Extension

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## ABSTRACT

**Background:** Recent studies evaluated the disease-modifying properties of lithium in mild cognitive impairment and dementia. Although potentially effective for these purposes, chronic lithium use in regard to safety in the elderly needs to be better explored.

**Objective:** To evaluate the effect of long-term lithium treatment at subtherapeutic doses on renal function in older adults. Secondary aims were to evaluate the clinical safety and tolerability of this treatment and its effects on thyroid, immune, and glycemic functions.

**Method:** Between February 2007 and October 2011, a 2-year randomized, double-blind, placebo-controlled trial followed by a single-blinded phase for an additional 2 years. Sixty-one patients with mild cognitive impairment (Mayo Clinic criteria) were randomized to receive lithium or placebo. Renal function was estimated by the abbreviated Modification of Diet in Renal Disease (aMDRD) and the Chronic Kidney Disease-Epidemiology study (CKD-EPI) equations. Leukocytes, serum thyroid-stimulating hormone (TSH) and free thyroxine ( $T_4$ ), and serum glucose and insulin were determined. Tolerability was evaluated at 3-month intervals through systematic clinical examinations and by the UKU Side Effect Rating Scale.

**Results:** Analysis of longitudinal regression indicated that no significant changes in renal function were detected by the aMDRD ( $P = .453$ ) and CKD-EPI ( $P = .213$ ) equations after 4 years of lithium treatment. Significant increases in the number of neutrophils ( $P = .038$ ), serum TSH ( $P = .034$ ), and body weight ( $P = .015$ ) were observed in the lithium group. The lithium group presented more overall adverse events ( $P = .045$ ), particularly interfering in daily activities ( $P < .001$ ). In addition, those patients had a higher incidence of diabetes mellitus ( $P = .037$ ) and arrhythmia ( $P = .028$ ).

**Conclusions:** Chronic use of lithium at low doses did not affect renal function and was clinically safe. However, some other potentially relevant adverse events were observed and others could not be ruled out due to limitations of the study design.

**Trial Registration:** ClinicalTrials.gov identifier: NCT01055392

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Lithium represents an important therapeutic choice in psychiatry, being effective in the management of bipolar disorder<sup>1</sup> and reducing both suicide and mortality in mood disorders.<sup>2,3</sup> More recently, novel biological properties of lithium have been emphasized, supporting it as a candidate drug for disease modification in Alzheimer's disease. In a recent study<sup>4</sup> conducted by our group, chronic lithium treatment of patients with mild cognitive impairment was associated with cognitive and functional stabilization, in addition to the modification of pathological markers of the disease.

Although most practice guidelines recommend lithium as a first-line drug for the long-term treatment of bipolar disorder, its use has decreased mostly because of safety concerns.<sup>5</sup> In fact, there are concerns related to the prescription of the drug, such as a narrow therapeutic window, the necessity of frequent determinations of serum levels, the incidence of potentially incapacitating adverse effects, the risk of teratogenicity, and the likelihood of organ damage, particularly in long-term use. In this context, renal dysfunction is a topic of special interest due to the potential development for severe renal impairment.<sup>5,6</sup>

Lithium commonly induces a tubular renal dysfunction compromising urinary concentrating capacity, which is often clinically expressed by polyuria with secondary thirst, and in some cases, diabetes insipidus.<sup>6,7</sup> Evidence shows a significant reduction of urinary concentrating ability, which may be irreversible.<sup>8,9</sup> A major concern is the possibility of lithium-induced glomerular dysfunction, resulting in renal impairment. As opposed to the widely accepted relationship between lithium use and tubular function, the available evidence supporting glomerular lesions is much more scarce and controversial. Although end-stage renal disease seems to be uncommon among chronic users (0.5%), recent studies report higher incidences (21%–55%) of stage III renal disease (ie, glomerular filtration rate below 60 mL/min/1.73 m<sup>2</sup>).<sup>10–15</sup> Moreover, recent systematic reviews yielded conflicting results about the extent of glomerular impairment and the actual long-term risk of renal failure.<sup>7,8</sup>

There are limited controlled data on the safety of lithium treatment, especially regarding renal function impairment.<sup>8</sup> This is particularly important for the elderly, in which renal dysfunction can be more common secondary to normal aging of the kidney and the association with hypertension and diabetes. Two recent trials<sup>16,17</sup> addressed safety and tolerability aspects of the prescription of lithium for patients with mild cognitive impairment and Alzheimer's disease, yet no systematic assessment of organ damage was provided.

- Low-dose lithium appears to be safe, especially regarding renal function in an older population.
- Older adults present mild impairments in daily activities with low-dose lithium.
- Periodic evaluation of at least the renal and endocrine functions is important to avoid organic lesions.

Given the potential benefit of using lithium salts for the adjunctive treatment of dementia, it is urgent to define its therapeutic window in the elderly. We hypothesize that lower lithium levels will not cause significant organ damage, especially renal impairment, among elderly patients. In this placebo-controlled study, we evaluated the effect of low-dose, long-term lithium treatment on renal function in elderly patients with mild cognitive impairment. We additionally investigated the effects of lithium on thyroid, immune, and glycemic function, along with overall tolerability.

## METHOD

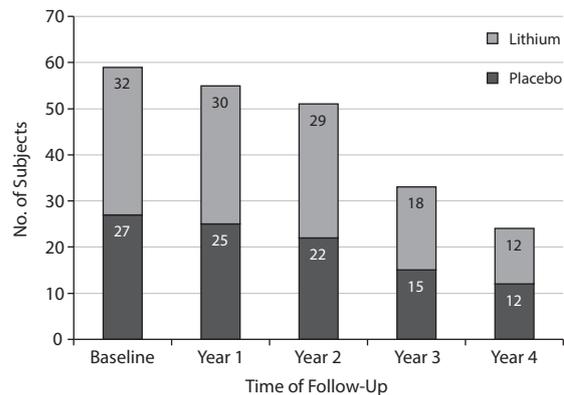
### Study Design and Participants

This was a single-center, randomized, double-blind, placebo-controlled study to assess the potential neuroprotective effects and the safety profile of chronic, low-dose lithium treatment in amnesic mild cognitive impairment. Participants were community-dwelling outpatients recruited from a cohort study<sup>18</sup> of cognitive aging at the Institute of Psychiatry, Faculty of Medicine, University of São Paulo, Brazil. Between February 2007 and October 2011, a total of 76 patients fulfilling the inclusion criteria were assigned to the present study. After initial recruitment, 15 patients declined participation. The remaining 61 patients were randomized to receive lithium or placebo and were longitudinally assessed for clinical, cognitive, and biological outcomes at 3-month intervals. Baseline laboratory data were missing for 2 patients, yielding an actual sample of 59 subjects (32 receiving lithium). Figure 1 displays the study flowchart, indicating the number of completers in each treatment group after 1, 2, 3, and 4 years of follow-up. Fifty-one of the initial sample of 59 participants (86%) completed the double-blind phase of the study after 2 years. Dropouts occurred for several reasons but were largely unrelated to the ongoing treatment (Table 1).

Preliminary data on cognitive and biological outcomes have been published previously,<sup>4</sup> and final analyses are underway. This study was approved by the local ethics committee and conducted in adherence with the Helsinki Declaration and Good Clinical Practice recommendations; the trial was registered at ClinicalTrials.gov: NCT01055392.

Participants were enrolled in this study after providing written informed consent. Inclusion criteria were an age of 60 years or older, diagnosis of amnesic mild cognitive impairment according to Mayo Clinic criteria<sup>19</sup> and no

**Figure 1. Study Flowchart With the Evaluation of Subjects During Follow-Up**



**Table 1. Dropout Distribution According to Study Phase and Treatment Group**

Study Phase	Lithium	Placebo
Double-blind (year 1)	Ischemic stroke (n = 1) Personal reasons (n = 1)	Died of pneumonia (n = 1) Personal reasons (n = 1)
Double-blind (year 2)	Lithium intolerance (n = 1)	Prostate cancer (n = 1) Severe hypertension (n = 1) Ventricular arrhythmia (n = 1)
Open extension (2 years)	Withdrew consent (n = 6) Recurrent falls (n = 1) Risk of drug interaction (n = 1) Requirement of diuretic use (n = 3) Supraventricular arrhythmia (n = 2) Cancer (n = 2) Major surgery (n = 1) Stroke (n = 1)	Withdrew consent (n = 3) Ventricular arrhythmia (n = 1) Cancer (n = 2) Major surgery (n = 2) Minor cerebrovascular events (n = 2)

evidence of ongoing psychiatric disorders, and no history of kidney disease or other relevant untreated clinical conditions. All participants were recruited, enrolled, monitored, and prescribed by a single investigator (O.V.F.) who did not take part in the assessment of baseline or outcome variables.

### Clinical Procedures and Safety Evaluation

All participants were interviewed and clinically examined for the detection of any adverse effects or organ damage at 3-month intervals. At each appointment, morbidity background was rechecked and potential drug interactions were examined. The evaluation of potential adverse events of treatment was based on the record of spontaneous complaints and the systematic assessment by the 56-item UKU Side Effect Rating Scale.<sup>20</sup> The UKU schedule estimates the likelihood of an association between the patient's complaints and the prescribed psychotropic drug based on the clinician's judgment, ie, adverse event(s) improbably, possibly, or probably related to the prescribed drug (or placebo). Additionally, the magnitude of the symptoms is rated as follows: 0 (symptom not present), 1 (mild), 2 (moderate), or 3

**Table 2. Baseline Characteristics of the Participants**

Characteristic	Lithium (n = 32)	Placebo (n = 27)	P
Age, mean (SD), y	71.6 (5.07)	74.8 (6.32)	.034 <sup>a</sup>
Education, mean (SD), y	9.47 (5.29)	9.04 (4.74)	.744 <sup>a</sup>
Female sex, n	23	19	.898 <sup>b</sup>
Race, n			.665 <sup>c</sup>
White	27	23	
Black	1	3	
Asian	4	1	
Comorbid diseases, n			
Hypertension	24	18	.677 <sup>b</sup>
Osteoarthritis	13	14	.388 <sup>b</sup>
Depression	10	8	.892 <sup>b</sup>
Dyslipidemia	8	11	.197 <sup>b</sup>
Hypothyroidism	8	7	.935 <sup>b</sup>
Diabetes	7	4	.487 <sup>b</sup>

<sup>a</sup>t test.<sup>b</sup> $\chi^2$  test.<sup>c</sup>Fisher test.

(severe). At the end of the UKU interview, both the physician investigator and the patient classified the overall impact of the reported symptoms (using the same 0–3 scale) on the ability to perform activities of daily living. At each visit, patients had their blood samples collected for a complete hemogram, renal function, electrolytes, hepatic enzymes, fasting glycemia and insulin (calculating the homeostasis model assessment of insulin resistance [HOMA-IR] index afterward), lipid profile, serum lithium, thyroid function tests (thyroid-stimulating hormone [TSH] and free thyroxine [ $T_4$ ] levels), and urinalysis. Other diagnostic tests (eg, electrocardiogram, ultrasound, tomography) were performed as needed according to the physician investigator's judgment. We did not perform specific tests to estimate the maximum concentrating capacity because the primary outcome was the longitudinal evaluation glomerular filtration rate and not the evaluation of tubular function.

### Lithium Dose Titration

The target lithium range defined was 0.25–0.5 mmol/L, which is lower than that commonly used for the treatment of affective disorders. This regimen was chosen to minimize the risk of adverse events and to reduce the rate of discontinuation due to side effects (for more information, see Forlenza et al<sup>4</sup>).

Identical tablets containing 150 mg, 300 mg, 450 mg, or 600 mg of lithium carbonate or placebo were produced at the pharmacy of the local university hospital and packaged into identical coded cases. After each visit, participants received from the pharmacist 2 batches of cases containing either lithium or placebo. Cases were identified for use in the morning and/or at bedtime, and patients were instructed to take 1 tablet daily or twice daily (accordingly), preferably with meals. Therefore, the prescribing physician investigator (O.V.E.) was able to titrate the daily doses of lithium or to maintain the placebo regimen by regulating the combinations of tablets, without needing to change the number of daily tablets.

After randomization, patients in the lithium group were started on daily doses of 150 mg of lithium, which was titrated at weekly visits to target serum levels. In case of

relevant side effects during the titration phase, the lithium dose was adjusted back to the highest tolerable dose within the treatment range. Serum lithium levels were determined weekly in the titration phase, 12 hours after the last dose. Once stable lithium levels were achieved, the prescription was maintained until the next visit, which was scheduled at 3-month intervals. Patients were instructed to report any adverse events or modifications made to other ongoing prescriptions; if necessary, the maintenance of lithium treatment was to be reevaluated.

### Assessment of Renal Function

Glomerular filtration rate was estimated according to 2 well-validated equations based on serum creatinine, namely the abbreviated Modification of Diet in Renal Disease (aMDRD) and the Chronic Kidney Disease-Epidemiology study (CKD-EPI).<sup>21</sup> The reason for using 2 equivalent indirect methods is the lack of a gold standard (ie, 24-hour inulin or creatinine clearance). Both equations are indicated for elderly patients and well correlated with the standards of renal function<sup>22</sup> and have the advantages of not requiring urinary storage or use of radiologic contrast materials. Any changes in serum creatinine, aMDRD, and/or CKD-EPI were further evaluated by the attending physician according to expert recommendations.<sup>23</sup>

### Statistical Analysis

Statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS) version 18. To assess the longitudinal changes in serum creatinine, CKD-EPI, aMDRD, TSH, free  $T_4$ , fasting serum glucose and insulin, HOMA-IR, and leukocyte/neutrophil count, we used a linear mixed effects model (longitudinal regression). Age was controlled in renal function variable (creatinine, aMDRD, and CKD-EPI) analyses. Fisher exact test was carried out to assess the incidence of new clinical diagnoses over time, and  $\chi^2$  test to evaluate symptoms discriminating lithium user from placebo.

## RESULTS

### Patients and Follow-Up

At baseline, patients in the lithium group were slightly younger (mean age = 71.6 years) compared to the placebo group (mean = 74.8 years,  $P = .034$ ). Other sociodemographic characteristics did not differ significantly (Table 2).

There were no significant differences between the 2 groups in the distribution of prevalent comorbid diseases (Table 2) or prescribed medications (not shown) at baseline. After 48 months of observation, new clinical diagnoses were established among participants in both groups: in the placebo group, 20% had incident dyslipidemia, 8% developed symptoms of gastritis, 8% were diagnosed with benign prostatic hyperplasia, and 12% evolved from amnesic mild cognitive impairment to Alzheimer's disease. In the lithium group, 40% developed dyslipidemia (nonsignificant), 20% acute gastritis (nonsignificant), 28% diabetes mellitus ( $P = .037$ ), and 20% arrhythmia ( $P = .028$ ). Eight patients

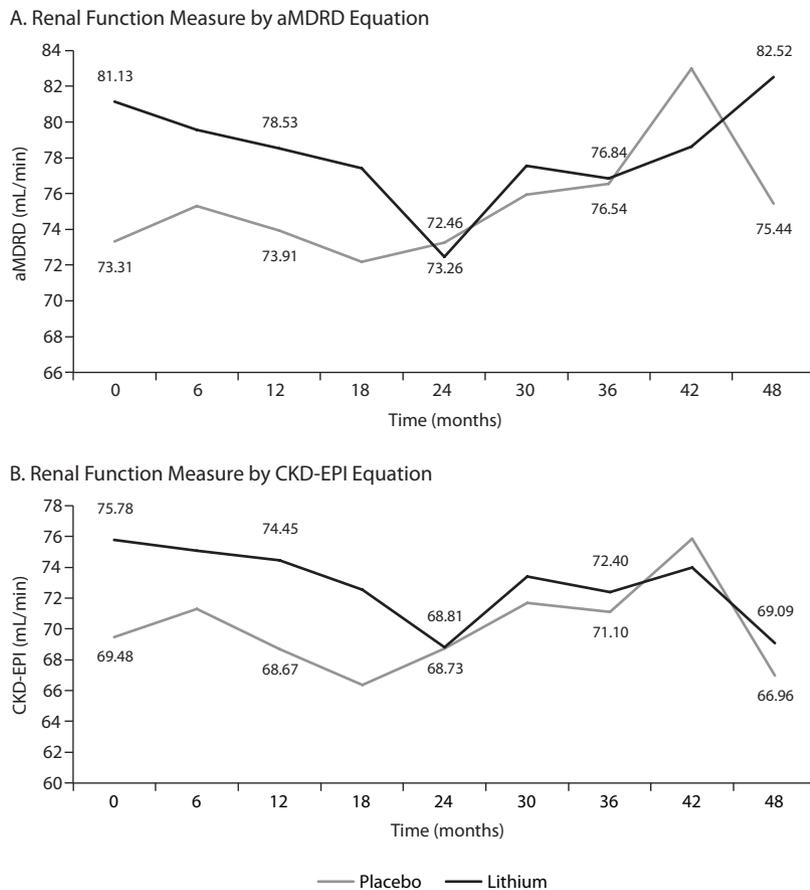
**Table 3. Baseline and Follow-Up Laboratory Variables According to Treatment Group**

Variable, Mean (SD)	Lithium		Placebo		P <sup>a</sup>
	Baseline	4-Year Follow-Up	Baseline	4-Year Follow-Up	
Creatinine, mg/dL	0.84 (0.20)	0.78 (0.13)	0.93 (0.27)	0.90 (0.25)	.333
aMDRD, mL/min/1.73 m <sup>2</sup>	81.12 (18.74)	82.51 (18.42)	73.31 (18.84)	75.43 (32.67)	.453
CKD-EPI, mL/min/1.73 m <sup>2</sup>	75.78 (14.92)	69.08 (18.68)	69.48 (17.83)	66.96 (26.53)	.213
TSH, $\mu$ U/mL	2.58 (2.06)	3.62 (1.92)	1.88 (1.59)	2.40 (1.54)	.471
Free T <sub>4</sub> , ng/mL	1.12 (0.28)	1.11 (0.17)	1.18 (0.27)	1.19 (0.19)	.945
Glucose, mg/dL	86.7 (15.88)	88.5 (14.29)	94.34 (40.96)	89.00 (26.43)	.511
Insulin, $\mu$ U/L	9.24 (5.74)	7.82 (3.40)	8.44 (6.70)	8.41 (2.91)	.241
HOMA-IR	1.04 (0.51)	1.01 (0.44)	1.16 (0.97)	1.04 (0.36)	.344
Leukocytes, unity/mm <sup>3</sup>	6,378.00 (1,568.99)	6,400.90 (2,447.96)	6,417.30 (1,466.37)	6,124.16 (1,831.74)	.026
Neutrophils, unity/mm <sup>3</sup>	3,703.33 (1,288.80)	4,181.81 (2,084.13)	3,715.38 (1,138.31)	3,700.00 (1,280.62)	.038

<sup>a</sup>Longitudinal regression interaction effect.

Abbreviations: aMDRD = abbreviated Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease-Epidemiology study, HOMA-IR = homeostasis model assessment of insulin resistance, T<sub>4</sub> = thyroxine, TSH = thyroid-stimulating hormone.

**Figure 2. Renal Function Measures by aMDRD and CKD-EPI From Baseline to 48 Months of Follow-Up**



Abbreviations: aMDRD = abbreviated Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease-Epidemiology study.

in the lithium group (25%) had a significant weight gain (ranging from 2 to 14 kg, median = 5.5 kg) ( $P = .015$ ), whereas no significant changes in weight were observed among patients in the placebo group. It is noteworthy that the patient with maximum weight increase had quit smoking just before presenting the weight gain, after already receiving lithium for 18 months. Only 2 patients with relevant weight gain (3 and 10 kg) developed diabetes mellitus after 1 and 2 years of continuous lithium use, respectively.

**Primary Outcome**

Mean serum creatinine levels were not significantly different between lithium and placebo groups throughout the follow-up ( $P = .333$ ; Table 3). The estimation of renal function using the aMDRD also indicated no significant differences between groups ( $P = .453$ ; Figure 2, Table 3). We also evaluated the potential influence of hypertension and diabetes mellitus on aMDRD results, finding no significant interferences of these confounders on renal function

across groups over time ( $P = .497$ ). When estimating renal function with the CKD-EPI equation, we found that patients in the placebo group presented with a mild but significant impairment in the first 2 years of follow-up ( $P = .011$ ). However, these changes did not remain significant in the long term, ie, after 3 and 4 years ( $P = .213$ ).

### Secondary Outcomes

There was no evidence of significant changes in glucose metabolism between groups over time, as indicated by serum glucose levels ( $P = .511$ ), fasting insulin ( $P = .241$ ), and insulin resistance using the formula HOMA-IR ( $P = .344$ ; Table 3). The number of total leukocytes increased significantly among subjects in the lithium group after 24–30 months ( $P = .026$ ; Table 3), but no significant differences were observed at the endpoint of the study. Evaluating specific groups of leukocytes, we observed a significant increase in the number of neutrophils at the end of the study ( $P = .038$ ).

In the evaluation of thyroid function, we observed significant elevation of thyrotropin in the lithium group compared to the placebo group ( $P = .034$ ). However, the increase in TSH levels was not significant when taking into account the interaction between the groups over the observation period of the study ( $P = .471$ ). The mean levels of free  $T_4$  were lower in users of lithium but not significantly different between groups or during the complete follow-up period ( $P = .945$ ; Table 3).

At baseline, the number of symptoms reported by patients in the lithium group was slightly higher than that reported by patients in the placebo group; however, the number of reported symptoms decreased in both groups during the follow-up. At the end of the trial, patients in placebo and lithium groups reported a mean of 4.07 and 4.98 symptoms, respectively ( $P = .045$ ). The difference in the total number of symptoms was also significantly different as an effect of time through follow-up ( $P = .005$ ), lithium users reporting more symptoms over time. However, no statistically significant differences were observed when the interaction between these factors was analyzed ( $P = .833$ ) in the mixed effects model. In the presence of memory complaints and/or mild depressive symptoms, patients in both groups reported significantly more UKU symptoms ( $P < .001$ ).

Symptoms presented by participants in both groups were mostly mild. The occurrence of moderately intense symptoms was rare, appearing on 19 occasions among lithium-treated patients and 15 times among those who received placebo. Increased dreaming (1.2%) was the only symptom that occurred in more than 1% of reports (lithium group). Severe symptoms were reported 3 times, exclusively by patients in the placebo group.

### DISCUSSION

After 4 years of continued lithium treatment, we found no indications of decline in renal function in the lithium as compared to the placebo group. There were no significant differences between the 2 treatment groups irrespective of the method used to ascertain renal function, even though

the aMDRD equation is reputedly better to estimate renal function in the elderly.<sup>21,22</sup> Mean aMDRD and CKD-EPI values remained virtually constant throughout the duration of the study, and the presence of hypertension or diabetes mellitus was not associated with renal impairment.

With respect to glomerular function, our results are in agreement with the majority of case-control studies published in the literature, which are represented by 6 studies, ie, 3 retrospective<sup>24–26</sup> and 3 prospective trials.<sup>10,27,28</sup> There is no randomized controlled trial evaluating safety issues among lithium users. The results from these studies are mixed, presenting both positive and negative findings regarding renal function. These studies were recently meta-analyzed by McKnight et al,<sup>8</sup> who concluded that no significant changes in glomerular function were observed after lithium use (weighted mean difference =  $-6.22$ ; 95% CI,  $-14.65$  to  $2.20$ ;  $P = .148$ ). Hullin et al<sup>24</sup> evaluated 106 patients with affective disorders who had been chronically treated with lithium at low serum concentrations for a mean period of 8 years. Creatinine clearance was not significantly different in a representative sample of 30 patients taking lithium and 30 matched patients taking other psychotropic drugs.<sup>24</sup> Coşkunol et al<sup>25</sup> compared 107 patients with bipolar disorder with 29 matched subjects with other psychiatric conditions and did not find a significant difference in renal function between these groups and no statistically significant correlations between creatinine clearance and duration of illness, duration of lithium treatment, and lithium dosage. In contrast, Turan et al<sup>26</sup> observed statistical evidence of renal dysfunction among long-term lithium users ( $> 3$  years), as compared to lithium-naive and short-term users ( $< 3$  years).

Considering the available prospective studies, none of these reported statistically significant differences in renal function among lithium users.<sup>10,27,28</sup> Bendz et al<sup>27</sup> examined 46 patients with mood disorders receiving lithium for 1 to 11 years, as compared to 32 matched controls. Renal function was evaluated cross-sectionally at the endpoint of lithium treatment and after about 3 months of withdrawal (from 7 weeks to 26 months). Although creatinine clearance was statistically similar across the 3 groups (ie, current lithium users, former users, and controls), glomerular function improved over time in the subset of patients who discontinued lithium.<sup>27</sup> In another study,<sup>28</sup> 32 patients receiving lithium for a mean period of 10 years had their renal function reassessed after 2 years; the comparison group was composed of 53 patients with mood disorders who had never been treated with lithium. Both at baseline and endpoint evaluations, there were no statistically significant differences of glomerular function between the 2 groups.<sup>28</sup> A similar result was also reported by Bendz et al<sup>10</sup> in a controlled study of 13 patients undertaking lithium for at least 15 years compared to 13 controls who had never been prescribed lithium salts. It is noteworthy that many observational studies with larger samples of long-term lithium users with greater treatment duration report loss of glomerular function.<sup>6</sup> Although they are not case-control or randomized trials, this evidence must be pointed out.

In our study, lithium users were slightly younger than those in the placebo group. Nevertheless, both groups had similar estimates of renal function at baseline, leading us to assume that the mean age difference of only 3 years may not have biased the results in favor of the lithium group. Lithium users presented a significant increase in weight, in addition to a higher incidence of arrhythmias and diabetes mellitus during the follow-up. Yet the reasons for these alterations remain unclear, but we should consider that these findings could be observational bias of our sample. The higher incidence of diabetes mellitus deserves further evaluation, given the lack of correlation either with the weight gain or with changes in glucose metabolism.<sup>29</sup> We also observed a significant tendency toward hypothyroidism among lithium users, but this abnormality did not persist through follow-up. The risk for clinical hypothyroidism is about 6-fold higher among lithium users, being related to the inhibition of iodine uptake, iodotyrosine coupling, and thyroxine secretion, resulting in increased secretion of TSH.<sup>6</sup> We speculate that the low-dose regimen may have minimized the aforementioned changes in thyroid homeostasis, particularly within the 4-year window of treatment. Finally, lithium treatment was associated with an increase in neutrophil count. It is accepted that lithium can induce the production of neutrophils by the blood marrow, resulting in a mean increase up to 1.5-fold<sup>6</sup>; nonetheless, the reasons for this effect on hematopoiesis remain unexplained. It is important to emphasize that our study design did not evaluate all potential adverse effects associated with lithium treatment.

Lithium treatment is undoubtedly associated with a higher incidence of unpleasant adverse effects. Such symptoms and complaints represent a major cause of treatment discontinuation, with reported estimates of 15%–20%.<sup>6</sup> In our study, such symptoms were largely mild and tolerable, with minimal interference in the ability to perform activities of daily living. Likewise, side effects of treatment were similar between the 2 groups and did not result in discontinuation of treatment. Again, we understand that the low-dose regimen in this trial was decisive for a good tolerability and compliance. Gastrointestinal symptoms are usually the most frequently reported complaints; yet, the predominant symptoms in the present study were neurologic and/or psychiatric, such as increased dreaming, depression, and memory complaints, which we hypothesize may be due to the fact that the present sample constituted older adults with mild cognitive impairment.

The peculiarities of our study group must be discussed as a potential limitation against the generalization of our findings. First of all, our study sample is small. The attrition rate after 2 years of follow-up (end of double-blind phase) was considerably high. Dropout rates were similar in both groups, suggesting that discontinuation was predominantly related to the duration of the trial rather than to adverse events of lithium. Regardless, this dropout rate may have critically affected the statistical power to detect differences between the 2 groups at the farthest endpoints (3 and 4 years of follow-up). Although clinically healthy at baseline,

many participants (in both groups) developed age-related medical comorbidities, unrelated to the treatment given the similar rates in both groups, but perhaps inevitable in view of the long duration of the trial. In addition, most studies addressing safety and tolerability of chronic lithium treatment have been conducted in samples of adult patients with mood disorders, who require not only a distinct therapeutic window of lithium but also the concomitant prescription of other psychotropic drugs. Therefore, the present findings may be more suited to extrapolation with caution to the treatment of elderly bipolar patients, who are more likely to receive a low-dose regimen. Finally, our study was not designed to perform a gold standard evaluation of renal function with inulin or 24-hour urinary creatinine clearance; the complexity of this method would probably impact negatively on compliance.

In conclusion, our controlled data support the position that low-dose lithium is tolerable and safe for the long-term treatment of clinically healthy older adults. We have recently published preliminary results of this placebo-controlled trial indicating that long-term, low-dose lithium treatment may be clinically beneficial to patients with mild cognitive impairment, in addition to modifying certain biological parameters related with the pathophysiological process of Alzheimer's disease.<sup>4</sup> We therefore believe that the present analysis may have relevant implications for safe prescription of lithium to older adults with mild cognitive impairment and bipolar disorder.

**Drug names:** lithium (Lithobid and others).

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