Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2023 Jan-Feb;45(1):46-49
doi:10.47626/1516-4446-2022-2767
Brazilian Psychiatric Association
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BRIEF COMMUNICATION

Revisiting global cognitive and functional state 13 years after a clinical trial of lithium for mild cognitive impairment

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Objectives: To re-evaluate a sample of older adults enrolled in a randomized controlled trial of lithium for amnestic mild cognitive impairment (MCI) after 11 to 15 years, re-assessing their current (or last available) global cognitive and functional state.
Methods: We recalled all former participants of the Lithium-MCI trial conducted by our group between 2009 and 2012 to perform a single-blinded, cross-sectional evaluation of their global clinical state to compare the long-term outcome of those who received lithium vs. those who received placebo.
Results: Of the original sample (n=61), we were able to reach 36 participants (59% of retention), of whom 22 had previously received lithium (61% of the recall sample) and 14 (39%) had received placebo. Since 30.5% of the recalled sample was deceased, psychometric data were collected only for 69.5% of the participants. We found statistically significant differences in current mean Mini Mental State Examination score according to previous treatment group (25.5 [SD, 5.3] vs. 18.3 [SD, 10.9], $p = 0.04$). The lithium group also had better performance in the phonemic Verbal Fluency Test than the control group (34.4 [SD, 14.4] vs. 11.6 [SD, 10.10], $p < 0.001$). Differences in these measures also had large effect sizes, as shown by Cohen's *d* values of 0.92 and 1.78, respectively.
Conclusion: This data set suggests that older adults with amnestic MCI who had been treated with lithium during a previous randomized controlled trial had a better long-term global cognitive outcome than those from a matched sample who did not receive the intervention.

Keywords: Alzheimer's disease; clinical trial; lithium; mild cognitive impairment; treatment

Introduction

Epidemiological studies suggest that chronic lithium use may be associated with a reduced prevalence of dementia in both the general population[1] and older adults with bipolar disorder.[2-4] Such findings may have important implications for the treatment and prevention of neurodegenerative disorders including, but not limited to, Alzheimer's disease (AD). Although there is a large body of evidence from experimental models supporting the potential neurotrophic and protective effects of lithium in AD, clinical evidence of this benefit is still scarce. The feasibility of lithium as a treatment for dementia due to AD was tested in an early clinical trial conducted in the United Kingdom,[5,6] although a subsequent short-term, single-blinded, multi-center study conducted in Europe found no evidence that clinical and biological parameters were modified after 10 weeks of lithium therapy.[5,6] Our group successfully performed the first double-blind, randomized controlled trial to evaluate the effects of long-term lithium treatment on clinical and biological outcomes in a sample of older adults with amnestic mild cognitive impairment (MCI),[7,8] a clinically-defined condition reputed to have a high risk of progressing to dementia (AD) in subsequent years. In this single-center study, 61 community-dwelling older adults with amnestic MCI were randomized to receive lithium or placebo for up to 4 years. Doses of lithium carbonate were individually adjusted to achieve sub-therapeutic serum concentrations (0.2-0.5 mEq/L). The first 2 years of follow-up represented the double-blinded phase of the study, and the remaining 2 years of the trial were single-blinded, i.e., the participants were made aware of their group allocation and were allowed to decide whether to remain in the study or withdraw consent. Compared to baseline, the cognitive and functional state of lithium-treated patients remained stable after 12 and 24 months of follow-up, whereas the control group had a significant decline in these functions.

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Submitted Jul 05 2022, accepted Aug 26 2022.

How to cite this article: Damiano RF, Loureiro JC, Pais MV, Pereira RF, Corradi MM, Di Santi T, et al. Revisiting global cognitive and functional state 13 years after a clinical trial of lithium for mild cognitive impairment. Braz J Psychiatry. 2023;45:46-49. http://doi.org/10.47626/1516-4446-2022-2767

Furthermore, lithium treatment was associated with significant changes in AD-related cerebrospinal fluid (CSF) biomarkers, i.e., reduction of CSF concentrations of ^{181}Thr-phosphoTau after 12 months,[7,8] and increased concentrations of amyloid-$\beta_{1\text{-}42}$ after 36 months.[7,8] We concluded that long-term lithium treatment was associated with stabilization of cognitive-functional decline and biological changes suggestive of disease modification in the MCI-AD continuum.

The aim of the present study was to evaluate the participants of the aforementioned randomized controlled trial more than a decade after the study endpoint (11 to 15 years) by re-assessing their current (or last available) global cognitive and functional state.

Methods

We recalled all former participants of the Lithium-MCI trial conducted by our group between 2009 and 2012[7,8] to perform a single-blinded, cross-sectional evaluation of their global clinical state in order to compare the long-term outcomes of the lithium and placebo groups. Although changes in AD-related CSF biomarkers were used as intervention outcome measures, the inclusion of participants was not restricted to a biological diagnosis of MCI due to AD. Therefore, all participants enrolled in the Lithium-MCI study had a ''clinical'' diagnosis of amnestic MCI at baseline, and this criterion was retained for the present analysis irrespective of a pattern of CSF biomarkers compatible with AD upon enrollment. Patients and/or their respective caregivers were approached by telephone or letter and invited to participate in this recall study. Assessments were performed through face-to-face interviews of approximately 30 minutes during home visits (preferentially) or by teleconsultation. Raters were unaware of prior group allocation. The assessment protocol consisted of a brief psychiatric interview and a set of screening tests, including the Informant Questionnaire on Cognitive Decline in Elderly (IQCODE)[9,10]; the Clinical Dementia Rating Scale (CDR),[11] rating the Global Score and the Sum of Boxes; the Functional Assessment Staging Tool (FAST) for Dementia[12]; the Montgomery-Åsberg Depression Rating Scale[13]; the Mini Mental State Examination[14]; the Verbal Fluency Test[15]; and the Clock Drawing Test.[16] A close relative was also inquired about the patient's global cognitive, functional, and neuropsychiatric symptoms (depression, anxiety, irritability, apathy, impulsivity, agitation, aggressivity, sleep disturbances, appetite problems), and this was the only source of information when the patients were unable to communicate or were deceased. In such cases, information about the patient's *antemortem* cognitive and functional state was obtained by compiling data from the neuropsychiatric anamnesis and the CDR, FAST, and IQCODE results. The closest caregiver was asked all of the questions about the last month of the patient's life. Time until the onset of decline in basic or instrumental activities of daily living since the trial was also computed as an intervention outcome.

Descriptive statistics were used for the sociodemographic and clinical characteristics of participants, and an inferential approach was used to evaluate group-wise differences in specific outcomes. Previous allocation to the lithium or control group was defined as the independent variable, whereas mean psychometric test scores (and other outcomes) were regarded as dependent (response) variables. Normality was determined using the Shapiro-Wilk test and, according to the results, Student's *t*-tests or Mann-Whitney *U* tests were used to compare the means of continuous variables related to the lithium and control groups. The distribution of categorial outcome variables was assessed with chi-square tests. Alpha was set at 5%. Effect sizes were calculated using Cohen's *d* or rank-biserial correlation for variables with normal or non-normal distribution, respectively.

Results

The recall effort reached 36 of the 61 participants in the original trial (59%), of whom 22 had previously received lithium (61% of the recall sample) and 14 (39%) had received placebo. The mean time between enrollment in the randomized controlled trial and the present assessment was 13.6 years (SD, 1.1; min: 11.0, max: 15.0 years). Previous allocation to the lithium group was significantly associated with recall success: 71% of the lithium group (22/31) vs. 46.7% (14/30) of the control group ($\chi^2 = 3.72$; $p = 0.05$). Dementia (CDR Global Score $\geqslant 1$) was more prevalent in controls than the lithium group (45.5%, 50%; $p = 0.79$). Table 1 summarizes the distribution of clinical and sociodemographic variables according to treatment group, indicating that the differences were not statistically significant. Eleven of the 36 participants were deceased by the time of re-assessment

Table 1 Sociodemographic and clinical characteristics of participants according to treatment group (n=36)

	Lithium (n=22)	Control (n=14)	p-value
Age, mean (SD)	85.2 (5.9)	86.8 (6.7)	0.54
Sex (% women)	54.5	57.1	0.88
Education (years), mean (SD)	10.4 (5.6)	8.3 (4.8)	0.26
Deceased (%)	27.3	35.7	0.59
Need for caregiver (%)	50.0	57.1	0.68
Dementia (%)	45.5	50.0	0.79
Any neuropsychiatric symptoms[†] (%)	90.9	78.6	0.30

Data presented as percentage, unless otherwise specified.
[†] Depression, anxiety, irritability, apathy, impulsivity, agitation, aggressivity, sleep disturbances, appetite problems.

Table 2 Associations between lithium use and neuropsychiatric/cognitive outcome measures

	Lithium				95%CI	
Outcome measures	No	Yes	p-value	Effect size	Lower	Upper
FAST†	4 (1-13)	4 (1-14)	0.92	0.02‡	-	-
MADRS Total†	6.5 (3-22)	5 (0-41)	0.50	0.18‡	-	-
CDR GS†	0.75 (0-3)	0.5 (0-3)	0.97	0.01‡	-	-
CDR SoB†	3.75 (0-18)	4.75 (0-18)	0.83	0.05‡	-	-
MMSE	**18.3 (10.9)**	**25.5 (5.3)**	**0.04**	**0.92**§	**0.02**	**1.80**
VFT (animals)	10 (8.2)	13.1 (4.5)	0.25	0.50§	-0.35	1.34
VFT (FAS)	**11.6 (10.1)**	**34.7 (14.4)**	**< 0.001**	**1.78**§	**0.71**	**2.82**
CDT	1.44 (1.3)	2.27 (1.1)	0.12	0.69§	-0.18	1.54
IQCODE	3.83 (0.7)	3.84 (0.7)	0.96	-0.01§	-0.69	0.65
Time to BADL decline (years)‖	7 (4.1)	10.8 (1.5)	0.05	-1.20§	-2.44	0.11
Time to IADL decline (years)‖	7.9 (4.9)	5.6 (4.6)	0.34	-0.47§	-1.43	0.50

Bold type denotes $p < 0.05$.
BADL = basic activities of daily living; CDR = Clinical Dementia Rating; CDT = Clock Drawing Test; FAS = phonemic Verbal Fluency Test (VFT); FAST = Functional Assessment Staging Tool; GS = Global Score; IADL = Instrumental activities of daily living; IQCODE = Informant Questionnaire on Cognitive Decline in Elderly; MADRS = Montgomery-Åsberg Depression Rating Scale; MMSE = Mini Mental State Examination; SoB = Sum of Boxes.
† Test score values shown as median/range (min-max) and statistics calculated with the Mann-Whitney *U* test or as means/SD calculated with Student's *t*-test.
‡ Rank biserial correlation.
§ Cohen's *d*.
‖ Time to decline in autonomy (estimated in years after participation in the trial).

(30.5%), with an even distribution across treatment groups (six and five individuals from the lithium and placebo groups, respectively; p = 0.59). There was no significant difference between groups for the presence of any neuropsychiatric symptoms (90.9, 78.6; p = 0.30) or for any individual symptoms.

Table 2 presents inferential statistics in the recall sample related to neuropsychiatric and cognitive outcomes. We found statistically significant differences in current mean Mini Mental State Examination scores according to previous treatment groups, with higher scores obtained the lithium group than the control group (25.5 [SD, 5.3] vs. 18.3 [SD, 10.9], p = 0.04). The lithium group also had better performance in the phonemic Verbal Fluency Test than the control group (34.4 [SD, 14.4] vs. 11.6 [SD, 10.10], $p < 0.001$). Differences in these measures also had large effect sizes, as shown by Cohen's *d* values of 0.92 and 1.78, respectively. In contrast, no significant differences were found between the groups regarding depressive symptoms (Montgomery-Åsberg Depression Rating Scale), functional state (IQCODE, CDR-Global Score, CDR-Sum of Boxes, and FAST), or estimated time to decline in instrumental or basic activities of daily living. Estimates of global functional state yielded similar results irrespective of the test in sub-samples of living or deceased subjects (data not shown).

Discussion

According to the present set of data, older adults with amnestic MCI who had been treated with lithium during a previous randomized controlled trial had a better long-term global cognitive outcome than those from a matched sample who did not receive the intervention. Significant differences were found in mean Mini Mental State Examination and phonemic Verbal Fluency Test scores, which could be used to discriminate between the two groups. Of note, these test scores refer to objective evaluation of the participants we were able to access in this recall study. Estimates of the global functional state obtained through patient caregiver interviews yielded no significant differences between the groups. This could illustrate the poor general health of participants from both groups in the months prior to death, the window of time for informant questionnaires. Another possibility is recall bias, i.e., caregiver information was of insufficient quality to provide a clear picture of the patient's status in the months prior to death.

It appears that the clinical benefits of lithium treatment continued beyond the trial, persisting for several years after exposure to the drug. The present findings are in keeping with the better clinical status of lithium-treated patients observed at the endpoint of the Lithium-MCI trial, and further support the notion that lithium treatment may be associated with long-term and enduring neuroprotective effects. Lithium has been shown to modify critical biological mechanisms that pertain to the pathogenesis of AD and, for this reason, is regarded as a candidate drug for disease modification. Lithium is a potent inhibitor of glycogen synthase kinase 3-beta (GSK3β), and this effect is associated with reduced tau phosphorylation and subsequent formation of neurofibrillary tangles.[17,18] One of the main biological outcomes of the Lithium-MCI trial was the reduction of ^{181}P-tau concentrations in CSF.[8] This effect was observed after 12 months of continuous lithium treatment and could represent a mechanism through which lithium might modify the disease. Another central component of AD pathogenesis, also related to overactive GSK3β,[19] is the overproduction of amyloid-beta ($A\beta_{42}$) peptide and its accumulation into neuritic plaques. This process is accompanied by a reduced concentration of $A\beta_{42}$.[20] Another promising biological finding from the trial was an "increase" of $A\beta_{42}$

concentrations in CSF, suggesting improved amyloid clearance from the brain.[7] Thus, through this effect, lithium might also contribute to the attenuation of Aβ neurotoxicity[21] in the MCI-AD continuum.

We acknowledge the many limitations of the present study. First, 41% of the original sample was lost to follow-up, rendering the current sample relatively small. Nevertheless, such attrition could be regarded as acceptable in view of the long interval between the trial and the reassessment. In addition, only 69.5% of the recalled sample could be assessed using objective information (acquired through patient examination); for the remaining 30.5%, information about the patient's functional status prior to death was acquired indirectly through close informants, regardless of the fact that validated instruments were used (e.g., IQCODE, FAST, and part of the CDR). It was these tests that failed to show significant differences between the groups. Therefore, we must consider the possibility that indirect, informant-based estimates introduced recall bias, jeopardizing the reliability of results. However, objective assessment of the participants with a set of cognitive screening tests (the Mini Mental State Examination and the phonemic Verbal Fluency Test) consistently indicated better performance by lithium-treated patients. Furthermore, given that we did not obtain recent medical history data, variations in treatment after the trial (and in particular during the last 1-2 years) could also affected the outcomes. Finally, no *a priori* selection of primary and secondary cognitive outcome measures was made. In spite of these limitations, we point out that the present study-group is unique, given: 1) the precise diagnostic characterization at baseline; 2) exposure to lithium was controlled for up to 4 years; 3) the ability to recall a good proportion (three-fifths) of the original patient group after a long interval; and 4) the use of objective screening tests and validated, informant-based questionnaires to ascertain the global cognitive and functional state of the participants. Thus, we tried to make the best use of the available information, aiming to reinforce the long-term benefits of lithium use in older adults at risk of dementia.

Acknowledgements

The authors would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (2019/08507-3, 2014/50873-3), the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; 4654 12/2014-9), and the Associação Beneficente Alzira Denise Hertzog da Silva (ABADHS).

Disclosure

The authors report no conflicts of interest.

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