Received: 5 May 2023 | Accepted: 4 September 2023

DOI: 10.1002/gps.6002

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Effects of lithium on serum Brain-Derived Neurotrophic Factor in Alzheimer's patients with agitation

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Funding information
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Abstract

Background: There is ample evidence in animal models that lithium increases Brain-Derived Neurotrophic Factor (BDNF) with supporting evidence in human studies. Little is known, however, about the effects of lithium on BDNF in Alzheimer's Dementia (AD). In one study of patients with Mild Cognitive Impairment, serum BDNF increased after treatment with lithium. These patients also showed mild improvement in cognitive function.

Objectives: To evaluate low-dose lithium treatment of agitation in Alzheimer's disease (AD).

Method: We measured levels of BDNF in patients treated with lithium prior to and after a 12-week randomized placebo-controlled trial.

Results: BDNF levels did not change significantly and were not associated with improvement in overall neuropsychiatric symptoms or in cognitive function.

Conclusions: More research is needed to understand the potential effects of lithium on BDNF in AD including whether its use might be dependent on the stage of cognitive decline and dementia.

KEYWORDS
agitation, Alzheimer's disease, BDNF, brain-derived neurotrophic factor, dementia, lithium, mild cognitive impairment, neuropsychiatric symptoms, psychiatry

Key points

- Lithium is known to increase Brain-Derived Neurotrophic Factor (BDNF) levels.
- BDNF has neuroprotective properties.
- Decreased levels of BDNF have been found in the brains of people with AD.
- Little is known about the association between the effects of Lithium on BDNF in patients with AD.

1 | INTRODUCTION

Alzheimer's Dementia is associated with accumulation of beta amyloid (Aβ) and development of neurofibrillary tangles composed of abnormally phosphorylated tau protein[1,2] as well as reduction in synaptic strength, synaptic loss, and neurodegeneration.

Brain Derived Neurotrophic Factor, a neurotrophin that may have neuroprotective properties, shows reduced serum concentration in patients with AD[3–5] and has been studied extensively in this population.[6–8] There is consistent evidence in animal studies that lithium increases levels of BDNF in the brain.[9–13] In several animal models, lithium has been shown to mediate this process by stimulating synthesis and release of BDNF,[9,14–17] but there has been limited investigation of lithium's effects on BDNF in clinical trials with human subjects. DeSousa and colleagues[18] found increased serum BDNF levels in patients with acute bipolar mania after 4 weeks of treatment with lithium. To our knowledge, only one study has assessed the effects of lithium treatment on serum BDNF in patients with AD. In this 10-week randomized double-blind study of patients with early AD, Leyhe and colleagues[19] demonstrated statistically significant increases in serum levels of BDNF in patients treated with lithium compared to those taking placebo. Additionally, patients treated with lithium had significantly lower ADAS-Cog sum scores than at baseline when compared with patients taking placebo.

We performed a study examining the effects of low-dose lithium treatment of agitation in patients with AD. Behavioral and cognitive outcomes in this cohort were previously reported[20] from this randomized, double-blind, placebo-controlled, 12-week trial. Serum BDNF levels were measured before and after 12 weeks of treatment with lithium or placebo to determine whether treatment with lithium influenced BDNF levels and to assess the association of change in BDNF with neuropsychiatric symptoms and changes in cognition.

2 | SUBJECTS AND METHODS

The study design has been described in detail elsewhere.[20] Seventy-seven patients were enrolled at four sites: Columbia University Irving Medical Center/New York State Psychiatric Institute (NYSPI) (lead coordinating site), University of Miami, McLean Hospital, and University of Texas Southwestern from May 2014 until January 2020. The following were the main inclusion criteria: probable AD diagnosis by National Institute on Aging (NIA) criteria, Folstein Mini-Mental State Examination (MMSE) score of 5–26 inclusive, Neuropsychiatric Inventory (NPI) domain score for agitation/aggression ≥4, and an available informant. The main exclusion criteria were as follows: current major psychiatric diagnosis (major depression, bipolar, schizophrenia, schizoaffective disorder), contraindicated medications (e.g. medications known to have adverse renal effects in combination with lithium), bradycardia (heart rate <50/BPM), creatinine level greater than 1.5 mg/100 mL or a Glomerular Filtration Rate (GFR) <44 mL/min/1.73 m^2, alcohol or substance dependence in the prior 6 months, and major neurological disorders other than dementia.

Patients were randomly assigned to low dose lithium (150–600 mg/day) or placebo. Generic lithium carbonate 150 mg tablets were purchased and over-encapsulated by the NYSPI research pharmacy to match placebo capsules with inert filler. Patients were stratified by site, for 12 weeks. Randomization was developed by the statistician, executed by the NYSPI pharmacy, and stratified within each site by the presence of psychosis (NPI score ≥4 on delusions or hallucinations) with randomization sequences balanced in blocks of four. All study personnel and patients were masked to treatment assignment.[20] In this double-blind study, the lithium dose was initiated at 150 mg/day and then adjusted based on the patient's clinical response and/or side effects with real or sham (placebo) lithium blood levels communicated by an independent psychiatrist to the treatment team. Serum lithium levels of 0.2–0.6 mmol/L were targeted. Procedures included physical examination at all visits, neuropsychiatric assessment with the NPI at all visits, electrocardiogram at screen and 12 weeks, Basic Metabolic Panel at screen, 6 and 12 weeks, Complete Blood Count at screen and 12 weeks, GFR at screen, 6 weeks, and 12 weeks, serum lithium levels throughout weeks 2–12 and follow up, and neuropsychological tests (Severe Impairment Battery (SIB) at baseline and 12 weeks, and MMSE at screen and 12 weeks). Serum for BDNF assay was collected at baseline and week 12, that is, pre-, and post-treatment respectively.

We used the CONSORT reporting guidelines for this publication.[21]

3 | BRAIN-DERIVED NEUROTROPHIC FACTOR LEVELS

Blood samples collected were allowed to coagulate for 30 min at room temperature and then were centrifuged at 1000xg for 10 min 1.5 mL of BDNF serum was then pipetted into a cryogenic tube and stored at −80°C until further analysis. Brain-Derived Neurotrophic Factor serum levels were obtained using the ChemiKine BDNF Sandwich ELISA Kit Emanuel Merck, Darmstadt Millipore, St. Charles MO and Total BDNF Quantikine ELISA Kit R&D Systems, Minneapolis MN—following the manufacturers' instructions. Multiple independent samples t-test (two-tailed significance $\alpha = 0.05$) showed that results did not differ across kits (t [148] = 0.399; $p > 0.05$). Intra and inter-assay coefficients of variation were <6.0% and <12.0% respectively.

4 | STATISTICAL ANALYSES

All statistical analyses were performed using the R package (v.4.1.1).[22] We report mean with standard deviation and frequency with percentage as appropriate for descriptive statistics. We used linear mixed effect models to test whether the primary variables of interest (BDNF serum levels, MMSE scores, SIB scores, NPI scores) changed over time, and whether the changes differed by treatment group (placebo vs. lithium). Each model included time (baseline and

follow-up), group (placebo vs. lithium), and time × group interaction as fixed effects and a random intercept of subject to account for correlation due to repeated measurements. If the *p*-value of the time × group interaction was less than 0.05, we concluded that the change differed by group. To quantify pre-post- changes in the outcomes, we performed the least mean square difference analysis as implemented in the emmeans R package. To evaluate the relationship between changes in BDNF serum levels, MMSE scores, and SIB scores, we performed Pearson's correlation analyses for all samples as well as stratified by placebo and lithium groups. The actual sample size included in statistical analysis was 72 patients. Five patients out of 77 withdrew from the study before gathering week 12 BDNF levels.

We evaluated whether baseline changes in BDNF were associated with primary efficacy outcomes, including NPI total score, agitation/aggression domain, and psychosis domain, using linear regression for the continuous outcomes and logistic regression for the binary outcomes. All statistical tests were two-tailed at significance level alpha = 0.05.

5 | RESULTS

Patient characteristics at baseline did not differ significantly between the two treatment groups. Seventy-two of 77 patients (72/77 = 93.5%) completed the BDNF component of the study. Considering gender, race, and marital status, both groups were comparable (Table 1. Patient Demographics).

The change in BDNF serum levels pre- and post-treatment is presented in Table 2. Brain-Derived Neurotrophic Factor levels pre-treatment were mean 27.7 ng/mL (SD 15.8) for patients treated with lithium (n = 37) and mean of 32.6 ng/mL (SD 18.1) for patients treated with placebo (n = 35). Brain-Derived Neurotrophic Factor pre-treatment levels did not significantly differ between patients receiving lithium versus placebo (F [1,70] = 1.5, p = 0.223; $p > 0.05$). Brain-Derived Neurotrophic Factor levels post-treatment had a mean value of 24.4 ng/mL (SD 17.2) for patients treated with lithium (n = 37) and a mean value of 31.1 ng/mL (SD 15.6) for patients treated with placebo (n = 35). This difference was not statistically significant (p = 0.095; $p > 0.05$). In the total sample (N = 72), and in the lithium treatment group (N = 37), and placebo treatment group (N = 35), there were no significant changes in BDNF from baseline to week 12 (placebo: beta = −1.4, t (68) = −0.57, p = 0.94; $p > 0.05$; lithium: beta = −3.65, t (68) = −1.47, p = 0.46; $p > 0.05$). Additionally, there was no difference in post-treatment BDNF levels between the randomized lithium and placebo groups (beta = 2.2 t (69) = 0.62, p = 0.54; $p > 0.05$) (Table 2. Brain-Derived Neurotrophic Factor levels pre-and post-lithium treatment v. placebo).

The correlation between change in BDNF and change in total NPI scores (and agitation and psychosis scores) from 0 to 12 weeks was not significant in the total sample. Total NPI scores did not significantly change in the placebo group (p = 0.996; $p > 0.05$) and in the lithium treatment group (p = 0.281; $p > 0.05$). Agitation scores did not significantly change for both the placebo (p = 1.000; $p > 0.05$) and lithium treatment groups (p = 0.288; $p > 0.05$). Change in psychosis scores were not significant, placebo group, p = 1.000; $p > 0.05$, and lithium treatment group, p = 0.074; $p > 0.05$. Efficacy for NPI total, agitation/aggression domain, and psychosis domain scores were evaluated. For all three measures, *p*-values suggested no statistically significant differences between lithium and placebo treatment groups. In ancillary analyses, change in none of the 12 individual NPI domain scores was significantly associated with change in BDNF levels. In the lithium-treated group, psychosis tended to decrease from 0 to 12 weeks (p = 0.074; $p > 0.05$.), a non-significant change.

Mini-Mental State Examination scores did not change significantly from 0 to 12 weeks in either lithium (beta = −1.04, t (52) = −1.62, p = 0.10; $p > 0.05$) or placebo (beta = −1.04, t (52) = −1.60, p = 0.12; $p > 0.05$) groups. No significant group difference was found in MMSE score change (beta = 0.00, t (52) = 0.00, p = 0.99; $p > 0.05$). There was no correlation between changes in BDNF and MMSE scores in either lithium (r = 0.06, p = 0.79; $p > 0.05$) or placebo (r = 0.08, p = 0.73; $p > 0.05$) groups. In a split sample of patients with "high MMSE" (>14) versus "low MMSE" (≤14) we found no statistically significant difference between baseline and end-study levels of serum BDNF in either lithium or placebo groups. Statistical testing in the high MMSE group (n = 10) was severely underpowered and Common Gateway Interface analysis was not performed due to the cells being too small.

6 | DISCUSSION

In our cohort of agitated patients with AD using lithium v. placebo in a 12-week randomized controlled trial, we found no statistically significant change in serum BDNF in the lithium treated group by itself or when compared to placebo. We also found no statistically significant improvement in cognitive function as measured by MMSE scores after 12 weeks of treatment with lithium. Our findings contrast with those of Leyhe and colleagues,[19] the only other randomized controlled trial exploring the effects of lithium treatment on BDNF in AD, in which a significant increase in BDNF was observed in AD patients treated with lithium compared to placebo. They also found evidence of improved cognitive performance in the lithium treated group in which ADAS-Cog scores decreased in inverse correlation with serum lithium and BDNF levels, but they, too, found no evidence of change on the MMSE. Hampel and colleagues,[23] in a 10-week randomized, single-blind, placebo-controlled trial using lithium in AD found no change in ADAS-Cog or MMSE scores pre- and post-treatment.

Two notable differences between our study and that of Leyhe and colleagues might account for the differences in outcome. First, Leyhe and colleagues studied patients with early AD with an average MMSE of 23 at baseline, whereas we studied patients with agitation in AD with an average MMSE of 14 at baseline. Entry criteria for our protocol included baseline MMSE 5–26 but we did not do separate

TABLE 1 Patient demographics.

	Lithium (*N* = 37)	Placebo (*N* = 35)	Total (*N* = 72)
Age in years			
Mean (SD)	75.6 (8.4)	74.3 (7.2)	75.0 (7.8)
Range	53.0–93.0	59.0–92.0	53.0–93.0
Sex			
Female	22 (59.5%)	19 (54.3%)	41 (56.9%)
Male	15 (40.5%)	16 (45.7%)	31 (43.1%)
Race			
White	29 (78.4%)	28 (80.0%)	57 (79.2%)
Black or African American	4 (10.8%)	3 (8.6%)	7 (9.7%)
Asian	1 (2.7%)	2 (5.7%)	3 (4.2%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	3 (8.1%)	2 (5.7%)	5 (6.9%)
Marital status			
Married	24 (64.9%)	25 (71.4%)	49 (68.1%)
Never married	3 (8.1%)	1 (2.9%)	4 (5.6%)
Widowed	6 (16.2%)	6 (17.1%)	12 (16.7%)
Divorce	3 (8.1%)	3 (8.6%)	6 (8.3%)
Separated	1 (2.7%)	0 (0.0%)	1 (1.4%)
Years of education			
Mean (SD)	13.6 (4.5)	13.0 (3.9)	13.3 (4.2)
Range	3.0–23.0	4.0–20.0	3.0–23.0
Hospitalization associated with psychosis and/or agitation			
Psychosis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Agitation	16 (43.2%)	16 (45.7%)	32 (44.4%)
Psychosis and agitation	21 (56.8%)	19 (54.3%)	40 (55.6%)
Alzheimer's disease status			
Possible AD	8 (21.6%)	5 (14.3%)	13 (18.1%)
Probable AD	29 (78.4%)	30 (85.7%)	59 (81.9%)

TABLE 2 Brain-Derived Neurotrophic Factor (BDNF) levels pre and post lithium treatment versus placebo.

	DRUG (*N* = 37)	Placebo (*N* = 35)	Total (*N* = 72)	*p*-value
BDNF pre-treatment				
Mean (SD)	27.7 (15.8)	32.6 (18.1)	30.1 (17.0)	0.223
Range	7.7–76.0	6.4–94.6	6.4–94.6	
BDNF post-treatment				
Mean (SD)	24.4 (17.2)	31.1 (15.6)	27.7 (16.7)	0.095
Range	5.0–96.1	4.3–81.5	4.3–96.1	
Missing values (*N*)	2	1	3	
BDNF change (post-pre treatment)				
Mean (SD)	−3.9 (16.0)	−1.4 (13.3)	−2.6 (14.7)	0.489
Range	−54.1–29.4	−34.6–31.5	−54.1–31.5	
Missing values (*N*)	2	1	3	

analyses of BDNF levels for subgroups with lower v. higher MMSE scores. Nevertheless, our cohort included patients with later stage disease and more advanced neurodegenerative processes, presumably limiting neuronal capacity to produce BDNF. Second, Leyhe and colleagues aimed for a higher therapeutic serum level of lithium in their study than we did (0.5–0.8 mmol/L v. 0.2–0.6 mmol/L in our study), potentially accounting for a more robust BDNF response.

AD patients with agitation are often treated with other concomitant medications that affect BDNF levels. In medication naïve patients with schizophrenia, short-term treatment with quetiapine, risperidone, aripiprazole, and olanzapine (the four antipsychotics used by patients in our study) were shown to increase levels of serum BDNF.[24–28] Similarly, many antidepressants including selective serotonin reuptake inhibitor and mirtazapine increase serum BDNF levels in patients with depression[29–31] This potential bias was offset in our study by entry criteria requiring treatment with a stable dose of a concomitant medication for 1 month prior to randomization. Sixty of 77 (78%) of all patients in our study were on antipsychotics, antidepressants, or both. Seventy one percent of patients on atypical antipsychotics had no change in medication dose from baseline to end-study while 20% had dose reductions and 8% had dose increases by end-study. Similarly, 82% of patients on antidepressants had no change in medication dose from baseline to end-study while 12% had dose reduction and 4% had dose increases by end study. Since atypical antipsychotics and antidepressants are shown consistently to increase serum BDNF, our data suggests that use of these concomitant medications by our patients was not a likely factor in the study outcome.

Other short-term studies (<12 weeks) using lithium to treat patients with Mild Cognitive Impairment (MCI) or AD have shown no change in either AD biomarkers or cognitive function,[23,32,33] while some studies using lithium for 12 months or more showed statistically significant improvement in MMSE scores[15,34,35] and in AD biomarkers.[36] These studies suggest that potential therapeutic effects of lithium in AD may not be realized during short-term treatment such as ours. In addition, AD patients in these long-term studies were in a less advanced stage of the disease than those we studied.

Serum concentration of BDNF is widely thought to be stage dependent in AD,[3,4,37] decreasing as patients progress from MCI to more advanced stages of the disease. Leyhe and colleagues studied a sample of patients with MCI and no agitation. Our AD sample was more cognitively impaired, perhaps accounting for absence of significant improvement in BDNF or MMSE in our lithium treated patients.

Given the wealth of data showing lithium's association with increased BDNF in the animal brain and the discrepancies in the limited literature available on the effects of lithium on BDNF in AD, further investigation will be useful to determine the effects of lithium on serum BDNF levels in patients with AD, particularly to clarify whether lithium is associated with an increase in BDNF levels throughout the disease or only in its early clinical stages, and whether duration of treatment has an association with lithium causing elevations in serum BDNF.

ACKNOWLEDGMENTS

The study was supported by grant R01AG047146 from the NIA, NIH, Bethesda, MD, USA. This clinical trial is registered on ClinicalTrials.gov and may be identified by NCT02129348. The full trial protocol may be accessed using the provided NCT identifier on ClinicalTrials.gov, under "Study Documents (Full-Text)".[38]

CONFLICT OF INTEREST STATEMENT

Dr. Davangere P. Devanand- Research support: NIA; Alzheimer's Association. Scientific Adviser: Acadia; Corium; TauRx. DSMB: Bio-Excel. Dr. Brent Forester- Research Grants: NIA. Consulting: Ripple Care, Patina Health, CVS Health. Stock Options: Rippl Care, Patina Health. Dr. Mustafa Husain- Federal Grant Support: NIH, NIMH, NIA, NINDA, Brain Initiative. Stanley Medical Research Institute. Industry Research Grant Support: Abbott (ANM), Cyberonics, Neuronetics, Brainsway, NeoSync. Dr. Elizabeth Crocco- Grant Support previous 3 years: National Intitute on Aging, State of Florida Department of Elder Affairs, Health Services Research Administration, Otsuka, Novartis, Avanir, Neurim.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Scheltens P, Blennow K, Breteler M, et al. Alzheimer's disease [Internet]. *Lancet*. 2016;388(10043):505-517. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/26921134/
2. Selkoe DJ. Alzheimer's disease is a synaptic failure. *Science*. 2002;298(5594):789-791. https://doi.org/10.1126/science.1074069
3. Laske C, Stransky E, Leyhe T, et al. Stage-dependent BDNF serum concentrations in alzheimer's disease [Internet]. In: Richartz E, ed. *Journal of neural transmission*. U.S. National Library of Medicine; 1996. [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/16362629/
4. Ted Kheng Siang N, Su Hui Ho C, Wai San Tam W, Ee Heok K, Chun-Man Ho R. Decreased serum brain-derived neurotrophic factor (BDNF) levels in patients with alzheimer's disease (AD): a systematic review and meta-analysis [Internet]. *Int J Mol Sci*. 2019;20(2):257. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.3390/ijms20020257
5. Siuda J, Patalong-Ogiewa M, Żmuda W, et al. Cognitive impairment and BDNF serum levels [Internet]. *Neurol Neurochir Pol*. 2017;51(1):24-32. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1016/j.pjnns.2016.10.001
6. Alvarez XA, Alvarez I, Iglesias O, et al. Synergistic increase of serum BDNF in alzheimer patients treated with CEREBROLYSIN and Donepezil: association with Cognitive Improvement in APOE4 cases [Internet]. *Int J Neuropsychopharmacol*. 2016;19(6):pyw024. U.S. National Library of Medicine; [cited 2023Mar23]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4926802/
7. Laske C, Stellos K, Hoffman N, et al. Higher BDNF serum levels predict slower cognitive decline in alzheimer's disease patients [Internet]. *Int J Neuropsychopharmacol*. 2011;14(3):399-404. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/20860877/

8. Leyhe T, Stransky E, Eschweiler GW, Buchkremer G, Laske C. Increase of BDNF serum concentration during donepezil treatment of patients with early alzheimer's disease [Internet]. *Eur Arch Psychiatr Clin Neurosci*. 2008;258(2):124-128. U.S. National Library of Medicine; [cited 2023Mar23]. . https://doi.org/10.1007/s00406-007-0764-9
9. De-Paula VJ, Gattaz WF, Forlenza OV. Long-term lithium treatment increases intracellular and extracellular brain-derived neurotrophic factor (BDNF) in cortical and hippocampal neurons at subtherapeutic concentrations [Internet]. *Bipolar Disord*. 2016;18(8):692-695. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1111/bdi.12449
10. Dwivedi T, Zhang H. Lithium-induced neuroprotection is associated with epigenetic modification of specific BDNF gene promoter and altered expression of apoptotic-regulatory proteins [Internet]. *Front Neurosci*. 2015;8. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.3389/fnins.2014.00457
11. Malhi GS, Tanious M, Das P, Coulston CM, Berk M. Potential mechanisms of action of lithium in bipolar disorder. current understanding [Internet]. *CNS drugs*. 2013;27(2):135-153. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1007/s40263-013-0039-0
12. Torabi Z, Rezaie M, Aramvash A, et al. Interaction of lithium and sleep deprivation on memory performance and anxiety-like behavior in male wistar rats [Internet]. *Behav Brain Res*. 2022;428:113890. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1016/j.bbr.2022.113890
13. Young W. Review of lithium effects on brain and blood [Internet]. *Cell Transplant*. 2009;18(9):951-975. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.3727/096368909x471251
14. Chen G, Huang LD, Zeng WZ, Manji HK. Mood stabilizers regulate cytoprotective and mrna-binding proteins in the brain: long-term effects on cell survival and transcript stability [Internet]. *Int J Neuropsychopharmacol*. 2001;4(03). U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1017/s1461145701009567
15. Forlenza OV, De-Paula VJR, Diniz BSO. Neuroprotective effects of lithium: implications for the treatment of alzheimer's disease and related neurodegenerative disorders [Internet]. *ACS Chem Neurosci*. 2014;5(6):443-450. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1021/cn5000309
16. Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain [Internet]. *Psychopharmacology*. 2001;158(1):100-106. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1007/s002130100871
17. Hammonds MD, Shim SS. Effects of 4-week treatment with lithium and olanzapine on levels of brain-derived neurotrophic factor, B-cell CLL/lymphoma 2 and phosphorylated cyclic adenosine monophosphate response element-binding protein in the sub-regions of the hippocampus [Internet]. *Basic Clin Pharmacol Toxicol*. 2009;105:113-119. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1111/j.1742-7843.2009.00416.x
18. de Sousa RT, van de Bilt MT, Diniz BS, et al. Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study [Internet]. *Neurosci Lett*. 2011;494(1):54-56. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/21362460/
19. Leyhe T, Eschweiler GW, Stransky E, et al. Increase of BDNF serum concentration in lithium treated patients with early alzheimer's disease [Internet]. *J Alzheim Dis*. 2009;16(3):649-656. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/19276559/
20. Devanand DP, Crocco E, Forester BP, et al. Low dose lithium treatment of behavioral complications in alzheimer's disease: lit-AD randomized clinical trial [Internet]. *Am J Geriatri Psychiat*. 2022;30(1):32-42. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/34059401/
21. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8(18).
22. R Core Team. *R: A Language and Environment for Statistical Computing [Internet]*. R Foundation for statistical computing; 2021. [cited 2023Mar23]. https://www.scirp.org/(S(czeh2tfqw2orz553k1w0r45))/reference/referencespapers.aspx?referenceid=3131254
23. Hampel H, Ewers M, Burger K, et al. Lithium trial in alzheimer's disease: a randomized, single-blind, placebo-controlled, Multicenter 10-week study [Internet]. *J Clin psychiatry*. 2009;70(6):922-931. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.4088/jcp.08m04606
24. Liu J, Sun J, Shen X, et al. Effect of Quetiapine on Brain-Derived Neurotrophic Factors in Patients with First-Episode Schizophrenia [Internet]; 1970. [cited 2023 Aug 10]. https://pesquisa.bvsalud.org/portal/resource/pt/wpr-456774
25. Zhao T, Tang S, Gao X, et al. Association of serum brain-derived neurotrophic factor level and early response to antipsychotic drug in first-episode patients with schizophrenia [Internet]. *Int J Methods Psychiatr Res*. 2023;23:e1982. U.S. National Library of Medicine; [cited 2023 Aug 10]. https://pubmed.ncbi.nlm.nih.gov/37485797/
26. Yoshimura R, Hori H, Ikenouchi-Sugita A, et al. Aripiprazole altered plasma levels of brain-derived neurotrophic factor and catecholamine metabolites in first-episode untreated Japanese schizophrenia patients [Internet]. *Hum Psychopharmacol*. 2012;27(1):33-38. U.S. National Library of Medicine; [cited 2023 Aug 10]. https://pubmed.ncbi.nlm.nih.gov/22213405/
27. Han D, Sun D, Xiu M, et al. Association between the improvement in depressive symptoms and serum BDNF levels in drug-naive first episode patients with schizophrenia: a longitudinal follow-up [Internet]. *Psychoneuroendocrinology*. 2021;133:105392. U.S. National Library of Medicine; [cited 2023 Aug 10]. https://pubmed.ncbi.nlm.nih.gov/34428640/
28. Fernandes BS, Steiner J, Berk M, et al. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications [Internet]. *Mol Psychiatr*. 2015;20(9):1108-1119. U.S. National Library of Medicine; [cited 2023 Aug 10]. https://pubmed.ncbi.nlm.nih.gov/25266124/
29. Mosiołek A, Mosiołek J, Jakima S, Pięta A, Szulc A. Effects of antidepressant treatment on neurotrophic factors (BDNF and IGF-1) in patients with major depressive disorder (MDD) [Internet]. *J Clin Med*. 2021;10(15):3377. U.S. National Library of Medicine; [cited 2023 Aug 10]. https://pubmed.ncbi.nlm.nih.gov/34362162/
30. Yoshimura R, Mitoma M, Sugita A, et al. Effects of paroxetine or Milnacipran on serum brain-derived neurotrophic factor in depressed patients [Internet]. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2007;31(5):1034-1037. U.S. National Library of Medicine; [cited 2023 Aug 10]. https://pubmed.ncbi.nlm.nih.gov/17459550/
31. Deuschle M, Gilles M, Scharnholz B, Lederbogen F, Lang UE, Hellweg R. Changes of serum concentrations of brain-derived neurotrophic factor (BDNF) during treatment with Venlafaxine and mirtazapine: role of medication and response to treatment [Internet]. *Pharmacopsychiatry*. 2013;46(2):54-58. U.S. National Library of Medicine; [cited 2023 Aug 10]. https://pubmed.ncbi.nlm.nih.gov/22961097/
32. Macdonald A, Briggs K, Poppe M, Higgins A, Velayudhan L, Lovestone S. A feasibility and tolerability study of lithium in alzheimer's disease [Internet]. *Int J Geriatr Psychiatr*. 2008;23(7):704-711. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1002/gps.1964
33. Straten G, Saur R, Laske C, et al. Influence of lithium treatment on GDNF serum and CSF concentrations in patients with early alzheimer's disease [Internet]. *Curr Alzheimer Res*. 2011;8(8):853-859.

U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.2174/156720511798192754

34. Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial [Internet]. *Br J Psychiat*. 2011;198(5):351-356. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/21525519/
35. Nunes MA, Viel TA, Buck HS. Microdose lithium treatment stabilized cognitive impairment in patients with alzheimer's disease [Internet]. *Curr Alzheimer Res*. 2013;10(1):104-107. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/22746245/
36. Forlenza OV, Radanovic M, Talib LL, Gattaz WF. Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial [Internet]. *Br J Psychiat*. 2019;215(5):668-674. U.S. National Library of Medicine; [cited 2023Mar23]. https://pubmed.ncbi.nlm.nih.gov/30947755/
37. Diniz BS, Reynolds CF, Begley A, et al. Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: a longitudinal study [Internet]. *J Psychiatr Res*. 2014;49:96-101. U.S. National Library of Medicine; [cited 2023Mar23]. https://doi.org/10.1016/j.jpsychires.2013.11.004
38. Treatment of Psychosis and Agitation in Alzheimer's Disease [Internet]. [cited 2023 Aug 10]. https://classic.clinicaltrials.gov/ct2/show/NCT02129348

How to cite this article: Deliyannides DA, Graff JA, Niño I, et al. Effects of lithium on serum Brain-Derived Neurotrophic Factor in Alzheimer's patients with agitation. *Int J Geriatr Psychiatry*. 2023;e6002. https://doi.org/10.1002/gps.6002