International Journal of Clinical Trials
Vöhringer PA et al. Int J Clin Trials. 2025 May;12(2):121-126
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20251207

Protocol

Trace-dosage of lithium for prevention of cognitive declining in mood illnesses: a randomized double-blind, placebo-controlled, study protocol

Paul A. Vöhringer[1-3]*, Bárbara A. Palma[1], Álvaro A. Provoste[1], M. Ignacia Carrasco[1], M. Graciela Rojas[1,3], S. Nassir Ghaemi[2,4]

[1]Clínica Psiquiátrica Universitaria, Hospital Clínico Universidad de Chile, Santiago, Chile
[2]Department of Psychiatry, Tufts University School of Medicine, Boston, MA, USA
[3]Millennium Institute for Depression and Personality Research. MIDAP, Santiago, Chile
[4]Harvard Medical School, Boston, MA, USA

Received: 03 January 2025
Accepted: 09 April 2025

***Correspondence:**
Dr. Paul A. Vöhringer,
E-mail: pvohringer@mail.harvard.edu

ABSTRACT

Background: Mood disorders [bipolar disorder (BD) and recurrent unipolar depression] are among the most common mental health conditions worldwide, and are recognized as significant risk factor for development of mild cognitive impairment (MCI) and dementia. Lithium, the gold standard treatment for these mood disorders, has also been suggested as a potential neuroprotective agent, even at trace doses. This study aims to evaluate the effect of trace doses of lithium in preventing cognitive decline in individuals with mood disorders.
Methods: This is randomized, double-blind, placebo-controlled trial involving 250 participants aged 55 to 75 years, all of whom have mood disorders and are not currently receiving lithium therapy. Participants will be randomized into either trace dose lithium (50 mg oral tablets daily) or placebo group, with 125 subjects in each group. All participants will continue their usual clinical treatment and will be followed every six month for five years. The primary outcome measure will be the incidence of MCI or worsening of pre-existing MCI, defined as change from baseline clinical dementia rating scale (CDR) score of 0 to 0.5 (MCI).
Conclusions: If this research demonstrates that trace doses of lithium can prevent the onset or progression of MCI or dementia in patients with mood disorders, it could offer a new therapeutic approach for addressing cognitive decline in this high-risk population, with significant public health implications.
Trial registration: clinicaltrials.gov: NCT06662526.

Keywords: Lithium trace doses, Mood disorders, Cognitive declining prevention, Dementia prevention

INTRODUCTION

Mood disorders, BD and recurrent unipolar depression are among the most common mental health conditions worldwide. Research estimates that the international lifetime prevalence of BD is 0.8% for type 1 and up to 2% for type 2, while for major depressive disorder (MDD), prevalence rates stand between 6.4%.[1] In Chile lifetime prevalence for MMD is 9.2 and 2% for any BD.[2]

MCI, for instance, is an intermediate stage between the expected cognitive decline of normal aging and the more serious decline of dementia.[3] It is considered a transitional-preclinical stage between healthy aging and dementia. While not all individuals with mild MCI will go on to develop dementia, evidence suggests that those with this condition are at a higher risk, with annual conversion rates ranging from 8% to 15% per year.[4] This is why detecting and treating MCI represents a critical opportunity for early intervention and potentially preventing or delaying the onset of more severe neurodegenerative diseases. Dementia, by the other hand, is a general term to describe a condition characterized for a group cognitive and behavioral symptom, observed in

several conditions. Among all causes of dementia, Alzheimer disease (AD) is the most common form, representing 60-80% of cases.[5]

There is a substantial body of evidence showing that individuals with affective disorders exhibits a markedly higher risk of developing dementia and other neurodegenerative conditions, compared to the general population. Specifically, the risk estimates for developing dementia range from 1.90 to 3.02 for MDD, and 2.36 to 5.58 for BD.[6-11] People suffering affective disorders have also a 2.5 times higher risk of developing dementia when compared to other medical conditions like osteoarthritis of diabetes.[8,9] This increased risk is thought to be associated with factors such as the chronic nature of BD, the impact of mood episodes on cognitive function, and the potential shared underlying pathophysiological mechanisms between the two conditions.[10] Another important clinical aspect with this high risk of MCI and dementia group is pertained with earlier presentation of cases when compared with the general population.[12,13]

Lithium evidence as cognitive protector agent

In recent years, growing body of evidence has suggested that lithium may possess neuroprotective properties, which could be leveraged to address the pressing challenges of dementia, MCI and other neurodegenerative disorders like Parkinson disease among others.[14-18]

Research investigating the underlying mechanisms of lithium's potential neuroprotective effects has revealed a broad spectrum of targets. Its neuroprotective properties are thought to stem from its ability to modulate several critical cellular pathways involved in the pathogenesis of neurodegenerative diseases. These include the inhibition of the glycogen synthase kinase-3 (GSK-3), enhancement of the brain-derived neurotrophic factor (BDNF) activity and a range of anti-inflammatory, antioxidant and neuroprotective effects.[15] Lithium may also promote neuronal survival by increasing the levels of the anti-apoptotic factor Bcl-2, thus mitigating neuronal death, as demonstrated in various in vitro and in vivo models of neurodegenerative disorders. Additionally, lithium has been shown to influence oxidative stress, mitochondrial function and neuroinflammation-key factors implicated onset and progression of these diseases.[19] By targeting these multiple interconnected pathways, lithium presents a promising therapeutic avenue for the prevention and treatment of dementia and other neurodegenerative conditions.

Neuroprotective role of lithium in the prevention of dementia in affective disorders

One of the earliest pieces of evidence suggesting the neuroprotective effects of lithium in dementia comes from the seminal study by Angst et al. In 2007, after following a cohort of patients with mood disorders for over twenty years, they found that the prevalence of Alzheimer's disease was significantly lower in elderly euthymic patients with BD who were in long-term lithium therapy, compared with patients who did not receive lithium.[20] Another case-control study found that the prevalence of Alzheimer's disease was significantly lower in elderly euthymic patients with BD who were on long-term lithium therapy compared to those who were not.[21] Recent research also suggests that low-dose lithium (ranging from 300 mcgr to 50 mg/day) may offer neuroprotective benefits with minimal side effects. This low dose is thought to be sufficient to activate neuroprotective pathways while minimizing toxicity.[22]

Interesting evidence supporting the potential neuroprotective effects of low-dose lithium comes from the northern Chilean region of Tarapacá. Figueroa et al assessed lithium levels in the general population of this area, where the concentration of lithium in drinking water is among the highest in the world, finding lithium concentrations of approximately 0.05 meq/L.[23] The official dementia prevalence in the region, as reported by the Chilean ministry of health, is 4.3%, significantly lower than the national average of 8.4 for individuals aged 75-79.[24] Considering that the standard clinical dosage of lithium for mood disorders is 900 mg per day, yielding an average serum concentration of approximately 0.8 meq/L, the observed serum level of 0.05 meq/L in the Tarapacá population would correspond to an estimated daily dosage of 50 mg per day. This finding suggests that the trace dosage of 50 mg per day may be sufficient to activate neuroprotective pathways while minimizing the risk of toxicity. These effects appear analogous to those observed in populations exposed to trace lithium levels in this the region.

Aim of study

The aim of this research protocol is to examine the effectiveness of lithium in prevention of MCI in patients with the high-risk factor of preexisting mood illnesses (i.e., unipolar depression or bipolar illness). The primary outcome is incidence of newly diagnosed MCI or worsening of preexisting MCI. Furthermore, by exploratory analyses, to evaluate clinical predictors of good lithium response in this sample. These analyses will also assess lithium effects on suicide, mortality, quality of life, functional impairment, and overall medical morbidity.

It is expected that patients with mood conditions exposed to trace lithium dosage will have a smaller incidence of MCI or less worsening of preexisting MCI compared with patients receiving placebo. Specifically, we expect that a) trace dosage of lithium (50 mg/day) will be efficacious in preventing newly diagnosed MCI or worsening in existing MCI, in patients with mood conditions compared with patients receiving placebo, b) there will not be a differential rate of adverse events related to trace lithium dosage compared with placebo

and that c) there will be clinical features that may predict the lithium response in the active arm.

METHODS

Eligible subjects will be invited to participate in the study as part of their primary care psychiatry. In case of interest, they will be contacted by one of the study's researchers to confirm that the eligibility criteria are met. Those subjects who meet the inclusion criteria and do not meet the exclusion criteria at baseline assessment will be included in the trial. After giving consent, subjects will be invited to undergo the baseline assessment.

All participants will receive their usual clinical medical treatment during the time the study is conducted. All psychotropic medications will be allowed to be given per standard of care except lithium. The study defined randomization to lithium or placebo arms as adjuncts to other medications.

Inclusion criteria

Eligible participants will be adults of aged 55 to 70 years of either sex. Subjects must have DSM-5 diagnosis of MDD or BD (types I or II), current or lifetime. Prior to participation in this study, each subject must sign an informed consent.

Exclusion criteria

Subjects with current mood treatment with lithium, alcohol dependency within the past month, current serious unstable medical conditions or history of medical illness that would contraindicate a trial of lithium, current or past severe kidney disease or baseline creatinine >1.5 mg/dl, active suicidal ideation with plan and intent (Columbia suicide severity rating scale screen version -C-SSRS screen->3 points), current or past severe thyroid disease or baseline TSH >5.0 uUI/dl and current diagnosis of dementia of any kind were excluded.

Assessments

In both groups, the assessments will be carried out at the baseline and subsequently every six months over the next four years by blind researchers. Research study investigators will base this diagnosis on interviews with the patient, caregivers, clinicians, and/or chart assessments.

Study outcomes

Primary outcome: incidence of MCI

Incidence of MCI on a yearly basis from year one until the end of the study (year five). This primary outcome will be defined as change from patients initially with a CDR score of 0 to 0.5 (MCI), or a change from baseline CDR score of 0.5 to 1. The CDR is a numerical scale used to quantify the severity of symptoms of dementia. It is used for assessing six cognitive and functional domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR scale helps in categorizing the stages of dementia from no dementia (CDR 0) to severe dementia (CDR 3), providing a standardized measure for the severity of dementia.[25] The primary analysis will employ a Cox regression model to analyze the time to first clinical diagnosis of MCI.

Secondary outcome: clinical predictors of lithium response

Sheehan disability scale (SDS): is a self-administered psychological assessment tool that measures functional impairment in three inter-related domains: work/school, social, and family life.[26]

Columbia suicide severity rating scale (C-SSRS): A tool used for the assessment of suicidal ideation and behavior. It is designed to evaluate the severity of suicidal ideation and the presence of suicidal behavior in individuals.[27]

Patient health questionnaire-9 (PHQ-9): A widely used nine-item self-administered instrument for screening, diagnosing, monitoring and measuring the severity of depression.[28] It was validated in Chile.[29]

Altman self-rating mania scale (ASMS): Self-report questionnaire used to assess the presence and severity of mania symptoms. It is commonly used in both clinical and research settings to monitor manic episodes in individuals with mood disorders.[30]

Shahin mixed depression scale (SMDS): This instrument is specifically designed to measure non-DSM mixed features in depression. It was developed to address gaps in the traditional DSM-5 criteria, which may not fully capture the spectrum of mixed symptoms in depressive disorders.[31]

Beck anxiety inventory (BAI): This is a self-report assessment tool designed to evaluate the presence and severity of anxiety symptoms such as nervousness, trembling, fear, and physical symptoms. It is widely used because of its robustness and validity in measuring anxiety.[32]

Montreal cognitive assessment (MoCA): Clinical screening instrument designed to detect MCIs. It is primarily used to evaluate memory, orientation, concentration, and executive functions among other cognitive abilities.[33] It has been validated in Chile.[34]

INECO frontal screening scale (IFS): A neuropsychological test specifically designed to assess various frontal lobe functions including abstraction, mental flexibility, motor programming, working memory, and inhibitory control. The IFS is particularly useful for

detecting early signs of executive dysfunction in neurological diseases such as frontotemporal dementia and Alzheimer's disease.[35] It has been validated in Chile.[36]

Free and cued selective reminding test (FCSRT): This is an episodic memory test. It has a good discriminative ability to predict the development of Alzheimer's disease up to 5 years before its clinical onset among elderly subjects. Additionally, this test is minimally influenced by schooling factors, making it an ideal tool to detect Alzheimer's disease in individuals with low literacy levels.[37]

EuroQol EQ-5D: This is a standardized five questions instrument for measuring an individual's self-reported health status. It encompasses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[38]

MINI-international neuropsychiatric interview: A brief structured diagnostic psychiatric interview for DSM-IV and ICD-10 psychiatric disorders. It will be used for the diagnosis of: 1. Alcohol dependency 2. Abuse of psychoactive substances 3. BD 4. MDDs.[39]

Data analysis

The primary analysis (by full intention-to-treat) will be a survival analysis of time to either detection of MCI or worsening of MCI as defined for the primary outcome during the scheduled treatment period of patients allocated to lithium versus placebo. Time to first event (newly diagnosed MCI or worsening of an already existing one) during the scheduled follow-up will be compared between the two groups. Follow-up time will be censored at the last available assessment in patients who will be lost to follow-up without having an event. Time from randomization to event will be summarized by Kaplan-Meier curves, and compared with the log rank test. Hazard ratios (HRs) with 95% CIs will be calculated with Cox's regression to estimate size of the treatment effect. The proportional hazards assumption will be tested formally with analysis of Schoenfeld residuals. All analyses will be performed with STATA.

Randomization

Participants will be randomized into one of two arms, a trace dose lithium or placebo, each group consisting of 125 subjects. Block randomization will be stratified by diagnosis (bipolar vs MDD), gender, decade of age, and presence or absence of any baseline cognitive impairment (defined clinically as the presence of executive dysfunction, attentional impairments, and/or poor working or short-term memory). Equipoise randomization, as has been implemented in other RCTs, will be used to minimize risks by allowing subjects and/or clinicians to exclude one of the two treatment arms if past clinical history and/or patient preferences indicate an undue risk for side effects in one of the arms.

Sample size and power

We plan to enroll a total of 250 participants in the study. Based on the effect size and variability observed in our pilot clinical data, we estimate that this sample size will provide 80% statistical power (α=0.05) to detect meaningful differences in outcomes. Angst et al. reported an odds ratio (OR) of 0.2 over a 5-year period, beginning in the third and fourth decades of life, with absolute rates of 22% in patients with mood disorders compared to 5% in non-mood disorder controls. The study population had a mean age of 68 years.[40] Using these findings as a reference, we project a HR of 0.7 in our overall sample of 250 participants.

DISCUSSION

Despite significant advances in understanding cognitive impairment and dementia over recent decades, we remain far from being able to effectively address these conditions at the scale and level of care required. With the anticipated rise in cognitive decline as a major global health challenge, particularly as the aging population increases, the need for effective preventative strategies has never been more urgent.

Lithium, a well-established treatment for mood disorders, has recently garnered attention for its potential neuroprotective effects, given its role in modulating key processes involved in neurodegeneration and cognitive decline.

To the best of our knowledge, this study is the first randomized controlled trial to investigate the effects of low-dose lithium in the prevention of MCI in individuals with affective disorders. We hypothesize that trace doses of lithium will reduce the incidence of MCI and prevent the progression of pre-existing MCI compared to the control group. If our study confirms these neuroprotective effects, it would provide a promising foundation for further research exploring lithium's potential in broader populations, including those with other psychiatric conditions, or even in the general population at risk for cognitive decline.

Potential limitations of this study include challenges common to long-term clinical trials, such as partial adherence to the drug regimen, incomplete follow-up visits, or participant dropout due to personal reasons or treatment dissatisfaction. These factors may influence the study's findings and will need to be considered in the interpretation of results.

CONCLUSION

This article presents the protocol for a randomized, double-blind, placebo-controlled trial aimed at evaluating

the effectiveness of trace doses of lithium in preventing the onset of mild cognitive impairment in patients with mood disorders, such as unipolar depression or BD. While existing evidence suggests that lithium may have neuroprotective properties, particularly in reducing the risk of cognitive decline, to our knowledge, this is the first controlled trial to investigate its effects specifically in this high risk population. If this study demonstrate that trace doses of lithium can effectively prevent neurocognitive impairment, it could open new avenues for research and therapeutic strategies, offering significant implications for the long-term management of mood disorders and their associated risks.

Funding: This work was funded by the ANID Millennium Science Initiative /Millennium Institute for Research on Depression and Personality-MIDAP ICS13_005
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Kessler RC, Hagop SA, Minnie A, Howard B, Paul G, Robert MAH, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. Am J Psychiatry. 2006;163(9):1561-8.
2. Vicente B, Robert K, Pedro R, Sandra S, Itzhak L, Silverio T. Lifetime and 12-month prevalence of DSM-III-R disorders in the Chile psychiatric prevalence study. Am J Psychiatry. 2006;163(8):1362-70.
3. Gillis C, Mirzaei F, Potashman M, Ikram MA, Maserejian N. The incidence of mild cognitive impairment: A systematic review and data synthesis. Alzheimers Dement Amst Neth. 2019;11:248-56.
4. Petersen RC. Mild Cognitive Impairment. Contin Lifelong Learn Neurol. 2016;22:404-18.
5. NA. Alzheimer's Association 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement. 2024;20(5):3708-821.
6. Chen MH, Cheng-Ta L, Chia-Fen T, Wei-Chen L, Wen-Han C, Tzeng-Ji C, et al. Risk of subsequent dementia among patients with bipolar disorder or major depression: a nationwide longitudinal study in Taiwan. J Am Med Dir Assoc. 2015;16(6):504-8.
7. Da Silva J, Gonçalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. Br J Psychiatry J Ment Sci. 2013;202(3):177-86.
8. Diniz BS, Antonio LT, Fei C, Ariel G, Jair CS, Meryl AB, et al. History of Bipolar disorder and the risk of dementia: a systematic review and meta-analysis. Am J Geriatr Psychiatry. 2017;25(4):357-62.
9. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63(5):530-8.
10. Velosa J, Delgado A, Finger E, Berk M, Kapczinski F, de Azevedo Cardoso T. Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. Acta Psychiatr Scand. 2020;141(6):510-21.
11. Wu KY, Chia-MC, Hsin-YL, Chi-Shin W, Erin CHW, Chia-Hsiang C, et al. Increased risk of developing dementia in patients with bipolar disorder: a nested matched case-control study. Bipolar Disord. 2013;15(7):787-94.
12. Pfennig A, Littmann E, Bauer M. Neurocognitive Impairment and Dementia in Mood Disorders. J Neuropsychiatry Clin Neurosci. 2007;19(4):373-82.
13. Yates JA, Clare L, Woods RT. Mild cognitive impairment and mood: a systematic review. Rev Clin Gerontol. 2013;23:317-56.
14. Forlenza OV, Breno SD, Márcia R, Franklin SS, Leda LT, Wagner FG. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry J Ment Sci. 2011;198(5):351-6.
15. Forlenza OV, De-Paula VJR, Diniz BSO. Neuroprotective Effects of Lithium: Implications for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders. ACS Chem Neurosci. 2014;5:443-50.
16. Kessing LV, Søndergård L, Forman JL, Andersen PK. Lithium treatment and risk of dementia. Arch Gen Psychiatry. 2008;65:1331-5.
17. Mauer S, Vergne D, Ghaemi SN. Standard and trace-dose lithium: a systematic review of dementia prevention and other behavioral benefits. Aust N Z J Psychiatry. 2014;48(9):809-18.
18. Singulani MP, Ana Flávia FF, Paulina SF, Iván CV, Leda LT, Luiz RB, et al. Lithium and disease modification: A systematic review and meta-analysis in Alzheimer's and Parkinson's disease. Ageing Res Rev. 2024;95:102231.
19. Haupt M, Bähr M, Doeppner TR. Lithium beyond psychiatric indications: the reincarnation of a new old drug. Neural Regen Res. 2021;16(12):2383.
20. Angst J, Gamma A, Gerber-Werder R, Zarate CA, Manji HK. Does long-term medication with lithium, clozapine or antidepressants prevent or attenuate dementia in bipolar and depressed patients? Int J Psychiatry Clin Pract. 2007;11:2-8.
21. Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. Br J Psychiatr. 2007;190:359-60.
22. Nunes MA, Viel TA, Buck HS. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. Curr Alzheimer Res. 2013;10(1):104-7.
23. Figueroa LT, Barton S, Schull W, Razmilic B, Zumaeta O, Young A, et al. Environmental lithium exposure in the north of Chile-Tissue exposure indices. Epidemiol Biostat Public Health. 2014;149(2):280-90.

24. Dependencia Personas Mayores 2009. 2009.
25. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatr J Ment Sci. 1982;140:566-72.
26. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11(3):89-95.
27. Posner K, Gregory KB, Barbara S, David AB, Kseniya VY, Maria AO, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatr. 2011;168:1266-77.
28. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.
29. Errazuriz A, Beltrán R, Torres R, Passi-Solar A. The Validity and Reliability of the PHQ-9 and PHQ-2 on Screening for Major Depression in Spanish Speaking Immigrants in Chile: A Cross-Sectional Study. Int J Environ Res Public Health. 2022;19(21):13975.
30. Altman EG, Hedeker D, Peterson JL, Davis JM. The Altman Self-Rating Mania Scale. Biol Psychiatr. 1997;42(10):948-55.
31. Shahin I, Bonnin CDM, Saleh E, Helmy K, Youssef UM, Vieta E. Validity of the Shahin Mixed Depression Scale: A Self-Rated Instrument Designed to Measure the Non-DSM Mixed Features in Depression. Neuropsychiatr Dis Treat. 2020;16:2209-19.
32. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol. 1988;56(6):893-7.
33. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.
34. Gaete M, Jorquera S, Bello-Lepe S, Mendoza YM, Véliz M, Alonso-Sanchez MF, et al. Resultados estandarizados del Montreal Cognitive Assessment (MoCA) para cribado neurocognitivo en población chilena. Neurología. 2020;38:246-55.
35. Torralva T, Roca M, Gleichgerrcht E, López P, Manes F. INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia–corrected version. J Int Neuropsychol Soc. 2009;15(5):777-86.
36. Ihnen J, Antivilo A, Muñoz-Neira C, Slachevsky A. Chilean version of the INECO Frontal Screening (IFS-Ch): Psychometric properties and diagnostic accuracy. Dement Neuropsychol. 2013;7(1):40-7.
37. Grober E, Hall C, Sanders AE, Lipton RB. Free and cued selective reminding distinguishes Alzheimer's disease from vascular dementia. J Am Geriatr Soc. 2008;56:944-6.
38. Rada I, Ortiz MS, Cabieses B. Calidad de vida relacionada con la salud en chilenos de comunas vulnerables. Gac Sanit. 2023;37:102328.
39. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatr. 1998;59(20):22-33.
40. Angst J, Gamma A, Neuenschwander M, Ajdacic-Gross V, Eich D, Rössler W, et al. Prevalence of mental disorders in the Zurich Cohort Study: a twenty year prospective study. Epidemiol Psychiatr Sci. 2005;14:68-76.

Cite this article as: Vöhringer PA, Palma BA, Provoste AA, Carrasco MI, Rojas MG, Ghaemi SN. Trace-dosage of lithium for prevention of cognitive declining in mood illnesses: a randomized double-blind, placebo-controlled, study protocol. Int J Clin Trials 2025;12(2):121-6.