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The effect of levetiracetam on cognition, a systemic review and meta-analysis of the double-blinded randomized placebo-controlled trials

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 July 2023 and was last updated on 01 July 2023.

INTRODUCTION

Review question / Objective The objective is to investigate the current evidence from randomized double-blinded placebo-controlled trials of levetiracetam on individual cognitive domains, and adverse events.

Rationale Levetiracetam is a well-tolerated anti-seizure medication that has been associated with improved cognitive function in people with epilepsy. Animal studies have shown its potential to improve cognitive function in human amyloid precursor protein mice models. Meanwhile, studies in human subjects have explored its potential to improve mild cognitive impairment and Alzheimer's disease. However, the specific cognitive domains associated with improvement remain inconclusive.

Condition being studied The PICO (population, intervention, comparison, and outcome) setting for the current meta-analysis will be as follows: (1) P: human subjects; (2) I: levetiracetam; (3) C: placebo; and (4) O: the difference in scores on the selected cognitive domain test.

METHODS

Search strategy The following keywords will be used in combination for literature searching: levetiracetam, cognitive, cognition, memory, learning, language, visuospatial, attention, random, randomized, and randomised.

Participant or population Human subjects.

Intervention Levetiracetam.

Comparator Placebo.

Study designs to be included Randomized double-blinded placebo-controlled trials.

Eligibility criteria The following inclusion criteria will be used: (1) Randomized placebo-controlled trials (RCTs) enrolling human subjects, (2) Double-blinded RCTs, (3) RCTs investigating the quantitative difference in cognitive function between levetiracetam and placebo. The following exclusion criteria will be applied: (1) Studies that were not RCTs, (2) Open-labeled studies, (3) RCTs that lacked cognitive assessment of either levetiracetam or placebo.

Information sources A literature search will be conducted in PubMed (US National Library of Medicine), Embase (Wolter Kluwer Ovid), and Cochrane CENTRAL (Cochrane Collaboration) for randomized double-blinded placebo-controlled trials that explore changes in cognitive function test outcomes between levetiracetam and placebo following treatment. The reference list of available review articles and meta-analyses will also be examined for additional candidates. Animal studies, non-randomized, non-double blinded, and non-placebo controlled studies will be excluded from the present meta-analysis.

Main outcome(s) The primary results of this study will be the variations in cognitive function test outcomes between the levetiracetam and placebo treatments following the therapy. The cognitive function test will include seven categories: multi-domain, executive function, processing speed, working memory, verbal memory/learning, visuospatial memory/learning, and language.

Additional outcome(s) The secondary outcomes of this study will include adverse events such as somnolence, fatigue, dizziness, headache, irritability, and cognitive adverse events.

Data management Two independent authors, C.-Y.L. and H.-J.J., will extract data from the included studies. This includes demographic information, study design parameters, statistical methods, and primary and secondary outcomes. If data is not available in published articles, we will contact corresponding authors to obtain the original data.

Quality assessment / Risk of bias analysis The methodological quality will be assessed using the Cochrane Risk-of-Bias tool for randomized trials, version 2 (RoB 2), which includes six main items: randomization process, intervention adherence, missing outcome data, outcome measurement, selective reporting, and overall risk of bias. For crossover trials, period/carryover effect will also be included. In the intervention adherence section of RoB 2, the per-protocol method will be used for literature assessment. There are two options available: intention-to-treat (intervention assignment) or per-protocol (intervention adherence).

Strategy of data synthesis A random-effects model will be used for this meta-analysis, which will be conducted using Comprehensive Meta-Analysis software (version 3, Biostat, Englewood, NJ, United States). Hedges' g and 95% confidence intervals (CIs) will quantify primary study outcomes (changes in cognitive scores), with effect sizes of 0.2, 0.5, and 0.8 considered small, moderate, and large, respectively. Odds ratios (ORs) and their associated 95% CIs will be used to investigate secondary outcomes. The degree of heterogeneity across studies will be evaluated using I2 and Cochran's Q statistics, where I2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively.

Subgroup analysis The subgroup analysis will be conducted based on population (epilepsy and non-epilepsy), age group (pediatric and adult), dosage, and study design (parallel versus crossover).

Sensitivity analysis Sensitivity analysis will be conducted by substituting the representative test with an assessment within the same test domain. The results will be analyzed to explore if the association between the intervention and outcome differs significantly.

Language restriction There will be no language restrictions imposed.

Country(ies) involved Taiwan.

Keywords levetiracetam; cognition; clinical trials, meta-analysis; systemic review.

Contributions of each author

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