INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Efficacy of pharmacological treatment in poststroke apathy: a protocol for systematic review and network meta-analysis

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Review question / Objective: **Although evidence suggests that dopaminergic drugs, acetylcholinesterase inhibitors, antipsychotics and psychostimulants show clinical efficacy in poststroke apathy. However, there is no published evidence comparing the efficacy of different pharmacotherapeutic interventions in poststroke apathy.**
Eligibility criteria: **Types of studies. This systematic review and network meta-analysis will include all randomized controlled trials (RCTs) that using pharmacological treatment on poststroke apathy. Quasi-RCTs, Non-RCTs, or case report will be excluded. It would be only in English, regardless of the sample size, publication status, or location.Type of participant. Patients (aged > 18 years) who were diagnosed with poststroke apathy will be included, with no restrictions on gender, race, nationality or occupation.Type of interventions. The intervention group received any type of pharmacological treatment for poststroke apathy. The control group was treated with placebo. When studies combine pharmacological treatment with other active therapies, both intervention and control groups are required to receive the same active therapy.Type of outcomes. The primary outcomes included efficacy rate of apathy and change score of a standardized 14-item Apathy Evaluation Scale12. The secondary outcome measures included Barthel Index (BI), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and Mini-Mental State Examination (MMSE).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 February 2023 and was last updated on 15 February 2023 (registration number INPLASY202320065).

INTRODUCTION

Review question / Objective: **Although evidence suggests that dopaminergic drugs, acetylcholinesterase inhibitors, antipsychotics and psychostimulants show clinical efficacy in poststroke apathy. However, there is no published evidence comparing the efficacy of different**

pharmacotherapeutic interventions in poststroke apathy.

Condition being studied: Stroke is the leading cause of death from cardiovascular and cerebrovascular diseases, and its incidence continues to increase, which seriously threatens the health and safety of peoples. It is important to note, however, that patients may suffer from a variety of sequelae after stroke, which may hinder their recovery in some degree. Apathy is a common symptom after stroke, and it has been estimated that 29.5%-40.2% of stroke survivors experience apathy. Apathy is a multidimensional syndrome characterized by diminished goal-directed cognition and emotional concomitants. Importantly, poststroke apathy have a negative impact on the recovery of physical function, activities of daily living and mental health, and increased burden on families and cost for society. However, there are few effective treatments for stroke apathy.

It is usually difficult to diagnose poststroke apathy and depression can also confound the assessment of apathy. Therefore, many clinical patients with poststroke apathy often are not treated in a timely manner. At present, none of the current medications are approved for the treatment of apathy. Numerous preclinical and clinical evidence indicates that dysfunction of the frontal-subcortical projection system is an important cause of apathy, including monoaminergic, glutamatergic, and monoaminergic pathways. Therefore, pharmacotherapeutic interventions targeting these systems may be feasible. Pharmacologic agents most frequently administered to apathetic patients include dopaminergic drugs, acetylcholinesterase inhibitors, antipsychotics and psychostimulants. However, the difference in efficacy between different pharmacological treatment on poststroke apathy is still uncertain. Different from traditional pairwise meta-analysis, network meta-analysis can be used to test for heterogeneity in the effect of any given treatment as well as for inconsistency between pairs of treatments. Therefore, the goal of this study is to compare the efficacy of the different pharmacological therapies for poststroke apathy, it is expected to provide optimal option for clinical decision-making.

METHODS

Search strategy: Following databases will be used: Web of Science, EMBASE, Cochrane Library and Pubmed. We systematic retrieval the eligible studies about the effect of pharmacological treatment on poststroke apathy from their inception to January 1, 2023. In addition, the references cited by the relevant articles will be hand-searched to identify any additional articles. We will search additional gray databases including Google Scholar and Greynet. All published English RCTs were included. The search strategy used will be a combination of keywords and medical subject headings terms, including “stroke, ischemic stroke, cerebral infarction, cerebrovascular disease, apathy, nefiracetam, fluoxetine, escitalopram, bupropion, donepezil, galantamine”.

Participant or population: Patients (aged > 18 years) who were diagnosed with poststroke apathy will be included, with no restrictions on gender, race, nationality or occupation.

Intervention: The intervention group received any type of pharmacological treatment for poststroke apathy.

Comparator: The control group was treated with placebo.

Study designs to be included: This systematic review and network meta-analysis will include all randomized controlled trials (RCTs) that using pharmacological treatment on poststroke apathy. Quasi-RCTs, Non-RCTs, or case report will be excluded. It would be only in English, regardless of the sample size, publication status, or location.

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Information sources: Following databases will be used: Web of Science, EMBASE, Cochrane Library and Pubmed. We systematic retrieval the eligible studies about the effect of pharmacological treatment on poststroke apathy from their inception to January 1, 2023. In addition, the references cited by the relevant articles will be hand-searched to identify any additional articles. We will search additional gray databases including Google Scholar and Greynet.

Main outcome(s): The primary outcomes included efficacy rate of apathy and change score of a standardized 14-item Apathy Evaluation Scale. The secondary outcome measures included Barthel Index (BI), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and Mini-Mental State Examination (MMSE).

Quality assessment / Risk of bias analysis: Quality of evidence - The quality of the evidence for main outcomes was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Quality of evidence will be carried out through the GRADEpro (https://gradepro.org/). A consensus will be reached with the third investigator if there are any disagreements.
Risk of bias assessment - A Cochrane risk-of-bias tool for randomized trials version 2 will be used by two reviewers to assess the risk of bias of all included trials. The random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases will be evaluated. There were three categories of risk of bias for each domain: low-risk, unclear-risk, and high-risk. A consensus will be reached with the third investigator if there are any disagreements.

Strategy of data synthesis: Review Manager 5.3 will be used to perform the pairwise meta-analysis. The odds ratios (OR) with 95% confidence interval (95% CI) or mean differences (MDs) with 95%CI was presented the pooled estimates. The heterogeneity of each comparison will be presented by an I2 statistic, with values over 50% indicating considerable heterogeneity. The funnel plot and Egger's test to detect publication bias if at least ten studies were available. Additionally, a sensitivity analysis will also be conducted in order to enhance the credibility of the outcome.
The network meta-analyses were performed to synthesize direct and indirect evidence using STATA 16.0 and WinBUGS 1.4.3. The random-effects and fixed-effects models for the network meta-analysis, the deviance information criterion will be used to select the appropriate model. Using Markov chains Monte Carlo, a effect estimate with a 95% credible interval (CrI) was calculated for each comparison. The simulation will be conducted using two chains that are built through Markov Chain Monte Carlo iterations of 100,000, annealed after the first 50,000 iterations. If the PSRF is close to 1 or equal to it, the model is stable, and the data analysis can proceed. Closed loops are assessed using a node-split model; values of P>.05. If there are no local inconsistencies, a design-by-treatment interaction model is used. The

surface under the cumulative ranking curve and the distribution of ranking probabilities are used to determine the relative rank of pharmacological therapies for each outcome. To detect any publication bias in the network meta-analysis, we also plotted a comparison-adjusted funnel plot.

Subgroup analysis: If necessary, subgroup analysis and meta-regression was performed for pairwise meta-analyses and network meta-analysis to examine the influence of potential effect modifiers.

Sensitivity analysis: Sensitivity analysis will also be conducted in order to enhance the credibility of the outcome.

Language restriction: The language will be restricted in English.

Country(ies) involved: China.

Keywords: stroke, apathy, meta-analysis, network.

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