INTRODUCTION

Review question / Objective: We aimed to perform an umbrella review to evaluate the efficacy and safety of PSCI therapies.

Condition being studied: Post-stroke cognitive impairment (PSCI) is a leading cause of morbidity and mortality after stroke worldwide. Numerous studies have evaluated the efficacy and safety of PSCI therapies, but clinical data were largely inconsistent. Therefore, it is necessary to summarize and analyze the published clinical research data in the field.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 November 2022 and was last updated on 26 November 2022 (registration number INPLASY2022110139).
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METHODS

Participant or population: Two independent authors search for meta-analyses and systematic reviews on PubMed, the Cochrane Library and Web of Science to address this issue. We examined neurological function deficit and cognitive function scores, Montreal Cognitive Assessment (MoCA), Activities of daily living (ADL) as efficacy endpoints, and the incidence of adverse events as safety profiles.

Intervention: Nineteen eligible papers including 312 studies, were included in the umbrella review. The results showed that angiotensin-converting enzyme inhibitors (ACEI) inhibitors and N-methyl-D-aspartate (NMDA) antagonists, cell therapies, Acupuncture, EGB76 can improve the neurological deficits and activities of daily living, and the adverse effects were mild for the treatment of PSCI. Moreover, antiplatelet agents (aspirin, clopidogrel), Vinpocetine, Oxiracetam, Citicoline, thrombolytic therapy, Actovegin, DL-3-n-Butylphthalide, Nimodipine showed adverse events or low article quality in PSCI patients, Research evidence is not exact, and further research is needed.

Comparator: The AMSTAR2 tool was used to evaluate systematic reviews and meta-analyses(9). The methodological quality of the studies was determined by the percentage of AMSTAR2 score. The percentage of AMSTAR2 score was classified into 0–15.8%, 15.8–21.05%, and 21.05%–100% indicating low quality, medium quality, and high quality, respectively.

Information sources: PubMed, Web of Science and the Cochrane Library.

Main outcome(s): Our study demonstrated that ACEI inhibitors (Donepezil) and NMDA antagonists (Memantine), EGB76, Acupuncture are the optimum neurological function and activities of daily living medication for patients with PSCI. Moreover, antiplatelet agents (aspirin, clopidogrel), Vinpocetine, Oxiracetam, Citicoline, thrombolytic therapy, Actovegin, DL-3-n-Butylphthalide, Nimodipine showed adverse events or low article quality in PSCI patients, Research evidence is not exact, and further research is needed.

Quality assessment / Risk of bias analysis: Nineteen eligible papers including 312 studies, were included in the umbrella review. The results showed that angiotensin-converting enzyme inhibitors (ACEI) inhibitors and N-methyl-D-aspartate (NMDA) antagonists, cell therapies, Acupuncture, EGB76 can improve the neurological deficits and activities of daily living, and the adverse effects were mild for the treatment of PSCI. Moreover, antiplatelet agents (aspirin, clopidogrel), Vinpocetine, Oxiracetam, Citicoline, thrombolytic therapy, Actovegin, DL-3-n-Butylphthalide, Nimodipine showed adverse events or low article quality in PSCI patients, Research evidence is not exact, and further research is needed.

Strategy of data synthesis: We searched for related articles using keywords and filtering titles, and two investigators screened the literature independently. Articles were downloaded and the
abstracts screened using inclusion criteria, deleting any irrelevant or repetitive articles. Thereafter, we manually searched the reference lists of the chosen papers for any other relevant studies not found in our initial search. Finally, a full-text search was performed to extract and then analysis the data from articles.

**Subgroup analysis:** According to the following criteria, three investigators (Yongbiao Li, xx, xx) independently selected those trials that met the inclusion criteria. The main characteristics of the selected study were extracted in a table including year of publication, study design, number of studies, and regimens for the treatment. We included results evaluating the efficacy of drugs in patients with at least one of the clinical assessment scales: 1) baseline mini-mental state examination (MMSE) scores; 2) the primary outcomes included: global neurological deficit scores such as the National Institutes of Health Stroke Scale(NIHSS) score ≤1 and Montreal Cognitive Assessment (MoCA); 3) Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); 4) dependence assessed by Clinical Global Impression of Change (CIBIC-plus or CGI); 5) Activities of Daily Living scale (ADL); 6) clinical effect, defined according to the nationally approved criteria, is divided into essentially recovered, significant improvement, improvement, no change, deterioration; cognitive function scoring; quality of life as activities of daily living. All data analyses were performed using graphpad prism 8 software. The results were expressed as MD ± SD (standard deviation). The adverse events were assessed incidence of adverse events, and the OR were calculated. Therefore, mean difference or odds ratio with 95% CI and P values were used to assess the efficacy and safety of the study medications.

**Language restriction:** English.

**Country(ies) involved:** China.

**Keywords:** Post-stroke cognitive impairment, clinical trial, systematic review, umbrella review, neurological functional.

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**Sensitivity analysis:** The sample size and mean difference were used to calculate the four clinical assessment scales. NIHSS/BI/scores were used to evaluate of neurological status, behavioral symptoms in patients were calculated by ADL/MMSE/ADAS. We focused on the clinical effect is divided into essentially recovered, significant improvement, no change, deterioration; cognitive function scoring; quality of life as activities of daily living. All data analyses were performed using graphpad prism 8 software. The results were expressed as MD ± SD (standard deviation). The adverse events were assessed incidence of adverse events, and the OR were calculated. Therefore, mean difference or odds ratio with 95% CI and P values were used to assess the efficacy and safety of the study medications.