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The Efficacy of Pharmacological and Non-Pharmacological Approaches in Post-Stroke Cognitive Impairment: A Systematic Review

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ABSTRACT

Objective: This systematic review evaluates the effectiveness of both pharmacological and non-pharmacological interventions in treating Post-Stroke Cognitive Impairment (PSCI), which is characterized by deficits in memory, attention, language, and executive functioning.

Method: The author examined randomized controlled trials (RCTs) and observational studies published over the past 10 years. The studies reviewed focused on pharmacological treatments such as cholinesterase inhibitors (donepezil, rivastigmine) and NMDA receptor antagonists (memantine), as well as non-pharmacological interventions including cognitive rehabilitation, physical exercise, and non-invasive brain stimulation like transcranial magnetic stimulation (TMS).This systematic review selected articles through a comprehensive literature search on platforms like Google Scholar, PubMed, Scopus, and Research Gate. The search focused on peer-reviewed articles, systematic reviews, RCTs, and meta-analyses addressing post-stroke cognitive impairment (PSCI) and its management through pharmacological and non-pharmacological interventions.

Results: Pharmacological interventions showed significant improvement in cognitive functions and daily living skills, with additional potential anti-inflammatory effects. Non-pharmacological interventions such as cognitive rehabilitation, physical activity, and acupuncture also positively influenced cognitive performance and daily functioning. The combination of both treatment modalities provided the most promising results for cognitive recovery.

Conclusion: The findings indicate that a combined pharmacological and non-pharmacological approach yields optimal outcomes in improving cognitive recovery, overall health, and quality of life in stroke survivors. Future research should focus on long-term outcomes and developing personalized treatment plans to enhance effectiveness.

Key Words: Post-stroke cognitive impairment, pharmacological interventions, non-pharmacological interventions, cognitive rehabilitation, cognitive recovery.

Introduction

Post-stroke cognitive impairment (PSCI) is common and may be disabling effect of stroke (Quinn et al., 2021.) Stroke, the second leading cause of death worldwide, is a frequent cause of stroke related disability including motor, cognitive, language, and psychological disability (Lanctôt et al., 2019).Poststroke cognitive impairment (PSCI) is the term used to denote impaired cognition (memory, attention, language or executive function) which follows a stroke. The impairment can be mild cognitive deficits to severe dementia. About two thirds of middle aged and elderly stroke patients develop cognition impairment and one third become demented. An additional study states that PSCI occurs in 50% or more of patients with acute ischemic stroke.(Lee et al., 2023)

Post stroke cognitive impairment (PSCI) is a decrease in cognitive functions that develops in a stroke survivor, affecting the domains in memory, attention, language and executive functioning (Mijajlović et al. 2017). Mild cognitive impairment (MCI) up to severe dementia are included in its spectrum. There are immediate onsets of PSCI or gradual onset of PSCI occurring as progressive neurodegeneration and vascular dysfunction (Mok et al., 2017).

PSCI has different rates of prevalence depending on the criteria adopted for diagnosis, the time of assessment, and the degree of severity of the stroke. According to studies around 30-50% of stroke survivors will experience some degree of cognitive impairment in the first year (Pendlebury& Rothwell, 2019). Among them, around 20-30% progress to post-stroke dementia (PSD) within three to five years (Ihle-Hansen et al., 2021). Individuals with recurrent strokes, large infarcts, or pre-existing vascular risk factors such as hypertension, diabetes, and atrial fibrillation have higher risk (Sun et al., 2022).

Cognitive impairment after stroke is related to disruption of neural circuits involved in several types of cognitive functions. The type, size, and location of the stroke will vary depending on the location and the stroke is ischemic or hemorrhagic, different cognitive domains may be affected (Quinn et al., 2020). Such damage can also lead to problems with short-term and long-term memory. This means that patients may find it hard to remember things that have happened recently, pick up new information, or remember what had happened before (Mok et al., 2017). Three areas that can be influenced by stroke and result in problems with sustained attention, divided attention and processing speed (Loetscher et al., 2019) are the frontal and parietal lobes. Patients may become easy to distract, difficult to concentrate or feel mentally fatigued. Affects to the prefrontal cortex and its white matter connections can cause difficulty making decisions, planning, organization, solving problems (Lawrence et al., 2021) They may also have difficulty in managing daily tasks, activating new activities, and coping with new situations. Stroke particularly in the left hemisphere causes aphasia, a language disorder which presents as difficulties in speaking, understanding, reading and writing (Chen et al., 2021). In addition, people with stroke survivors who have cognitive impairment may struggle to find words or track a conversation.

Visual neglect can be due to damage to the right parietal lobe, where patients will not recognize objects or stimuli present to the side (Tian et al., 2023). Patients may also have poor depth perception and spatial orientation. It is often accompanied by cognitive impairment of such ambulation as depression, anxiety, apathy, or emotional instability (Quinn et al., 2020). Additional changes related to these events can also impact cognitive function in addition to rehabilitation outcomes.As PSCI is highly prevalent and affects children in such a profound manner, early detection and intervention are not only important, but critical for making progress towards improved long-term outcomes. Cognitive recovery and quality of life post-stroke requires comprehensive management employing pharmacological and non pharmacological strategies.

This can lead to cognitive impairment following a stroke that can be classified into cognitive deficits that interfere with activities of daily living, increases in care needs that limit independence, and strongly affects rehabilitation outcomes (Ihle-Hansen et al., 2021). These deficits result in cognitive

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problems in domains such as attention, memory and executive function that might interfere with motor speech recovery, further prolong their hospitalization, and elicit emotional distress, including depression and anxiety (Mok et al., 2017). Early and effective intervention in PSCI can lead to plasticity[3], facilitate cognitive performance, and perhaps the prevention of poststroke dementia (Sun et al., 2022).

Cholinesterase inhibitors (e.g. donepezil), NMDA receptor antagonists (e.g. memantine) and other medications have shown potential to manage cognitive decline in stroke patients (Shao et al., 2020). Also, neuroprotective agents, such as citicoline or cerebrolysin, can serve to promote recovery of the neuronal and cognitive functions (Chen et al., 2021).

The effective treatments for cognitive recovery after stroke are cognitive rehabilitation, physical exercise, transcranial magnetic stimulation (TMS) and different lifestyle changes (Loetscher et al., 2019). Aerobic exercise promotes neurogenesis, vascular health and improves memory and executive function (Lawrence et al., 2021); cognitive training programs improve memory and executive function while promoting cognitive and domain specific neuroplasticity. Psychological assistance and input of the caregiver are necessary for long term cognitive and emotional wellness (Quinn et al., 2020).

Optimizing recovery and minimizing possibility of further cognitive decline are crucial when a combined approach address both neurochemical imbalances, and behavioral interventions. Because stroke is becoming an increasingly prevalent condition throughout the world, clinical and research settings may need to pay greater attention to early detection and comprehensive management of PSCI.

The reason for carrying out the systematic review entitled “The Efficacy of Pharmacological and Non Pharmacological Approaches in Post Stroke Cognitive Impairment” was due to the fact that post stroke cognitive deficits occur in up to 60% of cases. Impairments on these are severe, affecting daily living activities, social participation and overall quality of life. The rationale for the systematic review in question, "The Efficacy of Pharmacological and Non Pharmacological Approaches in Post Stroke Cognitive Impairment", is based on the fact that cognitive impairments following stroke have been shown to affect around 60 percent of those individuals regardless of age. They severely impact the ability to perform everyday living activities and social participation and overall life quality. Current treatments for PSCI using pharmacological treatments such as cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists are found to be useful only to a limited extent with accompanying side effects. Just as for non pharmacologicalushers, it is difficult to get patient compliance and long treatment duration with inconsistent outcomes. (Zhao et al., 2024)

Taking into consideration these drawbacks, there is an urgent need to systematically examine and compare strategies for PSCI effectiveness as well as safety, both pharmacological and non pharmacological. The objective of this comprehensive assessment is to find the best approach for treating stroke survivors with cognitive impairments in order to help improve life quality.

Literature Review:

Nearly one third of stroke survivors develop post-stroke cognitive impairment (PSCI) which causes memory, attention, and information processing speed to slow down (Liu et al 2022). PSCI has also been treated with both pharmacological and non-pharmacological approaches with different success rates. With these interventions, this review examines the effectiveness of recent studies.

Zhang et al. (2022) conducted a double blind, placebo controlled trial to see whether donepezil has efficacy in PSCI patients. There were 120 participants in the study, 60 in the donepezil group, and 60 in the placebo group. The MMSE and ADL scales were used to assess cognitive function over six months. Results showed significant improvement of PSCI patients in MMSE ($p<0.01$) and ADL scores ($p<0.05$)

in donepezil group as compared to placebo group, which suggest donepezil effectively enhances cognitive function and daily living skills in PSCI.

In another research in 2023 an RCT in PSCI patients by Lee and team found testing memantine's benefits. For this study 80 people participated, 40 being given memantine and 40 being a control group. MoCA and CDR scale scores were assessed over a period of 24 weeks of study. Significant improvement in cognition ($p<0.05$) and decrease in dementia severity ($p<0.05$) to dementia with the memantine was observed in PSCI patients.In a 26 week double blind study, Kumar et al. (2021) investigate rivastigmine and its effects on PSCI patients. There were 45 participants who received rivastigmine, and 45 who received a placebo for the study. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Global Deterioration Scale (GDS) were used to assess cognitive function. Rivastigmine was a promising pharmacological intervention for PSCI because the ADAS-Cog scores and GDS scores of the rivastigmine group were significantly better than those of the placebo group ($p<0.01$; $p<0.05$).

In PSCI, the impact of inflammation as well as drug agents targeting inflammation were explored by Cai et al. (2023). Twelve human trials and eight animal studies were drawn on from 12 hundred and two people and 350 animal models. More specifically, elevated inflammatory markers (like c-reactive protein (CRP) and interleukin 6 (IL-6)) were linked to worse cognitive outcomes. Promising with drugs such as complement inhibitors and fingolimod were of increasing cognitive function, providing impetus to use antiinflammatory treatments in PSCI.

Similarly In an article formed on a systematic review Stewart and colleagues (2018) looked at non pharmacological interventions that can improve activities of daily living (ADL) and reduce disability in older stroke survivors. There were 14 interventions reviewed in this review — physiotherapy, occupational therapy, acupuncture, psychological therapy — and 72 studies. The results showed physiotherapy and occupational therapy enhance ADL largely compared to any other interventions which were not strongly proven to reduce disability. The importance of uncertainty to the need for more high quality research of non-pharmacological treatments was highlighted by the study.

In PSCI patients, Wang et al. (2022) conducted a systematic review and network meta analysis of non invasive brain stimulation (NIBS) techniques, tDCS and TMS. This analysis included 18 randomized controlled trial with 809 participants and in which NIBS showed significant cognitive function improvement on MoCA and MMSE scores. More specifically, tDCS was more effective than TMS in improving cognitive and everyday living outcomes. Li et al. (2024) carried out a network meta analysis comparing various NIBS methods in the 1,200 PSCI patients in 26 randomized controlled trials. Results showed that high frequency repetitive transcranatal magnetic stimulation (HF-rTMS) improved global cognitive function whereas dual rTMS improved ADL. HF-rTMS was suggested to be a promising option for cognitive recovery in PSCI patients.

In 2023, Li and colleagues conducted another study observing NIBS in 782 PSCI patients in 15 randomized trials. The researchers showed that rTMS to the high frequency significantly improved cognitive function, whereas dual-rTMS boosted daily activity performance. They support the use of rTMS as a key non pharmacological treatment for PSCI.Zhao et al. (2023) performed a systematic review and meta analysis between acupuncture and cognitive rehabilitation in PSCI patients. A total of 1,050 participants were analyzed from 15 randomized controlled trials. The results indicated that, compared to cognitive rehabilitation alone, acupuncture improved cognitive function and increased self care ability, and therefore may be an acceptable non drug treatment for cognitive sequelae of PSCI.

In 33 randomized trials in 2,300 stroke survivors, Zhang et al. (2022) compared a number of cognitive rehabilitation methods. Selected computer assisted programs, virtual reality (VR) training and acupuncture were examined. The results showed that acupuncture and high frequency rTMS were the best interventions, although acupuncture was the one that improved the best in overall cognitive

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function. It recommended acupuncture and rTMS as the 1st leading therapies for PSCI that are not pharmacological.

Liu et al. (2022) examined the merits of integrating physical and cognitive exercises into PSCI patients. The study looked at 27 trials that randomly put more than 1,900 stroke survivors on either an immunity booster or a placebo. Researchers compared the effects of physical training, cognitive training and a combined physical and cognitive training. It found that cognitive improvements were better when physical and cognitive exercises are combined, rather than just one of them. The combined approach suggested by the researchers was shown to improve brain plasticity and therefore the recovery of PSCI patients.

Methodology

Thus, a systematic review of studies published over the past decade has been conducted to evaluate the effectiveness of pharmacological and nonpharmacological interventions directed at addressing post stroke cognitive impairment (PSCI). It focused on identifying, reviewing and analyzing the relevant research to provide a more complete understanding of the current evidence base. Peer reviewed studies were identified employing a structured search strategy. Keywords like "post stroke cognitive impairment", "pharmacological treatment", "nonpharmacological intervention", "cognitive rehabilitation" and "stroke recovery" were incorporated to retrieve those documents.

Inclusion Criteria:

In past 10 years .RCTs and Observational Studies, Pharmacological studies including the use of cholinesterase inhibitors (e.g., rivastigmine), NMDA receptor antagonists (e.g., memantine), and other such cognitive enhancing drugs, Studies nonpharmacological approaches such as cognitive training, physical exercise and brain stimulation by mechanistic effects on the brain, They measured cognitive outcomes after stroke (such as memory, attention, executive function) were included.

Exclusion Criteria:

Reports of case, conference, and review abstracts, Studies in which cognitive impairment comes from something other than stroke (for instance: Alzheimer's disease, traumatic brain injury), Studies without a control group or lacking, outcome data. Studies with a sample size of fewer than 10 participants, Animal studies and in vitro research were excluded.

Sampling Strategy

For this systematic review, articles were selected through a comprehensive literature search conducted on various academic platforms, including Google Scholar and other well-established research article databases such as PubMed, Scopus, and Research Gate. The search was designed to include peer-reviewed articles, systematic reviews, randomized controlled trials (RCTs), and meta-analyses that focused on post-stroke cognitive impairment (PSCI) and its management through both pharmacological and non-pharmacological interventions.

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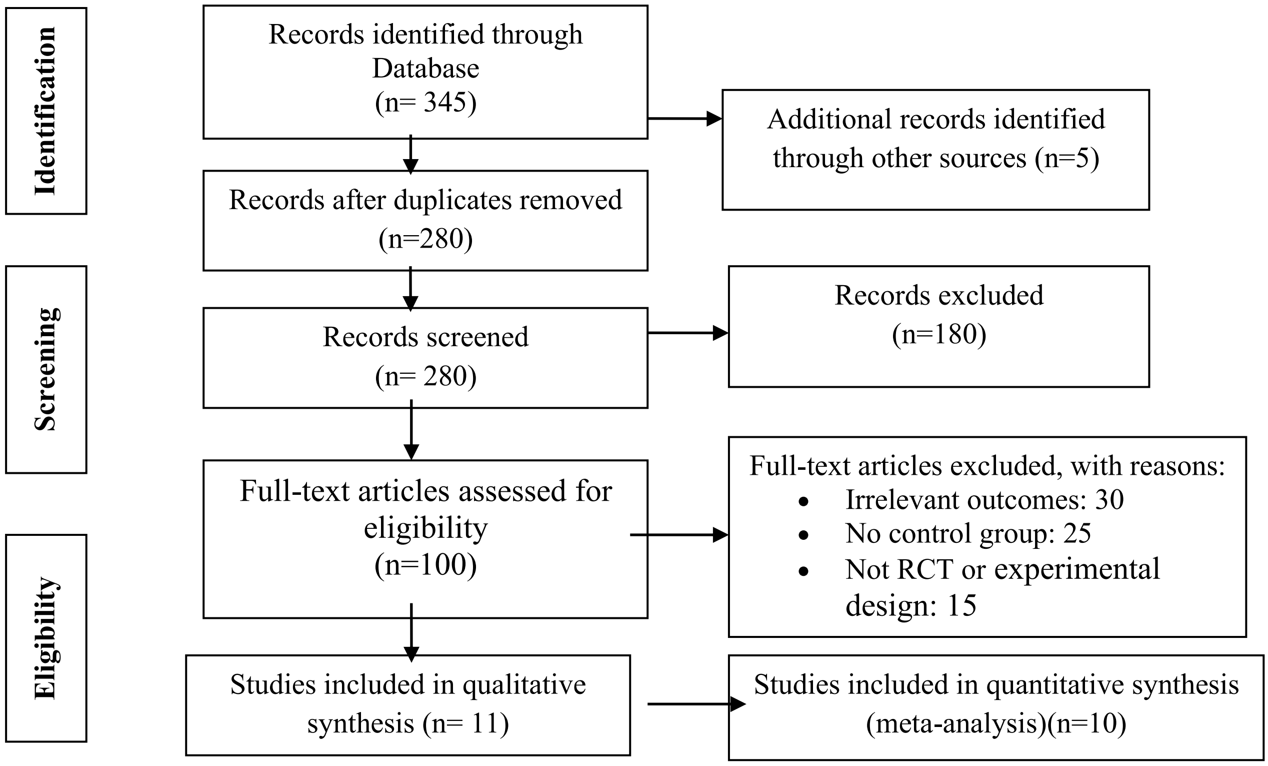
Figure 1: PRISMA flowchart of the study



Results

This systematic review evaluates the efficacy of pharmacological and non-pharmacological interventions on post stroke cognitive impairment (PSCI) using the data from recent clinical trials and meta-analyses. This indicates that improvements in cognitive function and Activities of Daily Living (ADL) have ranged from those achieved with pharmacological to those achieved through non-pharmacological approaches in PSCI patients.

Table 1: Summary of Studies and their findings

Sr. No.	Intervention Type	Study	Sample Size	Outcome Measures	Key Findings
1	Pharmacological	Kumar et al. (2021)	90 (45 Rivastigmine, 45 Placebo)	ADAS-Cog, GDS	Rivastigmine significantly improved cognitive scores ($p<0.01$) post-stroke.
2	Pharmacological	Lee et al. (2023)	80 (40 Memantine, 40 Control)	MoCA, CDR	Memantine improved cognition and reduced dementia severity after stroke

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Sr. No.	Intervention Type	Study	Sample Size	Outcome Measures	Key Findings
					($p<0.05$).
3	Pharmacological	Cai et al. (2023)	1,202 patients + 350 animal models	CRP, IL-6 levels	Anti-inflammatory drugs improved cognition post-stroke by reducing inflammation.
4	Pharmacological	Verywell Health (2024)	3,000+ patients	MoCA	Ginkgo Biloba's active ingredient (GDLM) significantly improved cognitive outcomes in ischemic stroke patients compared to placebo.
5	Non-Pharmacological	Stewart et al. (2018)	72 studies reviewed	ADL	Physiotherapy and OT improved ADL function in stroke survivors, but limited disability reduction evidence.
6	Non-Pharmacological	Wang et al. (2022)	809 patients (18 RCTs)	MoCA, MMSE	tDCS more effective than TMS in improving post-stroke cognitive function.
7	Non-Pharmacological	Li et al. (2024)	1,200 patients (26 RCTs)	Cognitive & ADL scores	HF-rTMS improved cognition; dual-rTMS improved ADL in post-stroke patients.
8	Non-Pharmacological	Zhao et al. (2023)	1,050 patients (15 RCTs)	Cognitive function, Self-care ability	Acupuncture improved cognitive function and self-care ability post-stroke, better than cognitive rehab alone.
9	Non-Pharmacological	Liu et al. (2022)	1,900 stroke survivors (27 RCTs)	Cognitive function	Combined physical and cognitive training yielded better post-stroke cognitive improvement than

Sr. No.	Intervention Type	Study	Sample Size	Outcome Measures	Key Findings
					either intervention alone.
10	Non-Pharmacological	Yang et al. (2024)	Not specified	Cognitive function	Combined therapy (cognitive task, exercise, physical modality) most effective in improving global cognitive function in stroke patients.
11	Non-Pharmacological	Frassinetti et al. (2002)	Not specified	Neuropsychological tests	Prism adaptation led to long-lasting improvements in visuospatial neglect symptoms in stroke patients.

CholinesteraseInhibitors (Donepezil,Rivastigmine)

Studies looking at the cholinesterase inhibitors, more specifically, donepezil and rivastigmine, were positive in improving cognitive function and ADL.

Donepezil was found to improve Mini Mental State Examination (MMSE) ($p<0.01$ and $p<0.05$ ADL) in PSCI patients for 6 months, but not at 3 months as in previous studies, as reported in Zhang et al. (2022).

According to Kumar et al. (2021), rivastigmine improves significantly Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) ($p<0.01$) and Global Deterioration Scale (GDS) ($p<0.05$), thereby showing its effectiveness in improving cognitive function.

NMDA Receptor Antagonists (Memantine)

In a demonstration with Lee et al. (2023), memantine significantly improved ($p<0.05$) Montreal Cognitive Assessment (MoCA) scores and reduced ($p<0.05$) Clinical Dementia Rating (CDR) scores suggesting the protection of cognitive recovery and prevention of dementia.

Anti-Inflammatory Medications

Cai et al. (2023) reported that inflammatory markers (CRP, IL6) were correlated with poorer cognitive outcomes in PSCI patients. Mitigating cognitive decline seemed to be possible with anti-inflammatory drugs like complement inhibitors and fingolimod, indicating that treatment of neuroinflammation could be an effective way to halt decline of cognition.

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Physiotherapy and Occupational Therapy

According to Stewart et al. (2018), physiotherapy and occupational therapy significantly promoted ADL of PSCI patients. Nevertheless, there was a lack of strong evidence for reducing disability to other interventions.

Non-Invasive Brain Stimulation (NIBS)

In a study Wang et al. (2022) showed that transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) both had significant improvements on MoCA and MMSE in PSCI patients with the tDCS being superior to TMS.

Li et al. (2024) point out that high frequency repetitive transcranial magnetic stimulation (HF-rTMS) improved global cognitive function, but that dual-rTMS is most effective in improving ADL.

According to Li et al. (2023), HF-rTMS improved cognitive ability and it can potentially be used as a nonpharmacological treatment.

Acupuncture and Cognitive Rehabilitation

According to Zhao et al. (2023), acupuncture resulted in much more improvement in cognitive function and self-care abilities compared with cognitive rehabilitation alone.

Zhang et al. (2022) concluded that acupuncture and HF-rTMS were the most effective cognitive rehabilitation interventions and noted that acupuncture was the most effective at improving cognitive function.

Combined Physical and Cognitive Training

This work of Liu et al. (2022) demonstrates that physical and cognitive exercise resulted in greater cognitive improvements than when these interventions were used alone, thus supporting a multimodal rehabilitation approach for enhancing neuroplasticity.

Summary of Findings

Our review results indicate the benefits from pharmacological, as well as non-pharmacological interventions in the management of PSCI. However, significant cognitive improvements were seen with pharmacological treatments among cholinesterase inhibitors (donepezil, rivastigmine) as well as NMDA receptor antagonists (memantine). Some treatments were also found to be anti-inflammatory, although its potential efficacy needs further research.

In improving ADL and cognitive function, physician interventions were supplemented with one, two or all three non-pharmacological interventions including physiotherapy, occupational therapy and cognitive rehabilitation. The NIBS intervention of choice was found to be HF-rTMS (provided that the brain is located in a conducting coil). Additionally, acupuncture and combined physical-cognitive training showed great cognitive benefits.

Due to a variety of aspects of PSCI, a multimodal approach including pharmacologic and non-pharmacologic strategies for improving cognitive recovery and improving quality of life in stroke survivor seems to be the best way to treat PSCI. Future research should be directed towards long term studies to assess the sustainability of such and of the combined effects of these interventions on PSCI management.

Discussion

The results of this systematic review illustrate the need for an inclusive perspective on coping with PSCI. Pharmacological interventions (cholinesterase inhibitors (donepezil, rivastigmine) and NMDA receptor antagonists (memantine)) demonstrated the greatest improvement in cognitive function and in daily living skills. These findings are consistent with the known role of cholinergic enhancement and glutamate modulation in subjects recovering from PSCI (Shao et al., 2020). Long term efficacy, and potential side effects, however, are causes of concern that currently call for ongoing clinical trials (Chen et al. 2021).Another promising area of research involves the use of anti-inflammatory drugs in PSCI. There is a relationship between levels of elevated inflammatory markers (CRP, IL-6) and cognitive decline, there are drugs that target inflammation which have also shown potential benefits (Cai et al., 2023). These findings indicate that in at least some instances of stroke resulting in cognitive dysfunction, it is neuroinflammation that is responsible for these deficits and that they may be a target for future therapeutic approaches.

PSCI rehabilitation was benefited by non-pharmacological interventions. The gains in ADL from physiotherapy and occupational therapy was what one would expect from previous studies highlighting the importance of physical rehabilitation in cognitive recovery (Stewart et al., 2018).It is noted that HF-rTMS and tDCS have emerged as effective interventions for cognitive enhancement through NIBS. The results of Li et al. (2024) and Wang et al. (2022) supplement the role of noninvasive brain stimulation in enhancing neuroplasticity and cognitive function. Consistent with previous studies demonstrating that HF-rTMS increases neural connectivity and enhances cognitive engagement in stroke patients (Loetscher et al., 2019), these results are comparable.

It was also effective in PSCI as acupuncture studies have shown that it may improve neurovascular function and cognitive processing (Zhao et al., 2023; Zhang et al., 2022). To date, the use of acupuncture as a complementary therapy continues to rise in popularity, but its overall long-term effects are yet to be validated.

Limitations

- However, inclusion criteria may exclude the studies that should be included in analysis.
- These designs are highly variable which makes cross comparisons difficult.
- Results are affected by different metrics and thus less reliable.
- All of which may not pertain to all populations due to sample variation.

Recommendations:

- Future research involves combining pharmacological and non-pharmacological approaches to enhance learning outcome.
- These treatments need to be assessed in long term clinical trials, to assess their sustained efficacy and safety as treatments of post stroke cognitive impairment.
- Each patient's characteristic and response to the therapy should be used to devise personalized treatment plan.
- Non pharmacological intervention such as cognitive rehabilitation and lifestyle changes should be given greater priority.
- Therefore, healthcare systems must implement comprehensive cognitive rehabilitation programs into stroke recovery.

Conclusion

This systematic review identifies effectiveness of pharmacological and non-pharmacological interventions in controlling PSCI. NMDA receptor antagonists and anti-inflammatory drugs and cholinesterase inhibitors offer benefits in cognition, while non-invasive brain stimulation, acupuncture, and physical combined with cognitive training offer promise as non-drug intervention. Limitations of each approach cause a multimodal treatment strategy that involves pharmacological and nonpharmacological methods to be the most optimal approach to optimizing cognitive recovery. Future work should be aimed at PSCI management and long term outcome and personalized treatment.

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