

What are the effects of pharmacological, non-invasive brain stimulation and psychological interventions, and their combination, in the treatment of post-stroke depression? A Cochrane Review summary with commentary

Ekin Ilke Sen*

Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Abstract.

BACKGROUND: Post-stroke depression (PSD) is a prevalent condition that can significantly influence the recovery process.

OBJECTIVE: To assess the effects of pharmacological, non-invasive brain stimulation and psychological interventions, and their combination on PSD.

METHODS: A summary of the Cochrane Review by Allida et al. (2023), with comments from a rehabilitation perspective.

RESULTS: Sixty-one studies with 5831 participants were included in the Cochrane Review. Very low-certainty evidence indicated favorable treatment effects of pharmacological interventions, psychological therapies, and the combination of pharmacological intervention and non-invasive brain stimulation on PSD. Pharmacological intervention has resulted in increased side effects associated with the central nervous system and gastrointestinal system, with very low-certainty evidence.

CONCLUSION: Evidence for the effectiveness of pharmacological, psychological, and combination therapies for the management of PSD is uncertain, as the quality of the evidence has been assessed as very low. Therefore, further studies with improved methods should investigate pharmacological and non-pharmacological interventions for the treatment of depression in stroke survivors.

Keywords: Depression, stroke, drug intervention, non-invasive brain stimulation, psychological intervention

*Address for correspondence: Ekin Ilke Sen, MD, Associate Professor, Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, 34093 Capa, Istanbul, Turkey. E-mail: ekinozgorgu@gmail.com.

The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review “Pharmacological, non-invasive brain stimulation and psychological interventions, and their combination, for treating depression after stroke” (Allida et al., 2020) by Allida, Hsieh, Cox, Patel, Rouncefield-Swales, Lightbody, House & Hackett.^a, published by the Cochrane Stroke Group. This Cochrane Corner is produced in agreement with NeuroRehabilitation by Cochrane Rehabilitation with views* of the review summary author in the “implications for practice” section.

1. Background

Post-stroke depression (PSD) is a prevalent psychological complication following stroke, significantly contributing to elevated morbidity and premature mortality, and hindering patients’ functional recovery. Therefore, there is a pressing need to establish efficient strategies for identifying and treating PSD. A recent Cochrane Review by Allida et al. (2023), has specifically focused on assessing the effectiveness of pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression among stroke survivors.

Pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression after stroke

(Allida, Hsieh, Cox, Patel, Rouncefield-Swales, Lightbody, House & Hackett, 2023)

2. Objective

The aim of this Cochrane Review was to assess the effects of pharmacological intervention, non-invasive brain stimulation, psychological therapy, or their combinations for treating PSD.

^aThis summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2023, Issue 7, Art. No.: CD003437, DOI: 10.1002/14651858.CD003437.pub5 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

*The views expressed in the summary with commentary are those of the Cochrane Corner author (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

2.1. What was studied and methods

The population addressed in this review was stroke patients with depression. The interventions studied evaluated the effects of pharmacological intervention, psychological intervention, non-invasive brain stimulation, or their combinations in treating depression after a stroke. The control interventions included placebo treatment, sham stimulation, standard/usual care, and attention control. The primary outcomes included the number of individuals meeting depression criteria and with inadequate treatment responses (scoring below 50% of the predetermined scoring threshold) at the end of treatment. The secondary outcomes included depression severity (mean scores at the end of treatment), meeting the criteria for depression at the end of follow-up, psychological distress, anxiety, cognitive function, activities of daily living, disability, neurological function, and adverse events. The review authors searched for relevant randomized controlled trials (RCTs) published until February 2022 in multiple databases.

3. Results

This review included 61 studies with a total of 5831 participants. The findings were as follows:

- Pharmacological interventions reduced the number of stroke survivors who met the criteria for depression at the end of treatment (RR 0.70, 95% CI 0.55 to 0.88; eight RCTs) and were more effective than placebo in decreasing the number of stroke survivors who exhibited an inadequate response to treatment (RR 0.47, 95% CI 0.32 to 0.70; six RCTs) with very low-certainty evidence.
- A greater number of adverse events affecting the central nervous system (RR 1.55, 95% CI 1.12 to 2.15; five RCTs) and gastrointestinal system (RR 1.62, 95% CI 1.19 to 2.19; four RCTs) were observed with the pharmacological intervention than with placebo (very low-certainty evidence).
- Non-invasive brain stimulation had no effect on the number of stroke survivors who met the criteria for depression at the end of treatment (RR 0.67, 95% CI 0.39 to 1.14; two RCTs) or who had an inadequate response to treatment (RR 0.84, 95% CI 0.52 to 1.37; two RCTs) compared to sham stimulation (very low-certainty evidence).

- Psychological therapy reduced the number of stroke survivors who met the criteria for depression at the end of the treatment (RR 0.77, 95% CI 0.62 to 0.95; six RCTs) when compared to usual care or attention control (very low-certainty evidence).
- The combination of pharmacological intervention and non-invasive brain stimulation reduced the number of stroke survivors who met the criteria for depression after stroke at the end of the treatment (RR 0.77, 95% CI 0.64 to 0.91; three RCTs; low-certainty evidence) compared to pharmacological intervention and sham stimulation or usual care. However, it had no impact on those with an inadequate response to treatment (RR 0.95, 95% CI 0.69 to 1.30; three RCTs; very low-certainty evidence) compared to pharmacological intervention alone.
- Primary outcomes were not reported in RCTs examining other combinations of therapies, including pharmacological interventions in conjunction with psychological therapy and non-invasive brain stimulation with psychological therapy.

4. Conclusions

The authors concluded that pharmacological and psychological therapies and their combination may have the potential to decrease the prevalence of PSD based on very low-certainty evidence. They also found very low-certainty evidence that pharmacological intervention increased the risk of central nervous system and gastrointestinal side effects, highlighting the importance of using these drugs with caution. Moreover, there was little evidence for the effectiveness of non-invasive brain stimulation treating depression and the combination of pharmacological intervention with non-invasive brain stimulation in alleviating depressive symptoms after a stroke.

4.1. *Implications for practice in neurorehabilitation*

Since the certainty of the evidence from the RCTs included in the Cochrane Review (Allida et al., 2023) was assessed as very low, it remains uncertain whether pharmacological and psychological interventions and combination therapies, effectively improve PSD. Therefore, it is necessary to conduct adequately powered clinical trials that use clinically

useful primary endpoints, clearly defined treatment protocols, and comprehensively record and report side effects to determine the balance of benefit and risk of interventions to treat PSD.

From a rehabilitation perspective, individuals with PSD face challenges such as increased disability, cognitive impairment, reduced participation in rehabilitation, and less favorable rehabilitation outcomes, ultimately leading to a deterioration in their health-related quality of life (Perna & Harik, 2020). Rehabilitation plays a crucial role in addressing the physical, emotional, and psychological aspects of recovery. Therefore, there is significant uncertainty to warrant research on the effectiveness of rehabilitation interventions, such as exercise (Li et al., 2022), virtual reality-based interventions (Liu et al., 2023), and their combinations with pharmacological, psychological, and non-invasive brain stimulation interventions for treating PSD. Furthermore, incorporating patient-centered outcomes, such as assessing activities of daily living, participation, and health-related quality of life, can facilitate a comprehensive analysis of the effectiveness of these interventions on distinct aspects of disability. In this regard, the Cochrane Review by Legg et al. (2021) extensively evaluates the use of selective serotonin reuptake inhibitors within the first-year post-stroke, specifically focusing on disability and independence outcomes. The insights from studies assessing functioning and disability provide crucial information for clinicians to make informed decisions on tailored treatment options for individuals with PSD.

Conflict of interest

The author declares no conflicts of interest.

Acknowledgments

The author thanks Cochrane Rehabilitation and the corresponding author of the original Cochrane Review, Professor Maree Hackett, for reviewing the contents of the Cochrane Corner.

References

- Allida, S. M., Hsieh, C. F., Cox, K. L., Patel, K., Rouncefield-Swales, A., Lightbody, C. E., House, A., & Hackett, M. L. (2023). Pharmacological, non-invasive brain stimulation and

- psychological interventions, and their combination, for treating depression after stroke. *The Cochrane Database of Systematic Reviews*, 7(7), CD003437.
- Perna, R., & Harik, L. (2020). The role of rehabilitation psychology in stroke care described through case examples. *NeuroRehabilitation*, 46(2), 195–204.
- Li, C., Zhao, M., Sun, T., Guo, J., Wu, M., Li, Y., Luo, H., Wang, X., & Li, J. (2022). Treatment effect of exercise training on post-stroke depression in middle-aged and older adults: A meta-analysis. *International Journal of Geriatric Psychiatry*, 37(9), 10.1002/gps.5798.
- Liu, H., Cheng, Z., Wang, S., & Jia, Y. (2023). Effects of virtual reality-based intervention on depression in stroke patients: A meta-analysis. *Scientific Reports*, 13(1), 4381.
- Legg, L. A., Rudberg, A. S., Hua, X., Wu, S., Hackett, M. L., Tilney, R., Lindgren, L., Kutlubaev, M. A., Hsieh, C. F., Barugh, A. J., Hankey, G. J., Lundström, E., Dennis, M., & Mead, G. E. (2021). Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *The Cochrane Database of Systematic Reviews*, 11(11), CD009286.