

Are antiepileptic drugs effective for the primary and secondary prevention of seizures after stroke? A Cochrane Review summary with commentary

Farooq Azam Rathore^{a,*} and Shaikh Nabi Bukhsh Nazir^b

^a*Armed Forces Institute of Rehabilitation Medicine (AFIRM), Rawalpindi, Pakistan*

^b*Department of Health, Physical Education and Sports Sciences, University of Karachi, Karachi, Pakistan*

Abstract.

BACKGROUND: In post stroke patients, seizures can complicate the recovery process and lead to poor outcomes. It is unclear whether antiepileptic drugs (AEDs) can prevent seizures after a stroke.

OBJECTIVE: To summarize the evidence on the effects of AEDs on the primary and secondary prevention of post stroke seizures.

METHODS: The authors searched the Cochrane Register of Studies and MEDLINE (last search on 9 March 2021), checked the reference lists of articles retrieved and contacted the corresponding authors of the study where needed. Only randomized controlled trials were included (RCT). There were no language and time limits.

RESULTS: Two RCTs with 856 adult participants with a clinical diagnosis of stroke were included. There was moderate-certainty evidence that the AEDs were not effective for primary prevention of post stroke seizures (Relative effect, 95% CI = RR 0.65, 95% CI 0.34 to 1.26). They also did not affect the mortality rate (RR 1.03, 95% CI 0.78 to 1.36). Both studies were at low risk of bias and certainty of the evidence was low to moderate.

CONCLUSION: The evidence for routine use of AED for the primary and secondary prophylaxis of post stroke seizures is unclear. There is a need for high-quality trials to address this question using a larger sample size.

Keywords: Rehabilitation, stroke, epilepsy, mortality

The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review “Antiepileptic drugs for the primary and secondary prevention of seizures after stroke” (Chang,

2022) by Chang et al.^a, published by Cochrane Epilepsy Group. This Cochrane Corner is produced

^aThis summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2022, Issue 2, Art. No.: CD005398. DOI: 10.1002/14651858.CD005398.pub4. (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.

*Address for correspondence: Dr. Farooq Azam Rathore, Consultant, Armed Forces Institute of Rehabilitation Medicine (AFIRM), Rawalpindi, Pakistan. E-mail: farooqrathore@gmail.com.

in agreement with NeuroRehabilitation by Cochrane Rehabilitation with views* of the review summary authors in the “implications for practice” section.

1. Background

Post stroke seizure is defined as a single or multiple convulsive episodes (fits) following a stroke, regardless of the time at which the seizures occur after the stroke.

It is an important post stroke complication which can lead to increased infarct size, mortality, and limited functional recovery (Galovic et al., 2021). Early seizures occur within first week of a stroke, while late seizures occur after first week. Approximately 2% to 6% of people with a stroke experience early seizure, and 3% to 5% have late seizures (Lamy C, 2003).

Antiepileptic drugs (AEDs) are commonly used and are effective in the management of seizures. However, their role in post-stroke seizures is unclear. In addition, they can be potentially harmful due to certain adverse effects and drug interactions. Their exact role in primary and secondary prophylaxis of post-stroke seizures needs to be elucidated.

Antiepileptic drugs for the primary and secondary prevention of seizures after stroke

(Chang RS, Leung WCY, Vassallo M, Sykes L, Battersby Wood E, Kwan J; 2022)

2. Objective

The aim of this Cochrane Review (Chang, 2022) was to summarise the evidence on the effects of antiepileptic drugs for the primary and secondary prevention of seizures after stroke.

2.1. What was studied in the Cochrane review?

This is an updated version of the Cochrane Review previously published in 2014. The review considered only randomised and quasi-randomised controlled trials (RCT) in which participants were assigned to either treatment or control groups. Participants of all ages, with a clinical diagnosis of stroke (ischaemic or haemorrhagic stroke) and any seizure type were included. Studies focusing only on cases of

neurosurgery, subarachnoid haemorrhage, subdural haemorrhage, extradural haemorrhage, or other non-stroke diagnoses such as tumour or infection-related infarction or haemorrhage were excluded. The interventions included antiepileptic drugs. Intervention was compared with placebo or no drug. The primary outcome studied was the number of participants experiencing post-stroke seizures during the follow-up period. Secondary outcomes included proportion of participants who achieved remission of seizures, dropouts from allocated treatment, mortality rate, proportion of dependent or independent post-stroke survivors, US National Institutes of Health Stroke Scale (NIHSS) upon follow-up, quality of life (QoL), duration of stay for the acute phase of stroke recovery and optimal duration of treatment.

2.2. Search methodology of the Cochrane review

The authors searched the Cochrane Register of Studies and MEDLINE (last search on 9 March 2021), checked the reference lists of articles retrieved and contacted the corresponding authors of the study where needed.

3. Results

The review included two RCTs with a total of 856 adult (>18 years) participants. There was moderate-certainty evidence that the AEDs were not effective for primary prevention of post stroke seizures (Relative effect, 95% CI = RR 0.65, 95% CI 0.34 to 1.26). They also did not affect the mortality rate (RR 1.03, 95% CI 0.78 to 1.36). Both studies were at low risk of bias and certainty of the evidence was low to moderate.

3.1. Valproic acid versus placebo

Valproic acid was compared with placebo for primary seizure prevention up to one year after stroke. Oral valproic acid 400 mg twice daily or placebo was given for one month. The study included 72 adults with intracerebral hemorrhage. Risk of post-stroke seizures (RR 0.88, 95% CI 0.35 to 2.16) and mortality rate (RR 1.20, 95% CI 0.40 to 3.58) did not differ. At 12 months, the mean NIHSS score of the valproic acid group was lower at than the placebo group. [4.4 (+/- 4.1) Vs. 8.6 (+/- 6.1)] ($P = 0.002$).

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

3.2. Diazepam versus placebo

In 784 adults with acute stroke, a three-day diazepam treatment was compared to a placebo for primary seizure prevention up to three months after stroke. Rectal diazepam 10 mg or placebo was given within 12 hours after stroke onset, followed by oral 10 mg tablets twice daily for three days. Neither the hemorrhagic nor ischemic stroke subgroups (RR for all strokes 0.47, 95% CI 0.18 to 1.22) showed a difference in the risk of post-stroke seizures. Post-stroke seizures were reduced by primary prophylaxis with diazepam in a subgroup analysis of anterior circulation cortical infarcts. There was no difference between groups in mortality between diazepam and placebo at two weeks and three months follow-up.

Neither study reported data on secondary prevention of post-stroke seizure, proportion of participants who achieved remission, QoL, duration of stay for the acute phase of stroke recovery and optimal duration of treatment.

4. Conclusions

The authors concluded that there is moderate-certainty evidence suggesting that there is no difference between AEDs and placebo in the primary prophylaxis of post-stroke seizure. They suggest conducting better quality RCTs to address this question using larger sample size and using clinically meaningful outcome measures.

4.1. Implications for practice in neurorehabilitation

Patients with stroke after medical stabilization are referred or transferred to rehabilitation wards for comprehensive multidisciplinary stroke rehabilitation. They are primarily under the care of physiatrists and rehabilitation team. These patient during their stay in rehabilitation are at high risk of developing seizures which can adversely affect the rehabilitation process. Some AED like phenytoin, valproate, and carbamazepine can adversely affect cognitive and motor recovery after stroke (Kaur, 2019). It is therefore, important for the rehabilitation professionals

not only to identify patients at risk for developing post stroke seizures but also to optimize their medical management to reduce the risk of post stroke seizures and to enhance the recovery. The evidence regarding the appropriate selection, dosage, and duration of AEDs for post stroke seizures is not clear. It is important for rehabilitation professionals to collaborate with neurologists in research to gain a deeper understanding of the neuro-physiological processes focusing on the need to include cognitive and motor functional outcomes.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors thank Cochrane Rehabilitation and the corresponding author of the original Cochrane review for reviewing the contents of the Cochrane Corner.

References

- Chang, R. S., Leung, W. C., Vassallo, M., Sykes, L., Battersby Wood, E., & Kwan, J. (2022). Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. *The Cochrane Database of Systematic Reviews*, 2(2), CD005398. <https://doi.org/10.1002/14651858.CD005398.pub4>
- Galovic, M., Ferreira-Atuesta, C., Abreira, L., et al. (2021). Seizures and epilepsy after stroke: Epidemiology, biomarkers and management. *Drugs Aging*, 38, 285-299.
- Kaur, U., Chauhan, I., Gambhir, I. S., & Chakrabarti, S. S. (2019). Antiepileptic drug therapy in the elderly: A clinical pharmacological review. *Acta Neurologica Belgica*, 119, 163-173.
- Lamy, C., Domingo, V., Semah, F., Arquizan, C., Trystram, D., Coste, J., et al. (2003). Early and late seizures after cryptogenic ischemic stroke in young adults. *Neurology*, 60(3), 400-404.