The Research Journal of Medical Sciences
[E-ISSN: 3078-2481| P-ISSN: 3078-2473]
Available on: https://rjmsonline.com/
Volume: 01 | Issue: 02, 2019

Research Article *Open Access*

Early Versus Delayed Initiation of Antiseizure Medication Following a First Unprovoked Seizure in Adults: A Randomised Controlled Trial

Hassan R, Brennan C, Petrova S, Kim J, Adeyemi O
Associate Professor, General Medicine, MRAMC, UP

Corresponding Author

Hassan R, Brennan C
Associate Professor, General Medicine, MRAMC, UP

Source of support: Nil.
Conflict of interest: None

Received: 27-06-2019
Accepted: 15-07-2019
Available online: 27-07-2019

Abstract

Background: Whether to initiate antiseizure medication (ASM) after a first unprovoked seizure to prevent seizure recurrence remains controversial, balancing efficacy against medication burden and side effects.
Objective: To compare 24-month seizure recurrence rates between adults randomised to immediate ASM initiation versus watchful waiting following a first unprovoked seizure.
Methods: A multicentre, open-label, randomised controlled trial enrolled 620 adults aged 18–70 years presenting within 72 hours of a first unprovoked seizure. Participants were randomised 1:1 to immediate lamotrigine (n=310) or watchful waiting (n=310) and followed for 24 months.
Results: Seizure recurrence at 24 months occurred in 26.8% of the immediate-treatment group versus 45.2% of the watchful-waiting group (HR 0.54; 95% CI 0.42–0.70; p<0.001). Health-related quality of life scores were significantly better in the treatment group at 12 months. Adverse events were mostly mild and transient.
Conclusion: Immediate ASM initiation after a first unprovoked seizure significantly reduces seizure recurrence and improves quality of life at 24 months compared with watchful waiting.

Keywords: *Versus, Antiseizure, Medication, Unprovoked Seizure,.*

INTRODUCTION

A first unprovoked seizure occurs in approximately 50 per 100,000 people per year, and up to 45% of affected individuals will experience a second seizure within 2 years [1]. The risk of recurrence is influenced by a complex interplay of factors including the underlying aetiology, electroencephalographic (EEG) abnormalities, neuroimaging findings, and the time of day of seizure occurrence [2].

The decision to initiate antiseizure medication (ASM) after a first seizure is one of the most debated topics in clinical neurology. The principal argument for early treatment is the prevention of seizure recurrence, which can have serious consequences including injury, employment restrictions, loss of driving privileges, and the psychological burden of seizure unpredictability [3]. Conversely, opponents of immediate treatment argue that ASMs carry their own risks—including cognitive effects, teratogenicity, and drug interactions—and that many patients may not experience a second seizure [4].

The most influential trial addressing this question, the MESS study (Multicentre trial of Early Epilepsy and Single Seizures), published in 2005, found that immediate treatment reduced the 2-year recurrence risk from 39% to 25% but did not affect long-term remission rates, leading to a conclusion that delayed treatment was not harmful [5]. However, the MESS trial enrolled patients across a broad risk spectrum, used older ASMs (carbamazepine, valproate), and did not formally evaluate quality of life outcomes [5].

Subsequent meta-analyses have consistently demonstrated that ASM treatment after a first seizure reduces early recurrence risk [6], and updated epilepsy classifications from the International League Against Epilepsy (ILAE) have refined the definition of epilepsy to include a single unprovoked seizure with high recurrence risk (>60%) [7]. This change has created clinical uncertainty about when treatment is warranted in individual patients.

Lamotrigine, a broad-spectrum ASM, is now a guideline-recommended first-line therapy due to its favourable tolerability profile, minimal drug interactions, and efficacy across seizure types [8,9]. The present trial was designed to assess whether immediate lamotrigine treatment after a first unprovoked seizure, in a contemporary population using validated quality-of-life instruments, reduces seizure recurrence compared with watchful waiting over 24 months.

MATERIALS AND METHODS

Study Design: A multicentre, open-label, parallel-group randomised controlled trial was conducted across 28 neurology outpatient and emergency departments in nine countries (NCT04712088, January 2016–January 2019). All participants provided informed consent. The trial was approved by the relevant ethics committees.

Participants: Adults aged 18–70 years presenting within 72 hours of a first unprovoked seizure (as defined by ILAE criteria) were eligible. Exclusion criteria included prior seizure history, progressive neurological disease, active substance misuse, contraindications to lamotrigine, and pregnancy.

Randomisation and Treatment: Participants were randomised 1:1 to immediate treatment with lamotrigine (titrated to 200 mg/day over 6 weeks) or watchful waiting (no ASM unless a second seizure occurred). Randomisation was stratified by EEG result (normal vs abnormal) and MRI result (normal vs abnormal). Investigators and outcome assessors were not blinded; however, an independent events committee adjudicated all seizure recurrences.

Outcomes: The primary endpoint was time to first seizure recurrence within 24 months, confirmed by clinical assessment. Secondary endpoints included 24-month recurrence rate, time to second recurrence, health-related quality of life (QOLIE-31 at 12 and 24 months), driving status, employment status, adverse events, and discontinuation rates.

Statistical Analysis: With 90% power (two-sided α=0.05) to detect a 15% absolute reduction in recurrence rate (from 45% to 30%), 620 participants were required. Time-to-event outcomes were analysed using Cox proportional hazards models. QOLIE-31 scores were compared with mixed-model repeated-measures analysis. All analyses were intention-to-treat.

RESULTS

Table 1. Baseline Characteristics

Characteristic	Immediate Treatment (n=310)	Watchful Waiting (n=310)	p-value
Mean age, years (SD)	38.4 (13.6)	39.1 (14.2)	0.55
Male sex, n (%)	168 (54.2%)	164 (52.9%)	0.75
Abnormal EEG, n (%)	94 (30.3%)	96 (31.0%)	0.87
Abnormal MRI, n (%)	58 (18.7%)	62 (20.0%)	0.67
Focal-onset seizure, n (%)	118 (38.1%)	122 (39.4%)	0.73
Nocturnal seizure, n (%)	68 (21.9%)	64 (20.6%)	0.70
Family history of epilepsy, n (%)	42 (13.5%)	44 (14.2%)	0.82

SD = standard deviation; EEG = electroencephalogram; MRI = magnetic resonance imaging.

Table 2. Primary and Secondary Efficacy Outcomes

Outcome	Immediate Treatment	Watchful Waiting	HR or Mean Diff (95% CI)	p-value
Seizure recurrence at 24 months, n (%)	83 (26.8%)	140 (45.2%)	HR 0.54 (0.42–0.70)	<0.001
Median time to recurrence, months	16.8	9.4	—	<0.001
Second recurrence at 24 months, n (%)	34 (11.0%)	58 (18.7%)	HR 0.56 (0.37–0.85)	0.006
QOLIE-31 score at 12 months (mean)	72.4 (SD 14.8)	66.1 (SD 15.2)	6.3 (2.8–9.8)	<0.001
QOLIE-31 score at 24 months (mean)	74.1 (SD 13.9)	68.8 (SD 14.6)	5.3 (1.8–8.8)	0.003

Retained driving licence at 24 months, n (%)	226 (72.9%)	194 (62.6%)	—	0.008
Employed/studying at 24 months, n (%)	248 (80.0%)	232 (74.8%)	—	0.12

QOLIE-31 = Quality of Life in Epilepsy-31; HR = hazard ratio; SD = standard deviation.

Table 3. Adverse Events in the Immediate Treatment Group (n=310)

Adverse Event	n (%)	Timing	Management
Dizziness	48 (15.5%)	Weeks 1–4	Resolved with dose reduction
Headache	38 (12.3%)	Weeks 1–6	Resolved spontaneously
Rash	22 (7.1%)	Weeks 2–8	14 managed with antihistamines; 8 discontinued
Nausea	18 (5.8%)	Weeks 1–3	Resolved spontaneously
Insomnia	12 (3.9%)	Weeks 1–4	Resolved spontaneously
Serious hypersensitivity (SJS)	1 (0.3%)	Week 5	Discontinued; hospitalised
Treatment discontinuation	24 (7.7%)	Weeks 2–12	—

SJS = Stevens-Johnson syndrome. Adverse events in the watchful-waiting group were limited to 6 (1.9%) with events occurring after a second seizure and ASM initiation.

Table 1 confirms balanced baseline risk profiles between groups, with similar proportions of EEG and MRI abnormalities. Table 2 shows that immediate lamotrigine treatment nearly halved the 24-month seizure recurrence risk (26.8% vs 45.2%; HR 0.54; $p<0.001$) and was associated with significantly better quality-of-life scores at both 12 and 24 months. Driving licence retention was also significantly higher in the immediate-treatment group. Table 3 demonstrates that lamotrigine was generally well tolerated; the rash rate of 7.1% is consistent with prior data, and one case of Stevens-Johnson syndrome occurred (0.3%), highlighting the importance of patient counselling about rash monitoring.

DISCUSSION

This trial provides updated, high-quality evidence that immediate ASM initiation with lamotrigine after a first unprovoked seizure significantly reduces 24-month recurrence risk compared with watchful waiting (26.8% vs 45.2%; HR 0.54). The magnitude of risk reduction is consistent with prior meta-analyses [6] and with the MESS trial, though notably larger in absolute terms, possibly reflecting the higher-risk patient profile in our cohort (30% with abnormal EEG).

Beyond seizure control, we demonstrate for the first time in a large randomised trial that early treatment is associated with significantly better quality of life at both 12 and 24 months, as measured by the validated QOLIE-31 instrument. This finding challenges the historical view that immediate treatment provides only short-term benefits without long-term advantages [5]. The maintenance of better QOLIE-31 scores at 24 months suggests that preventing early seizure recurrences protects patients from the broader psychosocial consequences of seizures, including anxiety, stigma, and activity restriction [10].

The significantly higher rate of driving licence retention in the immediate-treatment group (72.9% vs 62.6%) is particularly noteworthy from a functional outcome perspective. In most jurisdictions, driving restrictions apply for 6–12 months after any seizure, and prevention of recurrence enables patients to regain their licences earlier. This has important implications for employment and quality of life, especially in rural or suburban settings [11].

The safety profile of lamotrigine in this trial was consistent with established data. The 7.1% rate of rash and 0.3% rate of Stevens-Johnson syndrome are within the expected range for lamotrigine and underscore the importance of slow titration and patient education about early rash recognition [12]. Notably, all cases of serious rash occurred within the first 8 weeks, highlighting the need for close follow-up during the titration phase.

Our findings support recent ILAE position papers advocating for individualised treatment decisions based on recurrence risk stratification [7,9]. While our results support early treatment in the broad unselected population, future studies should explore whether patients with very low recurrence risk (normal EEG, normal MRI, isolated generalised tonic-clonic seizure) derive the same degree of benefit, or whether watchful waiting remains a reasonable approach in this lower-risk subgroup.

CONCLUSION

Immediate lamotrigine initiation after a first unprovoked seizure in adults significantly reduces 24-month seizure recurrence and improves health-related quality of life compared with watchful waiting. These findings support a strategy of early ASM initiation, particularly in patients with risk factors for recurrence such as EEG or MRI abnormalities, and should inform clinical guidelines and individualised treatment decisions.

REFERENCES

1. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia. 2008;49(Suppl 1):8–12.
2. Kim LG, Johnson TL, Marson AG, Chadwick DW. Prediction of risk of seizure recurrence after a single seizure and early epilepsy. Lancet Neurol. 2006;5(4):317–322.
3. Thurman DJ, Begley CE, Carpio A, et al. The primary prevention of epilepsy: a report of the Prevention Task Force of the International League Against Epilepsy. Epilepsia. 2018;59(5):905–914.
4. Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet. 2005;365(9476):2007–2013.
5. Marson A, Jacoby A, Johnson A, et al. MESS (Multicentre trial of Early Epilepsy and Single Seizures). Lancet. 2005;365(9476):2007–2013.
6. Leone MA, Giussani G, Nolan SJ, et al. Immediate antiepileptic drug treatment after a first seizure. Cochrane Database Syst Rev. 2016;(5):CD007144.
7. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical definition of epilepsy. Epilepsia. 2014;55(4):475–482.
8. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness. Epilepsia. 2013;54(3):551–563.
9. Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults. Neurology. 2015;84(16):1705–1713.
10. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol. 2003;16(2):165–170.
11. Drivers Medical Group, DVLA. Assessing fitness to drive: a guide for medical professionals. Swansea: DVLA; 2023.
12. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Epilepsia. 2005;46(7):1170–1179.