RESEARCH ARTICLE

Effectiveness of Levetiracetam vs Valproic Acid for Poststroke Seizure

A Population-Based Study Using a Target Trial Emulation Framework

Hsin-Yi Huang[1,2] and Chi-Chuan Wang[2,3,4]

Neurology® 2025;105:e214319. doi:10.1212/WNL.0000000000214319

Correspondence
Dr. Wang
chicwang@ntu.edu.tw

Abstract

Background and Objectives

Evidence on levetiracetam for poststroke seizures is limited. Understanding whether levetiracetam effectively manages poststroke seizures is important for improving prognosis and preventing further complications in stroke patients. The aim of this study was to assess the risk of seizure rehospitalization between levetiracetam and valproic acid in patients with poststroke seizures.

Methods

Using data from Taiwan's National Health Insurance Research Database, this observational retrospective cohort study followed the target trial emulation framework to emulate a hypothetical randomized trial estimating the effect of levetiracetam for poststroke seizure management. Eligible patients were those who were hospitalized for their first seizure event (index seizure) between January 1, 2012, and December 31, 2020, and were newly prescribed levetiracetam or valproic acid monotherapy before discharge. Patients should have had a stroke-related hospitalization within 2 years before the seizure. Patients prescribed levetiracetam were assigned to the exposure group, whereas those prescribed valproic acid were assigned to the reference group, based on their first prescription after the index seizure. Inverse probability–weighted marginal structural models were used to assess outcomes between levetiracetam and valproic acid, including seizure rehospitalization as the primary outcome. Secondary outcomes included all-cause mortality and a composite of seizure rehospitalization and all-cause mortality. Both baseline and time-varying confounders were adjusted in the models.

Results

The final sample included 740 levetiracetam users (48.5%) and 786 valproic acid users, with a mean age of 67.2 years in both groups and a similar proportion of men (59.9% for levetiracetam; 61.3% for valproic acid). In the primary outcome analysis, levetiracetam use was associated with a lower risk of seizure rehospitalization compared with valproic acid (hazard ratio 0.78; 95% CI 0.64–0.95). In secondary outcome analyses, no significant differences were observed in all-cause mortality or the composite of seizure rehospitalization and all-cause mortality.

Discussion

Levetiracetam was associated with a lower risk of seizure rehospitalization, with no significant difference in the risk of all-cause mortality. These findings support levetiracetam as a potentially suitable treatment option for patients with poststroke seizures. As this study focused on monotherapy, future investigations should further explore combination antiseizure medication regimens involving levetiracetam.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Supplementary Material

[1]Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Health Care Institute, Boston, MA; [2]School of Pharmacy, College of Medicine, National Taiwan University, Taipei; [3]Department of Pharmacy, National Taiwan University Hospital, Taipei; and [4]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei.

Glossary

ASM = antiseizure medication; **DAG** = directed acyclic graph; **HR** = hazard ratio; **ICD-9-CM/10-CM** = International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification; **IPTW** = inverse probability of treatment weighting; **IPW** = inverse probability–weighted; **NHIRD** = National Health and Insurance Research Database; **SIPTW** = stabilized inverse probability weighting.

Classification of Evidence

This study provides Class II evidence that levetiracetam is associated with a lower risk of seizure rehospitalization compared with valproic acid in patients with post-stroke seizures.

Introduction

Post-stroke seizures are a common complication that often occurs after a cerebrovascular stroke.[1] Understanding the optimal antiseizure medication (ASM) regimen for patients with post-stroke seizure is crucial for improving prognosis and preventing further complications associated with seizures. Poorly controlled post-stroke seizures can affect quality of life, worsen functional outcomes, and increase risk of all-cause mortality.[2,3] Despite ASM treatment, more than one-third of patients with post-stroke seizure continue to experience uncontrolled seizures.[4] Therefore, choosing an effective ASM regimen remains challenging but is crucial for improving long-term outcomes in patients with post-stroke seizures.

Levetiracetam offers advantages in treating patients with post-stroke seizure because of its safety profile and stable pharmacokinetic properties. As a newer-generation ASM with a broad-spectrum antiseizure effect, levetiracetam was approved for managing various type of seizures.[5-9] Compared with older-generation ASMs, levetiracetam has fewer drug-drug interactions and adverse effects.[6] Given that stroke patients often have multiple comorbidities and receive polypharmacy, it is important to be aware of the potential drug interactions and serious adverse effects from ASMs.[10,11] Therefore, levetiracetam seems to be an ideal choice of ASM for patients with post-stroke seizure.

It is not fully understood whether levetiracetam is comparable to older-generation ASMs, such as valproic acid, in managing post-stroke seizures. The PROgnosis of Post-Stroke Epilepsy study reported a lower seizure recurrence rate associated with newer-generation ASMs compared with the older-generation ASMs,[12] but it did not specifically focus on levetiracetam. A population-based study found that both valproic acid and newer-generation ASMs were associated with a lower risk of seizure rehospitalization compared with phenytoin.[13] However, there is a lack of direct comparison between levetiracetam and valproic acid. Currently, both levetiracetam (a newer-generation ASM) and valproic acid (an older-generation ASM) are commonly prescribed for patients with post-stroke seizures.[14] Hence, it is necessary to conduct a longitudinal study that directly compares effectiveness of levetiracetam and valproic acid in patients with post-stroke seizures.

This population-based, real-world, observational study followed a target trial emulation framework[15] to directly compare levetiracetam with valproic acid in patients with post-stroke seizures. The primary research question was whether treatment with levetiracetam, compared with valproic acid, is associated with a lower risk of seizure rehospitalization in patients with post-stroke seizures. The findings from this study provide clinical insights into the suitability of levetiracetam for treating post-stroke seizures.

Methods

This study followed a 2-step target trial emulation framework.[15,16] First, we defined a hypothetical randomized clinical trial (target trial) to estimate the effect of levetiracetam vs valproic acid monotherapy for post-stroke seizure management. In the second step, we emulated the target trial protocol using real-world observational data.

Hypothetical Randomized Clinical Trial

In this hypothetical randomized clinical trial, eligible participants would be patients aged 18 years or older who experienced their first seizure hospitalization after a previous stroke within the past 2 years. To meet the eligibility criteria, patients must have undergone a washout period of at least 6 months without any ASM use before enrollment. Participants would be randomly assigned to receive either levetiracetam or valproic acid monotherapy on hospital discharge and followed prospectively for seizure-related outcomes, including seizure rehospitalization, all-cause mortality, a composite of seizure rehospitalization and all-cause mortality, and changes in ASM regimen. Follow-up would continue from the hospital discharge until death or the end of the study period. Table 1 provides the detailed comparison of the protocol between the hypothetical randomized clinical trial and the target trial emulation using observational data.

Table 1 Comparison of the Protocol Between the Hypothetical Randomized Clinical Trial and the Target Trial Emulation Using Observational Data

Protocol	Hypothetical randomized clinical trial	Target trial emulation using observational data
Eligibility criteria	Adults (≥18 years old) hospitalized for a first seizure event	Adults (≥18 years old) with a first primary diagnosis of seizure recorded during emergency department visits or inpatient discharges between January 1, 2012, and December 31, 2020, as identified in the National Health Insurance Research Database in Taiwan
	Have had at least 1 stroke-related hospitalization within 2 y preceding the first seizure hospitalization	Same
	No previous use of levetiracetam, valproic acid, or any ASM within 6 mo before seizure hospitalization	Same
	Exclusion of patients with acute early-onset seizures occurring within 7 d of stroke	Same
	No history of conditions that could trigger seizures (e.g., CNS infections, encephalopathy, and traumatic brain injury)	Same
Treatment assignment	Participants were randomly assigned to levetiracetam or valproic acid monotherapy at hospital discharge	In observational data, treatment groups were determined based on the first prescribed levetiracetam or valproic acid monotherapy at discharge
Follow-up period	Followed from hospital discharge until death or the administrative end of study	Same
Outcomes	Seizure rehospitalization	Same
	All-cause mortality	Same
	Composite of seizure rehospitalization or all-cause mortality	Same
	Changes in ASM regimen (switching or augmentation)	Assessed only in sensitivity analyses using IPTW or SIPTW
Causal contrasts of interest	Intention-to-treat effect	(1) Main analysis using marginal structural models: Hypothetical sustained treatment effect: Using IPW marginal structural models to estimate the effect that would have been observed if all patients had remained on their initially assigned treatment, accounting for baseline treatment selection and treatment deviation weights. We modeled the probability of remaining on treatment and incorporated this into the weights, using both baseline and time-varying covariates. (2) Sensitivity analysis using IPTW or SIPTW: Intention-to-treat effect: Estimated using IPTW or SIPTW based on baseline covariates only.

Abbreviations: ASM = antiseizure medication; IPTW = inverse probability of treatment weighting; SIPTW = stabilized inverse probability of treatment weighting.

Emulating the Targeted Randomized Clinical Trial Using Observational Data

The Observational Database

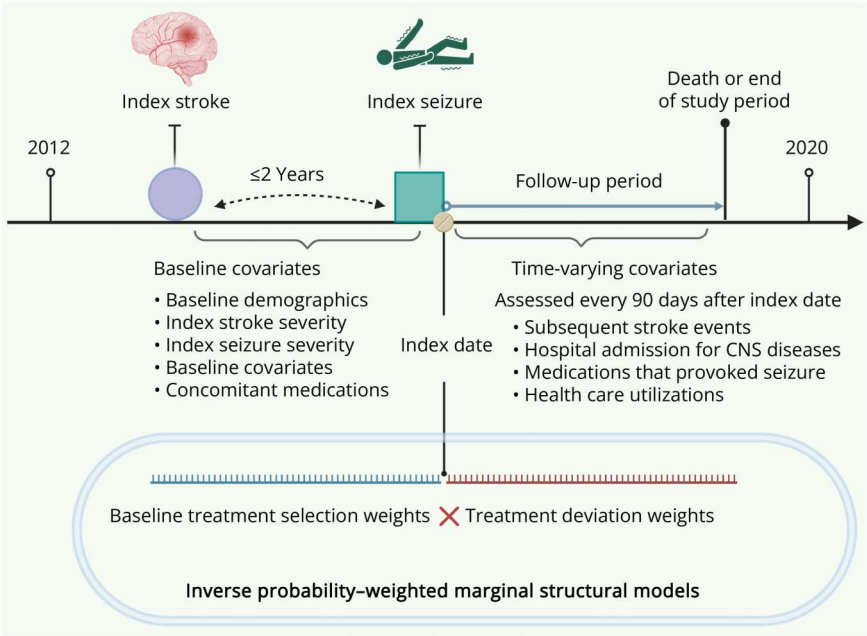
We used the full-population data of the National Health and Insurance Research Database (NHIRD) in Taiwan as the observational database for this study.[17] The NHIRD contains beneficiaries' inpatient and outpatient diagnoses, drug prescriptions, pharmacy dispensing reports, procedures, social demographics, and insurance enrollment information for more than 23 million enrollees in Taiwan.[17] Data from 2010 to 2020 were used for this study.

Eligibility Criteria

Eligible patients were at least 18 years old and had a first primary diagnosis of seizure (ICD-9-CM: 345.x; ICD-10-CM: G40.x, G41.x) recorded during emergency department visits or inpatient discharges between January 1, 2012, and December 31, 2020. Patients were newly prescribed with either monotherapy levetiracetam or valproic acid before discharge. To confirm the diagnosis of post-stroke seizures, patients must have had at least 1 stroke-related hospitalization within 2 years preceding the first seizure diagnosis. Stroke had to be the primary discharge diagnosis from an inpatient admission, including acute ischemic stroke (ICD-9-CM: 433.x, 434.x; ICD-10-CM: I63.x), intracranial hemorrhage (ICD-9-CM: 431.x; ICD-10-CM: I61.x, I62.x), or subarachnoid hemorrhage (ICD-9-CM: 430.x; ICD-10-CM: I60.x). Figure 1 illustrates the design of this emulated study using observational data. The first seizure hospitalization was defined as the "index seizure" while the discharge date from this hospitalization was designated as the "index date." The nearest stroke hospitalization occurring within 2 years preceding the index seizure was identified as the "index stroke." Patients were followed from the index date until death or the end of the available data period (December 31, 2020).

Patients were excluded if they had been prescribed levetiracetam, valproic acid, or any other ASMs, or had any seizure

Figure 1 Illustration of the Emulated Study Design Using Observational Data and the Implementation of Inverse Probability–Weighted Marginal Structural Models



diagnosis within 6 months before the index seizure. To ensure monotherapy with levetiracetam or valproic acid, patients were excluded if they were concomitantly prescribed both levetiracetam and valproic acid, or received any other ASMs during the index seizure hospitalization. In addition, patients were excluded if the index seizure occurred within 7 days of the index stroke, as these were likely acute early-onset seizures, which were not the focus of our study because of potentially different outcomes compared with seizures occurring after 7 days.[18,19] Patients were also excluded if they had conditions during the index seizure hospitalization that could trigger seizures, such as CNS infection, encephalitis, or traumatic brain injury.[20-22] Patients who died during the index seizure hospitalization were also excluded.

Exposure and Reference Groups

Patients prescribed monotherapy levetiracetam were assigned to the exposure group, whereas those prescribed monotherapy valproic acid were assigned to the reference group, based on their first prescription after the index seizure. Valproic acid was chosen as an active comparator because it is an older-generation ASM with a broad spectrum of antiseizure effects and serves a similar role to levetiracetam in seizure control.[23]

Outcome Measures

The primary outcome was seizure rehospitalization. Secondary outcomes included all-cause mortality and a composite of seizure rehospitalization and all-cause mortality. Seizure rehospitalization was defined as patients having a primary diagnosis of seizure during emergency department visits or inpatient admission after the index date. All-cause mortality was ascertained from Taiwan's National Cause of Death Database. The composite of seizure rehospitalization and all-cause mortality was included to reflect both seizure control and survival outcomes after initiating levetiracetam or valproic acid.

Covariates

Baseline Covariates

Baseline covariates were selected based on their potential to influence both choice of ASM regimen and seizure-related outcomes. These included demographic characteristics (e.g., age and sex); clinical timing (e.g., time from the index stroke to the index seizure); severity of the index stroke or index seizure; and relevant comorbidities and concomitant medications that may affect ASM treatment tolerability, risk of adverse effects, potential drug interactions, or seizure recurrence.

Index stroke severity and associated management were identified during the index stroke hospitalization, including year of the index stroke (e.g., 2010–2015 or 2016–2020), stroke subtypes (i.e., ischemic stroke, intracranial hemorrhage, and subarachnoid hemorrhage), receipt of intracranial surgery, and the risk score of post-stroke seizure development within 1 year after stroke (i.e., PSEiCARe score). The PSEiCARe score was derived and validated from the study using NHIRD.[24]

Covariates representing the severity of the index seizure and associated management were identified from the index seizure

hospitalization. These included types of hospitalization (e.g., seizures resulting in an inpatient admission or emergency department visit), length of hospital stay for index seizure, receipt of IV sedative agents (e.g., benzodiazepines, propofol, dexmedetomidine, ketamine, or pentobarbital), receipt of IV levetiracetam or valproic acid, and use of continuous electroencephalography monitoring. We adjusted for covariates such as the administration of IV sedative agents, IV study drugs, and use of continuous electroencephalography monitoring to account for the likelihood of status epilepticus, a severe type of seizure associated with poor prognosis.[25]

Baseline comorbidities, identified within 2 years before the index seizure, were selected because they may influence both treatment selection and seizure outcomes. The included comorbidities were hypertension, atrial fibrillation, ventricular arrhythmias, coronary artery disease, dyslipidemia, diabetes mellitus, dementia, liver diseases, chronic kidney diseases, psychiatric disorders, autoimmune diseases, and brain tumors. Baseline concomitant medications, identified within 90 days before the index date, were included to capture potential drug interactions and to serve as proxies for underlying clinical conditions that may influence ASM selection or seizure risk. The concomitant medications included benzodiazepines, antidepressants, antipsychotics, methylphenidate, carbapenem, cephalosporins, xanthine derivatives, tramadol, statins, warfarin, and non–vitamin K antagonists.

Time-Varying Covariates

Time-varying covariates were assessed every 90 days after the index date. We measured subsequent stroke events after the index date because these could further increase the risk of seizure recurrence. In addition, we measured subsequent hospitalizations for CNS infections, encephalitis, traumatic brain injury, and brain surgery because these events may alter seizure risk and ASM treatment strategies. We also measured the use of medications such as carbapenem, cephalosporin, tramadol, xanthine derivatives, and statins because these were associated with higher seizure risks. Health care utilization factors, including records of inpatient admission and emergency department visits within each 90-day interval, were also treated as time-varying covariates.

To support variable selection and clarify hypothesized causal relationships, a directed acyclic graph (DAG) is presented in eTable 1. The DAG illustrates the relationships among baseline and time-varying covariates, initial ASM selection, subsequent ASM treatment deviations, and outcomes.

Statistical Analysis

This study used secondary health care claims data and causal inference methods to understand a broad population-based real-world clinical effect. The secondary health care claims data were analyzed retrospectively within the targeted cohort. We used inverse probability–weighted (IPW) marginal structural models[26] to control for potential confounding that influences both the probability of initial treatment selection and subsequent treatment deviations. Marginal structural models enable the estimation of causal effects in the presence of both baseline and time-varying covariates.[27] Our main analysis estimated a hypothetical sustained treatment effect,[28,29] defined as the effect that would have been observed if all patients had remained on their initially assigned treatment throughout follow-up. Although this effect shares conceptual similarities to a per-protocol contrast, it differs in a key way: instead of censoring individuals at the time of treatment deviation, we retained all outcome data and modeled the probability of remaining on the assigned treatment. These probabilities were incorporated as weights in marginal structural models.[27-29]

The IPW marginal structural model analysis consisted of 2 main phases: weight estimation and outcome analysis. eTable 1 summarizes the specification of models used for weight estimation. In the weight estimation phase, inverse probability weights were constructed by multiplying 2 components: the baseline treatment selection weights and the treatment deviation weights.[30] Baseline treatment selection weights were estimated from baseline covariates using logistic regression models. Treatment deviation weights were derived to account for both baseline and time-varying covariates, using logistic regression models with generalized estimating equations to adjust for within-participant correlations due to repeated measures. To reflect distinct clinical scenarios and underlying implications, treatment deviation weights were constructed separately for different types of deviations: (1) switching or augmentation with an alternative ASM and (2) discontinuation of ASM treatment. These scenarios warranted separate modeling strategies: switching and augmentation often indicate suboptimal seizure control or tolerability issues requiring active treatment adjustment, whereas discontinuation may reflect a planned decision after seizure resolution. eFigure 1 illustrates the definitions of treatment deviation scenarios, including switching, augmentation, and discontinuation.

In the outcome analysis phase, the combined weights were incorporated into Cox proportional hazard models to estimate the time-to-event HRs and 95% CIs for outcomes of interest between the exposure and comparison groups. In addition, the combined weights were applied to Poisson regression models to estimate incidence rates for both groups. To visualize the adjusted survival curves for each outcome over time, we constructed inverse probability–weighted survival curves using the combined weights derived from the marginal structural models. All analyses in this study were conducted using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

Sensitivity Analysis

In the sensitivity analysis, 2 approaches, inverse probability of treatment weighting (IPTW) and stabilized inverse probability of treatment weighting (SIPTW), were applied separately to replicate the main analysis. The effect estimand in

both IPTW and SIPTW sensitivity analyses reflected an intention-to-treat contrast. These models did not use the marginal structural model framework; instead, they applied inverse probability treatment weights derived solely on baseline covariates. This allowed us to test the robustness of our findings and assess whether including time-varying covariates in the marginal structural model influenced the results. In addition to evaluating the same outcomes as in the main analysis, the IPTW and SIPTW sensitivity analyses also examined the risk of changes in ASM regimen, defined as switching to an alternative ASM or adding another ASM (augmentation) for seizure management. This outcome reflects the stability of ASM use and indicates potential need for further treatment adjustments in patients who experience adverse effects or seizure recurrence.[4]

Standard Protocol Approvals, Registrations, and Patient Consents

This study was reviewed and approved from the Research Ethics Committee A of the National Taiwan University Hospital (NTUH-REC No.: 202312122W) and conforms to the provisions of the Declaration of Helsinki. The participant consent was not required and waived by the Research Ethics Committee A of the National Taiwan University Hospital.

Data Availability

The data sets analyzed during this study are not publicly available because of legal restrictions by Taiwan's policy. Data are available from the corresponding author on reasonable request and with permission from the Health and Welfare Data Science Center, Ministry of Health and Welfare in Taiwan.

Results

A total of 1,526 patients experienced post-stroke seizures between January 1, 2012, and December 31, 2020, and met the study criteria. Among them, 740 (48.5%) were levetiracetam users and 786 (51.5%) were valproic acid users. Figure 2 displays the cohort inclusion and exclusion flowcharts. Levetiracetam users had a more recent index stroke year (i.e., 2016–2020) compared with valproic acid users, along with higher rates of liver diseases and greater concomitant use of tramadol and non–vitamin K antagonists at baseline. By contrast, valproic acid users were more likely to undergo intracranial surgery during the index stroke and had a higher prevalence of autoimmune diseases at baseline compared with levetiracetam users. Table 2 presents the baseline characteristics of the cohort.

Table 3 presents the estimated events, incidence rates, and hazard ratios (HRs) for each outcome from the marginal structural model analysis, and eFigure 2 shows the inverse probability–weighted survival curves for each outcome. For the primary outcome, levetiracetam use was associated with a lower risk of seizure rehospitalization compared with valproic acid (HR 0.78; 95% CI 0.64–0.95; $p = 0.01$). No significant differences were observed between the 2 groups for the secondary outcomes of all-cause mortality or the composite of seizure rehospitalization and all-cause mortality.

In the sensitivity analysis using the IPTW and SIPTW approaches without considering time-varying covariates, the findings were generally consistent with the main analysis. Baseline characteristics were well balanced after applying both IPTW and SIPTW approaches, with an absolute standardized mean difference <0.1 for all covariates. eTables 2 and 3 summarize the baseline characteristics of the study cohort after IPTW and SIPTW analyses. In the IPTW analysis (Table 4), levetiracetam was associated with a lower risk of seizure rehospitalization (HR 0.85; 95% CI 0.72–0.99; $p = 0.04$) and changes in ASM regimen (HR 0.66; 95% CI 0.57–0.77; $p < 0.001$). The risks of all-cause mortality and the composite of seizure rehospitalization and all-cause mortality did not differ significantly between the 2 groups. Similarly, in the SIPTW analysis (Table 4), levetiracetam was associated with a significantly lower risk of changes in ASM regimen compared with valproic acid (HR 0.66; 95% CI 0.53–0.82; $p < 0.001$). However, the risks of seizure rehospitalization, all-cause mortality, and the composite of seizure rehospitalization and all-cause mortality were not significantly different between the 2 groups.

Classification of Evidence

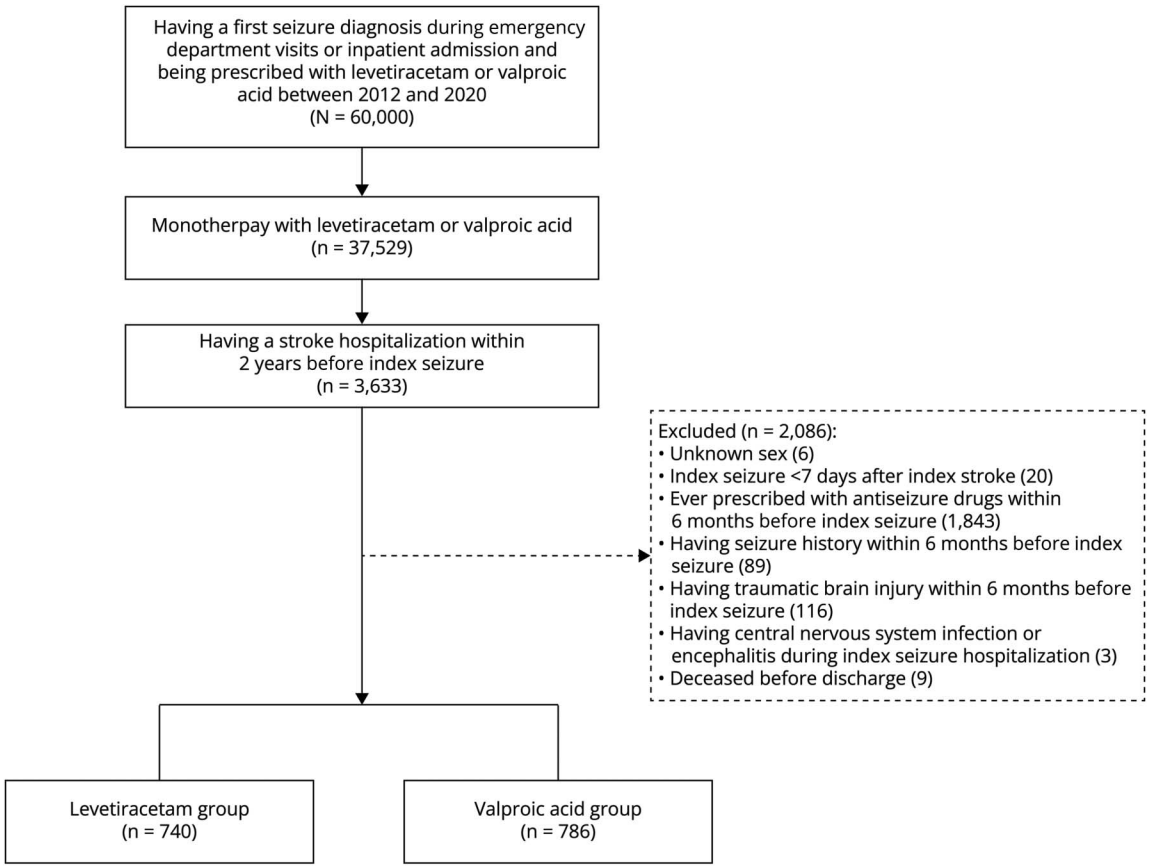
This study provides Class II evidence that levetiracetam is associated with a lower risk of seizure rehospitalization compared with valproic acid in patients with post-stroke seizures.

Discussion

Our study compared the newer-generation ASM, levetiracetam, with the older-generation ASM, valproic acid, for the treatment of new-onset post-stroke seizures. We found that levetiracetam was associated with lower risks of seizure rehospitalization, while demonstrating similar risks of all-cause mortality and the composite outcome of seizure rehospitalization and all-cause mortality compared with valproic acid. In sensitivity analyses, levetiracetam use was also associated with a lower risk of changes in ASM regimen. These findings contribute to the growing body of evidence supporting levetiracetam as a suitable option for managing post-stroke seizures.

Our findings that levetiracetam effectively controls seizures by reducing the risk of seizure rehospitalization align with previous studies. A network meta-analysis comparing 13 ASMs across 15 studies found that levetiracetam was associated with a lower risk of seizure recurrence and treatment discontinuation compared with valproic acid.[31] A randomized, open-label study comparing levetiracetam with an older-generation ASM, carbamazepine, in patients with post-stroke seizure

Figure 2 Cohort Inclusion and Exclusion Flowchart



found that the time to the first seizure recurrence was longer in the levetiracetam group.[32] However, the study was conducted 20 years ago, and seizure management strategies have since evolved.[23,33] Another prospective observational study suggested that levetiracetam could effectively control post-stroke seizure recurrence,[34] with 77% of patients remaining seizure-free during an 18-month follow-up. It is important to note that this study had a limited sample size of only 35 patients and did not provide comparisons with other ASMs or adjust for covariates to account for potential biases. Altogether, our study not only reinforces existing evidence supporting levetiracetam use in controlling post-stroke seizures but also builds on it by using a larger real-word cohort, incorporating contemporary seizure management strategies, and applying causal inference methods.

This study did not find a significant difference in all-cause mortality between levetiracetam and valproic acid, whereas a network meta-analysis[31] reported a significantly reduced mortality risk associated with levetiracetam compared with valproic acid. This discrepancy may be attributed to differences in study design, population characteristics, and analytic methods. Our use of a well-defined target trial emulation and causal inference methods may have addressed residual confounding differently from the traditional observational studies[35] contributing to the meta-analysis. Moreover, local prescribing practices and patient selection under Taiwan's reimbursement policies may have influenced the observed mortality risk, as clinicians may avoid prescribing valproic acid to frail or high-risk patients (e.g., those with hepatic dysfunction or significant drug interactions),[36] resulting in a more balanced risk profile between the 2 treatment groups.

The sensitivity analysis using both the IPTW and SIPTW approaches yielded findings consistent with our main analysis, supporting the robustness of our main study results. Both IPTW and SIPTW analyses reflected an intention-to-treat contrast and applied weights based on baseline covariates, without accounting for time-varying covariates. The consistency of these results indicates that the effectiveness of levetiracetam use in managing post-stroke seizures remains stable, regardless of the changes in patient characteristics or clinical factors over time. In addition, the sensitivity analyses also indicated that levetiracetam users were more likely to persist with their initial treatment without switching or augmenting therapy, reflecting greater treatment stability. This may be attributed to levetiracetam's favorable tolerability profile and lower risk of adverse effects, consistent with findings from network meta-analyses suggesting that valproic acid is more likely to be discontinued.[31] Overall, the findings across multiple sensitivity analyses reinforces the robustness of our conclusions and suggests that the observed benefits of

Table 2 Baseline Characteristics Before Marginal Structural Model Weighting Among Levetiracetam and Valproic Acid Users With Poststroke Seizures

	Levetiracetam		Valproic acid	
	N = 740	%	N = 786	%
Baseline demographics				
Age, y, mean (SD)	67.22	16.00	67.22	14.94
<65 y	316	42.7	334	42.49
65–84 y	316	42.7	346	44.02
≥85 y	108	14.59	106	13.49
Male	443	59.86	482	61.32
Average duration from stroke to seizure, mean (SD)	0.91	0.52	0.90	0.51
Index stroke hospitalization				
Index stroke year				
2010–2015	182	24.59	394	50.13
2016–2020	558	75.41	392	49.87
Stroke subtypes				
Ischemic stroke	523	70.68	555	70.61
Intracranial hemorrhage	197	26.62	205	26.08
Subarachnoid hemorrhage	20	2.7	26	3.31
PSEiCARe score, mean (SD)[a]	2.63	2.09	2.79	2.13
Received intracranial surgery	50	6.76	89	11.32
Index seizure hospitalization				
Types of hospitalization				
Inpatient admission	304	41.08	305	38.8
Emergency department	436	58.92	481	61.2
Length of hospital stay, mean (SD)	3.18	5.92	3.18	6.28
≤7 d	642	86.76	688	87.53
>7 d	98	13.24	98	12.47
Required ICU stays	52	7.03	53	6.74
Used IV sedatives[b]	325	43.92	354	45.04
Used IV levetiracetam or valproic acid	572	77.3	609	77.48
Continuous EEG monitoring	8	1.08	3	0.38
Baseline comorbidities[c]				
Hypertension	647	87.43	690	87.79
Atrial fibrillation	224	30.27	207	26.34
Ventricular arrhythmias	108	14.59	107	13.61
Coronary artery disease	178	24.05	219	27.86
Dyslipidemia	342	46.22	373	47.46
Diabetes mellitus	317	42.84	360	45.8
Dementia	172	23.24	208	26.46

Continued

Table 2 Baseline Characteristics Before Marginal Structural Model Weighting Among Levetiracetam and Valproic Acid Users With Poststroke Seizures *(continued)*

	Levetiracetam		Valproic acid	
	N = 740	%	N = 786	%
Liver diseases	115	15.54	92	11.7
Chronic kidney diseases	105	14.19	121	15.39
Psychiatric disorders	196	26.49	212	26.97
Autoimmune diseases	104	14.05	203	25.83
Brain tumor	15	2.03	19	2.42
Concomitant medications[d]				
Benzodiazepines	658	88.92	709	90.2
Antidepressants	260	35.14	284	36.13
Antipsychotics	360	48.65	410	52.16
Methylphenidate	13	1.76	20	2.54
Carbapenem	80	10.81	92	11.7
Cephalosporin	630	85.14	674	85.75
Xanthine derivatives	267	36.08	273	34.73
Tramadol	282	38.11	254	32.32
Statin	427	57.7	436	55.47
Warfarin	90	12.16	93	11.83
Non–vitamin K antagonists	184	24.86	125	15.9

Abbreviation: ICU = intensive care unit.
The value of absolute standardized mean difference <0.1 indicated that the baseline characteristics were balanced between groups.
[a] The PSEiCARe score is a risk score to estimate the risk of post-stroke seizure development within 1 year after a stroke. It was derived and validated from the study using National Health and Insurance Research Database in Taiwan. The PSEiCARe score calculation is based on the components that occur during index stroke admission, including prolonged hospital stays (2 points), early-onset seizure (6 points), age 80 and older (1 point), required intensive care (3 points), cognitive impairment (2 points), atrial fibrillation (2 points), and respiratory tract infection (1 point). The sum of these points will be categorized into low (score 0), medium (score 1–5), high (score 6–10), and very high (score ≥11) probabilities of experiencing a post-stroke seizure within 1 year after a stroke.
[b] Sedatives included benzodiazepines, propofol, dexmedetomidine, ketamine, or pentobarbital.
[c] Baseline comorbidities were identified through 2 years before the index seizure.
[d] Concomitant medications were identified through 90 days before the index date.

levetiracetam are unlikely to be dependent on specific modeling strategies, such as the use of time-varying covariates.

This study has several strengths. First, this study followed a target trial emulation framework and closely mirrored the design of the hypothetical randomized clinical trial to reduce potential selection biases and the immortal time bias by ensuring appropriate time-zero alignment for treatment initiation.[37] By structuring our study design based on well-defined eligibility criteria and treatment assignment strategies, we aimed to minimize biases commonly encountered in observational research. Second, we used marginal structural models with the inverse probability weights to strengthen the causal effects,[26] which considered not only the baseline covariates but also time-varying covariates that accounted for changes in seizure risks over time. This approach aimed to align with clinical situations, particularly when seizure risk factors changed during subsequent events. Third, this study used the nationwide full-population administrative claims data to directly compare levetiracetam with valproic acid in patients with post-stroke seizures. Results generated from these real-world data can reflect the actual utilization of ASMs in clinical practice and are more likely to extrapolate results to patients with post-stroke seizures across different ages and comorbidities. Finally, we applied the validated PSEiCARe score as a baseline covariate to estimate the annual risk of post-stroke seizure development,[24] which allowed us to better consider the risk of seizure recurrence and minimize potential imbalance in baseline seizure risks.

We acknowledge the limitations in this study. First, identifying a seizure attack in an observational claims database can sometimes be challenging because we cannot access the electroencephalography report from the NHIRD. However,

Table 3 Estimated Events, Incidence Rates, and Hazard Ratios for Each Outcome for Levetiracetam vs Valproic Acid Using the Inverse Probability–Weighted Marginal Structural Model Under the Sustained-Treatment Approach[a]

	Events		Incidence rates per 100 person-year (95% CI)			
	Levetiracetam (N = 763.63)	Valproic acid (N = 725.53)	Levetiracetam	Valproic acid	Hazard ratio[b] (95% CI)	*p* Value
Primary outcome						
Seizure rehospitalization	178.98	216.33	11.85 (11.68–12.03)	14.42 (14.23–14.61)	0.78 (0.64–0.95)[c]	0.01
Secondary outcomes						
All-cause mortality	264.67	257.08	14.04 (13.87–14.21)	12.40 (12.25–12.55)	1.09 (0.92–1.30)	0.31
Composite of seizure rehospitalization and all-cause mortality	387.35	405.12	25.65 (25.40–25.91)	27.00 (26.74–27.27)	0.92 (0.80–1.06)	0.24

Abbreviation: ASM = antiseizure medication.
[a] The inverse probability–weighted marginal structural model analysis incorporates inverse probability weights in the regression model to control for potential confounders affecting initial treatment selection and subsequent treatment deviation probabilities. Both baseline covariates and time-varying covariates were considered in estimating the inverse probability weights.
[b] Levetiracetam users were the exposure groups while valproic acid users were the reference group.
[c] Significant differences between levetiracetam and valproic acid.

we applied validated seizure diagnostic codes to ensure the accuracy of seizure diagnoses in our study.[38] Moreover, only seizure diagnoses in the primary position during hospitalization will be identified as seizure events in our study, making the diagnosis more definitive while not accounting for misdiagnosis. Second, unmeasured confounders may remain because the claims database did not include laboratory data. Consequently, we were unable to capture values such as serum creatinine, liver enzymes, and serum albumin, which could have provided important clinical context for distinguishing between the use of levetiracetam and valproic acid. Moreover, certain baseline differences, such as underlying liver disease or autoimmune conditions, may reflect complex biological mechanisms that cannot be fully captured through observed variables, potentially contributing to residual bias despite statistical adjustment. Third, the type of seizure could not be identified in our study, as the type and severity of seizures could potentially affect the risk of seizure recurrence. Fourth, lamotrigine was not included in our analysis because it is not reimbursed as a first-line ASM under

Table 4 Results From the Intention-to-Treat Sensitivity Analyses Using IPTW and SIPTW

	IPTW				SIPTW			
	Incidence rates per 100 person-year (95% CI)		Hazard ratio[a] (95% CI)	*p* Value	Incidence rates per 100 person-year (95% CI)		Hazard ratio[a] (95% CI)	*p* Value
	Levetiracetam	Valproic acid			Levetiracetam	Valproic acid		
Primary outcome								
Seizure rehospitalization	11.23 (11.10–11.37)	12.43 (12.30–12.57)	0.85 (0.72–0.99)[c]	0.04	11.23 (11.04–11.43)	12.43 (12.25–12.62)	0.85 (0.67–1.06)	0.15
Secondary outcomes								
All-cause mortality	15.11 (14.97–15.25)	15.37 (15.24–15.50)	0.95 (0.84–1.08)	0.45	15.11 (14.91–15.31)	15.37 (15.19–15.56)	0.95 (0.80–1.14)	0.60
Composite of seizure rehospitalization and all-cause mortality	26.83 (26.62–27.04)	28.32 (28.12–28.53)	0.91 (0.82–1.01)	0.08	26.83 (26.53–27.13)	28.32 (28.04–28.61)	0.91 (0.78–1.06)	0.22
Changes in ASM regimen[b]	11.97 (11.83–12.11)	17.74 (17.57–17.91)	0.66 (0.57–0.77)[c]	<0.001	11.97 (11.77–12.17)	17.74 (17.50–17.97)	0.66 (0.53–0.82)[c]	<0.001

Abbreviations: ASM = antiseizure medication; IPTW = inverse probability of treatment weighting; SIPTW = stabilized inverse probability weighting.
[a] Levetiracetam users were the exposure groups while valproic acid users were the reference group.
[b] Changes in the ASM regimen included switching to an alternative ASM or adding on another ASM for seizure management.
[c] Significant differences between levetiracetam and valproic acid.

Taiwan's reimbursement policy. As a result, we were unable to assess its effectiveness relative to levetiracetam. This may limit the generalizability of our findings to health care settings where broader access to lamotrigine exists. Lamotrigine is a commonly used ASM that has demonstrated superior treatment persistence and efficacy in the SANAD II trial.[39] In addition, a network meta-analysis reported comparable risks of seizure recurrence and drug discontinuation between lamotrigine and levetiracetam,[31] suggesting that lamotrigine may represent a more appropriate comparator in some contexts. Evaluating the real-world effectiveness of newer-generation ASMs, such as lamotrigine and zonisamide, is a valuable direction for future research. Fifth, the causal contrast from our sustained treatment approach should be interpreted with caution. Rather than censoring individuals at the time of treatment deviation, we retained all outcome data and modeled the probability of remaining on the initially assigned treatment. Although this approach avoids informative censoring and captures clinically meaningful post-deviation outcomes, it relies on assumptions that may not fully reflect clinical reality. Specifically, it assumes that person-time spent on a given treatment is associated with the same outcome risk, regardless of whether the treatment was initiated at baseline or after a switch. It also implies minimal treatment deviation interaction and presumes a linear dose-response relationship with time on treatment. Nevertheless, our intention-to-treat analysis yielded directionally consistent results, providing supportive evidence for the robustness of the sustained treatment findings. Still, it is important to recognize these assumptions when interpreting the results. Finally, this study only focused on assessing the effectiveness of monotherapy ASM use in managing post-stroke seizures. The results should be interpreted with caution when applied to patients with complex seizure conditions requiring more than 1 ASM for seizure control. Future investigations could focus directly on ASM combination regimens to better understand the role of levetiracetam in managing post-stroke seizures as a combination therapy.

Our study found that levetiracetam was associated with a lower risk of seizure rehospitalization compared with valproic acid, with no significant difference in the risk of mortality. Sensitivity analyses further suggested that levetiracetam users were more likely to persist with their medication without requiring alternative ASMs, potentially reflecting greater seizure treatment stability. In conclusion, levetiracetam may be a suitable treatment choice for patients with post-stroke seizures. Future randomized controlled trials could help confirm and build on the findings of our study.

Author Contributions

H.-Y. Huang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C.-C. Wang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This study was supported by the National Science and Technology Council of Taiwan under grant numbers MOST 111-2636-B-002-019 and NSTC 113-2320-B-002-054.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® March 24, 2025. Accepted in final form August 22, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Emily Johnson, MD, MPH.

References

1. Myint PK, Staufenberg EF, Sabanathan K. Post-stroke seizure and post-stroke epilepsy. *Postgrad Med J*. 2006;82(971):568-572. doi:10.1136/pgmj.2005.041426
2. Zelano J. Prognosis of poststroke epilepsy. *Epilepsy Behav*. 2020;104(pt B):106273. doi:10.1016/j.yebeh.2019.04.026
3. Ren Z, Wen Q, Yan X, Wang Y, Zhang Y. Post-stroke epilepsy and risk of all-cause mortality: a systematic review and meta-analysis of cohort studies. *Clin Neurol Neurosurg*. 2022;220:107362. doi:10.1016/j.clineuro.2022.107362
4. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol*. 2018;75(3):279-286. doi:10.1001/jamaneurol.2017.3949
5. Contreras-García IJ, Cárdenas-Rodríguez N, Romo-Mancillas A, et al. Levetiracetam mechanisms of action: from molecules to systems. *Pharmaceuticals (Basel)*. 2022;15(4):475. doi:10.3390/ph15040475
6. Abou-Khalil B. Levetiracetam in the treatment of epilepsy. *Neuropsychiatr Dis Treat*. 2008;4(3):507-523. doi:10.2147/ndt.s2937
7. Loikas D, Linnér L, Sundström A, Wettermark B, von Euler M. Post-stroke epilepsy and antiepileptic drug use in men and women. *Basic Clin Pharmacol Toxicol*. 2021;129(2):148-157. doi:10.1111/bcpt.13617
8. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381(22):2103-2113. doi:10.1056/NEJMoa1905795
9. Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane Database Syst Rev*. 2017;12(12):CD011412. doi:10.1002/14651858.CD011412.pub3
10. Hosoi T, Yamana H, Tamiya H, et al. Association between comprehensive geriatric assessment and polypharmacy at discharge in patients with ischaemic stroke: a nationwide, retrospective, cohort study. *EClinicalMedicine*. 2022;50:101528. doi:10.1016/j.eclinm.2022.101528
11. Elamy AH, Shuaib A, Carriere KC, Jeerakathil T. Common comorbidities of stroke in the Canadian population. *Can J Neurol Sci*. 2020;47(3):314-319. doi:10.1017/cjn.2020.17
12. Tanaka T, Fukuma K, Abe S, et al. Antiseizure medications for post-stroke epilepsy: a real-world prospective cohort study. *Brain Behav*. 2021;11(9):e2330. doi:10.1002/brb3.2330
13. Huang YH, Chi NF, Kuan YC, et al. Efficacy of phenytoin, valproic acid, carbamazepine and new antiepileptic drugs on control of late-onset post-stroke epilepsy in Taiwan. *Eur J Neurol*. 2015;22(11):1459-1468. doi:10.1111/ene.12766
14. Winter Y, Uphaus T, Sandner K, Klimpe S, Stuckrad-Barre SV, Groppa S. Efficacy and safety of antiseizure medication in post-stroke epilepsy. *Seizure*. 2022;100:109-114. doi:10.1016/j.seizure.2022.07.003
15. Hernán MA, Dahabreh IJ, Dickerman BA, Swanson SA. The target trial framework for causal inference from observational data: why and when is it helpful? *Ann Intern Med*. 2025;178(3):402-407. doi:10.7326/ANNALS-24-01871
16. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758-764. doi:10.1093/aje/kwv254
17. Health and Welfare Data Science Center, *Ministry of Health and Welfare* (HWDC, MOHW). Accessed October 7, 2025. https://dep.mohw.gov.tw/DOS/cp-5119-59201-113.html
18. Federico EM, Carroll K, McGrath M, et al. Incidence and risk factors of post-stroke seizure among ischemic stroke patients. *J Stroke Cerebrovasc Dis*. 2024;33(12):108072. doi:10.1016/j.jstrokecerebrovasdis.2024.108072
19. Nilo A, Pauletto G, Lorenzut S, et al. Post-stroke status epilepticus: time of occurrence may be the difference? *J Clin Med*. 2023;12(3):769. doi:10.3390/jcm12030769
20. Fordington S, Manford M. A review of seizures and epilepsy following traumatic brain injury. *J Neurol*. 2020;267(10):3105-3111. doi:10.1007/s00415-020-09926-w

21. Vezzani A, Fujinami RS, White HS, et al. Infections, inflammation and epilepsy. *Acta Neuropathol*. 2016;131(2):211-234. doi:10.1007/s00401-015-1481-5
22. Spatola M, Dalmau J. Seizures and risk of epilepsy in autoimmune and other inflammatory encephalitis. *Curr Opin Neurol*. 2017;30(3):345-353. doi:10.1097/WCO.0000000000000449
23. Doria JW, Forgacs PB. Incidence, implications, and management of seizures following ischemic and hemorrhagic stroke. *Curr Neurol Neurosci Rep*. 2019;19(7):37. doi:10.1007/s11910-019-0957-4
24. Chi NF, Kuan YC, Huang YH, et al. Development and validation of risk score to estimate 1-year late poststroke epilepsy risk in ischemic stroke patients. *Clin Epidemiol*. 2018;10:1001-1011. doi:10.2147/CLEP.S168169
25. Betjemann JP, Lowenstein DH. Status epilepticus in adults. *Lancet Neurol*. 2015;14(6):615-624. doi:10.1016/S1474-4422(15)00042-3
26. Breskin A, Cole SR, Westreich D. Exploring the subtleties of inverse probability weighting and marginal structural models. *Epidemiology*. 2018;29(3):352-355. doi:10.1097/EDE.0000000000000813
27. Miguel A Hernán JMR. *Causal Inference: What If*. Chapman & Hall/CRC; 2020.
28. Rochon J, Bhapkar M, Pieper CF, Kraus WE. Application of the marginal structural model to account for suboptimal adherence in a randomized controlled trial. *Contemp Clin Trials Commun*. 2016;4:222-228. doi:10.1016/j.conctc.2016.10.005
29. Lancet EA, Borrell LN, Holbrook J, Morabia A. Using marginal structural models to analyze randomized clinical trials with non-adherence and lost to follow up. *Ann Epidemiol*. 2021;63:22-28. doi:10.1016/j.annepidem.2021.07.001
30. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. doi:10.1093/aje/kwn164
31. Misra S, Wang S, Quinn TJ, et al. Antiseizure medications in poststroke seizures: a systematic review and network meta-analysis. *Neurology*. 2025;104(3):e210231. doi:10.1212/WNL.0000000000210231
32. Consoli D, Bosco D, Postorino P, et al. Levetiracetam versus carbamazepine in patients with late poststroke seizures: a multicenter prospective randomized open-label study (EpIC Project). *Cerebrovasc Dis*. 2012;34(4):282-289. doi:10.1159/000342669
33. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Epilepsy Curr*. 2018;18(4):269-278. doi:10.5698/1535-7597.18.4.269
34. Belcastro V, Costa C, Galletti F, et al. Levetiracetam in newly diagnosed late-onset post-stroke seizures: a prospective observational study. *Epilepsy Res*. 2008;82(2-3):223-226. doi:10.1016/j.eplepsyres.2008.08.008
35. Larsson D, Baftiu A, Johannessen Landmark C, et al. Association between antiseizure drug monotherapy and mortality for patients with poststroke epilepsy. *JAMA Neurol*. 2022;79(2):169-175. doi:10.1001/jamaneurol.2021.4584
36. Chiang KL, Liang CY, Hsieh LP, Chien LN. Analysis of trends and factors determining initial antiseizure medication choice for epilepsy in Taiwan. *Seizure*. 2021;93:145-153. doi:10.1016/j.seizure.2021.10.020
37. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;79:70-75. doi:10.1016/j.jclinepi.2016.04.014
38. Mbizvo GK, Bennett KH, Schnier C, Simpson CR, Duncan SE, Chin RFM. The accuracy of using administrative healthcare data to identify epilepsy cases: a systematic review of validation studies. *Epilepsia*. 2020;61(7):1319-1335. doi:10.1111/epi.16547
39. Marson A, Burnside G, Appleton R, et al. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. *Lancet*. 2021;397(10282):1363-1374. doi:10.1016/S0140-6736(21)00247-6