Treatment Persistence of Lacosamide, Perampanel and Brivaracetam: An Extended Real-World Analysis from the COMPARE Italian Cohort

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OBJECTIVES

Antiseizure medication (ASM) discontinuation is a frequent and clinically meaningful outcome in the treatment of epilepsy, often reflecting inadequate tolerability, limited effectiveness, or both[1, 2]. In this study, we reanalyzed data from the COMPARE Italian multicenter cohort previously published by Roberti et al[3].to investigate real-world outcomes in patients treated with the most recent add-on ASMs. Our aim was to compare treatment persistence among lacosamide, brivaracetam, and perampanel over time, and to assess how adverse events and clinical response influence the discontinuation process. In contrast to the original multivariable regression approach, we applied a propensity score weighting framework to better approximate causal effects and address residual confounding.

METHODS

We estimated stabilized inverse probability of treatment weights (IPTW) using a multinomial propensity score model based on age, sex, epilepsy duration, etiology, seizure type, prior ASM exposure, epilepsy surgery, and baseline polytherapy[4, 5]. Time to treatment discontinuation was analyzed through log-logistic accelerated failure time (AFT) models, which allow direct estimation of time ratios (TRs)[6]. Clinical response and adverse events were added as covariates to explore their potential mediating role. Interaction terms with log-transformed time were introduced to assess how treatment effects evolve longitudinally. Robustness was evaluated through sensitivity analyses using cluster-robust standard errors and symmetric weight trimming to exclude individuals with extreme propensity scores.

RESULTS

The analysis included 828 patients (250 lacosamide, 234 brivaracetam, 344 perampanel), with a maximum follow-up of 36 months. In unadjusted AFT models, brivaracetam (TR = 0.48, 95% CI: 0.27–0.84) and perampanel (TR = 0.46, 95% CI: 0.27–0.76) were associated with shorter persistence than lacosamide. After adjusting for adverse events and response, the association was attenuated for brivaracetam (TR = 0.68, 95% CI: 0.42–1.14), while perampanel remained significant (TR = 0.61, 95% CI: 0.38–0.97). Both adverse events (TR = 0.44, 95% CI: 0.30–0.66) and clinical response (TR = 4.25, 95% CI: 2.97–6.07) were independently associated with time to discontinuation, supporting their potential mediating role. Time-dependent models revealed that the initial disadvantage of brivaracetam (interaction TR = 2.50, 95% CI: 2.21–2.83) and perampanel (TR = 2.60, 95% CI: 2.34–2.88) diminished over time. Clinical response became increasingly protective, while the impact of adverse events waned. Sensitivity analyses confirmed the robustness of these findings.

CONCLUSIONS

The risk of treatment discontinuation evolves dynamically and differs among ASMs. Lacosamide showed greater early persistence, whereas brivaracetam and perampanel, despite being associated with earlier dropout, demonstrated improved retention among patients who tolerated them beyond the initial period. These findings suggest that the first weeks of treatment may be critical for identifying and managing tolerability issues, especially with brivaracetam and perampanel. Our results underscore the importance of adopting a dynamic, patient-centered approach to ASM selection, considering not only baseline characteristics but also longitudinal

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response and tolerability. Propensity score-based methods, when applied appropriately, can enhance causal inference in observational studies and provide clinically meaningful insights to guide therapeutic decisions in epilepsy care.

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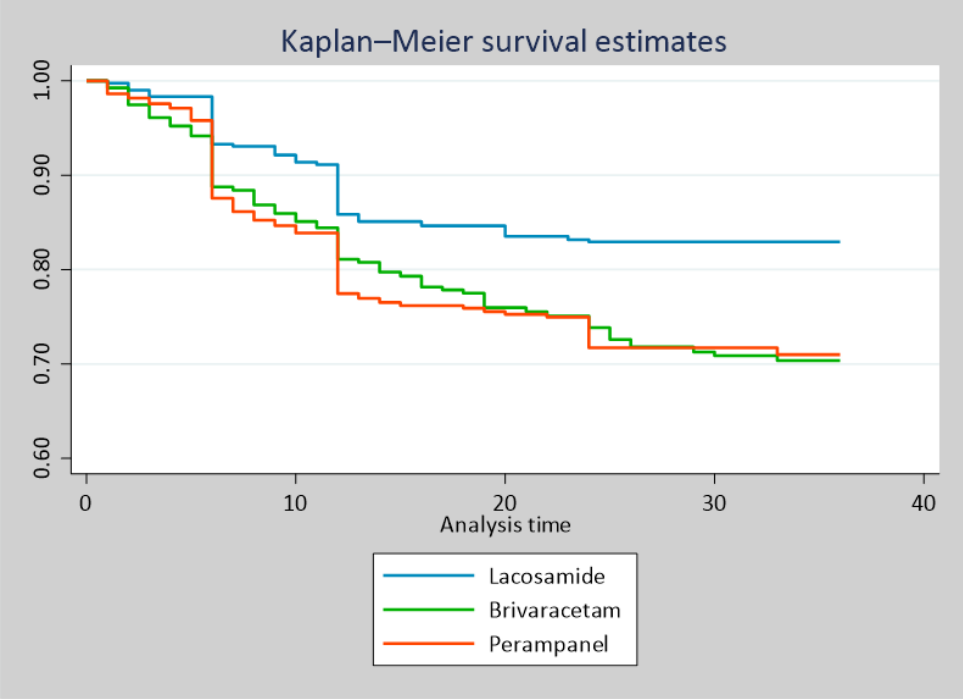

Figure 1. Kaplan–Meier survival curves showing time to treatment discontinuation for lacosamide, brivaracetam, and perampanel over a follow-up of up to 36 months. Lacosamide was associated with higher early treatment persistence.

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