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Mirror, Mirror on the Wall, Who's the Fairest Third Generation Anti-Seizure Medication of All?

A Real-World Comparison Among Third-Generation Antiseizure Medications: Results From the COMPARE Study

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Objective: There are few comparative data on the third-generation antiseizure medications (ASMs). We aimed to assess and compare the effectiveness of brivaracetam (BRV), eslicarbazepine acetate (ESL), lacosamide (LCM), and perampanel (PER) in people with epilepsy (PWE). Efficacy and tolerability were compared as secondary objectives. Methods: This multicenter, retrospective study collected data from 22 Italian neurology/epilepsy centers. All adult PWE who started add-on treatment with one of the studied ASMs between January 2018 and October 2021 were included. Retention rate was established as effectiveness measure and described using Kaplan-Meier curves and the best fitting survival model. The responder status and the occurrence of adverse events (AEs) were used to evaluate efficacy and safety, respectively. The odds of AEs and drug efficacy were estimated by 2 multilevel logistic models. Results: A total of 960 patients (52.92% females, median age = 43 years) met the inclusion criteria. They mainly suffered from structural epilepsy (52.29%) with monthly (46.2%) focal seizures (69.58%). Compared with LCM, all the studied ASMs had a higher dropout risk, statistically significant in the BRV levetiracetam (LEV)-naïve (hazard ratio [HR] = 1.97, 95% confidence interval [CI] = 1.17-3.29) and PER groups (HR = 1.64, 95% CI = 1.06-2.55). Women were at higher risk of discontinuing ESL (HR = 5.33, 95% CI = 1.71-16.61), as well as PER-treated patients with unknown epilepsy etiology versus those with structural etiology (HR = 1.74, 95% CI = 1.05-2.88). BRV with prior LEV therapy showed lower odds of efficacy (odds ratio [OR] = .08, 95% CI = .01-.48) versus LCM, whereas a higher efficacy was observed in women treated with BRV and LEV-naïve (OR = 10.32, 95% CI = 1.55-68.78) versus men. PER (OR = 6.93, 95% CI = 3.32-14.44) and BRV in LEV-naïve patients (OR = 6.80, 95% CI = 2.64-17.52) had a higher chance of AEs than LCM. Significance: Comparative evidence from real-world studies may help clinicians to tailor treatments according to patients' demographic and clinical characteristics.

Commentary

Anti-seizure medications (ASMs) constitute the first-line therapy in epilepsy. Yet, one third of patients remain drug-resistant, so the quest for new agents is paramount.[1] Over the last decade, several third generation ASMs have been introduced to the market.[2] Some are improved versions of old formulations, while others harness new mechanisms of action. Their efficacy and safety profiles were originally confirmed by randomized controlled trials (RCTs) and subsequently evaluated by long-term extension and post-marketing outcomes series. By abiding to high scientific standards, RCTs offer high internal validity and rigorous assessments of dose–response relationships.[3,4] Yet, due to their stringent eligibility criteria resulting often in unrepresentative patient samples, they suffer from lower external validity, and their duration is typically limited.[3,4] On the contrary, extension and post-marketing outcome studies evaluate safety during chronic exposure across a broader range of doses when concomitant ASMs can be adjusted, allowing for patient retention estimates as a reasonable index of long-term treatment outcome.[2] In this rapidly evolving landscape, clinicians are understandably on the lookout for comparative studies. Given that no head-to head comparison trials exist for third generation ASMs,[5] such information is derived indirectly by network meta-analyses (NMAs) and real-world evidence (RWE) studies.

The study at-hand by Di Gennaro et al[6] enriches our indirect comparative knowledge on third generation ASMs. By means of retrospectively collected data from 22 Italian epilepsy centers between January 2018 and October 2021, adult persons with epilepsy who were started on brivaracetam (BRV) [with or without prior use of levetiracetam (LEV)], eslicarbazepine acetate (ESL), lacosamide (LCM), and perampanel (PER) were assessed with regard to their overall retention rate, and the ASMs' efficacy and tolerability. A total of 960 patients were recruited (median age 43 years, 53% female), with the majority ($\sim$70%) experiencing focal seizures only, despite a median of 3 ASMs before enrollment and 2 concomitant ASMs during enrollment. Treatment duration ranged from 1 to 36 months, with nearly 40% of the patients being available at the end of the study period. Overall, 20% of patients discontinued treatment, mainly due to lack of efficacy (61%), followed by intolerable adverse events (AEs) (38%), mostly pertaining to the central nervous system (dizziness, irritability, and somnolence). Lacosamide had the higher retention rate throughout the 3-year study period. No serious AEs were encountered. Brivaracetam in LEV naïve patients had the lowest retention rate and LCM had the highest. Sex, age, epilepsy etiology, disease duration, and previously studied ASMs did not affect the overall retention time. Except for BRV patients previously treated with LEV, all other ASMs, including BRV in LEV naïve patients, exceeded 60% responder rate at some time point during the observation period, without statistically significant differences in the overall efficacy. Persons with epilepsy treated with $>$2 ASMs in the past had a lower probability of drug efficacy, while longer follow-up time was associated with increased efficacy. With regards to safety, a higher frequency of AEs was observed in those treated previously with more ASMs and with increasing age, but the probability of reporting AEs decreased over time. Perampanel and BRV in LEV naïve patients showed a higher chance of AEs than LCM. In the subgroup analyses, women demonstrated higher efficacy in LEV naïve BRV patients than men. Women also had a higher risk of discontinuing ESL, as well as PER-treated patients with unknown as opposed to structural epilepsy.

This study[6] affirms several key points about medical management in epilepsy. For a start, third generation ASMs demonstrate descent retention rates regardless of sex, age, epilepsy etiology, disease duration, and previously tried ASMs. Furthermore, they are efficacious as a group in nearly 2/3 of the patients who try them out. The half-empty viewpoint of this statement is that 1/3 remain drug-resistant, particularly those who failed several ASMs in the past. Except for the anticipated reduced efficacy in BRV patients previously treated with LEV, they do not demonstrate substantial individual differences in their efficacy. Moreover, AEs are seen in nearly 1/5 of patients who take them, increasing with prior ASMs attempts and with age, advocating for a start-low, go-slow approach, particularly in the elderly. Yet, third generation ASMs are relatively safe given that no serious AEs were observed. While there may be individual differences in retention rates with LCM emerging as the front-runner, one should be mindful that LCM had the lowest median number of previously tried ASMs, hence increasing the chances of response. Moreover, LCM had the lowest number of concomitant ASMs across the study population, and it was used at a moderate dose without prominent escalation during the study period, hence decreasing the chances of AEs. In addition to interesting sex- and etiology-related individual drug differences emerging in the subgroup analyses, the reduced efficacy of prior ASMs with similar mechanism of actions (e.g., BRV in previously treated patients with LEV) seems to provide leverage to rational polytherapy.

The greatest advantage of this study[6] is the real-world experience on a large sample size derived from a host of epilepsy centers over a 3-year period. Four of the most common third generation ASMs were evaluated, including special analysis for LEV-previously treated versus naïve patients. An effort was undertaken to adjudicate potential inconsistencies and numerous subgroup analyses were performed.

On the other hand, this study[6] is a single country, retrospective evaluation of practice habits on the management of epilepsy with a fraction of the marketed third generation ASMs, excluding special populations (e.g., pediatric or pregnant patients). Despite the documented drug resistance in most participants, 84% were strangely deemed not to be epilepsy surgery candidates. Although the median number and median dose of concomitant ASMs at baseline was logged, in addition to the administered median doses of the third generation ASMs under study, the exact titration scheme and, foremost, any pharmacokinetic interactions and synergistic effects were not explicitly scrutinized. The inevitable losses to follow-up required arbitrary assumptions about missing data. No formal power analysis nor adjustments for multiple comparisons were performed. Finally, outcomes naturally focused on patient retention by means of efficacy and tolerability, overlooking other important management parameters such as quality of life and cost-effectiveness.

Many of these findings and shortcomings are in line with prior comparative effectiveness studies on the medical management of epilepsy. For example, two NMAs of prior RCTs of the same third generation drugs, confirmed no efficacy differences among them.[7,8] In the earliest,[7] lower AEs were observed with high dose BRV compared to high dose ESL or PER, while in the latest,[8] BRV had the best safety profile. When cenobamate was added to the mix,[5] it was associated with higher response rate, while BRV and LCM emerged as the best tolerated treatments. Yet, NMAs have clinical and methodological limitations, such as the handling of heterogeneity.[9] Similarly, several smaller, single center RWE studies have corroborated the efficacy and tolerability of third generation ASMs, but they require medically comparable treatment groups to lessen patient- and physician-related bias, and counteract the lack of randomization.[9] Until direct head-to-head clinical trials between third and older generation ASMs and among third generation ASMs themselves are performed, we are in need of concerted, scientifically rigorous, comparative effectiveness studies, based on large sample sizes, broader, representative and well-characterized patient populations, adjusting for

potential confounders and holistically measuring clinically relevant outcomes in the treatment of epilepsy. In other words, the study of third generation ASMs merits regeneration to inform and guide prescriber decision-making before a champion can be declared.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The author has served as a consultant in a UCB health equity advisory board and a GSK research study.

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