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A Clinical Review of Eslicarbazepine Acetate

And Its Effectiveness as a First-line or Later Adjunctive Therapy in Patients With Partial-Onset Seizures

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INTRODUCTION

When managing seizures, physicians have multiple treatment choices developed over the past half century.[1,2] Partial-onset seizures (POS), or focal seizures (FS), represent the majority of cases.[3] Neurologists and primary care providers are tasked with choosing the first-, second-, or third-line option for monotherapy, and determining when treatment-refractory cases require adjunct treatment.[3-5] Two landmark studies in adults directly compared the so-called first-generation antiepilepsy drugs (AEDs) used in POS (carbamazepine [CBZ], phenytoin, phenobarbital, primidone, and valproate), leading to the understanding that efficacy was similar but differences in tolerability among these agents was a larger issue. Physicians needed to empirically base their selection on considerations of age, gender, comorbidities, and drug interactions.[6,7] As the newer, third-generation AEDs became available (albeit at higher cost), clinical trials showed fewer adverse effects, but a lack of direct comparison evidence added to the dilemma of choice, leaving clinical impression as a guide to assess the cost-vs-benefit value.[3,8,9]

Medical care is only part of the cost of epilepsy. The economic impact of absenteeism and lost productivity, as well as caregiver burden, add to the economic impact.[4,10] Additionally, seizures negatively impact development in children, contributing to an increase in all-cause healthcare utilization.[11,12] Disease severity as measured by epilepsy control and comorbidities dramatically increases the overall healthcare costs apart from AED expenditures in adults and children.[10,11] Hospitalization, outpatient, and emergency department costs are shown to decrease when epilepsy is well controlled, making recent studies of newer AEDs all the more impactful, given their faster seizure control and reduced adverse events when used as first-line or adjunct therapy.[10,11,13] It's time to rethink study measures that ultimately determine the rank these third-generation AEDs hold in the perceived hierarchy of treatment.

CHOOSING AMONG THE MANY AEDs

In clinical practice, treatment is initiated with a single AED using less-costly first- or second-generation AEDs.[4,5,14] Both the 2018 American Academy of Neurology/American Epilepsy Society (AAN/AES) and the National Institute for Health and Care Excellence (NICE) guidelines support CBZ from the first-generation AEDs and oxcarbazepine (OXC), lamotrigine (LTG), levetiracetam (LEV), and zonisamide (ZNS) from the second-generation AEDs as good first

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options.[5,14] If initial treatment is not effective at controlling seizures or causes unacceptable adverse effects, an alternative AED should be initiated, with tapering of the first medication to reduce overlapping side effects. Dual AED therapy is recommended only after 2 well-tolerated single agents at maximized doses prove ineffective, as supported by US and international guidelines.[4-6,14] Long-term studies show that 50 to 75% of patients achieve seizure control for ≥1 year when monotherapy is maximized.[15] Many physicians utilize the tactic of selection based upon mechanism of action, preferring to ensure a trial of differing and non-overlapping pharmacology when adding a drug.[8,16]

A 1985 placebo-controlled, multicenter study of first-generation AEDs highlighted CBZ as one of the better first-choice medications, and the subsequent follow-up study in 1992 comparing CBZ to valproate concluded that CBZ should be preferred.[6,7] However, no established algorithm backed by head-to-head trials (not required by regulatory agencies) assists prescribers in the sequence of choices for the next single AED or pairing of medications.[9] Prescribers now typically avoid CBZ altogether, preferring later AEDs that offer fewer drug interactions with reduced psychiatric and behavioral side effects, often using AEDs based on the tricyclic molecule (eg, OXC, eslicarbazepine acetate [ESL]).[1] The most commonly used in the United States, LEV and LTG, are among those with long half-lives and/or extended-release formulations that have proven to reduce economic burdens associated with missed doses and other adherence issues.[3,16-18] Unfortunately, psychiatric and behavioral effects, including anxiety, depression, psychosis, and aggressive manners, may limit the use of some AEDs, notably LEV.[4,19,20]

THE ACHILLES' HEEL OF TRIAL DESIGN

Phase 3 trials inherently hamper comparative decision-making given that new AEDs are usually tested as add-ons to baseline control medications, and stringent eligibility criteria select for patients who inadequately represent the more typical clinical populations affected by such issues as age and concomitant conditions.[2,9,16] Meta-analyses of randomized controlled trials (RCTs) and other post-approval real-world data offer some help, but may also suffer from limited sample size, variability of available data points, and inadequate summary data inclusion that affect the quality of meta-analysis interpretation.[9,21] Early attempts to rank AEDs through post-hoc analysis of pivotal trial data for the second-generation AEDs based on both efficacy ("likelihood of success ratios") and adverse events ("summary complaint scores") demonstrated that improved efficacy as measured by seizure frequency reduction (SFR) came at the cost of adverse effects.[2,21] These data revealed that the primary efficacy endpoints of randomized controlled registrational trials do not give a full clinical picture.

Registrational trials track SFR as the primary endpoint, but recent evaluations have included secondary endpoints such as quality of life and evaluation of individual seizure attributes.[22] Measures such as percentage of patients achieving ≥50% SFR fail to capture variability in populations.[21] It is also important that patients themselves may not find seizure reduction to be their quintessential problem.[23] Validated health-related quality of life (HRQOL) instruments such as the QOLIE-31 (Quality of Life in Epilepsy Inventory 31) correlate incrementally to SFR ≥50%, with greater overall SFR linked to statistically significant improvement in HRQOL scores.[22-24] Specific domains of the QOLIE-31 can exceed the calculated minimum clinically important difference (MCID), suggesting these areas as possible tools to compare results of various phase 3 clinical trials.[23]

To better understand treatment effect on the qualities of seizures, severity assessments have been developed to complement the seizure frequency endpoint.[25] The Seizure Severity Questionnaire (SSQ), completed by the patient and an observer (usually family), describes the severity and bothersomeness of components of seizures occurring during the past month, allowing for comparison between baseline and change in follow-up after a new treatment is initiated.[24] The questions assess (1) warnings; (2) ictal movement and consciousness; and (3) post-ictal cognitive, emotional, and physical effects, with scores categorized as clinically meaningful changes.[25]

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Establishing reliable MCIDs for each domain and overall results of the SSQ allows further study of the impact an adverse effect has on disabling factors related to seizure beyond frequency of occurrence.[25] Using the pooled data from 2 open-label studies of lacosamide (LCM), a third-generation sodium channel blocker, the SSQ was corroborated as sensitive enough to quantify how the patient experiences POS, especially in the post-ictal phase that is responsible for cognitive impairment.[25] Later analysis of the SSQ as employed in phase 3 trials of ESL, another third-generation sodium channel modulator, confirmed its ability to detect post-ictal cognitive, emotional, and physical improvements that are not reflected by simple lowering of SFR.[24] This highlights clinical benefits that could impact other healthcare-related expenses aside from seizure-related interventions.[3] Studies of ESL show dose-dependent, clinically meaningful improvements in seizure severity.[19]

ESLICARBAZEPINE IN THE TREATMENT LANDSCAPE

Following the results of 2 breakthrough trials establishing CBZ as a preferred AED, the Human Epilepsy Project further confirmed that the sustained-release product (CBZ-CR) conveyed better 6-month seizure freedom and reduced need for switch or additive therapy than LEV.[3,6,7] Once-daily ESL is the *S* enantiomer of the active metabolite for the prodrug OXC, a CBZ analog, theorized to have fewer adverse effects and cytochrome P450 interactions than breakdown products of CBZ, as well as improved crossing of the blood-brain barrier and reduced toxicity compared to OXC.[1] When adverse events are compared, ESL shows a lower incidence of rash and hyponatremia than CBZ and OXC, and a reduced incidence of nervousness, depression, and agitation compared to most second-generation AEDs.[1,23] A clinical comparison has shown at least noninferiority of ESL as initial treatment for POS vs CBZ-CR, and significant sustained efficacy when begun as, or transitioned to, monotherapy.[3]

Newer AEDs are frequently studied for approval as adjunct therapy in treatment-refractory patients, an indication of more severe disease, and not initially evaluated for first-line monotherapy or as add-on therapy in earlier stages of disease.[16] However, the use of SSQ in ESL trials has prompted the need to explore a more pronounced role for it earlier in therapy.[19,22,24] One post-hoc analysis of a phase 3 study saw the most significant improvements in SSQ occurring in patients receiving ESL who were only using 1 AED at baseline over those using 2 (P=0.06), indicating the potential impact of ESL on seizure severity, especially social functioning, when added earlier or with fewer adjuncts. The ESL 1200-mg dose exceeded the MCID at week 14 compared to placebo for total score (+0.51), as well as after-seizure (+0.54) and severity/bothersomeness subscale scores (+0.55). Importantly, no changes in depression scores occurred, showing a potential advantage over second-generation AEDs.[19]

Recent evidence on the addition of ESL to the typical first-line LTG or LEV as the first adjunct, rather than later in treatment, supports not only prior evidence from phase 3 and 4 trials of efficacy and safety but also the significant economic benefits of ESL use.[3,16] Two cohorts from insurance claims were reviewed for adult sufferers of POS: one received ESL monotherapy and the other used ESL as the first add-on AED. All-cause inpatient (IP), emergency room (ER), and outpatient (OP) visits and POS-related IP and OP visits were significantly reduced compared to baseline in the ESL monotherapy group, creating an overarching decrease in expenditures despite increased pharmacy costs that were largely due to POS medications. For the ESL adjunct cohort, statistically significant reductions occurred in all-cause IP and OP visits as well as POS-related OP trips, while numerical decreases in healthcare resource utilization charges were maintained despite the increased prescription costs.[3]

A retrospective review of commercial insurance (real-world patient) data further connects ESL as monotherapy or as an adjunct to significant reductions in healthcare utilization by comparing baseline usage against trends following ESL initiation. The ESL monotherapy group had tried a median of 2 prior AEDs and experienced significant reductions in all-cause and epilepsy-related care during the ESL treatment year, while the ESL adjunct therapy cohort had attempted a median of 3 prior AEDs and saw improvements in all-cause ER and OP visits.[13] The use of newer-generation AEDs with lower incidences of psychiatric and behavioral effects in children offers potential developmental benefits, and one longitudinal cohort analysis of real-world claims data from patients aged 4 to 17 with POS further confirmed that ESL not only reduced overall health expenditures but did so equally among those with or without preexisting neurocognitive disorders, confirming the efficacy and minimal psychiatric side effects of ESL.[12]

To better characterize the reasons for considering ESL earlier as an add-on, Hixson et al undertook an open-label efficacy and safety study comparing those beginning ESL together with either LEV or LTG only (arm 1) to those having ESL added to either LEV or LTG plus another AED (arm 2). Endpoints included retention rate as a primary measure of effectiveness, followed by SFR, responder rates (proportion achieving ≥50% SFR), safety and tolerability, and psychological and HRQOL changes.[16] Retention rates, SFR, treatment

responders, and seizure-free percentage were all greater in arm 1 (81.8%, 72.8%, 62.5%, and 25%, respectively) than arm 2 (63.8%, 22.8%, 38.5%, and 9.6%). Conversely, adverse events (most of mild to moderate severity) were more frequent in arm 2 than arm 1 (81% vs 73%). Subanalysis of AED combinations indicates improved efficacy and tolerability measures when ESL is combined with LEV rather than other medications possessing some additional level of sodium channel modulation.[16] Neither arm saw changes in depression, mood, or aggression from baseline, and the QOLIE-31 scores were undifferentiated in both groups. In short, ESL proved its greatest effect and safety as the first adjunct in a real-world population, yet also afforded benefit when added as a third AED, particularly when there is minimal sodium channel activity crossover.[16]

SUMMARY

With a plethora of AEDs now available, those most recently developed need a more equitable yet safer method to assess their utility. Regulatory agencies do not require head-to-head studies, and there is little incentive for companies to do so, leaving clinicians and payers the option to wait for anecdotal evidence that newer AEDs demonstrate clinical and cost advantages over older medications.[9,16] However, strong clinical arguments can be made for introducing third-generation AEDs when viewing the larger picture of impact on overall healthcare resource utilization, efficacy outcomes beyond seizure frequency, and improved pharmacologic and pharmacokinetic profiles. Of significant interest, the third-generation sodium channel blockers LCM and ESL have been assessed using the new SSQ instrument now accepted by regulatory bodies and found to positively affect the post-ictal phase of seizure quality.[24] Further evidence from real-world, phase 4 studies that ESL effectively reduces overall healthcare costs while proving safe and effective as both first-line monotherapy and early adjunct treatment gives considerable cause to contemplate a more immediate role for these high-performing AED options.

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