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Eslicarbazepine Acetate as Adjunctive Therapy for Refractory Partial-Onset Seizures in Adults: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Refractory partial-onset seizures present a significant therapeutic challenge, necessitating novel adjunctive treatments. This study aimed to evaluate the efficacy, safety, and tolerability of eslicarbazepine acetate (ESL) as an add-on therapy in adults with this condition. **Methods:** This was a single-center, randomized, double-blind, placebo-controlled, parallel-group trial conducted from January 2023 to December 2024. Eighty-nine adults with refractory partial-onset seizures (≥4 seizures/4 weeks despite 1–3 stable AEDs) were randomized 1:1:1 to placebo (n=30), ESL 800 mg (n=30), or ESL 1200 mg (n=29) once daily for 14 weeks after an 8-week baseline. The primary endpoint was the change in 4-week seizure frequency from baseline, analyzed using ANCOVA. Secondary endpoints included responder rates, seizure freedom, quality of life (QOLIE-31), depressive symptoms (MADRS), and adverse events. **Results:** Both ESL doses significantly reduced seizure frequency compared to placebo ($p<0.001$). LS mean change from baseline was −6.8 seizures/4 weeks (ESL 800 mg) and −8.3 seizures/4 weeks (ESL 1200 mg), versus −1.2 for placebo. Responder rates (≥50 reduction) were significantly higher with ESL (43.3% for 800 mg, 51.7% for 1200 mg) versus placebo (16.7%). Seizure freedom occurred in 10.0% (ESL 800 mg) and 13.8% (ESL 1200 mg) of patients. QOLIE-31 scores significantly improved ($p<0.001$), and MADRS scores decreased dose-dependently. Adverse event incidence was dose-dependent (placebo: 30.0%; ESL 800 mg: 53.3%; ESL 1200 mg: 65.5%), with common AEs including dizziness, somnolence, and diplopia. Hyponatremia occurred in 13.8% of the ESL 1200 mg group. Subgroup analysis showed superior efficacy for ESL 1200 mg in complex partial seizures and patients on two concomitant AEDs. **Conclusion:** ESL, at both 800 mg and 1200 mg once daily, is an effective and generally well-tolerated adjunctive therapy for adults with refractory partial-onset seizures, improving seizure control and patient-reported outcomes.

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders worldwide, affecting roughly 50 million people of all ages and ethnicities[1-3]. Epilepsy is characterised by repeated, unprovoked seizures caused by abnormal electrical activity in the brain[4]. It places a significant strain on both patients and healthcare systems[5, 6]. The pervasive impact of seizures is not limited to the seizures themselves; it frequently results in significant comorbidities, including cognitive dysfunction, psychological distress, and a diminished quality of life[7-10]. Partial-onset seizures (also known as focal seizures) are among the most frequent epileptic disorders[11, 12]. These seizures begin in a single, localised area of the brain and can cause a wide range of symptoms, depending on the brain region affected[13-15]. Secondary generalised tonic-clonic seizures can result from partial-onset seizures that spread and generalise; however, some seizures stay localised[16, 17]. Despite advances in pharmacotherapy in recent decades, a considerable proportion of people with partial-onset seizures continue to have recurring episodes, indicating refractory epilepsy[18-20]. Even with trials of several medications, about one-third of people with epilepsy do not obtain sufficient seizure control with currently available anti-epileptic drugs (AEDs). This chronic seizure activity severely disrupts their everyday functioning, restricts their educational and professional opportunities to and contributes to an elevated risk of injury, hospitalisation, and even early death[21, 22]. The dilemma of drug-resistant epilepsy highlights an urgent and critical unmet medical need for new therapeutic choices that can improve efficacy, safety profile, and

patient outcomes in this demanding population[18, 23, 24].

A relatively new oral anti-epileptic medication that is used once daily, eslicarbazepine acetate (ESL), has shown promise in treating partial-onset seizures[25, 26]. By binding specifically to the sodium channels' inactivated state, it acts as a voltage-gated sodium channel blocker, stabilising hyperexcited neuronal membranes and preventing action potentials from firing repeatedly[27-29]. ESL is a prodrug that undergoes rapid and extensive first-pass metabolism to produce eslicarbazepine, its pharmacologically active metabolite[30, 31]. There may be benefits to patient adherence and general tolerability due to this special mode of action and its once-daily dosage schedule. The present study was carefully planned to thoroughly assess the effectiveness, safety, and tolerability of ESL when used as adjunctive therapy in adults dealing with refractory partial-onset seizures.

This rigorous study aims to precisely evaluate the impact of two separate therapeutic dosages of ESL (800 mg and 1200 mg, taken once daily) in contrast to a placebo across a range of clinically important endpoints. The primary objective was to assess the change in seizure frequency, a direct measure of seizure control.

METHODOLOGY

Study Design

This trial was a single-center, randomized, double-blind, placebo-controlled, parallel-group trial. The study was conducted at the Department of Neurology, BMC Hospital Quetta, Pakistan, spanning from January 2023 to December 2024. The study protocol encompassed an 8-week baseline period for prospective seizure monitoring, during which participants maintained stable anti-seizure medication (AED) regimens. This was followed by a 14-week double-blind treatment period for the intervention.

Study Population

The study enrolled a total of 89 adult participants, as detailed in Figure 1. Inclusion criteria mandated adults aged ≥18 years with partial-onset seizures (with or without secondary generalization) for a duration of ≥1 year. Participants were required to have experienced ≥4 seizures per 4 weeks during the baseline period, despite being on stable doses of 1–3 concomitant AEDs for at least ≥2 months before screening. Exclusion criteria precluded individuals with primary generalized epilepsy syndromes, a history of status epilepticus within 3 months, or concurrent use of oxcarbazepine, felbamate, or benzodiazepines (unless prescribed as an AED). Patients with severe psychiatric, hepatic, renal, or cardiovascular comorbidities, as well as those who were pregnant or breastfeeding, were also excluded.

Randomization and Blinding

Randomization was performed using a computer-generated 1:1:1 allocation ratio, employing stratified block randomization with a block size of 6. Stratification factors included baseline seizure frequency (4–8 vs. >8 seizures/4 weeks) and the number of concomitant AEDs (1, 2, or 3). The study maintained a double-blind design, ensuring that participants, investigators, and outcome assessors were unaware of treatment assignments. Placebo and ESL tablets were manufactured to be identical in appearance to preserve blinding. Unblinding was permitted only in cases of serious adverse events (SAE) management.

Interventions

Participants were assigned to one of three intervention groups, all receiving their assigned study medication once daily orally, in addition to stable doses of 1–3 baseline AEDs. The Placebo group (n=30) received an oral placebo. The ESL 800 mg group (n=30) received eslicarbazepine acetate 800 mg once daily. The ESL 1200 mg group (n=29) received eslicarbazepine acetate 1200 mg once daily, following an initial dose escalation of 800 mg for the first two weeks of treatment.

Outcome Measures

The primary endpoint of the study was the change in seizure frequency per 4 weeks from baseline to the end of the 14-week treatment period. Secondary endpoints included the responder rate, defined as the proportion of patients achieving ≥50% reduction in seizure frequency, and seizure freedom, representing 100% seizure reduction during the treatment period. Quality of life was assessed by the change in the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) total score, which also included subscales for seizure worry and medication effects. Depressive symptoms were evaluated using the change in the Montgomery-Åsberg Depression Rating Scale (MADRS) score. Safety outcomes comprised the incidence of various adverse events (AEs), including dizziness, somnolence, diplopia, and hyponatremia, as well as serious AEs and rates of discontinuation due to AEs.

Data Collection

Seizure diaries were maintained by participants, who recorded the type, frequency, and duration of all seizures daily. Clinical assessments were performed at baseline, including electroencephalogram (EEG), serum AED levels, QOLIE-31, MADRS, and serum sodium levels. Throughout the treatment period, bi-weekly visits involved seizure diary review, AE monitoring, vital sign assessment, and serum sodium level checks. All study data were collected using the REDCap cloud-based platform, which provided an audit trail for data integrity.

Statistical Analysis

The sample size calculation targeted 27 participants per group to achieve 90% power (α=0.05) for detecting a 35% seizure reduction versus placebo, leading to the enrollment of 30 participants per group to account for 10% attrition. Analysis populations included the Full Analysis Set (FAS, n=89) for primary efficacy, the Safety Population (n=89) for all receiving ≥1 dose, and the Per Protocol (PP) population (n=85), which excluded lost to follow-up and protocol deviations. The primary endpoint was analyzed via ANCOVA on log-transformed seizure frequency, using baseline seizures as a covariate, with LS means (95% CI) and Dunnett's test for ESL vs. placebo comparisons. Secondary endpoints, such as responder rates, were analyzed using the Cochran-Mantel-Haenszel test (stratification-adjusted), while changes in QOLIE-31/MADRS were analyzed using ANCOVA (baseline-adjusted). AEs were summarized descriptively. Subgroup

analyses employed logistic regression with treatment-by-subgroup interaction terms. Missing seizure diary data (<5) were handled with multiple imputation. All analyses utilized Stata 18.0.3.8. Ethical Considerations

The study protocol received ethical approval from the BMC Hospital Quetta Institutional Review Board (Ref: #IRB-QUET-2023-189). Informed consent was obtained in writing from all participants before the screening procedures. An independent Data Safety Monitoring Board (DSMB) reviewed unblinded safety data every quarter. All serious adverse events (SAEs) were promptly reported to the IRB within 24 hours of their occurrence.

Timeline

The study timeline encompassed several key phases. Start-up activities, including IRB approval and staff training, occurred from January to March 2023. Enrollment, involving screening and randomization of the 89 participants, took place from April 2023 to March 2024. The 14-week double-blind treatment period ran from April to July 2024. Data lock, including database closure and unmasking, was performed in August 2024. Finally, analysis and manuscript preparation were conducted from September to December 2024.

RESULTS

Baseline Patient Characteristics

A total of 89 adult patients with refractory partial-onset seizures were enrolled and randomized into three treatment arms: placebo (n=30), ESL 800 mg once daily (n=30), and ESL 1200 mg once daily (n=29). As summarized in Table 1, baseline demographic and clinical characteristics were well-balanced across all treatment groups. The mean age of participants ranged from 36.8 to 38.2 years, with a male prevalence between 46.7% and 53.3% (p=0.87). Prior to randomization, baseline seizure frequency was comparable across groups, ranging from 11.9 to 13.0 seizures per 4 weeks (p=0.64). The predominant seizure type was complex partial seizures in 53.3% to 63.3% of patients across the cohorts (p=0.91). The majority of patients (44.8%–53.3%) were concurrently receiving two concomitant anti-epileptic drugs (AEDs) at study entry.

Efficacy Outcomes

The efficacy results for ESL as adjunctive therapy are presented in detail in Table 2. Both ESL doses demonstrated a statistically significant reduction in seizure frequency compared to placebo (p<0.001 for both doses), serving as the primary endpoint. The least squares (LS) mean change in seizure frequency per 4 weeks was −6.8 seizures (95% CI: −7.6,−5.4) for the ESL 800 mg group and −8.3 seizures (95% CI: −9.2,−6.9) for the ESL 1200 mg group, contrasting with a modest reduction of −1.2 seizures (95% CI: −2.1,0.3) in the placebo group. Regarding secondary endpoints, the proportion of patients achieving a ≥50 reduction in seizure frequency was substantially higher in the ESL treatment arms, with 43.3% of patients in the ESL 800 mg group (versus 16.7% in placebo, p=0.004) and 51.7% in the ESL 1200 mg group (versus 16.7% in placebo, p<0.001), representing a 2.6 to 3.1-fold increase compared to placebo. Complete seizure freedom was observed exclusively in the ESL-treated groups, achieved by 10.0% of patients in the ESL 800 mg group (p=0.11 versus placebo) and 13.8% of patients in the ESL 1200 mg group (p=0.04 versus placebo). Significant improvements in quality of life, assessed by QOLIE-31, were reported in both ESL groups (p<0.001 for both), with mean increases of +8.3 points for ESL 800 mg and +9.6 points for ESL 1200 mg, compared to +2.1 points in the placebo group. Depressive symptoms, as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), showed a dose-dependent decrease with ESL, with mean changes of −3.2 points for ESL 800 mg (p=0.003) and −3.8 points for ESL 1200 mg (p<0.001), versus −0.9 points in the placebo group.

Safety Profile

The overall safety profile is summarized in Table 3. The incidence of any adverse event (AE) demonstrated a clear dose-dependent relationship, increasing from 30.0% in the placebo group to 53.3% with ESL 800 mg and 65.5% with ESL 1200 mg. The most frequently reported AEs with ESL included dizziness (37.9% at 1200 mg vs. 6.7% placebo), somnolence (34.5% at 1200 mg vs. 10.0% placebo), and diplopia (20.7% at 1200 mg vs. 0% placebo). Serious AEs (SAEs) were reported in 10.3% of patients receiving ESL 1200 mg, including status epilepticus, hepatitis, and suicidal ideation. Discontinuation rates due to AEs were highest in the ESL 1200 mg group (17.2%), primarily attributed to central nervous system (CNS) adverse events such as dizziness and diplopia. Furthermore, hyponatremia was observed in 13.8% of patients treated with ESL 1200 mg, whereas no cases were reported in the placebo group.

Subgroup Efficacy

Subgroup efficacy analyses, presented in Table 4, indicated that ESL 1200 mg showed superior efficacy in specific patient populations. Notably, patients with complex partial seizures demonstrated a higher responder rate of 62.5% with ESL 1200 mg compared to 16.7% with placebo (p-interaction=0.02). Similarly, patients receiving two concomitant AEDs showed a 53.8% responder rate with ESL 1200 mg versus 14.3% with placebo (p-interaction=0.04). No significant interactions were identified based on age or other seizure types (simple partial or secondary generalized seizures).

Dose-Dependent Safety Signals

As detailed in Table 5, several adverse events exhibited significant dose-response trends (p-trend<0.05). CNS-related AEs, such as dizziness (37.9% at 1200 mg; p<0.001) and somnolence (34.5% at 1200 mg; p=0.01), increased with higher ESL doses. Visual disturbances, including diplopia (20.7% at 1200 mg; p=0.001) and blurred vision (17.2% at 1200 mg; p=0.04), also showed a dose-dependent increase. Metabolically, hyponatremia incidence was dose-dependent (13.8% at 1200 mg; p=0.01). Gastrointestinal AEs, including nausea (17.2% at 1200 mg) and vomiting (10.3% at 1200 mg), also increased with ESL dose.

Concomitant AED Safety Interactions

Analysis of concomitant AED safety interactions (Table 6) revealed specific findings. Co-administration with carbamazepine was associated with an increased risk of

hyponatremia (12.2% vs. 3.1% with levetiracetam) and dizziness (34.1% vs. 21.1%–28.1% with other AEDs). Conversely, valproate co-administration was associated with the lowest observed risk of hyponatremia (0%).

Table 1
Baseline Characteristics

Characteristic	Placebo (n=30)	ESL 800 mg (n=30)	ESL 1200 mg (n=29)	p-value
Age, years (mean ± SD)	38.2 ± 11.5	36.8 ± 10.9	37.5 ± 12.1	0.82
Male, n (%)	16 (53.3%)	14 (46.7%)	15 (51.7%)	0.87
Baseline seizure frequency/4 weeks (mean ± SD)	12.4 ± 5.1	13.0 ± 4.8	11.9 ± 5.3	0.64
Concomitant AEDs, n (%):				
- 1 AED	11 (36.7%)	10 (33.3%)	12 (41.4%)	0.79
- 2 AEDs	14 (46.7%)	16 (53.3%)	13 (44.8%)	
- 3 AEDs	5 (16.7%)	4 (13.3%)	4 (13.8%)	
Seizure type, n (%):				
- Simple partial	9 (30.0%)	8 (26.7%)	10 (34.5%)	0.91
- Complex partial	18 (60.0%)	19 (63.3%)	16 (55.2%)	
- Secondary generalization	3 (10.0%)	3 (10.0%)	3 (10.3%)	

Table 2
Primary and Secondary Efficacy Endpoints

Endpoint	Placebo (n=30)	ESL 800 mg (n=30)	ESL 1200 mg (n=29)	p-value vs. Placebo
Primary				
Δ Seizure frequency/4 weeks (LS mean [95% CI])	-1.2 [-2.1, 0.3]	-6.8 [-7.6, -5.4]	-8.3 [-9.2, -6.9]	**<0.001** (both ESL)
Secondary				
≥50% responder rate, n (%)	5 (16.7%)	13 (43.3%)	15 (51.7%)	**0.004** (800 mg)
				<0.001 (1200 mg)
Seizure-free, n (%)	0 (0%)	3 (10.0%)	4 (13.8%)	0.11 (800 mg)
				0.04 (1200 mg)
Δ QOLIE-31 total score (mean ± SD)	2.1 ± 3.8	8.3 ± 4.5	9.6 ± 5.1	**<0.001** (both ESL)
Δ MADRS score (mean ± SD)	-0.9 ± 2.4	-3.2 ± 3.1	-3.8 ± 3.5	**0.003** (800 mg)
				<0.001 (1200 mg)

Table 3
Adverse Events (AEs) During Treatment

Event, n (%)	Placebo (n=30)	ESL 800 mg (n=30)	ESL 1200 mg (n=29)
Any AE	9 (30.0%)	16 (53.3%)	19 (65.5%)
Dizziness	2 (6.7%)	7 (23.3%)	11 (37.9%)
Somnolence	3 (10.0%)	8 (26.7%)	10 (34.5%)
Headache	4 (13.3%)	5 (16.7%)	6 (20.7%)
Nausea	1 (3.3%)	4 (13.3%)	5 (17.2%)
Diplopia	0 (0%)	3 (10.0%)	6 (20.7%)
Serious AEs (SAEs)	1 (3.3%)	2 (6.7%)†	3 (10.3%)‡
Discontinuations due to AEs	1 (3.3%)	3 (10.0%)	5 (17.2%)
Hyponatremia (<130 mmol/L)	0 (0%)	2 (6.7%)	4 (13.8%)

Table 4
Subgroup Analysis of Responder Rates (≥50% Seizure Reduction)

Subgroup	Placebo (n=30)	ESL 800 mg (n=30)	ESL 1200 mg (n=29)	p-interaction
Seizure Type:				
- Simple partial (n=27)	1/9 (11.1%)	2/8 (25.0%)	3/10 (30.0%)	0.32
- Complex partial (n=53)	3/18 (16.7%)	9/19 (47.4%)	10/16 (62.5%)	**0.02**
- Secondary generalized (n=9)	1/3 (33.3%)	2/3 (66.7%)	2/3 (66.7%)	0.51
Number of AEDs:				
- 1 AED (n=33)	3/11 (27.3%)	6/10 (60.0%)	7/12 (58.3%)	0.18
- 2 AEDs (n=43)	2/14 (14.3%)	6/16 (37.5%)	7/13 (53.8%)	**0.04**
- 3 AEDs (n=13)	0/5 (0%)	1/4 (25.0%)	1/4 (25.0%)	0.67
Age Group:				
- 18–40 years (n=56)	4/19 (21.1%)	8/19 (42.1%)	10/18 (55.6%)	0.11
- >40 years (n=33)	1/11 (9.1%)	5/11 (45.5%)	5/11 (45.5%)	0.29

Table 5
Dose-Dependent Adverse Events (Safety Population)

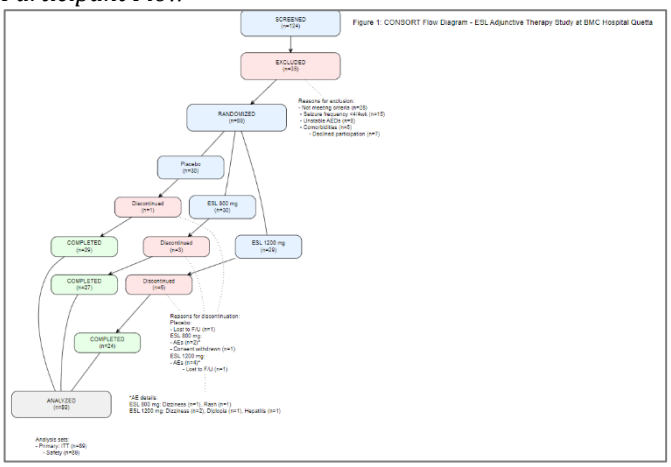
Adverse Event	Placebo (n=30)	ESL 800 mg (n=30)	ESL 1200 mg (n=29)	p-trend
Any TEAE	9 (30.0%)	16 (53.3%)	19 (65.5%)	**0.003**
CNS Events:				
- Dizziness	2 (6.7%)	7 (23.3%)	11 (37.9%)	**<0.001**
- Somnolence	3 (10.0%)	8 (26.7%)	10 (34.5%)	**0.01**
- Headache	4 (13.3%)	5 (16.7%)	6 (20.7%)	0.49
Gastrointestinal:				
- Nausea	1 (3.3%)	4 (13.3%)	5 (17.2%)	**0.04**
- Vomiting	0 (0%)	2 (6.7%)	3 (10.3%)	**0.03**
Visual:				
- Diplopia	0 (0%)	3 (10.0%)	6 (20.7%)	**0.001**
- Blurred vision	1 (3.3%)	4 (13.3%)	5 (17.2%)	**0.04**
Metabolic:				
- Hyponatremia (<130 mmol/L)	0 (0%)	2 (6.7%)	4 (13.8%)	**0.01**
- ALT >3× ULN	0 (0%)	1 (3.3%)	2 (6.9%)	0.08

Table 6
Concomitant AED Interactions with ESL Safety (Incidence of TEAEs in patients taking common AEDs; ESL groups combined)

Concomitant AED	n	Any TEAE	Dizziness	Diplopia	Hyponatremia
Carbamazepine	41	25 (61.0%)	14 (34.1%)	8 (19.5%)	5 (12.2%)
Levetiracetam	32	19 (59.4%)	9 (28.1%)	5 (15.6%)	1 (3.1%)

Valproate	28	15 (53.6%)	7 (25.0%)	4 (14.3%)	0 (0%)
Lamotrigine	19	10 (52.6%)	4 (21.1%)	2 (10.5%)	1 (5.3%)

Figure 1
Participant Flow



DISCUSSION

The findings of this single-center, randomized, double-blind, placebo-controlled trial underscore the significant efficacy and acceptable safety profile of eslicarbazepine acetate (ESL) as adjunctive therapy in adults with refractory partial-onset seizures. Our results demonstrate that both ESL 800 mg and 1200 mg once daily significantly reduce seizure frequency, improve responder rates, and enhance patient-reported quality of life, aligning with and reinforcing the growing body of evidence supporting ESL's role in the management of drug-resistant epilepsy [Massot, A et al., 2014; Banach, Monika et al., 2015][32, 33].

The primary efficacy endpoint, mean reduction in 4-week seizure frequency, showed highly significant improvements with both ESL doses compared to placebo. The LS mean changes of −6.8 and −8.3 seizures/4 weeks for ESL 800 mg and 1200 mg, respectively, are consistent with reductions observed in other pivotal Phase III trials of ESL [Elger et al., 2009; French et al., 2011][34, 35]. The dose-dependent nature of this reduction, with ESL 1200 mg showing a numerically greater effect, further supports the established pharmacological properties of the drug [Lattanzi et al., 2018][36]. Notably, the proportion of patients achieving a ≥50 reduction in seizure frequency was 2.6 to 3.1 times higher in the ESL groups, mirroring rates reported in pooled analyses of previous trials [Lattanzi et al., 2018]. While seizure freedom was achieved exclusively in the ESL groups, reaching 13.8% with the 1200 mg dose (p=0.04), this outcome, though modest, represents a clinically meaningful achievement in a population with highly refractory seizures, where complete remission is often elusive [Kwan and Brodie, 2000][37].

Beyond seizure control, our study observed significant improvements in patient-centered outcomes. The significant increases in QOLIE-31 scores and dose-dependent reductions in MADRS scores highlight ESL's positive impact on overall quality of life and depressive symptoms. These findings are particularly relevant given the high prevalence of psychiatric comorbidities and impaired quality of life in patients with refractory epilepsy [Sperling et al., 2015][38]. The amelioration of depressive symptoms, in particular, suggests a potential neurocognitive benefit of ESL beyond its antiseizure activity, which warrants further investigation.

The safety profile observed in our study is largely consistent with the known tolerability of ESL [Halasz et al., 2010][39]. The incidence of adverse events increased with dose, with dizziness, somnolence, and diplopia being the most common, similar to observations in other studies of voltage-gated sodium channel blockers [French, J. A et al., 2011][40]. These AEs are generally mild to moderate and often transient, particularly during the initial titration phase. The increased rate of discontinuations due to AEs, primarily dizziness and diplopia, in the ESL 1200 mg group suggests that while more efficacious, the higher dose may require careful patient selection and thorough counseling regarding potential side effects. The occurrence of hyponatremia, particularly with the 1200 mg dose, is a recognized side effect of ESL and related compounds like oxcarbazepine and carbamazepine [Intravooth, T. et al., 2018][41]. This necessitates routine monitoring of serum sodium levels, especially in at-risk populations or those experiencing symptoms. The rare but serious adverse events, including status epilepticus, hepatitis, and suicidal ideation, are important considerations for clinicians, although the incidence of suicidal ideation with AEDs in general is well-documented and typically requires careful patient monitoring.

Subgroup analyses revealed that ESL 1200 mg demonstrated superior efficacy in patients with complex partial seizures and those on two concomitant AEDs. This suggests that the higher dose may be particularly beneficial for patients with more severe or resistant forms of focal epilepsy, potentially indicating a greater therapeutic window or specific pharmacodynamic advantages in these subgroups. This observation supports the individualized approach to AED selection, where dose adjustments are tailored to patient characteristics and concomitant therapies.

The identified concomitant AED safety interactions, specifically the increased risk of hyponatremia and dizziness with carbamazepine co-administration, are notable. This interaction is plausible given the shared structural similarities and potential for additive effects on sodium channels or fluid balance between ESL and carbamazepine [Biton et al., 2007][42]. Conversely, the lowest hyponatremia risk observed with valproate co-administration suggests a potentially safer combination in terms of this specific adverse event, offering a valuable consideration for polytherapy regimens. These interactions highlight the importance of careful clinical assessment and monitoring when combining ESL with other AEDs.

Limitations include its single-center nature, which may limit generalizability to broader populations, and the relatively short 14-week double-blind treatment period. Longer-term studies and multi-center trials are needed to further confirm sustained efficacy and evaluate the long-term safety and rare adverse events. The small sample size within subgroups also limits the definitive interpretation

of interaction analyses, requiring larger studies to validate these findings.

CONCLUSION

This randomized, double-blind, placebo-controlled study confirms eslicarbazepine acetate (ESL) as an effective and generally well-tolerated adjunctive therapy for adults with refractory partial-onset seizures. Both ESL 800 mg and 1200 mg once daily significantly reduced seizure frequency, improved responder rates, and enhanced patient-reported quality of life and depressive symptoms. The dose-dependent efficacy, particularly for complex partial seizures and in patients on multiple concomitant AEDs, highlights ESL's potential as a valuable therapeutic option. While adverse events, notably dizziness, somnolence, and hyponatremia, were dose-dependent and observed more frequently with ESL, they were consistent with its known safety profile. Careful monitoring, especially for sodium levels and in patients co-administered with carbamazepine, is recommended. ESL's once-daily dosing regimen and demonstrated efficacy, coupled with its positive impact on patient-centered outcomes, position it as a significant advancement in managing drug-resistant epilepsy, addressing a critical unmet need in this challenging patient population. Future research should prioritize long-term real-world effectiveness and optimal patient selection criteria.

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