Depression and Antiepileptic Drug Use Do Not Affect Eslicarbazepine Efficacy in Patients With Partial-Onset Seizures

Written by Maria Vinall

When used as adjunctive treatment of refractory partial-onset seizures (POS), eslicarbazepine acetate (ESL) is strongly associated with significant reductions in seizure frequency [Sperling MR et al. *Epilepsia.* 2015]. T. Christopher Bond, PhD, and investigators from Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts, USA, and Covance Market Access Services, Gaithersburg, Maryland, USA, reported in a poster that the effect of ESL was not significantly modified by baseline depressive symptoms or use of concomitant antiepileptic drug (AED) therapy.

The purpose of this pooled analysis of 3 randomized double-blind phase 3 clinical trials [Sperling MR et al. *Epilepsia.* 2015; Ben-Menachem E et al. *Epilepsy Res.* 2010; Elger C et al. *Epilepsia.* 2009] was to determine whether the impact of adjunctive ESL on seizure frequency reduction (SFR) was influenced by the presence of depressive symptoms at baseline or by use of concomitant AEDs in patients with POS. A secondary assessment addressed the association between measures of depressive symptoms at baseline and SFR.

Patients with uncontrolled POS were randomized to either ESL (800 or 1200 mg QD) or placebo. Two binomial regression models were developed to evaluate the associations between baseline factors and treatment response. One included the 10-item Montgomery-Åsberg Depression Rating Scale (MADRS), in which scores ≥20 indicate moderate to severe depressive symptoms. The second was based on the 5-item Emotional Well-Being (EWB) subscale of the Quality of Life in Epilepsy Inventory–31 self-assessment questionnaire, in which a score ≤52 indicates the presence of depressive symptoms. A ≥50% SFR between baseline and the end of the 12-week maintenance period was defined as an ESL treatment response. Both models were controlled for multiple baseline factors and interactions. Demographic and baseline characteristics of the patients are shown in Table 1.

Mean number of AEDs used at baseline was 1.8, with carbamazepine being the most common (48.1%). With the MADRS model, <10% of patients were classified as having moderate to severe depressive symptoms, while almost 35% had depressive symptoms based on the EWB model. The presence of baseline depressive symptoms was significantly associated with treatment response in the MADRS model (OR, 1.57; 95% CI, 1.01 to 2.45; $P=.044$) but not in the EWB model (OR, 1.18; 95% CI, 0.86 to 1.60; $P=.311$). The effect of ESL was not significantly modified by depressive symptoms or baseline AED use in either model. Furthermore, treatment with ESL (both doses) was significantly associated with greater likelihood of treatment response on the basis of both models compared with placebo ($P<.001$; Table 2).

Treatment with adjunctive ESL significantly reduced seizure frequency, which was not modified by the presence of depressive symptoms or the use of other AEDs. The association between depressive symptoms and treatment response differed according to the instruments used to assess these symptoms.

Table 1. Demographic and Baseline Clinical Characteristics

Characteristic	n (%) / Mean ± SD
Age, y	38.0 ± 12.12
Female	594 (49.6)
Duration of epilepsy, y	21.4 ± 12.99
Body mass index, kg/m^2	25.5 ± 5.35
Seizure frequency	15.4 ± 21.37
Race	
Caucasian	933 (77.9)
Asian	126 (10.5)
Black	42 (3.51)
Hispanic	15 (1.25)
Other	81 (6.8)
Region	
Eastern Europe	371 (31.0)
Latin America	263 (22.0)
North America	224 (18.7)
Western Europe	160 (13.4)
Rest of world	179 (15.0)
MADRS≥20	113 (9.4)
EWB≤52	409 (34.2)
No. of AEDs at baseline	1.8 ± 0.49
Concomitant AEDs	
Carbamazepine	576 (48.1)
Lamotrigine	294 (24.6)
Valproic acid	266 (22.2)
Levetiracetam	234 (19.6)

Patients in the pooled modified intent-to-treat population with available seizure frequency reduction data (n = 1 197).

AEDs, antiepileptic drugs; EWB, Emotional Well-Being subscale; MADRS, Montgomery–Åsberg Depression Rating Scale.

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Table 2. ORs From Final Regression Models

Parameter	MADRS Model		EWB Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
ESL 1200 mg vs PBO	2.68 (1.94 to 3.69)	< .001	2.64 (1.92 to 3.64)	< .001
ESL 800 mg vs PBO	1.89 (1.37 to 2.62)	< .001	1.89 (1.37 to 2.61)	< .001

ESL, eslicarbazepine acetate; EWB, Emotional Well-Being subscale; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo.

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Levodopa-Carbidopa Intestinal Gel Shows Promise in Advanced Parkinson Disease

Written by Maria Vinall

Interim data from an ongoing phase 3b trial, presented in a poster by Jordan Dubow, MD, AbbVie, Inc., North Chicago, Illinois, USA, indicated that treatment with levodopa-carbidopa intestinal gel (LCIG) significantly improved nonmotor symptoms (NMSs) in patients with advanced Parkinson disease (PD).

NMSs play an important role, clearly affecting health-related quality of life (HRQOL) of patients with PD. LCIG (carbidopa-levodopa enteral suspension) is an effective treatment option for motor fluctuations in advanced refractory PD [Olanow CW et al. *Lancet Neurol.* 2014]. Open-label studies have shown that LCIG is associated with significant improvements in NMSs and HRQOL in patients with advanced PD [Fasano A et al. *Eur Rev Med Pharmacol Sci.* 2012; Reddy P et al. *Clin Neuropharmacol.* 2012].

This phase 3b, open-label, multicenter study [NCT01736176] included patients aged ≥30 years with levodopa-responsive idiopathic PD and severe motor fluctuations with ≥3 hours of "off" time/day (despite individually optimized therapy). After conversion to oral levodopa-carbidopa, all patients underwent a percutaneous endoscopic gastrostomy-jejunostomy placement procedure. The study included an initial 12-week LCIG treatment period and a 48-week long-term treatment period. The primary end point was the change in NMSs from baseline to week 12 as measured by the Non-Motor Symptoms Scale (NMSS) total score. Secondary end points included the change from baseline to week 12 in the 9 NMSS domains. Adverse events (AEs) were recorded. Interim analysis was completed for the first 17 of 36 participants.

Patients had a mean age of 64 years (range, 45-76), 65% were men, and 94% were white. Mean exposure to LCIG was 180 days (range, 5-368 days). Fourteen of 17 patients had a reduction in NMSS total score between baseline and final evaluation; the mean reduction was 38.3% (–20.7; $P = .001$).

Significant decreases were noted in 3 of the 9 NMSS domains: sleep/fatigue (–6.7; $P = .008$), sexual function (–2.5; $P = .011$), and miscellaneous (–4.9; $P = .002$).

At least 1 treatment-emergent AE was reported for 16 patients, and 2 patients discontinued due to AEs. The most frequently reported AEs were procedural pain (65%) and anxiety (24%). Serious AEs were reported for 2 patients; neither was considered related to LCIG.

This study provides additional evidence that LCIG can be a safe and effective treatment for NMSs in patients with advanced PD.

Brivaracetam Reduces Seizure Frequency in Patients With Partial-Onset Seizures

Written by Maria Vinall

Pavel Klein, MD, Mid-Atlantic Epilepsy and Sleep Center, Bethesda, Maryland, USA, presented the results of a phase 3 trial [NCT01261325] showing that adjunctive treatment with brivaracetam is associated with a significant reduction in the frequency of partial-onset seizures (POS) and improved response.

Brivaracetam is a selective high-affinity synaptic vesicle protein 2A ligand in clinical development for the treatment of epilepsy. The objective of this multicountry phase 3 study was to evaluate the efficacy, safety, and tolerability of brivaracetam compared with placebo as an adjunctive therapy in adult patients with focal epilepsy. Patients enrolled in this study had POS not fully controlled, despite treatment with 1 or 2 concomitant antiepileptic drugs. The study consisted of an 8-week baseline observational period and a 12-week treatment period, after which patients could undergo a 4-week down titration or enter into an open-label follow-up study. The co–primary efficacy outcomes were percentage reduction over placebo in 28-day adjusted seizure frequency and ≥50% responder rate based on percentage reduction in seizure frequency from baseline to the treatment period.

Patients aged ≥16 to 80 years with refractory POS who experienced ≥8 POS during the 8-week baseline period and ≥2 POS per month, with or without secondary generalization, during the 3 months prior to screening were recruited. Eligible patients were randomized 1:1:1 to placebo or brivaracetam 100 or 200 mg/d BID. During the 12 weeks of treatment, the rate of discontinuation was low and mostly due to adverse events (AEs; 3.8% in the placebo group and 8.3% and 6.8% among patients in the