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Brief Communication

Eslicarbazepine acetate as a replacement for levetiracetam in people with epilepsy developing behavioral adverse events

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ABSTRACT

Background: Psychiatric and behavioral side effects (PBSEs) are a major cause of antiepileptic drug (AED) withdrawal. Levetiracetam (LEV) is a recognized first-line AED with good seizure outcomes but recognized with PBSEs. Eslicarbazepine (ESL) is considered to function similarly to an active metabolite of the commonly used carbamazepine (CBZ). Carbamazepine is used as psychotropic medication to assist in various psychiatric illnesses such as mood disorders, aggression, and anxiety.
Aim: The aim was to evaluate the psychiatric profile of ESL in people who had LEV withdrawn due to PBSEs in routine clinical practice to see if ESL can be used as a possible alternative to LEV.
Methods: A retrospective observational review was conducted in two UK epilepsy centers looking at all cases exposed to ESL since its licensing in 2010. The ESL group was all patients with treatment-resistant epilepsy who developed intolerable PBSEs to LEV, subsequently trialed on ESL. The ESL group was matched to a group who tolerated LEV without intolerable PBSEs. Psychiatric disorders were identified from case notes. The Hamilton Depression Scale (HAM-D) was used to outcome change in mood. Clinical diagnoses of a mental disorder were compared between groups using the Fisher's exact test. Group differences in HAM-D scores were assessed using the independent samples *t*-test (alpha = 0.05).
Results: The total number of people with active epilepsy in the two centers was 2142 of whom 46 had been exposed to ESL. Twenty-six had previous exposure to LEV and had intolerable PBSEs who were matched to a person tolerating LEV. There was no statistical differences in the two groups for mental disorders including mood as measured by HAM-D (Chi-square test: $p = 0.28$).
Conclusion: The ESL was well tolerated and did not produce significant PBSEs in those who had PBSEs with LEV leading to withdrawal of the drug. Though numbers were small, the findings suggest that ESL could be a treatment option in those who develop PBSEs with LEV and possibly other AEDs.

1. Background

Epilepsy is a neurological condition with an enduring predisposition to generate seizures and is associated with cognitive, psychological, and social issues [1]. Neuropsychiatric disorders are also more prevalent in people with epilepsy than in the general population [2,3]. There is, however, still ambiguity as to whether these comorbidities are the result of a direct link such as a genetic predisposition or structural cause leading to seizures and psychiatric problems or if seizures over time lead to psychiatric symptoms [4].

Treatment strategies in epilepsy need to be tailored to the individual and in particular, clinicians when choosing the appropriate antiepileptic drug (AED) medication need to pay attention not only to seizure patterns but also to a number of different parameters such as age, gender, comorbidities, and cognitive state.

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Up to 75% of people with epilepsy may at some point have mental health issues. Antiepileptic drugs also have the potential to impact on mental health and cognition [5,6], and treatment with some AEDs is associated with the occurrence of psychiatric and behavioral side effects (PBSEs) while other may have beneficial psychotropic effects [7–10]. The PBSEs are often overlooked in epilepsy management and, withdrawal of an AED occurs only if the impact of these symptoms is significant and usually a risk to self or others.

Understanding psychotropic effects of (AEDs) is crucial but knowledge is limited. Carbamazepine (CBZ)-purported mode of action is via the modulation of voltage-sensitive sodium channels. Apart from antiepileptic action, CBZ is also used as a mood stabilizer and has proven efficacy in affective disorders. Oxcarbazepine (OXB) is structurally related to CBZ and is a prodrug that is converted into licarbazepine. The active form licarbazepine is the S enantiomer, known as eslicarbazepine (ESL). The presumed mechanism of action is as for CBZ. Conversely, OXB has never been proven to work as a mood stabilizer. In view of similarities of the postulated mechanism of action but a better tolerability profile, OXB has been used "off label" in mood management.

Levetiracetam (LEV), a commonly prescribed AED in the UK, is associated with PBSEs including irritability, depression, and anxiety [9,11]. A study suggested that PBSEs occurred in around 17% of people exposed to commonly used AEDs. Nearly 1 in 5 study participants on LEV reported PBSEs to LEV. However for CBZ the reported PBSEs were significantly lower [11]. The ESL did not figure in this study. Another study suggested that PBSEs with ESL were <2.5%. While side effects such as irritability, anxiety, and aggressive behavior have been associated with other AEDs, rates of aggression and agitation were comparable between ESL and placebo [12].

2. Aim

The aim was to evaluate the psychiatric profile of ESL in people who had LEV withdrawn due to perceived PBSEs in routine clinical practice.

3. Material and methods

3.1. ESL group (cases)

The study design was a retrospective case note review of those who satisfied the International League Against Epilepsy (ILAE) criteria of drug-resistant epilepsy [13] in two UK epilepsy secondary care centers (Cornwall and Stafford). All adults treated with ESL between 2010, when it was initially licensed, and 2016 were identified. Reasons for stopping ESL were established in those that came off it. In this subgroup, those exposed to LEV were identified and we ascertained if they were still continuing on LEV, and for those who had LEV withdrawn causes were established for the withdrawal. The final ESL group was of those who had ESL introduced after LEV withdrawal due to PBSEs.

3.2. LEV group

The LEV group was those on LEV who did not have PBSEs or if these were not severe enough to lead to discontinuation of the drug. For each individual in the ESL group, another on LEV from either center was selected as a match. Individuals were matched for clinical and demographic characteristics and time of exposure to LEV using a formal matching algorithm. It was ensured that the selected people were not on monotherapy when LEV was started.

3.3. Characteristics and evaluation of ESL and LEV groups

Demographic and clinical characteristics including etiology, seizure types, epileptic syndrome, seizure frequency, and AEDs were obtained for all. Clinical records including primary care profiles of all subjects were checked for history and type of diagnosed psychiatric disorders and alcohol problems. This included both pre- and posttreatment of ESL or LEV. Seizure response was defined as a change of seizure frequency of at least 50% vs baseline over an observation interval of 3 months. Of the major mental disorders, presentations such as psychosis or mania would be clinically recognized. Some individuals had more than one diagnoses but only the most significant diagnosis was taken. Only people who had taken ESL or LEV for over 6 months were included into the final ESL and LEV groups as this was felt adequate to achieve any dose titrations needed and reflect any identifiable associations of emergent psychiatric side effects. The ESL and LEV group participants received a Hamilton Depression Scale (HAM-D) to screen for depressive symptoms. The HAM-D was administered at the time of the last clinical review prior data collection to all participants of the project and was done posttreatment.

It is recognized that the HAM-D is a screening instrument. The HAM-D has a Sensitivity of 86.4% and Specificity of 92.2% to pick up depression. The internal consistency of the HAM-D is reported to be 0.76–0.92, and the inter-rater reliability on HAM-D is 0.87–0.95. It was felt that a recognized scale to help provide structured and objective feedback of the two groups would avoid clinical ambiguity around diagnosis of depression. Further, in recognition that there might be ambivalence around scores where HAM-D is in the range of screening for mild depression, normal–mild scores were taken as one cohort unlikely to have clinical depression and moderate–severe scores as representative of high likelihood of clinical depression.

3.4. Statistical analysis

We used descriptive statistics to assess frequencies and distributions. Clinical diagnoses of a mental disorder, alcohol misuse/dependence, and other categorical variables both pre- and posttreatment were compared between groups using Fisher's exact test. Group differences in HAM-D scores and other quantitative variables, including age, seizure frequency, and use of AEDs, were assessed using the independent samples *t*-test. The level of statistical significance was set at alpha = 0.05.

The study was approved as a clinical audit to ascertain PBSEs and potential benefits of ESL.

4. Results

The total number of people with active epilepsy in the two centers was 2142 of whom 46 had been exposed to ESL. Two had withdrawn ESL before 6 months due to nonpsychiatric effects (dizziness and nausea). A further three were withdrawn due to perceived lack of effect. Of the 41 remaining in the ESL group, three were coprescribed LEV, and thus, excluded. Twenty-six of the remaining 38 in the ESL group had previous exposure to LEV. The study design results are provided in Fig. 1.

The PBSEs which led to withdrawal of LEV included one drug-induced psychosis, six for hypomania, 18 for aggressive behavior and other personality changes such as agitation, anger, and hostility, one for personality disorder worsening, four for anxiety disorders & panic disorders, and one each for clinical depression, Post Traumatic Stress Disorder (PTSD), and depersonalization, respectively. These people subsequently received ESL (the ESL group) and tolerated it. Though all 26 had a noticeable adverse mental state change, only 10 had the symptom cluster for a diagnosable clinical psychiatric disorder pretreatment with ESL.

Each of the 26 people on ESL was matched with a person on LEV. Generalized tonic–clonic seizures (GTCS) were matched to 22 cases (85%) with 4 cases matched to focal seizures.

Demographic and baseline clinical detail summary for both the ESL and LEV group are provided in Table 1. Patients on LEV had a lower mean seizure frequency and number of AEDs used during the pretreatment period than the patients on ESL ($p < 0.01$). Table 2 provides

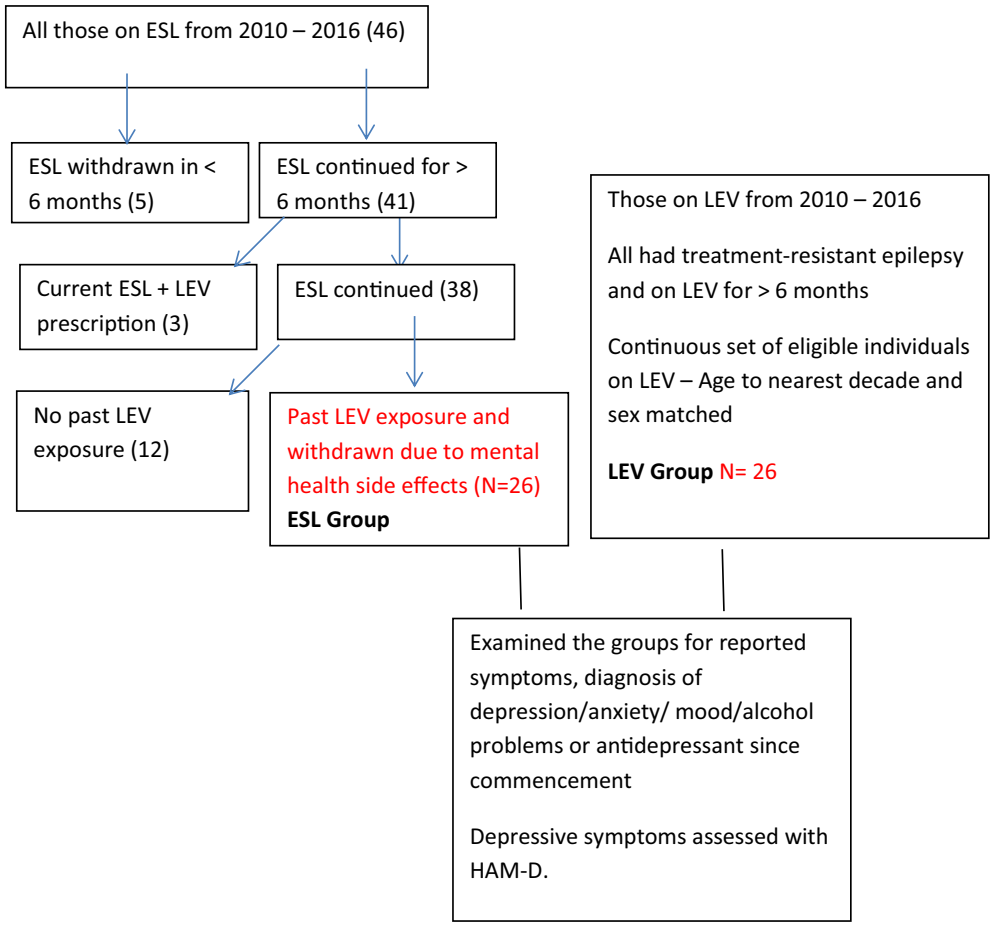

Fig. 1. Study flow chart.

posttreatment comparisons between the two groups. Patients on LEV had a higher response rate at 3 months than the patients on ESL ($p = 0.01$).

Lamotrigine was the most common concomitant AED used by 19 of the 26. The dose of ESL was 800 mg/day in 21 individuals (81%), while four (15%) were on 400 mg/day and one on 1200 mg/day. The 10 participants with past psychiatric disorders had PTSD in 1, clinical depression (moderate) in 1, transient psychosis in 1, anxiety/panic disorders in 6, and personality disorder in 1.

Common concurrent AEDs with LEV were lamotrigine and sodium valproate being the commonest (each used by 12 people). The LEV dose ranged from 750 to 4000 mg/day. The seven with psychiatric history included previous clinical depression (mild–moderate) in 4, social phobia in 1, panic attacks in 1, and Attention Deficit Hyperactivity Disorder (ADHD) in 1.

There was no statistical difference in mean HAM-D score between the two groups ($p = 0.28$) (Fig. 2).

Table 1
Comparison between the ESL and the LEV groups – pretreatment.

Variables	ESL (N = 26)	LEV (N = 26)	p-Value
Age in years: mean (SD)	45.8 (15.7)	49.2 (17.1)	0.63
Females	13 (50%)	13 (50%)	1.00
Structural cause apparent	12 (48%)	9 (36%)	0.57
Prior AEDs used: mean (SD)	10 (2.4)	5 (1.5)	<0.01
Prior seizure frequency: mean (SD)	5.5 (3.2)	2.8 (2.3)	<0.01
Past psychiatric history	10 (38%)	7 (27%)	0.56
Alcohol misuse/dependence	5 (19%)	10 (38%)	0.22
Concurrent AED: mean (SD)	3.2 (1.1)	2.7 (0.8)	0.10

5. Discussion

This pragmatic study compared the psychiatric profile of people who could not tolerate LEV but tolerated ESL with a group who tolerated LEV. The strengths include robust case selection and predefined criteria. The PBSEs which led to LEV withdrawal in the ESL group were similar to those previously reported [11,14].

There were no differences in psychiatric diagnoses or depressive symptoms between the ESL and LEV groups suggesting that ESL might be better tolerated by those who encounter intolerable PBSEs to LEV. Though some of the previous studies indicate that the overall tolerability of ESL is low compared with LEV, the incidence of PBSEs has been shown to be lower in ESL compared with LEV [15], consistent with our findings. We found that ESL was well tolerated and did not produce significant PBSE in those who had PBSE with LEV leading to withdrawal of the drug. Contrary to our finding, a study had found that LEV was better than ESL in terms of adverse events leading to withdrawal of AEDs [16]. Though our numbers were small, the findings suggest that ESL could be a treatment option in those who develop PBSE with LEV and other similar drugs.

Table 2
Comparison between the ESL and the LEV groups – posttreatment.

Variables	ESL (N = 26)	LEV (N = 26)	p-Value
Concurrent AED: mean (SD)	3.2 (1.1)	2.7 (0.8)	0.10
3-month responder rate at 3 months	23.1%	61.5%	0.01
3-month responder rate at 6 months	30.8%	57.7%	0.09
HAM-D – normal to mild (0–13)	12	14	0.78
HAM-D – moderate to severe (14+)	14	12	0.78

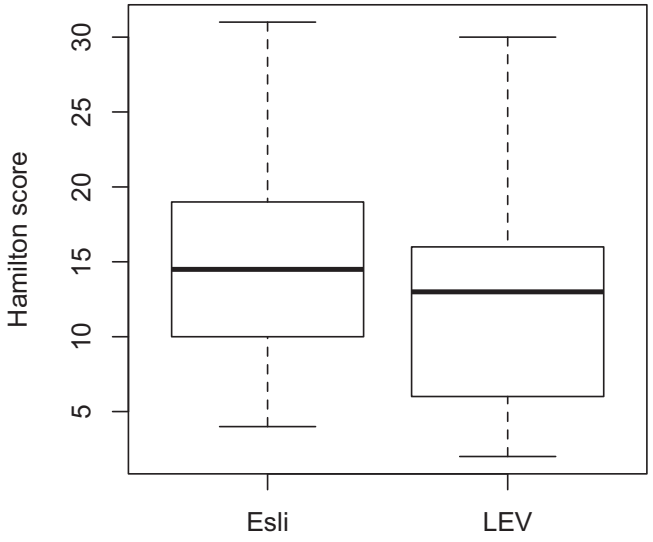

Fig. 2. Comparison of HAM-D scores in the ESL and LEV groups.

Previous studies indicate that the incidence of PBSE is higher in those with past psychiatric history and focal seizures [11]. The ESL or other sodium channel-blocking drugs rather than LEV or related compounds could be considered as treatment option in such individuals.

We acknowledge several limitations. These included a retrospective design, dependence mostly on case notes and a lack of a standardized psychiatric assessment before exposure to either drug. Efforts were however made to mitigate this by using two different sources, i.e., the primary care records and the epilepsy case notes to confirm consistency of clinical data in particular the psychiatric issues.

There were challenges in the LEV group matching. There was a difference between the two groups in terms of structural cause (48% vs 36%), prior seizure frequency (144 vs 73), and number of previous AED (10 vs 5) though we attempted to match for etiology of seizures. These factors which could not be controlled could also be the reason for better treatment response in the LEV group. The responder rates of the LEV group were twice of the ESL group. A possible explanation for this is that LEV had been used sooner than ESL in the new treatment-resistant population. People on ESL had gone through a greater number of AEDs including LEV suggesting the poorer response may be because the ESL group represents a more severe end of the treatment-resistance spectrum. Even though the ESL group has significantly more seizures, it is not associated with more psychiatric concerns. This study analyzes a cohort of patients who already are on the medication for greater than 6 months so it is possible that the 5 patients who discontinued the medication prior and thus not eligible for the study had psychiatric or behavioral symptoms not otherwise noted in the case notes.

A further confounder is the possibilities of other medication people are on which can influence mental state as a side effect. Information on nonpsychotropic medication was not collected. However, even if collected, it would be difficult to ascertain influences as side effects can be diverse and of differing likelihood. This would require a complex set of analysis.

The low numbers in our groups may also introduce errors of not finding statistical differences when they may be present. To make the study meaningful, it was imperative to look at whole populations. Of the 46, initially eligible 20 were ruled out thus leaving only 26 (56%) for the ESL population thus accounting for the low numbers. Ideally, the design of the study should also have looked to recruit four controls for each ESL subject. However, this was an explorative study. Further, there were practical challenges of identifying suitable matching controls from the population of the two centers satisfying prerequisite criteria which was strictly defined. It was felt that a 1:1 participant representation of the ESL to the LEV groups would help identify possibly associations to consider future larger studies if there were any interesting areas to explore.

The study did yield some interesting findings but these should be seen as provisional and require replication before mandating a change in clinical practice.

6. Conclusion

The findings from our study indicate that ESL was tolerated by those in whom LEV had to be withdrawn due to PBSE. The ESL, thus, could be considered a viable alternative to individuals who encounter intolerable PBSEs. A further large scale study is required to confirm findings from our study.

Conflicts of interest

There is no identified conflict of interest to any author other than Dr Ahmed who is an employee of Bial which is responsible for the manufacture and marketing of Eslicarbazepine Acetate.

Disclosures

This study was initiated, designed, and sponsored in association with Bial - Eisai Europe Ltd. Eisai & Bial were involved in the review of this manuscript. Dr. Ahmed is an employee of Bial Pharma Ltd. UK. RS and BNMcL have received institutional and research support and personal fees from LivaNova, UCB, Eisai, Special Products, Bial, and Desitin outside the submitted work. MP and PT have received educational grants from UCB, Special Products, Eisai, and Bial. MP has received support from Bial and Eisai to present this work as a poster at the European Neurology Conference 2017 at Amsterdam. JWS has received departmental research support from Eisai and UCB Pharma and has been consulted by and received fees for lectures from Bial, Eisai, Janssen, and UCB Pharma outside the submitted work.

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