Assessing long-term effects of eslicarbazepine acetate on lipid metabolism profile, sodium values and liver function tests

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A B S T R A C T
Introduction: Older dibenzazepines with a carboxamide substitution have been demonstrated to cause deleterious effects on lipid metabolism profile, as well as frequent hyponatremia. The aim of our study is to assess the effects of eslicarbazepine acetate, a novel AED, on lipid metabolism profile, sodium values and liver function tests, as well as to compare them with previous effects of carbamazepine and oxcarbazepine.

Methods: This report describes a retrospective cohort study of 108 patients who were treated with eslicarbazepine. Of these patients, 52% had switched to eslicarbazepine from prior treatment with carbamazepine or oxcarbazepine. Laboratory values concerning lipid metabolism profile, liver function tests and sodium were assessed before and after beginning/switching treatment. Patients who began treatment or whose treatment for dyslipidemia was modified during the study period were excluded from the analysis. Co-medications that could impact lipid metabolism profile, sodium or hepatic function were kept stable during the study period.

Results: The mean total cholesterol of the entire group decreased significantly from prior pathological to normal values after beginning/switching treatment. The percentage of patients with pathological values decreased. Patients switching from prior carboxamides also showed significant reductions in mean LDL and triglycerides. Patients beginning treatment without prior carboxamides did not develop dyslipidemia after titration. A tendency for an increased percentage of patients with hyponatremia was detected in both groups.

Conclusions: Compared with older carboxamides, eslicarbazepine acetate exhibits a safer profile related to lipid metabolism. No relevant changes were detected in liver function tests. Consequently, a vascular risk factor could be avoided in patients with chronic epilepsy, while hyponatremia still needs to be ruled out. Prospective studies are still needed.

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1. Introduction

Eslicarbazepine acetate (ESL) is a new antiepileptic drug (AED) indicated for the treatment of focal onset seizures with or without tonic–clonic bilateral evolution (Gil-Nagel et al., 2013). After intake, ESL is extensively (<95%) hydrolyzed to eslicarbazepine (Almeida and Soares-da-Silva, 2007). The primary metabolic

Abbreviations: ESL, eslicarbazepine acetate; CBZ, carbamazepine; OXC, oxcarbazepine; CoT, total cholesterol; LDL, low-density lipoproteins; TGC, triglycerides; HDL, high-density lipoproteins; GGT, glutamicoxalacetic transaminase; GPT, glutamic-piruvic transaminase; GGT, gammaglutamyl transpeptidase.

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functions have been detected (Milovan et al., 2010). In terms of lipid metabolism, an interaction between ESL and rosuvastatin or simvastatin has been described, which results in lower levels of statins (Falcão et al., 2013). This finding suggests that dose-adjustment of simvastatin could be needed after titration of treatment with ESL, if changes on lipid metabolism profile are noted when combining these drugs. However, no direct effects of ESL on lipid metabolism profile were concluded in those studies. Prior studies have demonstrated adverse effects of other dibenzazepines and other metabolic inducers on lipid metabolism profile (Chuang et al., 2012; Nikolaos et al., 2004), while authors have suggested a milder but still deleterious effect of OXC (Franzoni et al., 2006; Garoufi et al., 2014; Papacostas, 2000; Yis and Doğan, 2012), and little is known regarding the effects of ESL. In patients with epilepsy presence of dyslipidemia related to chronic use of AEDs represents a chronic vascular risk factor (Cockerell et al., 1994), with the consequent increased mortality due in part to the increased vascular risk (Chuang et al., 2012). Thus, avoidance of a vascular risk factor could lead to increased life expectancy, quality of life and reduced requirements of medical care in patients with epilepsy. In the case of patients with previous treatment with older dibenzazepines, preliminary data has suggested that an abrupt switch from treatment with OXC to ESL could be performed (Steinhoff et al., 2011), regardless of the need for sodium values controls. Nonetheless, the small sample size and short follow-up of works published thus far warrant prospective studies. However, there are no data comparing progressive/abrupt switching from OXC or CBZ to ESL, and the clinical and laboratory changes related to this switch have not been properly detailed. Hence, the effects of switching from CBZ/OXC to ESL on lipid metabolism profile, liver function tests, vitamin D or hormonal values still need to be assessed (Brown and El-Mallakh, 2010).

In phase III clinical trials, ESL showed no effects on clinically relevant laboratory parameters concerning hematolig, blood chemistry, urine and coagulation. Low sodium levels shifting from normal values were detected in 3.1–8.8% in the different groups, and no changes were detected in cholesterol fractions or triglycerides. Post-authorization studies have suggested that ESL has no effects on lipid metabolism (Massot et al., 2014), as well as a good efficacy related to seizures (Mauri-Llerda, 2012; Serrano-Castro et al., 2013; Villanueva et al., 2014). Taken together, these data offer a promising profile of ESL with respect to lipid metabolism compared to older drugs, such as CBZ or OXC. Nonetheless, all of these studies were not designed to evaluate the long-term effects of ESL on lipid metabolism profile.

The objective of our study is to assess the long-term effects of ESL on lipid metabolism profiles, sodium values and liver function tests, as well as to compare them with previous effects of CBZ or OXC, in a group of patients treated in our comprehensive epilepsy center since the introduction of ESL to the market.

2. Methods

2.1. Patients and study design

We performed an observational, retrospective cohort study of patients who attended our outpatient epilepsy clinic from February 2011 to July 2014. The patients were evaluated by epileptologists, who assessed the patients’ clinical variables and decided to begin treatment with ESL as an add-on de novo treatment, or by switching from another AED to ESL. Titration or discontinuation of treatment with ESL was independent from study inclusion. The patients’ laboratory values were systematically assessed before and during treatment with ESL, with blood test performed at least once during the last year before treatment with ESL (inclusion criteria), between 3 and 6 months after treatment initiation, and then yearly. ESL dosage was selected based on clinical criteria of efficacy and tolerability. The duration of treatment was variable, and determined by the clinical assessment of the individual patients. Data related to lipid metabolism profile, sodium values and liver function tests were retrospectively recollected from clinical diaries. The inclusion criteria for the analysis were as follows: patients over 18 years old, focal onset seizures, treatment with ESL during at least three months and existing laboratory parameters concerning lipid metabolism, liver function tests or sodium values during the last year previous and during treatment with the drug. The exclusion criteria were as follows: patients under 18 years old, pregnancy, systemic disease with life expectancy less than one year, treatment with ESL for less than three months and titration or dose changes of treatment with drugs that could affect the patient’s lipid metabolism profile during treatment with the drug.

The lab values assessed prior and during treatment were as follows: total cholesterol, triglycerides (TGC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), glutamic-oxalacetic transaminase (GOT), glutamic-piruvic transaminase (GPT), gamma-glutamal transeptandase (GGT) and plasma sodium values. Multiple determinations of each single value were available in the majority of patients, and variability was analyzed. When multiple lab value determinations were available, the last lab value before and during treatment was taken in account for the analysis. All values were determined in the same laboratory to avoid methodological bias that could interfere with the results. Blood extractions were always performed during the morning and before breakfast. Treatment with other AEDs was not an exclusion criteria because ESL was approved exclusively as an add-on treatment during the study period. Titration or tapering of other AEDs or switching from one AED to another was assessed and monitored, especially with regards to metabolic inducers. For the analysis of lab values, patients were subdivided into two groups, titration of treatment with ESL without prior treatment with older dibenzazepines and switching to treatment with ESL from CBZ/OXC. Concomitant treatment with statins, colestiramine, colestopil, gemfibrozil, ezetimibe, nitrinic acid and fibrates was strictly assessed. If these drugs were titrated or the doses were modified during the study period, the patients were excluded from the analysis. Other factors that could affect a patient’s lipid metabolism profile, such as presence or absence of diabetes mellitus and changes in the treatment, presence or absence of familiar hypercholesterolemia or hypertriglyceridemia, beta-blocking agents or thiazides, were assessed and documented. Demographic data, epilepsy concerning data, seizure outcome and other than AEDs epilepsy treatments were also assessed but were not used as primary endpoints.

2.2. Statistics

Statistical analysis was performed with SPSS 19.0. For continuous variables, the Saphiro–Wilk test was used to distinguish between normal and abnormal distributions. Normally and non-normally distributed variables were analyzed by using the Student t and the Mann–Whitney U-tests for the comparison of means and medians, respectively. Paired sample T and Wilcoxon’s tests were used to compare laboratory values before and during treatment with ESL in the same group of patients. The X2 test was used for the comparison of proportions. With regards to lab values, the patients were subdivided in two groups for the analysis, switching to ESL from CBZ/OXC or beginning treatment with ESL de novo and without prior treatment with older dibenzazepines. Univariate and multivariate analysis were performed to detect statistically significant correlations. Two-sided p values <0.05 were considered significant.
Table 1

Patient demographics and characteristics (N = 108).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD age, years</th>
<th>Gender, % patients</th>
<th>Drug-resistant, % patients</th>
<th>ESL dose, % patients</th>
<th>Number of concomitant AEDs, % patients</th>
<th>Concomitant medications, % patients</th>
<th>Epilepsy diagnosis, n (% patients)</th>
<th>DM, % patients</th>
<th>DLP, % patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.9 ± 14.6</td>
<td>Women</td>
<td>57.3%</td>
<td>400 mg/day</td>
<td>0%</td>
<td>1%</td>
<td>GGE/GSE</td>
<td>0%</td>
<td>65.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>800 mg/day</td>
<td>3.7%</td>
<td>2%</td>
<td>STILE</td>
<td>48 (44.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1200 mg/day</td>
<td>35.2%</td>
<td>3%</td>
<td>SFLE</td>
<td>12 (11.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1600 mg/day</td>
<td>48.1%</td>
<td>4%</td>
<td>SPCE</td>
<td>7 (6.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2000 mg/day</td>
<td>12.0%</td>
<td>5%</td>
<td>UTLE</td>
<td>19 (17.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean ± SD (range) follow up, months</td>
<td>23.1 ± 12.8 (1–41)</td>
<td>15%</td>
<td>SFLE</td>
<td>13 (12.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DM, % patients</td>
<td>0.90%</td>
<td>1%</td>
<td>UFE</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DLP, % patients</td>
<td>57.3%</td>
<td>5%</td>
<td>UPCE</td>
<td>5 (4.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of concomitant AEDs, % patients</td>
<td>65.7%</td>
<td>3%</td>
<td>EM</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>AEDs, number of current antiepileptic drugs concomitant to eslicarbazepine acetate; DM, diabetes mellitus; DLP, dyslipidemia; EM, structural/metabolic multifocal epilepsy; GGE, generalized genetic epilepsy; GSE, generalized structural/metabolic epilepsy; Other drugs, other drugs with known effect on lipid profile used by patients during treatment with eslicarbazepine acetate; SFLE, structural/metabolic frontal lobe epilepsy; SPCE, structural/metabolic posterior cortex epilepsy; STILE, structural/metabolic temporal lobe epilepsy; UFE, unknown etiology frontal lobe epilepsy; UIE, unknown etiology insular epilepsy; UPCE, unknown etiology posterior cortex epilepsy; UTLE, unknown etiology temporal lobe epilepsy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Results

We evaluated 843 patients in our outpatient epilepsy clinic between February 2011 and July 2014. Of them, 108 were included in the analysis. The patients’ demographic and clinical data showed that 65.7% of patients were previously diagnosed with dyslipidemia (Table 1). However, only 15.7% were on previous pharmacological treatment for this vascular risk factor. In this small group of patients, the treatment for dyslipidemia was not modified during the study period.

After a medium duration of treatment with ESL of 23.1 months (range 3–41 months), the mean total cholesterol values decreased significantly (p = 0.015) in the entire group, switching from previous pathological (>200 mg/dL) to normal values (<200 mg/dL) during treatment. The percentage of patients with hypercholesterolemia was also higher before treatment with ESL (from 53.2% to 40.7%), but this difference was not statistically significant. The GGT and TGC median values changed significantly, but in both cases, the values were normal before and during treatment and the changes were clinically irrelevant (median GGT from 42 to 29 IU; p = 0.038; median TGC from 80 to 82 mg/dL; p = 0.02; Fig. 1). No statistically significant changes were detected in other mean/median values of the lipid metabolism profile, sodium or liver function tests, which were also normal before and during treatment (Fig. 1). The percentage of patients with pathological values in these variables did not vary significantly, but the proportion of patients with hyponatremia (Na < 135 mmol/L) showed a non-significant tendency to increase (from 3.7% to 14.8%; p = 0.5). Specifically, we detected 14 patients with hyponatremia during treatment with ESL compared to four previous cases, and 13 of them were incident new cases. Only one case was symptomatic and needed the treatment to be suspended.

As the significant decrease in mean total cholesterol values could have been caused by switching to ESL from prior treatment with older dibenzazepines or other metabolic inducers, we divided the patients into two groups for the analysis. In the subdivision, 48.1% began treatment with ESL without prior treatment with older dibenzazepines (CBZ, OXC), and 51.9% were switched to ESL from prior CBZ/OXC. In the first group of patients, no other AEDs were withdrawn to titrate treatment with ESL in 65% of the group (34 patients), and some other AEDs different from CBZ/OXC were withdrawn to titrate ESL in 35% of the group (18 patients) (withdrawn AEDs in this group: lamotrigine, levetiracetam and topiramate [all n = 3]; gabapentine, lacosamide, valproic acid and vigabatrine [all n = 2]; phenobarbital [n = 1]). No patients were switched to ESL from prior phenytoin during the study period. Patients switching from prior CBZ/OXC were slightly older than patients beginning treatment de novo (46 years vs 40 years; p < 0.05). In this group, 57% of patients were switched to ESL from CBZ and 43% from OXC. Gender and other demographic data did not show any statistically significant differences between the groups.

The patients that began treatment with ESL “de novo” and did not switch from prior CBZ/OXC showed normal mean/median values, without significant changes, on all main variables. Only their mean/median values of HDL, GOT and sodium changed significantly. However, these values were normal prior and after treatment titration, and the changes were minimum and clinically irrelevant (Table 2). No statistically significant changes were detected in the percentage of patients with hypertriglyceridemia, hypercholesterolemia or hyponatremia before and after treatment titration. Nonetheless, hyponatremia was detected in 4.1% of patients before and in 16.3% after beginning treatment, with one case being clinically relevant, indicating a trend toward an increase.

As the most relevant findings of this study, patients switching from CBZ/OXC to ESL showed a significant decrease in mean/median values of TGC and LDL (p < 0.05), and mean total cholesterol showed a marked tendency to decrease from prior pathological values (>200 mg/dL) to normal values (<200 mg/dL).
Table 2
Mean ± standard deviation and median (interquartile range) lipid profile values and number of subjects for comparison before and during treatment with eslicarbazepine acetate in patients without prior treatment with carbamazepine/oxcarbazepine.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre ESL</th>
<th>During ESL</th>
<th>N</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TGC (mg/dl)</td>
<td>78 (63–111)</td>
<td>88 (58–118)</td>
<td>38</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean LDL (mg/dl)</td>
<td>115.8 ± 36.7</td>
<td>133 ± 46.3</td>
<td>16</td>
<td>0.115</td>
</tr>
<tr>
<td>Mean HDL (mg/dl)</td>
<td>61.3 ± 20.9</td>
<td>70.1 ± 25.0</td>
<td>16</td>
<td>0.022</td>
</tr>
<tr>
<td>Mean total cholesterol (mg/dl)</td>
<td>217.3 ± 50.2</td>
<td>201.0 ± 36.0</td>
<td>40</td>
<td>0.082</td>
</tr>
<tr>
<td>Median GGT (IU)</td>
<td>19 (15–25)</td>
<td>18.5 (14–23)</td>
<td>38</td>
<td>0.014</td>
</tr>
<tr>
<td>Median GPT (IU)</td>
<td>18 (11–34)</td>
<td>18 (12–26)</td>
<td>40</td>
<td>0.413</td>
</tr>
<tr>
<td>Median GGT (IU)</td>
<td>42 (26–67)</td>
<td>39 (22–48)</td>
<td>31</td>
<td>0.713</td>
</tr>
<tr>
<td>Mean sodium (mmol/l)</td>
<td>140.0 ± 3.7</td>
<td>138.4 ± 4.1</td>
<td>37</td>
<td>0.023</td>
</tr>
</tbody>
</table>

ESL, eslicarbazepine acetate; GGT, gamma-glutamyl transpeptidase; GOT, glutamic-oxalacetic transaminase; GPT, glutamic-pyruvic transaminase; HDL, high density lipoproteins; LDL, low density lipoproteins; TGS, triglycerides.

Table 3
Mean ± standard deviation and median (interquartile range) lipid profile values and number of subjects for comparison before and after switching treatment in patients switching to eslicarbazepine acetate from carbamazepine/oxcarbazepine.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre ESL</th>
<th>During ESL</th>
<th>N</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TGC (mg/dl)</td>
<td>81 (59–115.2)</td>
<td>76 (57–104)</td>
<td>45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean LDL (mg/dl)</td>
<td>137.6 ± 31.6</td>
<td>121.2 ± 18.7</td>
<td>21</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean HDL (mg/dl)</td>
<td>72.7 ± 27.7</td>
<td>71.6 ± 26.1</td>
<td>21</td>
<td>0.745</td>
</tr>
<tr>
<td>Mean total cholesterol (mg/dl)</td>
<td>207.4 ± 41.2</td>
<td>197.4 ± 29.9</td>
<td>47</td>
<td>0.053</td>
</tr>
<tr>
<td>Median GGT (IU)</td>
<td>18 (13–23)</td>
<td>17.5 (14.2–24)</td>
<td>45</td>
<td>0.701</td>
</tr>
<tr>
<td>Median GPT (IU)</td>
<td>15 (10–22)</td>
<td>17 (12–23)</td>
<td>46</td>
<td>0.595</td>
</tr>
<tr>
<td>Median GGT (IU)</td>
<td>48 (26.5–66)</td>
<td>29 (24–38)</td>
<td>31</td>
<td>0.010</td>
</tr>
<tr>
<td>Mean sodium (mmol/l)</td>
<td>139.8 ± 3.6</td>
<td>138.9 ± 3.4</td>
<td>46</td>
<td>0.661</td>
</tr>
</tbody>
</table>

ESL, eslicarbazepine acetate; GGT, gamma-glutamyl transpeptidase; GOT, glutamic-oxalacetic transaminase; GPT, glutamic-pyruvic transaminase; HDL, high density lipoproteins; LDL, low density lipoproteins; TGS, triglycerides.

After switching treatment (p = 0.053), GGT median values decreased significantly, but were normal before and after treatment switching. No differences were detected in other mean lab values, including sodium (Table 3). A statistically significant difference was detected between the percentage of patients with hypertriglyceridemia and hypercholesterolemia before and after switching treatment (Fig. 2). No statistically significant changes were detected in the percentage of patients with hyponatremia after switching treatment, but a trend was detected (from 3% to 12.5%). In this group, the relative risk of hypertriglyceridemia and hypercholesterolemia before switching treatment was 6.0 and 1.57, respectively, when comparing the patients’ values before and after switching treatment. Hence, hypertriglyceridemia and hypercholesterolemia were more frequent before switching from treatment with CBZ/OXC to ESL, while hyponatremia was present at least the same degree. Furthermore, by sub-analyzing patients who switched from CBZ to ESL a statistically significant decrease in mean/median values of TGC, total cholesterol, GOT and GPT were detected, while statistical significance was nearly reached in LDL, and HDL increased significantly. However, previous pathological switching to normal values were only observed for total cholesterol and LDL. In the same way, patients switching from OXC to ESL also showed a statistically significant decrease in mean/median values of TGC, total cholesterol, GPT and GGT, while statistical significance was also almost reached in LDL, and HDL also significantly increased. However, in contrast to CBZ, in this case, the values were always normal prior to and after switching treatment. As such, a milder, but still deleterious, prior effect of OXC could be suggested when comparing OXC with CBZ in our survey.

4. Discussion

The results from Phase III clinical trials and post-marketing studies have shown ESL to be a safe and effective drug in patients with focal onset seizures. In our survey, ESL was used as an add-on treatment, and it was mostly used in drug resistant patients, who represented 90.7% of the entire group. As ESL was only authorized as an add-on treatment during the study period, we were not able to assess ESL effects on lipid profiles, sodium and liver functions tests in patients under monotherapy regimens.

Focusing on lab values, the mean total cholesterol values of the entire group decreased significantly during treatment with ESL, switching from prior pathological to normal values during treatment with the drug. The percentage of patients with pathological values also showed a trend toward a decrease. This suggests that ESL is possibly a safe drug that does not deleteriously affect, or only mildly affect, the lipid metabolism profile in our patients after a medium follow up of near to two years. This represents a difference from CBZ, OXC and other AEDs that are metabolic inducers (Chuang et al., 2012; Nikolaos et al., 2004). The significant increase

![Fig. 2. Percentage of patients with normal or elevated levels of total cholesterol and triglycerides before and after switching treatment from carbamazepine/oxcarbazepine to eslicarbazepine acetate (ESL).](image-url)
in the median values of TGC was not considered clinically relevant because the patients' values were normal before and during treatment with ESL, and the changes were minimal (from 80 to 82.5 mg/dL; \( p = 0.02 \)). Furthermore, with the exception of TGC, the values of the patients' lipid metabolism profiles showed a tendency toward improvement. Obviously, this finding is not caused by ESL but could be a consequence of switching from CBZ/OXC to ESL because near half of the patients were switched from prior CBZ/OXC regimens. The tendency toward improvements in lipid metabolism profiles was probably due to the previous deleterious effects of CBZ/OXC, which do not seem to be present, or were present to a lesser degree, with ESL treatment.

In the subdivision of groups, patients switching from prior CBZ/OXC were slightly older than patients beginning treatment without prior CBZ/OXC. However, as the patients were compared to themselves before and after beginning/switching treatment, this difference was not considered to be relevant for the analysis and interpretation of data.

In patients without prior treatment with older dibenzazepines, dyslipidemia did not develop after beginning treatment with ESL.

Patients with prior treatment with CBZ/OXC showed a significant reduction of mean/median LDL and TGC after switching treatment, as well as a marked tendency toward the normalization of their values of mean total cholesterol. The number of patients in this group was probably too small to achieve statistical significance related to mean total cholesterol values because a tendency was detected and significance was nearly reached (\( p = 0.053 \)). Nonetheless, the mean values of LDL decreased significantly from prior pathological to normal values after switching treatment. The significant decrease in median TGC observed in this group was not considered to be clinically relevant because the values were normal prior and after switching treatment. With regards to the percentage of patients with pathological values, a significant decrease in patients with hypertriglyceridemia and hypercholesterolemia was detected after switching treatment. The relative risk of hypertriglyceridemia and hypercholesterolemia were also markedly higher before switching treatment, and the deleterious effects were more evident with CBZ than with OXC. We consider these data relevant in the comparison of ESL with older dibenzazepines because a vascular risk factor could be avoided in patients with chronic epilepsy. However, in our survey, when analyzing the data from the entire group, as well as when analyzing the subgroups, the percentage of patients with hypercholesterolemia after beginning/switching treatment with ESL was still higher than the prevalence in the general population (Pedro-Botet et al., 2014). As such, a very mild effect of ESL or effects of other AEDs cannot be completely ruled out.

In the analysis of the data from the entire group we consider that only the decrease in total cholesterol values is relevant for our results. While the subdivision of groups showed ESL to be safer than CBZ and OXC in terms of its effects on lipid metabolism profile. Natrium results were non-significant in our survey, so prospective studies are warranted to achieve to conclusions about this value. Lastly, our work shows the weaknesses of all retrospective observational studies.

### 5. Conclusions

In conclusion, ESL did not show a deleterious effect on the lipid metabolism profile of patients in our survey, and switching from CBZ or OXC to ESL could generate a positive effect on the lipid metabolism profile of patients with chronic epilepsy. Prospective and systematic long-term studies about the effects of ESL on lipid metabolism profiles, sodium values and liver functions tests, in the scenario of monotherapy or polytherapy regimens, as well as regarding the effects of switching from CBZ/OXC to ESL on lab values, are still warranted.

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### Conflict of interest

The authors have no conflicts of interest to declare.

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