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Neurological adverse events of new generation sodium blocker antiepileptic drugs. Meta-analysis of randomized, double-blinded studies with eslicarbazepine acetate, lacosamide and oxcarbazepine

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ABSTRACT

Purpose: Analysis of overall tolerability and neurological adverse effects (AEs) of eslicarbazepine acetate (ESL), lacosamide (LCM) and oxcarbazepine (OXC) from double-blind, placebo-controlled trials. Indirect comparisons of patients withdrawing because of AEs, and the incidence of some vestibulocerebellar AEs between these three antiepileptic dugs (AEDs).

Methods: We searched MEDLINE for all randomized, double-blind, placebo-controlled trials investigating therapeutic effects of fixed oral doses of ESL, LCM and OXC in patients with drug resistant epilepsy.

Withdrawal rate due to AEs, percentages of patients with serious AEs, and the proportion of patients experiencing any neurological AE, nausea and vomiting were assessed for their association with the experimental drug.

Analyses were performed between recommended daily doses of each AED according to the approved summary of product characteristics (SPC). Risk differences were used to evaluate the association of any AE [99% confidence intervals (CIs)] or study withdrawals because of AEs (95% CIs) with the experimental drug. Indirect comparisons between withdrawal rate and AEs dizziness, coordination abnormal/ataxia and diplopia were estimated according to network meta-analysis (Net-MA).

Results: Eight randomized, placebo-controlled, double-blind trials (4 with ESL, 3 with LCM, and 1 with OXC) were included in our analysis.

At high doses (OXC 1200 mg, ESL 1200 mg and LCM 400 mg) there was an increased risk of AE-related study withdrawals compared to placebo for all drugs. Several AEs were associated with the experimental drug. Both number and frequency of AEs were dose-related.

At high recommended doses, patients treated with OXC withdrew from the experimental treatment significantly more frequently than patients treated with ESL and LCM. Furthermore, the AEs coordination abnormal/ataxia and diplopia were significantly more frequently observed in patients treated with OXC compared to patients treated with LCM and ESL.

Conclusions: The overall tolerability of AEDs and the incidence of several neurological AEs were clearly dose-dependent. Indirect comparisons between these AEDs, taking into account dose-effect, showed that OXC may be associated with more frequent neurological AEs than LCM and ESL.

1. Introduction

Neurological adverse events (AEs) are frequently observed in patients treated with antiepileptic drugs (AEDs) and are often responsible of treatment failure and poor quality of life.[1,2] Amongst these AEs, the most common is sedation, which is observed with almost all AEDs, and brain stem, and vestibulocerebellar AEs, which are most often observed with voltage-gated sodium channels (VGSC) blocker AEDs.[3]

Vestibulocerebellar AEs may be characterized by objective involvement of gait and motor coordination (which in clinical trials are named ataxia, unsteadiness, abnormal gait, balance disturbance, imbalance, coordination disturbance)[4] or by subjective signs such as dizziness or vertigo. Other signs expression of brain stem involvement are those affecting ocular motor functions such as diplopia, blurred vision, and nystagmus.[3]

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This meta-analysis aimed to evaluate the differences in the neurological tolerability profile of oxcarbazepine (OXC) and two other recently approved VGSC blockers AEDs – lacosamide (LCM) and eslicarbazepine acetate (ESL) – at their recommended daily dosages for the adjunctive treatment of partial-onset seizures (POS) in adults, based on data from phase III clinical studies performed with each drug in this patient population.

2. Methods

2.1. Criteria for considering studies for this review

We included randomized, double-blinded, placebo-controlled trials investigating therapeutic effects of fixed doses of oral ESL, LCM and OXC as adjunctive therapy of POS in adults. Full journal publication was required, with brief abstracts not included. All other types of studies, including non-randomized trials, case reports, or clinical observations, were excluded.

We focused this meta-analysis on adjunctive treatment of POS, since tolerability of these drugs in patients with other diseases than epilepsy and as monotherapy is different from that observed in drug resistant epileptic patients.[5,6]

We searched in PubMed oxcarbazepine OR Trileptal, lacosamide OR Vimpat and eslicarbazepine acetate OR Zebinix with limits: ''Randomized controlled trial (or Clinical trial)'' and ''Humans''. Additional studies were sought in reference lists of retrieved articles and in The National Institutes of Health (NIH) clinical trial registry (www.clinicaltrial.gov). Eligibility was determined after reading each study identified by our search. All studies were read independently by two authors (G.Z. and A.V.) and agreement for inclusion/exclusion was reached after discussion

2.2. Comparison between recommended therapeutic dosages

Since neurological AEs are dose-dependent,[3,7,8] we considered that tolerability profile of the AEDs under analysis should be performed at equi-effective dosages. However, equally effective dosages are not available in the literature and therefore we decided to compare the tolerability profiles taking mainly into account the recommended daily dosages of each agent for the treatment of POS in adults, based on the approved summary of product characteristics (SPC).[9–13]

For the purpose of comparisons performed in this meta-analysis we have set the minimum effective recommended daily dosages to be OXC 600 mg, ESL 800 mg, and LCM 200 mg; the highest effective recommended daily dosage was set as OXC 1200 mg, ESL 1200 mg, and LCM 400 mg. Separate analyses per dose were performed (each dose arm was compared with placebo arm).

2.3. Outcome measures

Our primary outcome of interest was identification of specific neurological AEs and our secondary outcome was the comparison of percentages of patients withdrawing due to any AE. However, the secondary outcome will be discussed first.

2.3.1. Withdrawal rate due to AEs

We calculated placebo-subtracted percentages of patients withdrawing because of AEs. In a second step, we made an indirect comparison of placebo-subtracted percentages of patients withdrawing because of AEs.

2.3.2. Proportion of patients experiencing neurological AEs

We identified all neurological AEs significantly associated with the experimental drug in double-blinded studies with these AEDs. We included nausea and vomiting as neurological AEs because at least in some cases they are a consequence of neurological toxicity. We also performed an indirect comparison of placebo-subtracted percentages of three out of the most important AEs caused by vestibulocerebellar involvement: dizziness, coordination abnormal (or ataxia), and diplopia between these three AEDs.

These analyses were performed after the identification of synonyms – grouped under one main term – and the exclusion of rare AEs (i.e. those AEs observed in <5 patients among those randomized to the experimental drug or placebo).

2.4. Statistical analysis

Statistical heterogeneity was assessed using the I^2 test, with an $I^2 > 70\%$ indicating heterogeneity.[14] Provided that no significant heterogeneity was detected ($I^2 < 70\%$), analyses were carried out using a fixed-effect model. When I^2 was >70%, a random-effect model was used.

Risk differences (RDs) were used to estimate withdrawal rate and to identify AEs significantly associated with the experimental drug. A 95% confidence interval (CI) was used for the analysis of withdrawal rate and 99% (CI) for the analysis of AEs. In the last case, this conservative approach was aimed at minimizing the error rate.

All analyses were carried out with RevMan version 5.1.[15]

The statistical models for the indirect comparisons were based on the frequentist model described by Bucher and colleagues.[16] No heterogeneity was assessed for indirect comparisons; this assessment was restricted to direct comparisons (see I^2 test).

The RD (with 95% CI) for each indirect comparison was estimated according to the ITC software (Canadian Agency for Drugs and Technologies in Health, Indirect Treatment Comparison software, Ottawa, Ontario, Canada). This approach allows an indirect RD (with 95% CI) to be estimated upon the condition that both treatments included in the indirect comparison have been compared in actual trials against a common comparator (which in our case was placebo). Graphs were plotted using GRNETMA.EXE software (Società Italiana di Farmacia Ospedaliera, Milan, Italy) (www.osservatorioinnovazione.org).[17]

3. Results

3.1. Description of studies

3.1.1. Studies search results

A total of 95 references were identified through electronic databases searches (see Appendix 1). From this initial sample, we excluded non double-blinded studies, abstracts, active comparator-controlled studies, studies in which these drugs were administered intravenously, studies performed on children, healthy volunteers, or for indications other than epilepsy. Eight randomized, placebo-controlled, double-blind trials (1 with OXC, 3 with LCM and 4 with ESL) were carefully evaluated and included in our analysis (Table 1). For a detailed description of included studies see Appendix 2.

3.1.2. Characteristics of studies

The 8 studies included a total of 2732 subjects, 1858 of whom were randomized to active drug and 874 to placebo (Table 1). In all studies, patients received placebo or were titrated to a fixed dose regimen of the experimental drug.

In the 4 studies performed with ESL, 855 subjects were treated with active drug and 337 with placebo. Nine hundred-forty-four subjects were treated with LCM and 364 with placebo in the 3 LCM study. Finally, 519 subjects were treated with OXC and 173 with placebo in the OXC study.

Table 1
Double-blind studies performed with eslicarbazepine acetate, lacosamide and oxcarbazepine in patients with drug-resistant partial epilepsies.

Author	AEDs allowed (*n*)	Titration speed	Study duration (weeks)	Placebo (*n*)	Daily dose of the experimental drug		
					400 mg/d (*n*)	800 mg/d (*n*)	1200 mg/d (*n*)
Double-blind studies performed with eslicarbazepine acetate							
Ben-Menachem et al., 2010[18]	1–3	Starting dose: 400 mg or 800 mg/d. Pts randomized to 1200 mg/d achieved final dose within 2 wks	14	100	96	100	97
Elger et al., 2007[19]	1–2	Starting dose:400 mg/d. Final dose achieved within 4 wks	12	47	–	–	97[a]
Elger et al., 2009[20]	1–2	Starting dose:400 mg/d. Dose increments of 400 mg/d each week	12	102	100	98	102
Gil-Nagel, 2009[21]	1–2	Starting dose: 400 mg/d. Final dose achieved within 2 wks	14	88	–	85	80
Total				337	196	283	376

Author	AEDs allowed (*n*)	Titration speed	Study duration (weeks)	Placebo (*n*)	Daily dose of the experimental drug		
					200 mg/d (*n*)	400 mg/d (*n*)	600 mg/d (*n*)
Double-blind studies performed with lacosamide							
Ben-Menachem et al., 2007[22]	1–2	Starting dose100mg/d. Weekly increments of 100 mg up to the final dose	12	97	107	108	106
Chung et al., 2010[23]	1–3	Starting dose100mg/d. Weekly increments of 100 mg up to the final dose	18	104	–	204	97
Halàsz et al., 2009[24]	1–3	Starting dose100mg/d. Weekly increments of 100 mg up to the final dose	16	163	163	159	–
Total				364	270	471	203

Author	AEDs allowed (*n*)	Titration speed	Study duration (weeks)	Placebo (*n*)	Daily dose of the experimental drug		
					600 mg/d (*n*)	1200 mg/d (*n*)	2400/d (*n*)
Double-blind studies performed with oxcarbazepine							
[b]Barcs et al., 2000[25]	1–3	Six-hundred mg achieved within 2 days, 1200 mg/d achieved within 6 days, 2 400 mg/d achieved within 14 days	28 (2 + 24 + 2)	173	168	177	174

[a] QD and BID.
[b] During the study, since a large number of patients were discontinued because of AEs, a protocol amendment was prepared to allow for a blinded reduction to 1800 mg/d in the 2400 mg/d OXC treatment group either directly after randomization or on the occurrence of AEs. Forty-seven of the 174 patients randomized to 2400 mg/d were treated with a 1800 mg/d drug dose.

ESL was studied at 400 mg/day (two studies), 800 mg/day (3 studies) and 1200 mg/day (4 studies). LCM was studied at 200 mg/day (2 studies), 400 mg/day (3 studies), and 600 mg/day (2 studies). OXC was studied at 600 mg/day, 1200 mg/day and 2400 mg/day. All studies included patients with POS and treated with other AEDs. In all cases, efficacy and safety assessments were performed on patients who received at least one dose of drug.

In ESL studies, the experimental drug was started with a dose of 400 mg or 800 mg once daily and dose increments to 1200 mg/day were performed after one week or more slowly. LCM was started at 100 mg/daily dose with weekly increments to the final dose in all cases. In the study with OXC, drug dose was increased to 600 mg/day within 2 days and to 1200 mg/day within 6 days. A further increase to 2400 mg/day (or 1800 mg/day after a protocol amendment) was done after 2 weeks.

Risk of bias as regards incomplete reporting of outcome data (attrition bias), and selective reporting was considered low in all studies. Random sequence generation was described in all studies but three,[18,21,24] while was not given information on selection, performance, and detection bias in any of the studies.

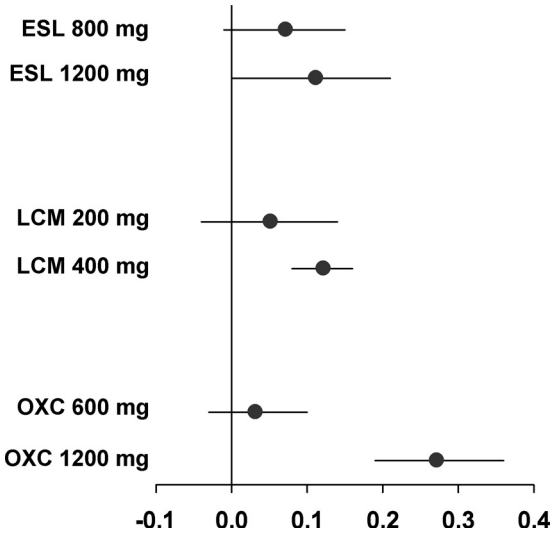


Fig. 1. Patients withdrawing because of adverse events in clinical studies with eslicarbazepine acetate, lacosamide and oxcarbazepine at low and high doses as reported in the SPC (for details, see text).

3.2. Tolerability assessment

3.2.1. Withdrawal rate due to AEs

Heterogeneity ($I^2 > 70\%$) was found with ESL at all doses and with LCM at 200 mg/d dose and in these cases a random model was adopted. In all other cases a fixed-effect model was used. High heterogeneity in ESL studies was mainly due to higher reporting in Ben-Menachem et al. study.[18]

At higher effective recommended daily dosage there was an increased risk of AE-related study withdrawals compared to placebo for all drugs. (see Fig. 1).

3.2.2. Proportion of patients experiencing neurological AEs

In the 4 studies with ESL, we found 18 AEs. Eleven were neurological. Amongst them, drowsiness was considered as synonymous of somnolence and merged with this AE. Convulsion, concentration impaired and insomnia were observed in less than 5 subjects and excluded from further analysis.

Seventeen AEs were observed in the 3 studies with LCM, nine of whom were considered neurological. Coordination abnormal was reported in 2 studies[22,23] while ataxia was only reported in one.[22] These AEs were considered as synonymous and merged as coordination abnormal/ataxia.

Fifteen AEs were reported in the OXC study and 10 were considered neurological. Abnormal gait and ataxia were considered as synonymous of coordination abnormal and merged as coordination abnormal/ataxia. For a detailed description of all neurological AEs, see Appendix 3.

3.2.3. Meta-analysis of neurological AEs observed in ESL studies

Evidence of heterogeneity ($I^2 > 70\%$) was found for coordination abnormal, diplopia and vomiting at the dose of 800 mg/day

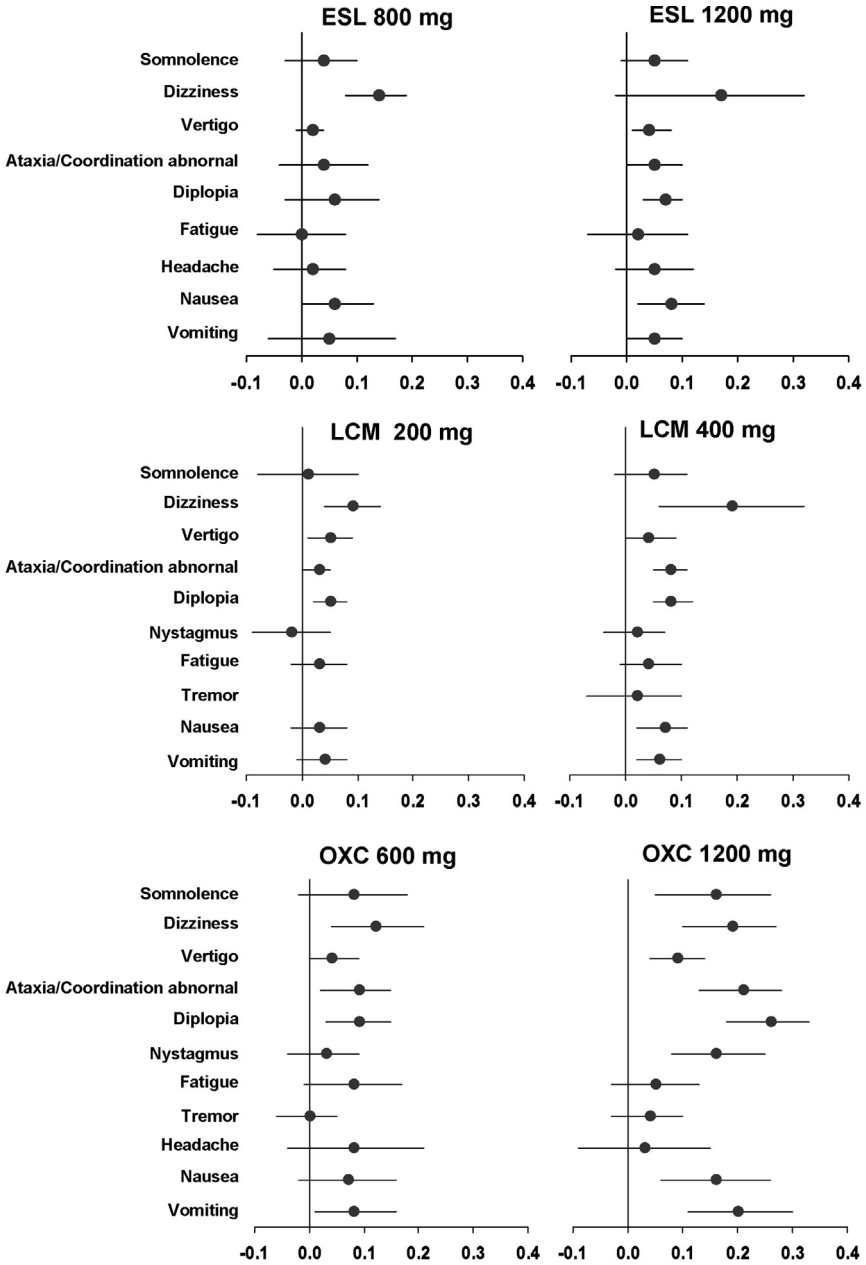


Fig. 2. Neurological adverse events observed in clinical studies with eslicarbazepine acetate, lacosamide and oxcarbazepine at low and high doses as reported in the SPC (for details, see text).

and for dizziness at 1200 mg/day. This heterogeneity was ascribed to a trend for higher percentage of patients with these AEs in one[18] study and lower reporting in two[19,21] and in these cases a random effect model was adopted. In all other cases, a fixed-effect model was used.

Dizziness at 800 mg/day, and diplopia and nausea at 1200 mg/day were significantly associated with the experimental drug (see Fig. 2 and Appendix 4).

3.2.4. Meta-analysis of neurological AEs observed in LCM studies

Heterogeneity ($I^2 > 70\%$) was observed for dizziness at 400 mg/day and in that case a random effect model was used. This was caused by higher reporting in one study.[22] In all other cases, a fixed-effect model was used.

At 200 mg/day, dizziness was significantly associated with LCM. At 400 mg/day AEs associated with the experimental drug were five, i.e. dizziness, ataxia/coordination abnormal, diplopia, nausea, and vomiting. (Fig. 2 and Appendix 4).

3.2.5. Meta-analysis of neurological AEs observed in OXC study

Three AEs (dizziness diplopia and vomiting) were significantly associated with the experimental drug at 600 mg daily dose. Eight AEs (somnolence, dizziness, vertigo, ataxia/coordination abnormal, diplopia, nystagmus, nausea and vomiting) were associated with a drug daily dose of 1200 mg (Fig. 2 and Appendix 4).

3.2.6. Indirect comparison of withdrawal rates due to AEs, and of proportion of patients experiencing neurological AEs

An indirect comparison of RDs (95% IC) of patients withdrawing because of AEs and of patients complaining of dizziness, coordination abnormal/ataxia and diplopia, was performed. At the minimum recommended daily dosages, indirect comparisons failed to evidence any significant difference between the three AEDs even though a non-significant trend favored OXC and LCM in the indirect comparison between LCM and ESL. (Patients withdrawing because of AEs: LCM vs OXC: 0.02 (−0.091, 0.131); ESL vs OXC: 0.04 (−0.063, 0.143); ESL vs LCM: 0.02 (−0.1, 0.14). See Table 2.

Table 2
Indirect comparisons of neurological AEs dizziness, ataxia/coordination abnormal, and diplopia between eslicarbazepine acetate, lacosamide and oxcarbazepine (RD (95% IC) at minimum recommended dosage (ESL: 800 mg/day, LCM 200 mg/day and OXC 600 mg/day) as reported in the SPC (for details, see text).

Dizziness	
ESL vs LCM[t]	0.05 [−0.024, 0.124]
LCM[t] vs OXC	−0.03 [−0.129, 0.069]
ESL vs OXC[t]	0.02 [−0.081, 0.121]
Ataxia/coordination abnormal	
ESL vs LCM[t]	0.01 [−0.074, 0.094]
LCM[t] vs OXC	−0.06 [−0.13, 0.01]
ESL[t] vs OXC	−0.05 [−0.153, 0.053]
Diplopia	
ESL vs LCM[t]	0.01 [−0.08, 0.1]
LCM[t] vs OXC	−0.04 [−0.107, 0.027]
ESL[t] vs OXC	−0.03 [−0.134, 0.074]

For explanations, see text.
[t] Treatment is favored by a trend in cases of no significant difference.

At high recommended doses it is shown that patients treated with OXC withdrew from the experimental treatment significantly more frequently than patients treated with ESL and LCM while between ESL and LCM, there was a non-significant trend in favor of ESL (Fig. 3).

The AEs coordination abnormal/ataxia and diplopia were significantly more frequently observed in patients treated with OXC compared to patients treated with LCM and ESL. Between ESL and LCM there was a non significant trend in favor of ESL. A non significant trend, always favoring LCM and ESL against OXC and ESL against LCM, was observed for the AE dizziness (Fig. 4).

This analysis was complemented by the computation of the number needed-to-harm (NNH) for dizziness, coordination abnormal/ataxia and diplopia associated with ESL, LCM, and OXC at high

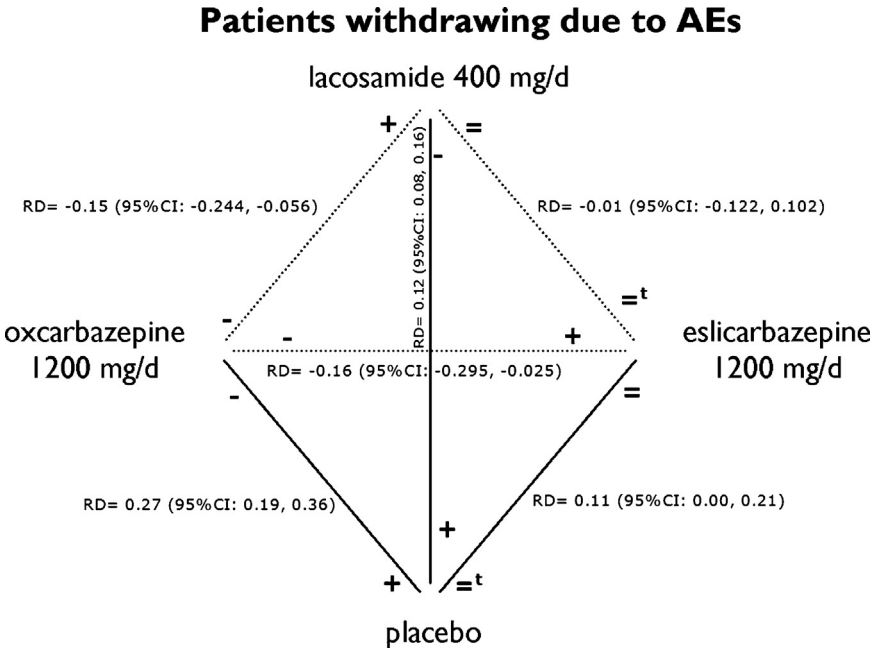
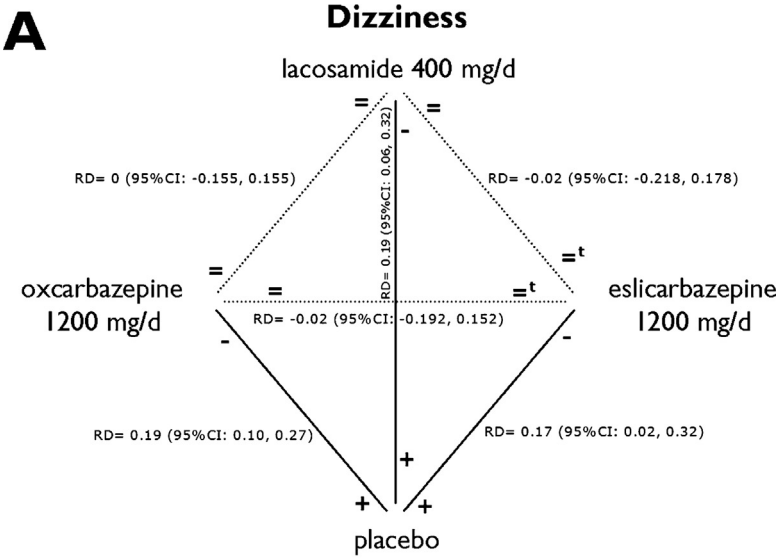
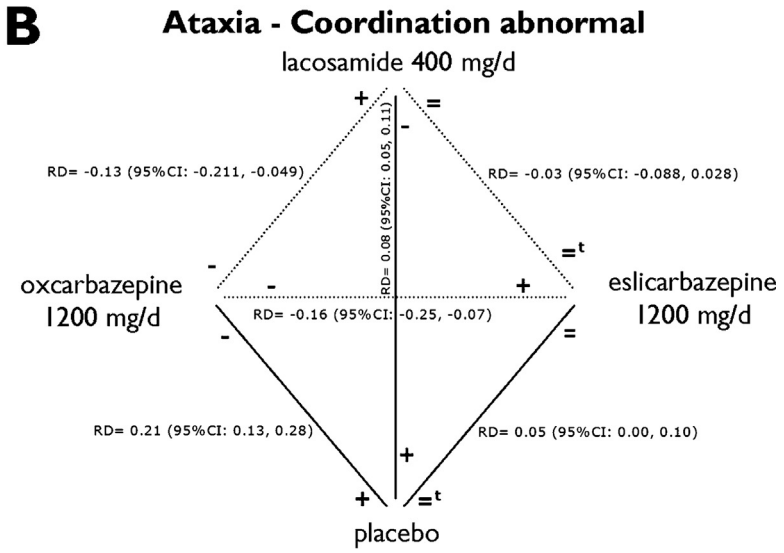


Fig. 3. Patients withdrawing because of AEs in clinical studies with eslicarbazepine acetate, lacosamide and oxcarbazepine. Indirect comparison (RD (95% IC)) at higher recommended dosages (ESL: 1200 mg/day, LCM 400 mg/day and OXC 1200 mg/day) as reported in the SPC. Each direct comparison is represented by a solid line and each indirect comparison by a dotted line. Statistical results of event rate ratio are presented as risk difference (RD) with 95% confidence interval (CI). The values of RD (with 95% CI) for direct and indirect comparisons were calculated according to the REVMAN and the ITC software, respectively. Symbols: '+'indicates which treatment is favored at levels of statistical significance, and vice versa for '−'; '=' denotes comparisons showing no significant difference; 't' indicates which treatment is favored by a trend in cases of no significant difference.





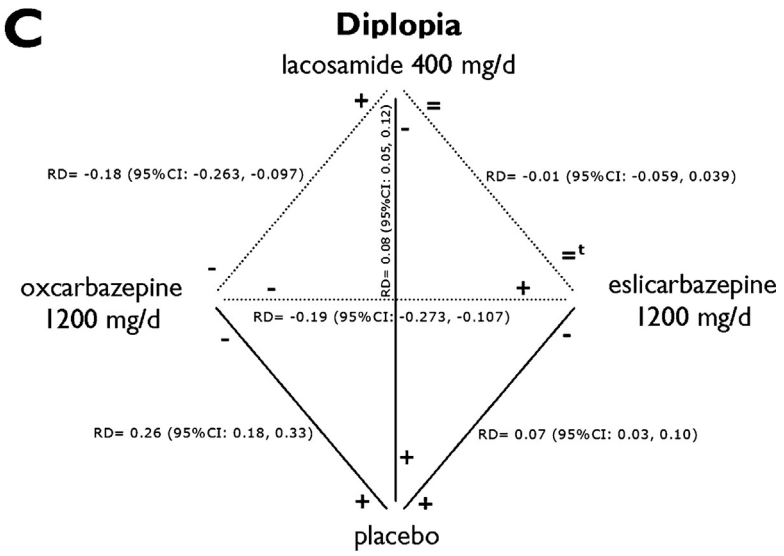


Fig. 4. Vestibulocerebellar AEs induced by eslicarbazepine acetate, lacosamide and oxcarbazepine in controlled studies. Indirect comparisons (RD (95% IC)) at higher recommended dosages (ESL: 1200 mg/day, LCM 400 mg/day and OXC 1200 mg/day) (for details, see text and Fig. 2).

recommended doses. NNH [95% IC] values respectively associated with ESL 1200 mg, LCM 400 mg, and OXC 1200 mg were: 6 [5,9]; 5 [4,6]; 5 [4,10] for dizziness, 19 [10,281]; 13 [9,21]; 5 [4,8] for ataxia/coordination abnormal, and 15 [9,30]; 12 [9,19]; 4 [3,5] for diplopia.

4. Discussion

The first finding of this meta-analysis of neurological AEs of ESL, LCM and OXC, is that there are several AEs for each AED that are influenced by dose. In fact, almost all treatment-emergent AEs were more frequently observed at higher doses. In a previous meta-analysis of all available randomized controlled trials (also those performed in patients with other disorders than epilepsy), we found that LCM treatment was associated with a range of neurological AEs which were clearly and significantly dose-dependent.[5] Recently, adjusted indirect comparisons of each drug were performed vs the pooled estimate effect of all other AEDs in three meta-analyses of placebo-controlled studies with some new AEDs[26] or newest AEDs.[27,28]

Even though equi-effective doses of drugs should ideally be compared for the assessment of the tolerability pattern of dose-dependent AEs, unlikely there is no way to establish equi-effective doses of these AEDs. For all these reasons, we decided to compare in our meta-analysis only those doses recommended in the approved SPCs excluding all other doses used in clinical trials. According to these indications, minimum recommended doses are 800 mg/day for ESL, 200 mg/day for LCM, and 600 mg/day for OXC, while maximum are 1200 mg/day, 400 mg/day and 1200 mg/day, for each AED respectively.

Although OXC was also studied at 2400 mg daily and the SPC mentions this can be an effective dosage, we decided not to include it as the highest recommended dosage. Firstly, because in the OXC study a large number of patients were discontinued because of AEs in the 2400 mg/daily group and a protocol amendment was prepared to allow for a blinded reduction to 1800 mg/daily either directly after randomization or on the occurrence of AEs; forty-seven of the 174 patients randomized to the 2400 mg/daily group were in fact treated with 1800 mg/daily which in our opinion does not allow an accurate evaluation of the 2400 mg/daily tolerability profile. Also of note, 128 (74%) patients in the 2400 mg/daily group prematurely discontinued treatment, which implies this dose may not provide the best risk/benefit ratio in clinical practice. Finally, a recent comparative pharmacokinetic study between ESL and OXC indicates that a ratio close to 1:1 is probably the best way to compare these drugs.[29]

ESL was studied at 400 mg/daily in two trials but in both failed to show significant improvements in seizure control as compared to placebo and hence the dosage is not recommended in the SPC.[11]

LCM was studied at 600 mg/daily in two trials but although the dosage was efficacious the risk/benefit was not considered favorable and the dosage is not recommended in the SPC.[12,13]

In our study, we made an indirect comparison of tolerability, through the analysis of placebo-subtracted percentage of patients who discontinue because of AEs, and a selected number of AEs: dizziness, coordination disturbance/ataxia, and diplopia which are a characteristic expression of vestibulocerebellar involvement. These neurological AEs are frequently associated with AEDs acting on voltage-gated sodium channels.

Looking at Figs. 3 and 4, we can see that at higher recommended doses, OXC caused significantly more withdrawals due to AEs and significantly more frequent coordination disturbances/ataxia and diplopia than ESL and LCM. Analysis of patients with dizziness, which is a subjective, and probably less specific sign of cerebellovestibular involvement, showed only a trend for a better tolerability of ESL and LCM compared to OXC. These data clearly indicate that, regarding these dose-dependent AEs, 1200 mg of OXC has a worse tolerability pattern than 1200 mg/day of ESL and 400 mg/day of LCM. Comparison between ESL and LCM, did not give significant results.

We think that these findings should be accepted with some criticism since two factors might have influenced tolerability of these AEDs: titration speed and possible differences between the populations of patients included in the studies. While OXC has been titrated to 1200 mg/day in only one week, both ESL and LCM were titrated more slowly to their respective effective recommended daily dosage (1200 mg/day and 400 mg/day). Regarding the population of patients included, the most important factor is, perhaps, the number of AEDs assumed by recruited patients. In the OXC study, up to 3 AEDS were allowed, while 2 studies with ESL and 1 study with LCM recruited only patients treated with no more than 2 AEDs (see Appendix 2). These factors may have contributed to worsen OXC tolerability profile although they cannot explain these findings. A further limit in the validity of our results may be searched in high values of heterogeneity which were found for some items. In this case the adoption of the random effect model may have been conservative and have hidden possible differences.

Regarding quality of studies included in this meta-analysis, we think that risk of bias is acceptable even though several details on study procedures were not available. For a description of risk of bias of such studies, see supplement document n 2. Finally, it has been hypothesized that tolerability of sodium blockers is worsened by other coadministered sodium blockers.[5] In this meta-analysis, we think that tolerability of OXC, LCM and ESL, which share a similar mechanism of action, may had been influenced in a similar way by other AEDs.

Why OXC at high recommended doses seems to display a worse profile than that observed with ESL and LCM? Mechanism of action of all these AEDs is at the level of voltage-dependent Na+ channels and it is known that all AEDs with this mechanism of action cause vestibulocerebellar AEs.[3] However, there are differences between these agents. It has been demonstrated that LCM determine a selective enhancement of slow inactivation but without apparent interaction with fast inactivation gating.[30]

Eslicarbazepine (the main active metabolite of both ESL acetate and OXC) has also recently shown not to share with carbamazepine and oxcarbazepine the ability to alter fast inactivation of VGSC, but rather appears to modify the kinetics and voltage-dependence of slow inactivation states.[29] Furthermore, eslicarbazepine has an affinity with the resting form of the channel about three times less than carbamazepine[31] and it has been suggested that eslicarbazepine is less likely to bind to normally active neurons and less likely to cause adverse neurological consequences.[32]

Perhaps, some different kinetic characteristics might better explain differences in the tolerability profile between these AEDs.

Fluctuations of drug levels in plasma may strongly affect susceptibility to some AEs.[32] It is well known that the traditional sodium blocker CBZ, mainly in induced subjects, has intermittent AEs time-locked with peak drug concentrations[33] and, for this reason, a controlled release CBZ formulation is better tolerated in patients with a short CBZ half-life.[34] Although much less data are available for OXC, also in this case it has been observed that several dose-dependent neurological AEs such as nystagmus, sedation, blurred vision, and dizziness occur intermittently during the day and mainly in the hours following drug administration.[35]

The main difference in terms of kinetic properties between ESL and OXC is that ESL is rapidly converted to eslicarbazepine,[31,36] while OXC – with a half-life of 1–2.5 h[37] before transformation in its active metabolite – is detectable in plasma and might per se determine an effect in the brain. In a recent study performed on

healthy volunteers[12] to investigate the kinetic of OXC, ESL, and its metabolites in plasma and cerebrospinal fluid, it was observed a peak concentration of OXC in plasma and cerebrospinal fluid after OXC but not after ESL administration. Thus, the quick increase of OXC levels in the brain might explain the occurrence of some time-locked and intermittent AEs after OXC administration. OXC acts primarily on fast inactivation VGSC (as mentioned before) and has a higher affinity with the resting state of the channel as compared with eslicarbazepine which may explain the occurrence of the neurological AEs associated with its peak in plasma and CSF.

This was the first meta-analysis aimed at comparing some aspects of tolerability of three AEDs. For a correct interpretation of our results, some methodological limits should be considered. First, network meta-analysis allow indirect comparisons between drugs used for the same indication but it should be kept in mind the possibility of biases which may be caused mainly by differences in the population of patients recruited in studies and also by differences in study protocols. Secondly, we focused our comparison of these three AEDs only on tolerability while we know that treatment decisions are made on the balance of effectiveness and harm and not harm alone. However, we are strongly convinced that several important methodological aspects – e.g. different ways to assess responder ratio (some studies considered all double-blind phase, other studies only maintenance phase), last observation carried forward (LOCF) analysis, and other aspects which have been carefully discussed by Rheims et al.[38] – limit comparison of efficacy of AEDs but these aspects do not influence the analysis of tolerability.[38]

In conclusion, all AEDs may cause neurological AEs which can limit their use and, ultimately, impair success of treatment. In this meta-analysis we observed that, at higher recommended doses, ESL and LCM were significantly associated with a lower withdrawal rate due to AEs and a lower percentage of neurological dose-dependent AEs than OXC.

Disclosure

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2013.03.016.

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