The evidence for switching dibenzazepines in people with epilepsy

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Abstract

The dibenzazepines particularly carbamazepine are associated with known adverse effects (AEs) and drug to drug interactions. Eslicarbazepine acetate (ESL) is structurally distinct from other members of the dibenzazepine family and has the advantage of once daily dosing. Observational and trial data report successful switching from older dibenzazepines to ESL. The evidence base for doing so is unclear and not standardised. This is a literature review following the PRISMA scoping guidelines identifying the evidence of switching dibenzazepines. Transition methods, ratios, tolerance to change, adverse effects and retention post change were evaluated. Study quality was assessed using the Oxford Centre for Evidence Based Medicine levels of evidence. Seven studies investigated the outcome of transition between carbamazepine and or oxcarbazepine to ESL, with specific data on the transition dose ratio and scheduling. The available data suggest that the overnight transition between oxcarbazepine and ESL in a 1:1 ratio (most common) is generally well tolerated with high retention rates. The transition showed improvement in adverse events associated with oxcarbazepine across a variety of domains. Almost 60% transitioned because of adverse events experienced no further symptoms at 12 months. There is less data on the transition from carbamazepine to ESL. The evidence available suggests an overnight transition in the ratio of 1:1.3-1.5. The retention rate following transition from carbamazepine to ESL was 69% (follow up of four months) with almost half of those transitioned because of adverse events experiencing no further symptoms. There is Grade C evidence available to help guide clinicians in the transition.

Introduction

The tolerability of AED regimes is crucial to treatment adherence, as non-concordance is a major cause of break-through seizures for people on long-term AEDs.[1] Now that there is significant 'real world' experience alongside trial data with a newer AED, eslicarbazepine acetate, we review the available efficacy and tolerability data, particularly in comparison with standard AEDs.

Eslicarbazepine acetate

Eslicarbazepine acetate (ESL) is licensed in the United States and Europe as an adjunctive treatment for focal-onset seizures with or without progression to bilateral tonic clonic seizures for people with epilepsy aged 6 years and older; it can also be used in monotherapy in adults. ESL is structurally distinct from other members of the dibenzazepine family (carbamazepine (CBZ) and oxcarbazepine (OXC)). There is evidence to suggest that ESL may be better tolerated and more efficacious than older dibenzazepines, and ESL may be an effective adjunct in individuals previously treated ineffectively with CBZ.[2] The dibenzazepines are associated with known adverse effects (AEs) including dizziness, nausea, hyponatraemia, osteopenia, and skin reactions. CBZ specifically has major potential for significant drug to drug interactions. CBZ is commonly associated with increased serum lipid levels, and there is potential for severe rebound seizures with both CBZ and OXC when adherence is low.[3,4] A key difference between ESL and CBZ is the pharmacokinetic profile and metabolism which conveys real clinical utility. Eslicarbazepine acetate has high bioavailability reaching peak concentration within two to three hours, with a significantly longer half-life of 20-24 hours (depending on population studied). This allows for once daily dosing and may minimise the risk of adverse events associated with CBZ and OXC, reduce the risk of drug to drug interactions, and increase concordance.[5]

Efficacy and Safety, and tolerability

A pooled analysis from four phase-3 randomised, double blind, placebo-controlled trials (N=1703) demonstrates that ESL was associated with a significant reduction in standardised seizure frequency ($P<0.0001$) at doses of 800mg (33%) and 1200mg (38%) when compared to placebo (18%). The responder rates (≥ 50% reduction in seizures over 4 weeks) were 34% (800mg) and 43% (1200mg) compared to 22% in the placebo group.[6] A post-hoc pooled analysis of three randomised, placebo-controlled trials in adults with treatment resistant focal onset seizures assessed the safety (N=1447) of adjunctive ESL.[7] ESL was generally well tolerated and treatment-related adverse events were dose related (lower incidence for those initiated at 400mg). Those adverse events leading to discontinuation were 28 (6.6%) in the placebo arm versus 179 (17.5%) in the ESL group. Adverse

events overall also appeared to be dose related (19/196 at 400mg, 104/410 at 1200mg). The overall incidence of serious adverse events was less than 10%. The most common events leading to discontinuation in the ESL group were dizziness, nausea, and vomiting.[7]

Monotherapy

In the monotherapy setting, two trials including a total of 332 patients from multiple centres have described the efficacy of ESL in patients who were switched from CBZ and/or other AEDs.[8] Patients on average, achieved a reduction of seizure frequency (calculated per 28 days) of 43% with ESL 1600 mg, and 36% with ESL 1200 mg. The magnitude of reduction was less for patients who were taking CBZ at baseline (12% on ESL 1200mg and 28% on ESL 1600mg) than for those who were not (45% on ESL 1200mg and 50% on ESL 1600mg).[8]

The largest cohort of patients from real-word experience was analysed in the Euro-ESLI study, which assessed the effectiveness, safety and tolerability of ESL when used in everyday clinical practice in Europe.[9] Data were obtained retrospectively from a number of heterogeneous clinical studies and pooled for analysis. Data from 2058 patients were included. A total of 2058 patients were assessed for safety and 1975 patients were assessed for effectiveness. AEs were reported for 34.0% of patients and led to discontinuation in 13.6% of patients. At 12 months the overall responder rate (≥ 50% reduction in seizures) was 76% with a seizure freedom rate of 41%. Of the 2058 patients included in the total analysis, 233 (11%) were transitioned from CBZ to ESL. 163 of the 233 patients (70%) were responders at 12 months and the seizure freedom rate was 31%. Among patients who transitioned from CBZ to ESL due to lack of efficacy, 11 patients out of 105 demonstrated unchanged or worsened seizure frequency at 12 months.[9]

The safety profile has also been reported in a small real-world study, which analysed 108 patients in Spain.[10] Among 108 patients, 52% switched from older dibenzazepines (either CBZ or OXC). Laboratory values concerning lipid metabolism profile, liver function tests (LFTs) and sodium was assessed before and after switching treatment. Patients switching from prior dibenzazepines showed significant reductions in mean low-density lipoproteins (LDL) and triglycerides ($p<0.05$). No differences were detected in other mean lab values, including sodium levels.[10] The Euro-ESLI data have undergone several further subgroup analyses, including specific investigation into monotherapy. The data are concordant with observational evidence such as the prospective multicentre study in 17 hospitals in Spain which demonstrated a responder rate of 83% (N=49) at 12 months, and adverse event rate of 15% (N=18).[11]

It is clear that clinicians are switching from CBZ and OXC to ESL but best practice for *how* to make the change is unclear. We review the evidence base for switching, specifically considering the mode of switching between AEDs (slow transition or immediate), dose ratio, and the impact upon safety, tolerability, and efficacy.

Methods

Inclusion/Exclusion criteria

The PRISMA scoping review guidelines were followed (supplementary information 1). This review included randomised controlled trials and uncontrolled prospective and retrospective cohort studies reporting outcomes from a 'switch' between CBZ and/or OXC and ESL, including information on how this transition was achieved. Studies were included if they reported: data observing dose titration method (ratio) of switching to ESL from CBZ and/or OXC and compared either efficacy and/or safety/tolerability before and after switching. Outcome measures included adverse events, retention rate, responder rate (≥ 50% reduction in seizures), change in seizure frequency, and quality of life according to validated general scales such as the 36-Item Short Form Health Survey (SF-36), EuroQol 5-Dimensions (EQ-5D), or epilepsy-specific scales such as the Quality Of Life In Epilepsy-31 (QOLIE-31). Exclusion criteria included; no data on transition between dibenzazepines', and lack of meaningful comparable outcome data.

Search strategy

A search was conducted on Medline (1946 to July 31st 2019), Embase, PsychINFO, and the Cochrane Library of Systematic Reviews using search terms and subject headings: eslicarbazepine and carbamazepine or oxcarbazepine with no language or date restrictions (appendix 1). We reviewed the reference lists of retrieved trials to check for additional reports of relevant studies and included grey literature.

Data collection and Analyses

We reviewed the outcome data from each study in detail with a view to pooling results to help consolidate the evidence available. There is dichotomous data available regarding responder rates, retention rates, and there are similar validated tools used to measure adverse events and quality of life outcomes across investigations. However, the heterogeneity of methodologies suggests that a descriptive review would be more appropriate. The barriers to pooling data include significant differences in; inclusion and exclusion criteria, follow-up period, ratio of transition between dibenzazepines, retrospective vs prospective data collection, and in some cases a lack of data available.

Results

We identified 841 records that fulfilled the search criteria. Animal studies (30) and duplicate studies (209) were removed leaving 602 records. These records were screened with 564 excluded based on title and abstract. Full text screening of the remaining 38 records led to 31 being excluded due to no data on transition ratio between dibenzazepines (11) review articles (5), ESL monotherapy (4), no ESL data (3), erratum responses (2), duplicate data (3), pharmacokinetic study (1), only data on children (1), only lipid data (1). Seven studies were included within this review (Table 1).

Table 1 [INSERT HERE]

All seven studies include data on the ratio and schedule of transition between dibenzazepines. Data are included on a total of 203 individuals; however two of the studies were sub-group analyses of larger populations. Of the seven studies, five were prospective, observational, uncontrolled, single-centre designs. A sub-group analysis from a larger retrospective, multicentre, uncontrolled observational investigation was also included. Because of limited data we also included conference abstracts (2) that met the inclusion criteria. All seven studies included some data on tolerability and adverse events. Four of the seven investigations included some data on efficacy. Seven studies reported on transition from OXC to ESL and two studies reported on the transition from CBZ to ESL. Due to heterogeneity in study design and dose schedules it was not possible to pool outcome data. The results are therefore presented as a narrative review.

Transition dose ratio between AEDs

No data on comparisons between switching regimes or dose ratio were identified for transitions between OXC and ESL, or CBZ and ESL.

OXC to ESL

The most common transition from OXC to ESL was an overnight switch in a ratio of 1:1 (5 studies, N=145). One prospective observational study (N=19) initially transitioned with an overnight switch ratio of 1:0.7 (OXC: ESL), and then increased ESL dose to a ratio of 1:1 after 3 days treatment.[12] Another prospective study included observed an overnight switch in a varying dose ratio between 1:1.1 and 1:1.9 (OXC: ESL).[13]

CBZ to ESL

The review identified less data on the ratio of switch between CBZ and ESL (2 studies, N=58). A sub-group analysis (N=13) of a prospective observational study transitioned overnight in a ratio of 1:1.3 (CBZ: ESL).[14] A retrospective, multicentre study sub-group analysis (N=45) observed an overnight transition in a ratio of 1:1.5 (CBZ: ESL).[15]

Efficacy

OXC to ESL

Three studies reported on efficacy outcomes in 84 patients switching from OXC to ESL. An open-label prospective observational study in Spain included 12 individuals as part of a larger cohort of 61 patients with treatment resistant epilepsy, on a variety of concomitant AEDs. The transition from OXC to ESL was conducted overnight in a dose ratio of approximately 1:1 (for example those prescribed OXC at 400mg were switched directly to ESL 400mg). Eleven of those included were followed up for at least 3 months (mean follow-up time 5.25 ± 2.3 months). One individual achieved seizure freedom, an additional 4 (36%) achieved ≥ 50 per cent reduction in seizure frequency, one experienced no change, and one experienced an increase in seizure frequency.[14]

A retrospective multicentre study (N=327) in Spain (ESLIBASE) investigating individuals with focal seizures across 12 hospital sites over a 2-year period included 48 individuals who switched from OXC to ESL. The transition from OXC to ESL was conducted overnight in a dose ratio of 1:1. Investigators observed a 12 month responder rate (≥ 50 per cent reduction in seizure frequency) of 46%, a seizure freedom rate of 31% (baseline before inclusion 16%), and epilepsy worsened in 17%.[15] A single centre study in Finland (N=23) followed individuals transitioned from OXC to ESL overnight in a dose ratio of 1:1. No significant change in seizure frequency was observed over a 1 to 3 month follow-up period.[16]

CBZ to ESL

The two Spanish studies discussed above also investigated the efficacy of switching from CBZ to ESL in a total of 58 participants. The larger retrospective investigation included 45 participants that transitioned from CBZ to ESL. This switch was made overnight in a dose ratio of 1:1.5 (CBZ: ESL). Investigators observed a 12-month responder rate of 39%, seizure freedom in 11% (baseline 13%), and epilepsy worsened in 17%.[15]

Thirteen people with treatment-resistant epilepsy were transitioned from CBZ to ESL in a post-authorisation observational study. The switch was made overnight in a dose ratio of 1:1.3 (CBZ: ESL). However, only 8 individuals who switched were monitored for at least 3 months. In these

cases one patient remained seizure free, one responded, three demonstrated no significant change, and a further three experienced an undefined increase in seizure frequency.[14]

Adverse Events

All seven studies involving a total of 203 participants included within this review included some outcome measure related to adverse events. In the prospective observational study conducted in Spain four of the 12 patients who switched from OXC to ESL (1:1 dose ratio) experienced the same adverse event: drowsiness. Two individuals reported that adverse events associated with OXC (dizziness and drowsiness) improved on switching to ESL. The retention rate for the OXC to ESL group was 100% (mean follow up time was approximately 5 months). In the CBZ to ESL (1:1.5 dose ratio) group 8 out of 13 patients' experienced adverse events (dizziness and nausea, 4; anxiety, 2; insomnia, 1; constipation, 1; pruritic rash, 1). The retention rate (mean follow up approximately 4 months) for the CBZ to ESL group was 69%.[14]

In the ESLIBASE subgroup analysis 26 individuals were switched to ESL from OXC (1:1 dose ratio) because of side effects. Of those switched, 15 out of 26 no longer had any adverse effects, while for 11 out of 26 the adverse effect continued. Seventeen individuals were switched from CBZ to ESL (1:1.5) because of side effects. Following transition 8 out of 17 no longer experienced adverse effects, 9 (53%) continued to experience adverse events.[15]

In a single centre prospective study in the inpatient setting, 23 patients were specifically identified for transition from OXC to ESL (1:1 dose ratio) because of adverse events related to OXC. Those included were most commonly on two other AEDs. The adverse events reported prior to the switch were most commonly fatigue (almost 50%), followed by vertigo and dizziness. Following the switch to ESL, 15 out of 23 patients experienced a significant reduction in adverse events. Following transition, almost all (93%) of the adverse events that presented in the morning resolved. The incidence of adverse events associated with ESL declined during follow up (39% at 1 month, 13% at 3 months). There was a 100% retention rate during the 3-month follow-up period.[16]

A small prospective observational study (N=19) has demonstrated that a switch to ESL (dose ratio 1:0.7, increased to 1:1 after 3 days) in individuals with focal epilepsy on high dose OXC, does not affect serum sodium levels.[12] An overnight switch from OXC to ESL (dose ratio 1:1) was examined prospectively over a 5 day period with standardised testing before and after transition (n=12). No significant differences were identified on measures of adverse events, quality of life, or alertness. Serum sodium level decreased in 9 out of 12 participants but never to a clinically significant level.[17]

A small (N=10) prospective observational investigation examined the tolerability of overnight switch (dose ratio variable 1:1.1 –1.9) in adults with uncontrolled focal seizures. The mean dose after switching was 800mg. Investigators applied the Adverse Event Profile (AEP), a standardized test for alertness, and the Quality of Life in Epilepsy Inventory-10 (QOLIE-10). At day-5 following the switch to ESL there was a significant reduction in AEP scores (P=0.005). There were no statistically significant differences on the other outcome measures.[13] A retrospective, single centre study (N=21) in patients with treatment resistant focal seizures (81% temporal lobe epilepsy) also used similar outcome measures. An overnight switch was performed between OXC and ESL (dose ratio 1:1) with AEP score and QOLIE-10 scores taken before the switch and 5 days post transition. There were statistically significant improvements in AEP score ($p<0.001$), QOLIE-10 ($p=0.001$), and alertness ($p<0.05$) in the short term, with no comment on clinical significance. The AEP score improved for all patients after switch. The QOLIE-10 scores remained the same or worsened for 4 out of 21 patients. The alertness score (reaction time) remained unchanged or worsened in 5 out of 21. There was no impact upon serum sodium level.[18]

Discussion

In contrast to CBZ and OXC it has been shown that Esli appears to lack any clinically meaningful interaction with other enzyme inducing AEDs.[5] This is of real clinical benefit in the management of treatment resistant epilepsy. CBZ in particular is known to be associated with a vast range of drug to drug interactions, some of which may affect the pharmacokinetics of CBZ leading to safety concerns due to the narrow therapeutic window. In addition, CBZ's potent enzyme inducing effects in the liver influence the metabolism of a wide range of drugs for many different conditions. The pharmacokinetic profile of Esli may offer particular benefit to people with multiple co-morbidities, concomitant medications, and the elderly.[19]

This review identified seven studies that investigated the outcome of transition between CBZ and or OXC and ESL, with specific data on the transition dose ratio and scheduling. The data available suggest that the overnight transition between OXC and ESL in a 1:1 ratio (most commonly) is generally well tolerated with retention rates between 70 and 100% (5 days to 5 months). The transition to ESL has also demonstrated improvement in adverse events associated with OXC across a variety of domains. Almost 60% of individuals' who transitioned from OXC to ESL because of adverse events experienced no further symptoms at 12 months.[15] Any adverse events associated with the introduction of ESL itself reduced with time. The data available suggests no negative impact upon seizure control and a responder rate (≥ 50% reduction in seizures) of almost half at 12-month follow-up.[15]

All of the papers included in this review expect one investigated the transition from immediate release OXC to ESL. There is evidence to demonstrate that OXC extended release formulation is associated with better tolerability.[20] However, the OXC extended release formation is not available in all regions and so this review is clinically relevant.

There is less data available for comparison on the transition from CBZ to ESL. The transition ratio varied between 1:1.3 and 1:1.5. Retention rate following transition has been reported as 69% with a mean follow up period of four months,[14] with almost half of those transitioned from CBZ to ESL because of adverse events experiencing no further symptoms.[15] The limited data from one investigation on efficacy reports a responder rate of almost 40% at 12 month follow up.[15]

Hyponatraemia is a clinically important consideration when prescribing dibenzazepines. This review only identifies limited data that may help inform prescribing choices. In a population of individuals (N=19) with pre-existing low sodium levels prescribed OXC, there was no significant impact upon serum sodium levels on long term follow up (1,6,12, and 18 months), even at higher dosege.[12] When

an immediate switch was conducted from OXC extended release formulation to ESL decreased serum sodium was observed at 5 days in nine of 12 participants. However, no one experienced hyponatraemia of a clinically concerning level requiring intervention or medication change.[17]

Non concordance with AEDs is a major contributing factor to treatment failure in epilepsy.[21] This can lead to significant risks to patient safety including injury, hospitalisation, and sudden unexpected death in epilepsy (SUDEP).[22] When patients experience side effects from prescribed medications adherence is poor.[23] Unfortunately the studies included in this review do not identify any specific markers of AED concordance such as serum AED levels. We can therefore only speculate based on surrogate markers such as seizure control and retention rates.

Limitations

The investigations identified are heterogeneous in terms of sample population, methodology, and outcome measures. Therefore, it has not been possible to pool any available data for further analysis. The studies are observational, with no comparative data such as different dosing ratios or schedules for switching between AEDs. The sample sizes in each study are small, and where samples are larger these consist of sub-groups derived from wider investigations. Inclusion and exclusion criteria vary between investigations, although the broad base of population characteristics is generally similar. These characteristics include diagnosis of epilepsy, with focal seizures, concomitant AED prescription, and treatment resistance- as may be expected given ESL licensing and indication. There is significant risk of inherent bias in all studies included due to the observational design, patient selection, sample sizes, short follow-up periods, and lack of comparative groups for a randomisation and blinding process. One positive regarding these observational studies is that outcomes may be more pragmatic. The nature of some of the studies included (conference proceedings) does not allow for formal assessment of bias due to lack of data.

Based on the findings in this review there is Grade C evidence[24] available to help guide clinicians on when and how to transition patients from CBZ or OXC to ESL. A Delphi Consensus paper has described recommendations (Table 2) on how to switch from CBZ and OXC to ESL.[25] This recommendation is based upon ESL clinical data and clinical practice experience of 54 epilepsy experts.

Table 2 [INSERT HERE]

This review does not provide significant new information to influence how transition from OXC or CBZ to ESL should be conducted. The evidence available is based on a transition from both OXC and CBZ overnight with some positive outcomes in the limited data set. There is a lack of data

comparing dosing regimens and titration periods. As discussed, the pharmacokinetic profile of ESL may be beneficial for certain populations with particular characteristics. However, to date there is a lack of robust evidence examining whether this benefit is observed in a clinically relevant way.

Conclusion

There is low level Grade C evidence[24] available based on data from heterogeneous observational cohort studies to support the method of transition between older dibenzazepines and ESL. The data that are available from pragmatic observational investigations demonstrates that transition from CBZ and or OXC to ESL may be effective, and it is in general well tolerated. The pharmacokinetic profile of ESL suggest that it may be beneficial for individuals experiencing side effects from other dibenzazepines, lack of efficacy, lowered adherence, and or risk of drug to drug interactions. However, at present data to support the switch in particular populations are not available. There is a clear need for a rigorous scientific investigation to be performed in large representative real-world cohorts across multiple sites, with comparative groups for transition ratio, schedule, and those who do not switch between AEDs.

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Appendix 1. Search strategy: Medline, PsychINFO, and the Cochrane Library of Systematic Reviews using search term and subject headings for 'Eslicarbazapine' and 'Carbamazapine' or 'Oxcarbazapine', with no language or date restrictions, including grey literature.

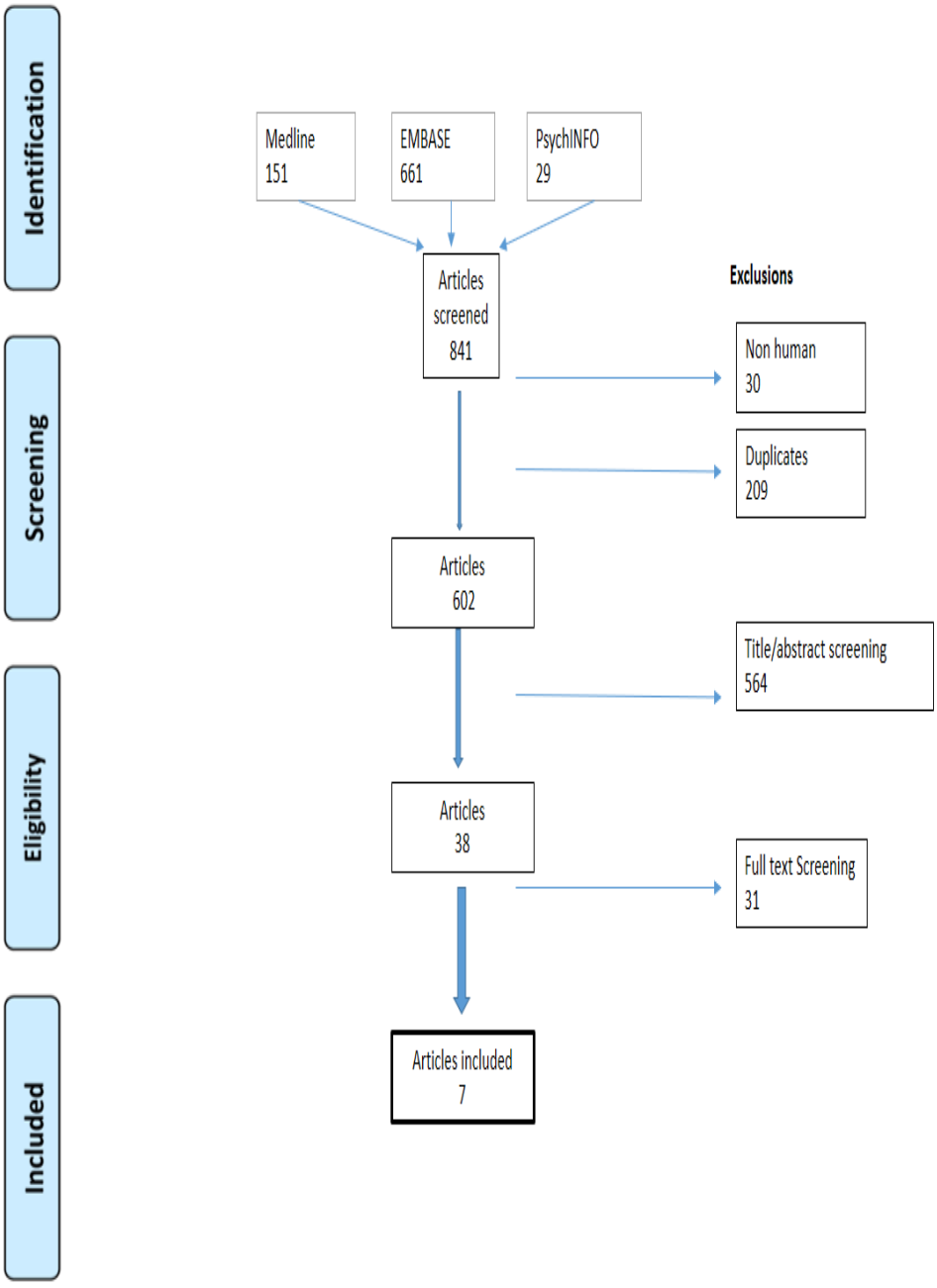

Table 1. Results of systematic literature search

Article	Setting	Sample	Transition Dose Ratio Schedule from OXC or CBZ to ESL	Results and Implications
Oehl *et al*, 2011[12] Conference Abstract	Prospective study patients with uncontrolled focal epilepsy (with low sodium levels)	N=19	OXC:ESL 1:0.7 initially 1:1 after 3 days	**Adverse events** No significant effect on serum sodium levels
Steinhoff et al, 2011[17]	Prospective investigation in adults with focal seizures	N=12	Overnight switch OXC:ESL 1:1 EXTENDED RELEASE FORMULATION	**Adverse events** No difference in AEs, Quality of Life scores, or alertness pre and post switch (5 days post switch) Decreased serum sodium in 9 of 12 (no clinical concern)
Hofler J. *et al* 2013[13] Conference Abstract	Adult patients with focal epilepsy not seizure free with adverse effects using OXC	N=10	OXC:ESL Range 1:1.1 to 1:1.9	**Adverse events:** (5 days post switch) Significantly lower Adverse Event Profile (AEP) ($p<0.005$) -reduction in unsteadiness, GI symptoms, weight gain, dizziness, diplopia, impaired concentration 70% retention rate

				QOLIE-10* and alertness-no significant changes
Massot *et al*, 2014[14]	A prospective post-authorisation observational study in adults with pharmacoresistant epilepsy inpatient and community	N=61 **Sub group**: N=25 Switch CBZ to ESL (N=13) Switch OXC to ESL (N=12)	Overnight switch CBZ:ESL 1:1.3 OXC:ESL 1:1	**Efficacy** *CBZ to ESL* (N=11 with at least 3 months follow up) Seizure freedom 1 (9%), responder (≥ 50% reduction in seizures) 4 (36.4%), no change 1 (9%), increase in seizure frequency 1(9%). *OXC to ESL* (N=8 with at least 3 months follow up) Seizure freedom 1 (12.5%), responder 1 (12.5%), no change 3 (37.5%), increase in seizure frequency 3 (37.5%). **Adverse events** *CBZ to ESL* (N=13) 8 experienced AEs (dizziness and nausea-4, anxiety-2, insomnia-1, constipation-1, pruritic rash-1) Retention rate -69% (mean follow up 4 months)

				OXC to ESL (N=12) 4 experienced AEs (drowsiness) 2 reported resolution of AEs on switching (dizziness and drowsiness) Retention rate -100% (5 months) 6.6% reduced sodium levels, none below 125mmol/L
Villanueva *et al*, 2014[15]	Retrospective multicentre study Focal seizures in 12 hospitals in Spain who initiated ESL between January 2010 and July 2012	N=327 **Sub Group**:N=93 CBZ (N=66) 45 (75%) switch to ESL OXC (N=50) 48(96%) switch to ESL	Overnight switch CBZ:ESL 1:1.5 OXC:ESL 1:1.	**Efficacy** CBZ to ESL 12-month responder rate 38.7% with 11.4% seizure free (baseline 13%) OXC to ESL 12 month responder rate 45.9% with 31.3% seizure free (baseline 16%) **Adverse events** CBZ to ESL 47.1% switch due to AEs had no further symptoms OXC to ESL 57.7% switch due to AEs had no further symptoms
Mäkinen *et al*, 2017[16]	A prospective single centre study of patients on OXC with side effects in a hospital inpatient setting in Finland	N=23	Overnight switch OXC:ESL 1:1	**Efficacy** 50% reduction n seizure frequency (1) 30% reduction in seizure frequency (1) 4 out of 12 reduction in seizure frequency or duration Increased seizure frequency (0)

				Adverse events 15 OXC-related AEs reduced significantly after transitioning. 93% of the AEs which presented in the morning resolved following transition 100% retention ESL related side effects were 39% at month 1 and 13% at month 3.
Schmid *et al*, 2017[18]	Retrospective, single-center study for patients with drug-resistant focal epilepsy on stable dose of OXC for at least 4 weeks.	N=21	Overnight switch Individual basis OXC:ESL 1:1 (most commonly)	**Adverse events** (5 days post switch) AEP score ($p<0.01$) and alertness (76%) ($p<0.5$) QOLIE-10* score improved in 81%

*(Quality of Life in Epilepsy Inventory -10)

Table 2. The EPICON[25] recommendations for transition from CBZ or OXC to ESL.

A switch from **CBZ to ESL** over a period of 1 to 3 weeks with a **CBZ:ESL dose ratio of 1:1.3.**
Patient characteristics:

- -Low concordance with medication
- -Patients working shift patterns/unusual hours
- -Patients on multiple medications
- -Cognitive problems
- -Severe osteoporosis or osteopenia
- -Dyslipidaemia
- -Liver disease other than acute liver failure
- -Men with erectile dysfunction caused by CBZ.

A switch from **OXC to ESL** is well tolerated even with an **overnight switch in a 1:1 ratio.**
Patient characteristics:

- -Low concordance with medication
- -Patients working shift patterns/unusual hours
- -Patients on multiple medications
- -Cognitive problems.

**Transition to ESL is not recommended for individuals with a rash associated with CBZ or OXC treatment.*