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Article type : Review Article

Antiepileptic Mono-therapy in Newly Diagnosed Focal Epilepsy. A network meta-analysis

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Running title: Antiepileptic Therapy in Newly Diagnosed Epilepsy

Supplemental material: Data Supplement
PRISMA statement

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ane.13025

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Key Words: Antiepileptic drugs; Focal Epilepsy; Mono-therapy; Network Meta-analysis

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Summary

Second and third generation AEDs have been directly compared to controlled-release carbamazepine (CBZ-CR) as initial monotherapy for new-onset focal epilepsy. Conversely, no head-to-head trials have been performed. The aim of this study was to estimate the comparative efficacy and tolerability of the antiepileptic monotherapies in adults with newly diagnosed focal epilepsy through a network meta-analysis (NMA).

Randomized, double blinded, parallel group, mono-therapy studies comparing any AED to CBZ-CR in adults with newly diagnosed untreated epilepsy with focal-onset seizures were identified. The outcome measures were the seizure freedom for 6 and 12 months, the occurrence of treatment-emergent adverse events (TEAEs), and the treatment withdrawal due to TEAEs. Mixed treatment comparisons were conducted by a Bayesian NMA using the Markov chain Monte Carlo methods. Effect sizes were calculated as odds ratios (ORs) with 95% credible intervals (CrIs).

Four trials were included involving 2856 participants, 1445 for CBZ-CR and 1411 for the comparative AEDs. Monotherapy AEDs compared to CBR-CR were levetiracetam (LEV), zonisamide (ZNS), lacosamide (LCM) and eslicarbazepine acetate (ESL). There were no statistically differences in the 6- and 12-month seizure freedom and TEAEs occurrence

between LEV, ZNS, LCM, ESL, and CBZ-CR. In the analysis of drug withdrawal due to TEAEs, LCM treatment was associated to a significantly lower discontinuation rate than CBZ-CR (OR 0.659, 95% CrI 0.428-0.950).

LEV, ZNS, LCM, and ESL are effective initial mono-therapy treatments in adult patients with newly diagnosed focal epilepsy and represent suitable alternatives to CBZ-CR.

Introduction

Epilepsy is one of the most common neurological disorders affecting approximately 70 million people worldwide.[1,2] It has age-adjusted prevalence estimates of 2.7 to 17.6 per 1000 and age-adjusted incidence of 16 to 51 per 100,000.[3] The major goal of medical management of epilepsy is achieving seizure freedom with minimal or no adverse effects, and monotherapy represents the best therapeutic option for newly diagnosed patients. Nonetheless, AEDs are initially licensed only for adjunctive use, and the authorization for monotherapy requires the comparison to a reference standard and can take several years. According to the recommendations of the US Food and Drug Administration, the approval is based on the evidence of efficacy and safety resulting from conversion-to-monotherapy trials with historical controls.[4] The European Medicines Agency (EMA), instead, requires randomized, double-blind, active-controlled, monotherapy studies in newly diagnosed epilepsy aimed to demonstrate a benefit/risk balance of the tested AED at least similar to that of an acknowledged standard at optimized dosage.[5] This type of study is commonly known as non-inferiority or equivalence study. The International League Against Epilepsy (ILAE) recommends a minimum trial duration of 48 weeks, without forced exit criteria, the assessment of efficacy based on seizure freedom for 24 weeks or more, and a sample size large enough to demonstrate non-inferiority with a ≤20% relative difference across the treatment arms.[6] Controlled-release carbamazepine (CBZ-CR) is commonly considered the primary standard and chosen as the active comparator since its efficacy as first-line

monotherapy for patients with newly diagnosed focal epilepsy has been established by several class I studies.[6-9]

In the recent years, second and third generation AEDs have been compared to CBZ-CR as initial monotherapy for patients with newly diagnosed focal epilepsy. Conversely, with the single exception of one randomized controlled trial (RCT) comparing pregabalin to lamotrigine (LMT) in newly diagnosed focal epilepsy,[10] no head-to-head trials have been performed, and comparative data on the efficacy and tolerability of these pharmacological options are not available. The network meta-analysis (NMA) is a new meta-analytical technique that has been proposed as an objective way of comparing alternative treatments where direct comparisons do not exist.[11,12] Hence, the aim of this study was to perform a systematic review and NMA of all currently available randomized control trials (RCTs) of AED monotherapy versus CBZ-CR in the non-inferiority design to compare the efficacy and tolerability of the different antiepileptic treatments in adult patients with newly diagnosed focal epilepsy.

Materials and methods

Search strategy. The study results were reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] We systematically searched (March week 3, 2018) MEDLINE (accessed through PubMed), CENTRAL (Cochrane Central Register of Controlled Trials), EMBASE, and the US National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov/) (search strategies are outlined in e-Appendix I); additional data were sought through the conference proceedings of the American Academy of Neurology and the International League Against Epilepsy. There were no date limitations or language restrictions. The

reference lists of retrieved studies were reviewed to search for additional reports of relevant trials. The protocol was not registered previously.

Eligibility criteria. Studies were selected when they met the following entry criteria: randomized, double blinded, parallel group, monotherapy studies comparing gabapentin, eslicarbazepine acetate, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, retigabine, tiagabine, topiramate, vigabatrin or zonisamide versus CBZ-CR. Participants had to meet the following criteria: any gender, any ethnicity, adult age (≥16 years), newly-diagnosed untreated epilepsy with focal-onset seizures (simple focal, complex focal or secondary generalized tonic-clonic seizures). Studies conducted exclusively in elderly patients (≥60 years) or using active comparators other than CBZ-CR were excluded.

Study selection, data extraction and assessment of the risk of bias. Two review authors (F.B. and E.G) independently assessed trials for inclusion and extracted the information from included trials. Any disagreement was resolved by discussion with a third review author (S.L.). The following trial data were extracted: main study author and age of publication; total number and demographics of participants for each group (age, sex, weight, height, body mass index, number of seizures in the past 3 months, number of seizures in the past 12 months, epilepsy duration, type of seizures); intervention details (study design; inclusion and exclusion criteria; description of study phases with details on starting and target dose, titration, and length of each phase; primary and secondary endpoints); trial methods (method of generation of random list; method of concealment of randomisation; blinding methods); definitions of intention-to-treat (ITT), per-protocol (PP) and safety population adopted in each study; proportion of patients achieving at least 26-weeks seizure freedom during the maintenance period; proportion of patients seizure-free for at least 52 consecutive weeks;

proportion of patients with treatment-emergent adverse events (TEAEs) during the treatment period; proportion of patients with TEAEs leading to drug withdrawal.

The risk of bias of the identified studies was assessed in accordance with the recommendations of the Cochrane Collaboration.[14] To evaluate whether studies were suitably similar to be synthesized into a NMA, we adopted the framework for assessing exchangeability assumption proposed by ICWG.[15]

Outcome measures. The efficacy outcomes were the proportion of patients achieving at least 26-weeks seizure freedom during the maintenance period and the proportion of seizure-free patients for at least 52 consecutive weeks. The ITT and PP population were used for the efficacy analyses. The safety endpoints (safety population) included the proportions of patients who experienced any TEAE during the treatment period and the proportion of patients with TEAEs leading to drug withdrawal.

Statistical analysis. Mixed treatment comparisons were conducted by a Bayesian network meta-analysis using the Markov chain Monte Carlo methods in WinBUGS 1.4 software package (MRC Biostatistics Unit at Cambridge, United Kingdom). Effect sizes were calculated as odds ratios (ORs) with 95% credible intervals (CrIs) for the posterior distribution of the binary outcomes using a fixed-effect model. The goodness of model fit has been confirmed by calculating the residual deviance and the deviance information criterion (DIC) (e-Appendix II).[16] Rank probabilities were generated for each outcome measure to determine the probability of each treatment being best and reported as histograms.

Results

Results of the search. A total of 1149 records were identified by database and trial registers searching. Four trials[17-20] were included in the review, all of which were included in the meta-

analysis (Figure 1). Monotherapy AEDs compared to CBR-CR were levetiracetam (LEV),[17] zonisamide (ZNS),[18] lacosamide (LCM),[19] and eslicarbazepine acetate (ESL).[20]

Characteristics of the included studies. All included trials were randomized, double-blind, multicentre, parallel group, and adopted a non-inferiority design. The studies included 2856 participants according to the ITT, 1445 for CBZ-CR and 1411 for the comparative AEDs. All patients were diagnosed with newly diagnosed untreated epilepsy with focal-onset unprovoked seizures, with or without secondarily generalization. Three RCTs included patients with generalized tonic-clonic seizures with percentages ranging from 9.3% to 20.3% of the entire study population.[17-19] Details of the included studies and participants are given in Table e-1 and Table 1, respectively. For each efficacy/tolerability endpoint, results were reported for ITT/safety population (consistently defined across studies as all randomized patients who received at least one dose of the study medication) and/or for PP population (defined as patients in the ITT population without protocol deviations impacting the interpretation of primary efficacy).

Risk of bias of the included studies. All trials applied centralised randomisation procedures with adequate methods of sequence generation and allocation concealment based on randomisation list or code generated by means of computerised techniques. We rated all included trials as low risk of performance and detection bias since blinding was ensured by matching trial medications and packaging, and neither the investigators nor the patients knew the identity of the study treatment being administered. The risks of attrition and selective reporting bias were judged low since patients lost to follow-up and withdrawals were documented, and there was no suspicion of selective outcome reporting. All trials were sponsored by the respective manufacturer of the AED that was compared to CBZ-CR. The risks of bias for each study were summarized in Table e-2.

Quantitative data synthesis. The proportions of seizure free patients for 6 and 12 months and the rates of TEAEs and drug withdrawal due to TEAEs for any given trial are reported in Table 2. In the ITT analysis, a total of 4 pairwise comparisons were available for each AED in any predefined outcome. There were no statistically differences in the 6- and 12-month seizure freedom and TEAEs occurrence between LEV, ZNS, LCM, ESL, and CBZ-CR. In the analysis of drug withdrawal due TEAEs, a statistically meaningful difference was observed in the comparison between LCM and CBZ-CR, with a significantly lower discontinuation rate associated with LCM than CBZ-CR treatment (OR 0.659, 95% CrI 0.428-0.950) (Figures 2-3). The estimated ORs with 95% CrIs of efficacy and tolerability endpoints are reported in Table 3 and Table 4. The PP analysis did not change the results (Table e-3). Rank analysis, which indicates the probability score that any drug is associated to the study outcome, is shown in the e-Appendix III.

Discussion

This NMA failed to demonstrate any significant difference in efficacy (seizure freedom at 6 and 12 months at the last assessed dose) within each new AEDs in adult patients with newly diagnosed focal epilepsy.

Approximately half of the patients newly diagnosed with epilepsy are expected to be seizure-free after the first treatment with an appropriate AED,[21] which might be maintained for life. This high response rate is reassuring, but it also translates into great responsibilities in the selection of the initial drug: it should control seizures, be safe and have a good tolerability with as few adverse effects as possible.

There is little evidence of how AEDs should be chosen, and practice recommendations are mostly empirical. In this respect, making use of what is already known about patient history and pharmacological profile can have direct clinical implications to tailor “rational

therapy":[22] treatment should be carefully individualized taking into account both patient-related variables, like age, childbearing potential, comorbidities and concomitant medications, and drug characteristics as tolerability profile, pharmacokinetics and ease of dosing. All these factors restrict the number of AEDs that can be actually used. Accordingly, although no AED has demonstrated to be superior to CBZ-CR in terms of efficacy, the identification of reliable alternatives for the first-line treatment of focal seizures would allow to overcome the suboptimal characteristics of any available drug and identify the best treatment for any given patient.

The results of this systematic review of AED monotherapy trials in newly diagnosed focal epilepsy are consistent with the previous evidence from unblinded trials,[23,24] which did not show a significant difference in efficacy with CBZ-CR. This does not completely rule out the possibility of false negative results due to statistical error type II: the wide CrIs around the estimates cannot exclude the likelihood of real differences between treatments. It is however noteworthy that findings of NMAs have been shown to be concordant with results of direct comparative trials in 93% of the cases, and their validity depends on the methodological quality and similarity of the studies being indirectly compared.[25] In this respect, all RCTs included in the present NMA were clinically and methodologically homogeneous. More specifically, they have been designed with adequate power for the assessment of non-inferiority and adopted a stepwise dose increment design, which was based on seizure control and tolerability and closely resembled the clinical practice. They have been performed in accordance with the recommendations of the EMA guidelines and the ILAE recommendations for class I studies,[5,6] which guarantee generalizability and robust statistical methodology. Seizure freedom at 6 and 12 months and discontinuation due to TEAEs represent strong outcome measures with high clinical relevance and sufficient duration to document a sustained response. Unlike add-on trials, change in seizure frequency is less

relevant for newly diagnosed epilepsy since most patients have had and will have only few seizures and the goal for the treatment of new-onset epilepsy is long-term seizure freedom.[26] When the efficacy profiles are quite similar among two AEDs, the overall effectiveness is often determined by tolerability, which is best measured by the rate of drug withdrawal due to TEAEs events.[26,27] Notably, this endpoint is more specific and less influenced by the nocebo effect than the occurrence of adverse events.[28] In the direct comparison, CBZ-CR has been associated with a higher rate of TEAEs leading to drug withdrawal than LCM. The older age of the population enrolled in the trial and the higher rate of patients over 65 years might partially explain this finding.[20] The selective enhancement of slow rather than fast inactivation of voltage-gated sodium channels operated by LCS might have also contributed, but no definitive conclusions could be drawn. Indeed, no clear-cut differences in withdrawal rates due to TEAEs have been observed between CBZ-CR and ESL, which resembles LCS in pharmacokinetic profile.[29,30]

The results of this meta-analysis share the limitations inherent to the non-inferiority trials without a placebo control. The assessment of the non-inferiority of the newer AEDs to CBZ-CR does not exclude that treatments could be not more effective than placebo.[31] In this respect, however, the efficacy of CBZ-CR as first-line monotherapy for focal epilepsy has been widely established and it is generally viewed as the best standard comparator.[6] We did not compare the outcomes according to the dose level tested or the first level of dosage that achieved a sustained seizure-freedom with any AED; furthermore, ESL and LCM were up-titrated to dosages higher than the highest effective recommended doses for adjunctive therapy.[32] Therefore, no dosing recommendations could be drawn from our study. It is also noteworthy that the population in the study investigating ESL versus CBZ-CR[20] had a higher number of pre-randomization seizures in comparison to patients enrolled in the other trials; however, since only means were reported and medians were not available, it could not be

ascertained whether the higher values observed in baseline seizure frequency were driven by the presence of outliers, which displaced the means, or actually reflected heterogeneity in recruited cohorts.

We undertook the NMA using summary data published in trials reports rather than data collected on each individual participant in randomized studies. A meta-analysis of individual participant data is usually more resource-intensive than a meta-analysis of aggregate data, and it can offer the potential either to perform more thorough and powerful analyses of time-based outcomes or explore the heterogeneity in treatment effects according to patient' s characteristics. Individual-level meta-analyses also allow to re-instate patients or include follow-up data that were excluded from published analyses; however, the likelihood to not obtain suitable data from all relevant studies is high and can lead to bias.[33] Recently, an individual-level NMA of AED monotherapy for epilepsy[34] indicated CBZ and LMT as suitable first-line treatments for individuals with partial onset seizures and LEV as a valid alternative. These conclusions were derived from the analyses of time-based endpoints: indeed, the primary outcome was the time to withdrawal of allocated treatment, and secondary outcomes included the times to achieve 12-month remission, 6-month remission and first seizure post-randomisation. Data for many of the pair-wise comparisons were however contributed by only a single trial or a small number of participants, and the pre-planned analysis of occurrence of adverse events was not performed due to variability in methods and details of reporting. Additionally, it is worth noticing that LCM and ESL were not considered by the review Authors as not licensed and used in clinical practice as monotherapy at the time of publication of the protocol.

Despite substantial homogeneity and similarity assumption between the included RCTs, indirect comparisons between AEDs should not be considered a substitute for head-to-head trials. In absence of RCTs directly comparing the different AEDs, we cannot keep out a

possible discrepancy in efficacy and tolerability within each new AED between direct and indirect comparisons. It is however unlikely that pragmatic direct comparisons will be sponsored by the industry in the future, as no drug company will carry the risk of performing a trial yielding unfavorable results to the own tested drug, and current EMA guidelines do only request a comparison against standard of care.

In summary, our NMA failed to demonstrate a significant difference in efficacy between different new AEDs as monotherapy treatment in adult patients with newly diagnosed focal epilepsy. Currently, the comprehensive knowledge of the pharmacological compounds should guide the clinical decision-making to provide the best individualized treatment and optimize resource allocation. Apart from possible differences in efficacy, other features including frequency of administration, pharmacokinetic properties, risk of drug-drug interactions, tolerability profile and patients´ preferences should be considered in the choice. In the future, the better understanding of the pathophysiology of seizure generation and innovative strategies to identify new molecular targets could allow to develop more effective drugs.[26,35]

Sources of funding. None

Conflict of interests. SL, FG, RN and MS declare no conflict of interest. GZ has received speaker's or consultancy fees from Eisai, Jansen-Cilag, Sanofi-Aventis, and UCB Pharma. EG is an employee of Eisai s.r.l. ET received speaker's honoraria from UCB, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, Sunovion Pharmaceuticals Inc., and Novartis; consultancy funds from UCB, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, Sunovion Pharmaceuticals Inc., and Novartis; directorship funds from Neuroconsult GmbH; and commercial funds from Biogen, Novartis, and Bayer. E. Trinka's Institution received grants from Biogen, Red Bull, Merck, UCB, European Union, FWF Österreichischer Fond

zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung. FB has received speakers' honoraria from Eisai and PeerVoice, payment for consultancy from Eisai, and travel support from Eisai, ITALFARMACO, and UCB Pharma. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Characteristics of study participants

	Brodie et al., 2007		Baulac et al., 2012		Baulac et al., 2017		Trinka et al., 2018	
Comparisons	LEV (n=285)	CBZ-CR (n=291)	ZNS (n=281)	CBZ-CR (n=300)	LCM (n=444)	CBZ-CR (n=442)	ESL (n=401)	CBZ-CR (n=412)
Age, years	39.8 (16.6)	39.0 (15.8)	37.1 (16.3)	35.6 (15.5)	41.9 (17.9)	41.8 (17.2)	37.6 (15.8)	38.7 (16.3)
Sex								
Male	146 (51%)	171 (59%)	174(62%)	172 (57%)	243 (55%)	232 (53%)	228 (57%)	220 (53%)
Female	139 (49%)	120 (41%)	107 (38%)	128 (43%)	201 (45%)	210 (47%)	173 (43%)	192 (47%)
Weight, kg	73.7 (16.8)	73.6 (15.2)	70.6 (17.0)	69.4 (16.5)	NA	NA	NA	NA
Height, cm	170.0 (9.7)	171.1 (9.7)	169 (10.2)	168.3 (10.3)	NA	NA	NA	NA
Body mass index, kg/m^2	25.5 (5.2)	25.1 (4.6)	24.6 (4.7)	24.4 (4.7)	25.10 (4.88)	25.70 (5.29)	25.2 (4.8)	25.4 (5.1)
Seizures in past year	4.0 [2.0-10.0]	3.0 [2.0-10.5]	3.0 (2.0-4.0)	3.0 (2.0-4.0)	4.0 [2.0-12.0]	4.0 [2.0-10.0]	20.0 (64.6)	19.0 (65.0)
Seizures in past 3 months	2.0 [1.0-4.5]	1.0 [1.0-5.0]	2.0 (1.0-3.0)	2.0 (1.0-3.0)	3.0 [1.0-6.0]	2.0 [2.0-5.0]	7.5 (17.8)	8.1 (33.3)
Epilepsy duration	0.8 [0.3-2.4]	0.8 [0.3-2.7]	2.6 (9.3)	3.0 (12.3)	29.0 [18.0-49.0]	27.0 [17.0-47.0]	NA	NA

	years	years	months	months	days	days		
Focal seizures	80%	79.7%	244 (87%)	262 (87%)	403 (90.8%)	302 (91.0%)	401 (100%)	412 (100%)
GTCS	20%	20.3%	37 (13%)	38 (13%)	47 (10.6%)	42 (9.3%)	0.0%	0.0%

Data are mean (standard deviation) or median [interquartile range].

Abbreviations: CBZ-CR=controlled-release carbamazepine, ESL=eslicarbazepine acetate, GTCS=generalized tonic clonic seizures, LCM=lacosamide, LEV=levetiracetam, NA=not available, Q1-Q3=first-third quintile, SD=standard deviation, ZNS=zonisamide.

Table 2. Efficacy and tolerability endpoints of the included trials

	Brodie et al., 2007		Baulac et al., 2012		Baulac et al., 2017		Trinka et al., 2018	
Comparisons	**LEV**	**CBZ-CR**	**ZNS**	**CBZ-CR**	**LCM**	**CBZ-CR**	**ESL**	**CBZ-CR**
Proportion of seizure free patients for 6 months, ITT	190/285 (66.7%)	194/291 (66.7%)	195/281 (69.4%)	224/300 (74.7%)	327/444 (73.6%)	308/442 (69.7%)	284/401 (70.8%)	305/412 (74.0%)
Proportion of seizure free patients for 6 months, PP	173/237 (73.0%)	171/235 (72.8%)	177/223 (79.4%)	195/233 (83.7%)	307/408 (75.2%)	285/397 (71.8%)	276/388 (71.1%)	300/397 (75.6%)
Proportion of seizure free patients for 12 months, ITT	142/285 (49.8%)	155/291 (53.3%)	157/281 (55.9%)	187/300 (62.3%)	264/444 (59%)	262/442 (59%)	256/388 (63.8%)	283/397 (68.7%)
Proportion of seizure free patients for 12 months, PP	129/228 (56.6%)	131/224 (58.5%)	146/216 (67.6%)	171/229 (74.7%)	NA	NA	251/388 (64.7%)	279/397 (70.3%)
Patients with TEAEs	227/285 (79.6%)	235/291 (80.8%)	170/281 (60%)	185/300 (62%)	328/444 (73.9%)	332/442 (75.1%)	302/401 (75.3%)	320/412 (77.7%)
Patients with TEAEs leading to discontinuation	41/285 (14.4%)	56/291 (19.2%)	31/281 (11%)	35/300 (12%)	47/444 (11%)	69/442 (16%)	54/401 (13.5%)	74/412 (18.0%)

Abbreviations: CBZ-CR=controlled-release carbamazepine, ESL=eslicarbazepine acetate, ITT=intention to treat, LCM=lacosamide, LEV=levetiracetam, NA=not available, PP=per protocol, TEAE=treatment emergent adverse event, ZNS=zonisamide.

Table 3. Efficacy of antiepileptic drugs in newly diagnosed focal epilepsy

	6-month seizure freedom	12-month seizure freedom
Comparison	**OR [95% CrI]**	**OR [95% CrI]**
CBZ-CR vs. LEV	1.016 [0.709, 1.414]	0.884 [0.633, 1.214]
CBZ-CR vs. ZNS	0.782 [0.534, 1.100]	0.773 [0.544, 1.061]
CBZ-CR vs. LCM	1.231 [0.911, 1.634]	1.020 [0.776, 1.323]
CBZ-CR vs. ESL	0.860 [0.624, 1.160]	0.813 [0.600, 1.080]
LEV vs. ZNS	0.793 [0.469, 1.271]	0.899 [0.546, 1.393]
LEV vs. LCM	1.249 [0.772, 1.922]	1.185 [0.761, 1.766]
LEV vs. ESL	0.873 [0.535, 1.352]	0.946 [0.591, 1.433]
ZNS vs. LCM	1.629 [0.996, 2.531]	1.358 [0.860, 2.042]
ZNS vs. ESL	1.138 [0.686, 1.782]	1.082 [0.677, 1.641]
LCM vs. ESL	0.715 [0.457, 1.075]	0.812 [0.535, 1.185]

Abbreviations: CBZ-CR=controlled-release carbamazepine, CrI=credible interval, ESL=eslicarbazepine acetate, LCM=lacosamide, LEV=levetiracetam, OR=odds ratio, ZNS=zonisamide.

Table 4. Tolerability of antiepileptic drugs in newly diagnosed focal epilepsy

	Treatment emergent adverse events	Withdrawal due to treatment emergent adverse events
Comparison	**OR [95% CrI]**	**OR [95% CrI]**
CBZ-CR vs. LEV	0.950 [0.618, 1.401]	0.718 [0.450, 1.086]
CBZ-CR vs. ZNS	0.967 [0.685, 1.331]	0.969 [0.560, 1.574]
CBZ-CR vs. LCM	0.950 [0.697, 1.275]	0.650 [0.428, 0.950]
CBZ-CR vs. ESL	0.838 [0.593, 1.151]	0.729 [0.492, 1.048]
LEV vs. ZNS	1.063 [0.606, 1.746]	1.420 [0.683, 2.610]
LEV vs. LCM	1.044 [0.609, 1.669]	0.953 [0.508, 1.655]
LEV vs. ESL	0.922 [0.522, 1.503]	1.068 [0.573, 1.814]
ZNS vs. LCM	1.012 [0.628, 1.555]	0.719 [0.354, 1.321]
ZNS vs. ESL	0.893 [0.543, 1.386]	0.805 [0.410, 1.440]
LCM vs. ESL	0.904 [0.559, 1.380]	1.169 [0.650, 1.944]

Abbreviations: CBZ-CR=controlled-release carbamazepine, CrI=credible interval, ESL=eslicarbazepine acetate, LCM=lacosamide, LEV=levetiracetam, OR=odds ratio, ZNS=zonisamide.

Figure 1. Flow diagram of study selection process

Figure 2. Efficacy of antiepileptic drugs in newly diagnosed focal epilepsy

A. 6-month seizure freedom

B. 12-month seizure freedom

Abbreviations: CBZ-CR=controlled-release carbamazepine, CrI=credible interval, ESL=eslicarbazepine acetate, LCM=lacosamide, LEV=levetiracetam, ZNS=zonisamide.

Figure 3. Tolerability of antiepileptic drugs in newly diagnosed focal epilepsy

A. Treatment emergent adverse events

B. Drug withdrawal due to treatment emergent adverse events

Abbreviations: CBZ-CR=controlled-release carbamazepine, CrI=credible interval, ESL=eslicarbazepine acetate, LCM=lacosamide, LEV=levetiracetam, ZNS=zonisamide.

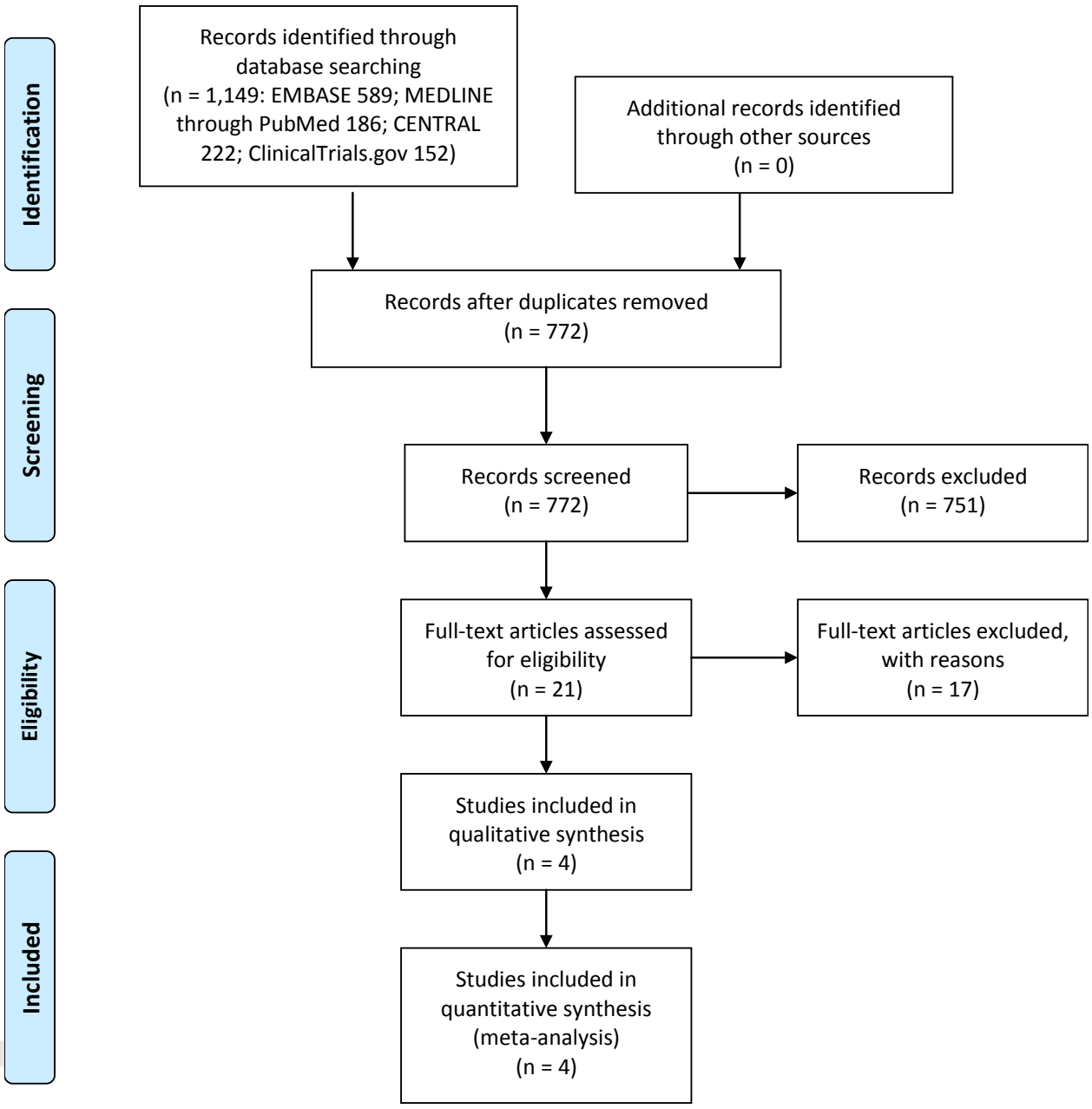
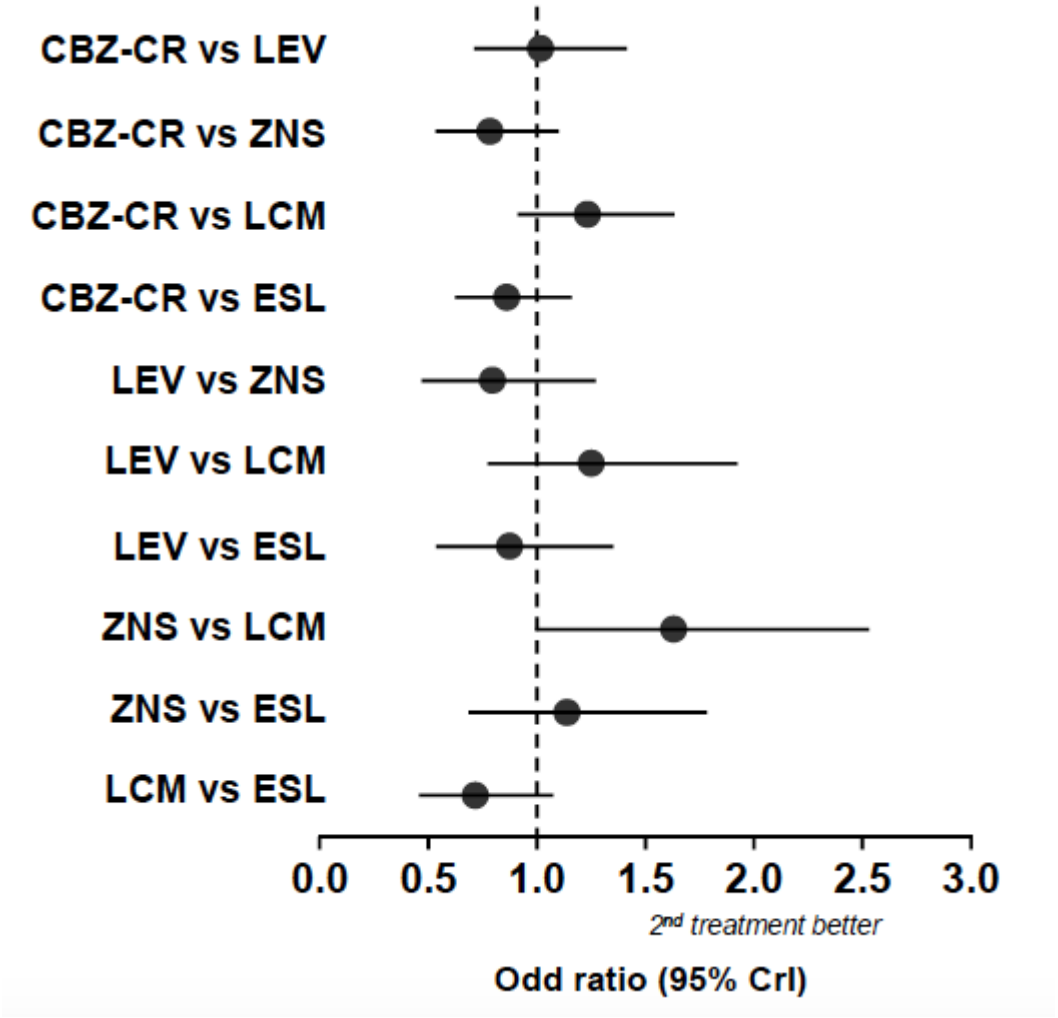


Figure 2A



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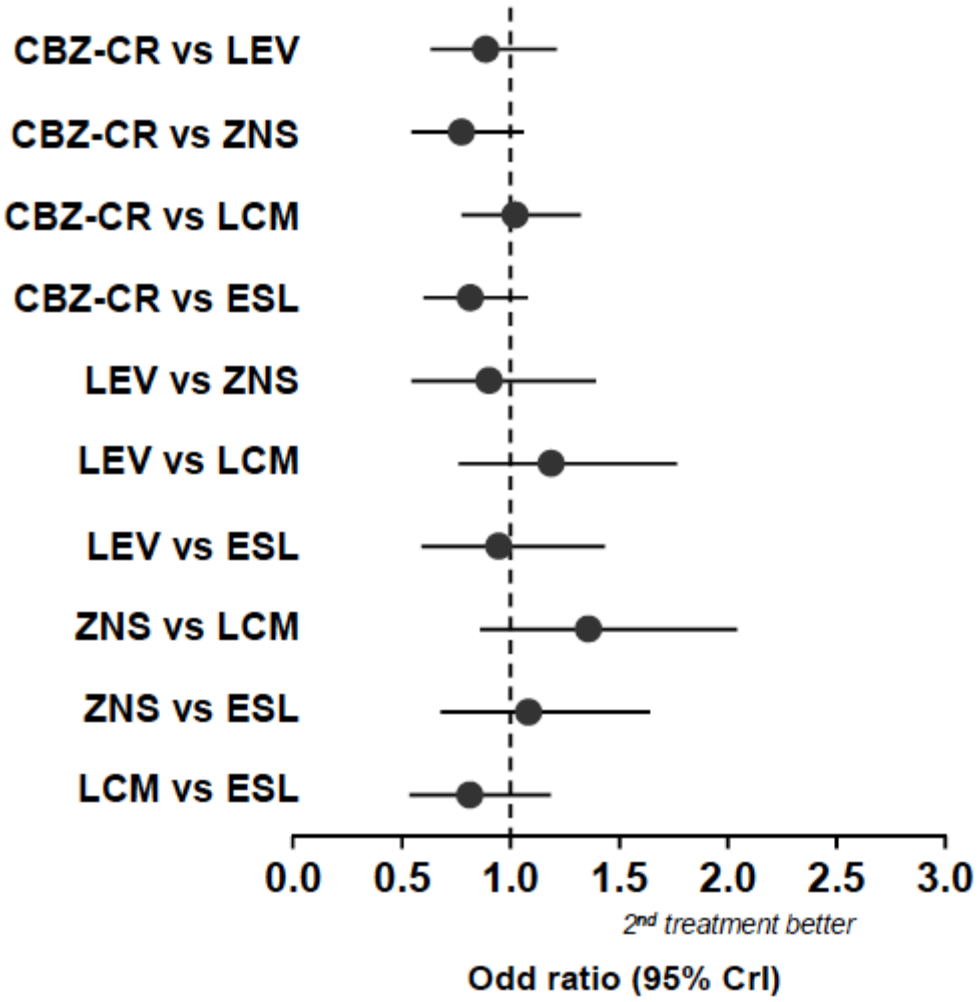

Figure 3A

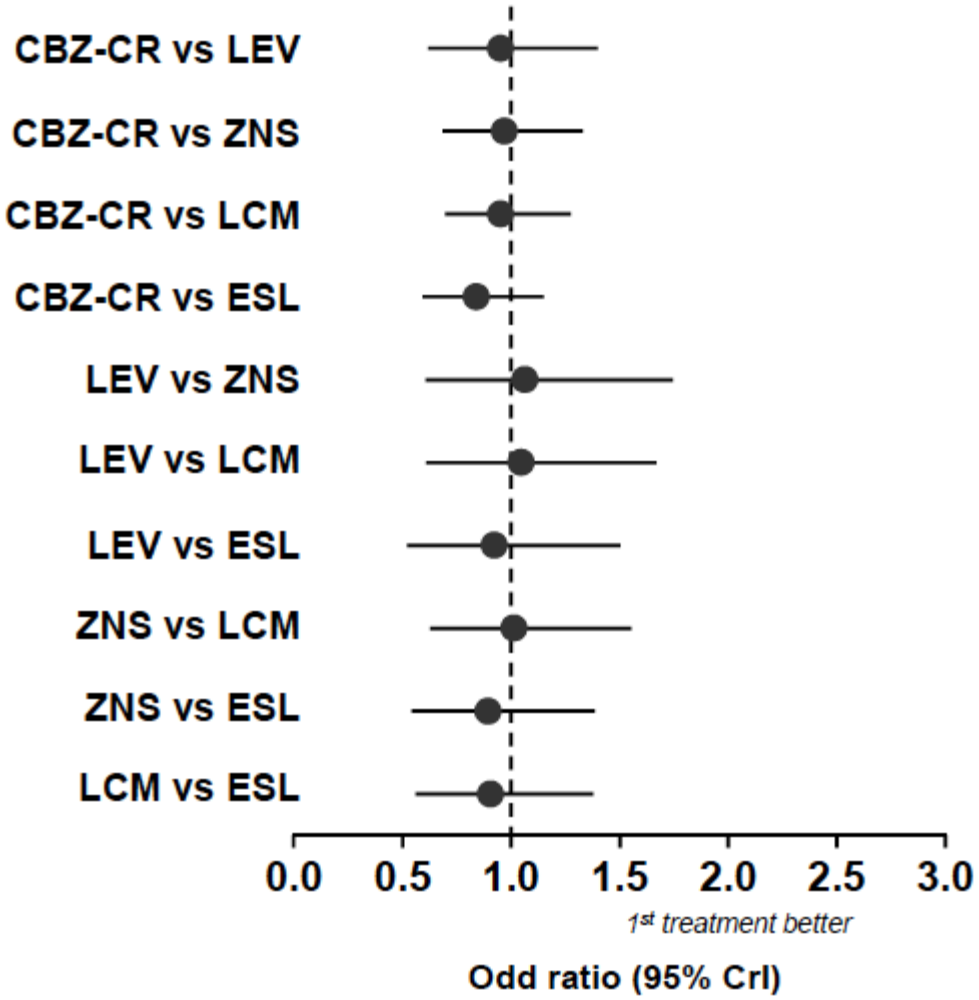

Figure 3B