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Review

The efficacy and safety of retigabine and other adjunctive treatments for refractory partial epilepsy: A systematic review and indirect comparison

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ABSTRACT

Introduction: Retigabine (RTG) is now approved in Europe and the US for the adjunctive treatment of partial-onset seizures in adults with epilepsy. To support submissions to EU reimbursement authorities, we explored its efficacy and tolerability relative to selected antiepileptic drugs (AEDs).
Methods: A systematic review was conducted to identify placebo-controlled trials of RTG and selected AEDs approved for use in a similar position in the management pathway of partial epilepsy (eslicarbazepine acetate [ESL], lacosamide [LCM], pregabalin [PGB], tiagabine [TGB] and zonisamide [ZNS]). Using conventional and network meta-analyses as appropriate, we report efficacy and tolerability outcomes for each AED versus placebo and the performance of RTG relative to other AEDs.
Results: Twenty studies met the inclusion criteria: three each for RTG, ESL, LCM, TGB and ZNS; five for PGB. Comparisons comprised 1–5 studies per AED. In the network meta-analysis, RTG was not found to be different from the other AEDs for responder rate (maintenance period), seizure freedom (maintenance period and double-blind period), withdrawals due to adverse events, and incidences of ataxia, dizziness, fatigue and nausea. Differences between RTG and other AEDs were found for a few comparisons, which did not reveal any trends: RTG was associated with a lower responder rate than PGB during the double-blind period, higher withdrawal rate due to any reason than ESL and a higher incidence of somnolence than TGB.
Conclusions: Findings suggest that the risk/benefit for RTG is similar to that for comparator AEDs. However, results should be interpreted in the context of the limitations of the analyses.

1. Introduction

Retigabine (RTG, international non-proprietary name) is the first potassium channel opener to be approved for the treatment of epilepsy. It is indicated in Europe for the adjunctive treatment of partial-onset seizures, with or without secondary generalization, in adults with epilepsy. RTG is also approved in other countries, including the US (under the US adopted name of ezogabine), where it is approved for the adjunctive treatment of partial-onset seizures. By targeting neuronal KCNQ (Kv7) ion channels, and thus stabilizing the resting membrane potential, RTG offers a novel treatment option for patients who have not previously attained an adequate response to other antiepileptic drugs (AEDs).[1]

When a new drug for the adjunctive treatment of partial-onset seizures becomes available, information on its efficacy and tolerability profile relative to other treatments may be required to inform the decision-making process for payers in the absence of head-to-head data. To support submissions to EU reimbursement authorities, a systematic review was conducted to compare the efficacy and tolerability of RTG relative to other selected adjunctive treatments approved for partial-onset seizures in adults with epilepsy.

The AEDs selected as appropriate comparators for RTG (eslicarbazepine acetate [ESL], lacosamide [LCM], pregabalin [PGB], tiagabine [TGB] and zonisamide [ZNS]) were those approved for use in Europe, over approximately the last 10 years, as adjunctive (but not mono-) therapy for partial epilepsy. RTG would be used in a similar position in the management pathway for partial-onset seizures as these comparator AEDs, and these

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agents, which are not licensed for use as monotherapy, would be considered as alternatives to RTG in pharmacy formularies. AEDs such as carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate, which are licensed for monotherapy in patients with partial-onset seizures, are also licensed for adjunctive use; however these well-established agents are generally used earlier in the adjunctive treatment pathway than the agents selected for this study and were therefore not considered appropriate comparators.[2]

The objective of this review was to evaluate the efficacy and tolerability of RTG relative to the selected drugs for the purposes of providing comparative data for EU reimbursement authorities. Using the best available data from randomized controlled trials, meta-analysis and indirect comparisons were employed for analyses.

The efficacy and tolerability of each drug compared with placebo and/or comparator AEDs were assessed for the following predefined outcomes: proportion of patients responding to treatment (≥50% reduction in seizure frequency), proportion of patients seizure-free over the treatment period, proportion of withdrawals (due to adverse events [AEs] and for any reason) and proportion of patients reporting specified AED-related AEs (ataxia, dizziness, fatigue, nausea and somnolence).[3]

2. Methods

The protocol used for the present review is available on www.yhec.co.uk/docs/retigabine_protocol.pdf.

2.1. Eligibility criteria

Randomized (head-to-head or placebo-controlled) studies of adjunctive therapy that used either a parallel group design or a crossover design, in which data from the first treatment period could be treated as a parallel study, were eligible for inclusion. Eligible studies included a treatment period at target dose (maintenance phase) of ≥8 weeks, with a prospective baseline period of ≥4 weeks, and reported change in seizure frequency and treatment withdrawal as outcomes. The population of interest was adults (≥18 years) with partial-onset epileptic seizures who had failed to respond adequately to previous AEDs (not controlled by one or more AEDs). Studies reported in any language and published in full or as abstracts or conference presentations were eligible for consideration for inclusion in the analysis.

2.2. Searches and study selection

All searches were conducted on 28th June 2010. The following databases were searched over the time periods specified to identify eligible studies: MEDLINE and MEDLINE In-process (OvidSP) (1950–2010/June week 3); EMBASE (1980–2010/week 25); Cochrane Database of Systematic Reviews (2010 Issue 6/2); Cochrane Central Register of Controlled Trials (2010 Issue 6/2); Database of Abstracts of Reviews of Effects (2010 Issue 6/2); Health Technology Assessment Database (2010 Issue 6/2); Science Citation Index (1899–2010/June 26th); and Conference Proceedings Citation Index – Science (1990–2010/June 26th). Other databases and internet resources were searched for all records available on the date of searching: National Guidelines Clearinghouse; National Library of Guidelines; National Horizon Scanning Centre; ClinicalTrials.gov; Current Controlled Trials Register; WHO International Clinical Trials Registry Platform; TRIP Database; OAIster; European Medicines Agency; and US Food and Drug Administration. Searches were limited to human studies; no methodological search filters were used and no date (within specified ranges) or language limits were applied. After removal of duplicates, records were screened for relevance and selected full-text articles assessed for eligibility; no abstracts or conference presentations were selected. In addition to data identified from the literature searches, unpublished data from four trial and regulatory reports made available by the study co-sponsors were included (GlaxoSmithKline [2009]. RTG: Summary of Clinical Efficacy [module 2.7.3] European Marketing Authorisation Application; Valeant Pharmaceuticals [2009]. Clinical Study Reports CSR-2065-205, CSR-301 and VRX-RET-E22-302).

2.3. Data collection

Details of the study, participant characteristics, intervention, analysis, outcomes and AEs were extracted from the selected publications by one researcher and independently checked by at least one other researcher. The quality of randomized controlled trials was assessed using seven questions that focus on the following methodological aspects: appropriate randomization, adequate concealment of treatment allocation, comparability of groups at baseline, blinding procedures, unexpected imbalances in dropouts, measured versus reported outcomes, and inclusion of an intent-to-treat analysis.[4]

2.4. Data analysis

The outcomes evaluated included the proportion of patients responding to treatment (defined as 50% responder rate, the proportion of patients who showed at least 50% reduction in seizure frequency relative to baseline), proportion of patients seizure-free over the treatment period, proportion of withdrawals (separate analyses for withdrawals due to AEs and for any reason) and proportion of patients reporting any of five specified AED-related AEs identified by the Cochrane Epilepsy Group[3]: ataxia, dizziness, fatigue, nausea and somnolence. When considering studies that measured responder rate and seizure freedom over different periods, separate analyses were undertaken for the efficacy outcomes for the fixed-dose maintenance phase of the treatment period (post-titration) and the full double-blind period (titration and maintenance).

AEDs were compared using two statistical methods. In a conventional meta-analysis (CMA), outcome measures reported for the treatment arm(s) were compared within trials against those for the comparator; comparisons were also conducted using pooled data from all the eligible trials for each of the selected AEDs. In a network meta-analysis (NMA), outcome measures from the treatment arm(s) were compared with those from the placebo arm, and each AED was compared with each other AED via the network.

A CMA of comparisons between treatment and placebo was initially undertaken using the Mantel–Haenszel and DerSimonian and Laird methods, employing Stata statistical software: Release 11 (StataCorp LP, College Station, TX). Pooled effect estimates as odds ratios (ORs) and relative risks were calculated using both fixed- and random-effects models; results described here are the ORs (and their associated 95% confidence intervals [CI]) from fixed-effects model analyses. Statistical heterogeneity was assessed using the Q statistic in conjunction with the I-squared (I^2) statistic[5] (I^2 value ≤50%, low; >50% to <75%, moderate; ≥75%, high heterogeneity). The I^2 statistic measures the extent of inconsistency among the results of different studies, and is interpreted as the approximate proportion of total variation in study estimates that is due to heterogeneity rather than sampling error.[5] Results of the CMA are presented in forest plots; data from random-effects model analyses and the weights contributed by each study to the pooled analysis for each AED are presented for information purposes. Potential publication bias was examined through funnel plot inspection[6] but was considered uninformative given the small

numbers of studies evaluating each of the included AEDs. Effect estimates from the CMA as *Z*-scores were considered statistically significant at $P \leq 0.05$.

A hierarchical Bayesian NMA was then undertaken using WinBUGS Version 14 (MRC Biostatistics Unit, Cambridge, UK). A fixed-effects approach to data synthesis was used, utilizing a fixed-effects logistic regression model with parameters estimated by Markov Chain Monte Carlo simulation. A random-effects model was also applied initially but, following convergence failure due to the small number of studies, is not presented. Results from the NMA are presented here as mean ORs and 95% credible intervals (95% CrI).

Inconsistency between the CMA and NMA was assessed by comparing the OR from the NMA with that from the CMA; evidence was assumed to be inconsistent if the OR from the NMA did not lie within the 95% CI of the corresponding OR from the CMA.

When placebo-controlled trials included multiple treatment arms that evaluated different doses of an AED, the events and patient numbers from the different treatment arms were initially combined to create a single, pooled comparison of drug versus placebo. Additional analyses were undertaken to take into consideration clinically relevant dose ranges; i.e. to exclude doses that were included in the trials but were not subsequently licensed (for LCM, 600 mg/day). The results presented here refer to the maintenance dose ranges approved in Europe (for LCM, 200–400 mg/day). Further analyses were undertaken to evaluate outcomes for individual doses of an AED but are not reported here.

Here, the performance of each AED relative to placebo and of RTG relative to other AEDs is reported.

3. Results

3.1. Studies

In total, 4387 records were identified for potential inclusion, and of these, 175 reports were assessed in detail for eligibility (Fig. 1). Following removal of duplicates and screening for eligibility, 20 trials met the eligibility criteria, all of which were placebo-controlled: three studies each for RTG,[7–9] ESL,[10–12] LCM,[13–15] TGB,[16–18] and ZNS[19–21]; and five studies for PGB.[22–26] The main reason for excluding reports (based on assessment of full-text papers) was that the data were reported in full elsewhere.

For each study, summary characteristics are presented in Table 1, and a quality assessment is presented in Table S1.

3.2. Efficacy outcomes

3.2.1. 50% responder rate during the fixed-dose maintenance period

Drug comparisons comprised one to three studies per AED: LCM, RTG and ZNS were each evaluated in three studies; ESL in two studies; and TGB in one study. None of the included studies reported this outcome for PGB.

In the CMA, there was a statistically significant difference in the 50% responder rate for all AEDs compared with placebo ($P < 0.001$), with the exception of TGB ($P = 0.122$) (Fig. 2a). Moderate heterogeneity was observed among RTG/placebo comparisons ($I^2 = 60.9\%$). All other comparisons displayed low heterogeneity ($I^2 = 0\%$).

Based on the results of the NMA, there was no evidence that RTG performed any better or worse than other AEDs with respect to this outcome (Table 2).

3.2.2. 50% responder rate during the double-blind period

Comparisons comprised two to five studies per AED: PGB was evaluated in five studies, RTG in three studies, and ESL and TGB in two studies each. None of the studies included reported this outcome for LCM or ZNS.

In the CMA, there was a statistically significant difference in the 50% responder rate for all AEDs compared with placebo ($P < 0.0001$) (Fig. 2b). Heterogeneity was low among most of the drug–placebo comparisons ($I^2 = 0\%$), with the exception of the five studies that evaluated PGB, which displayed moderate heterogeneity ($I^2 = 63.0\%$).

Based on the results of the NMA, RTG was comparable with the other AEDs, with the exception of PGB. There was a smaller effect for RTG than for PGB for this outcome (OR [CrI]: 0.65 [0.41–0.96]) (Table 2).

3.2.3. Seizure freedom during the fixed-dose maintenance period

Nine studies reported seizure freedom during the maintenance phase: three each for LCM and RTG, two for ESL and one for TGB. None of the included PGB or ZNS studies reported this outcome. Although TGB was considered for initial inclusion in the NMA, no patients in the placebo arm of the trial achieved seizure freedom during the maintenance period (zero events). TGB was excluded from this analysis because of problems with statistical convergence of the fixed-effect model.

Of the four AEDs evaluated in the CMA, only RTG was statistically significantly different from placebo (OR [95% CI]: 2.53 [1.11–5.76], $P = 0.026$) (Fig. 3a). Where estimable ($\geq$2 studies), low heterogeneity was observed ($I^2 = 0\%$). In the NMA, based on the ORs and their CrIs, RTG was not notably different from ESL and LCM with respect to seizure freedom assessed over the maintenance period (Table 2).

3.2.4. Seizure freedom during the double-blind period

A total of eight studies reported seizure freedom assessed over the full double-blind period: three for RTG, two each for PGB and ZNS, and one for ESL. This outcome was not reported in the included LCM or TGB studies. Due to sparse data (zero events in the placebo arm of the ESL study), model convergence of the fixed-effect model could not be attained. As such, ESL was not evaluated in the NMA for this outcome.

No statistically significant effects on seizure freedom assessed over the double-blind period were evident from the CMA of any drug-versus-placebo comparison (Fig. 3b). Low heterogeneity ($I^2 = 0\%$) was observed for comparisons for which heterogeneity could be estimated ($\geq$2 studies).

However, based on the results of the NMA, only RTG appeared to be more effective than placebo in achieving seizure freedom over the double-blind period (OR [95% CrI]: 3.74 [1.10–10.93]) but was not notably different from other AEDs (Table 2).

3.3. Study withdrawals

3.3.1. Withdrawals due to AEs

Study withdrawal data were available for 19 of the 20 studies: PGB was evaluated in 5 studies, ESL, LCM, RTG and TGB were each evaluated in 3 studies, and ZNS was evaluated in 2 studies.

From the CMA, all treatments resulted in a statistically significant higher rate of withdrawals due to AEs compared with placebo ($P < 0.002$) (Fig. 4a). Overall, low levels of heterogeneity were observed among all comparisons of drug versus placebo, with the exception of the three TGB studies, which displayed moderate heterogeneity ($I^2 = 61.2\%$).

Based on the NMA, RTG was not notably any better or worse than the other AEDs in terms of withdrawals due to AEs (Table 2).

3.3.2. Withdrawals due to any reason

Of the 20 studies included, 19 reported numbers of patients completing the trial, from which overall total withdrawals could be

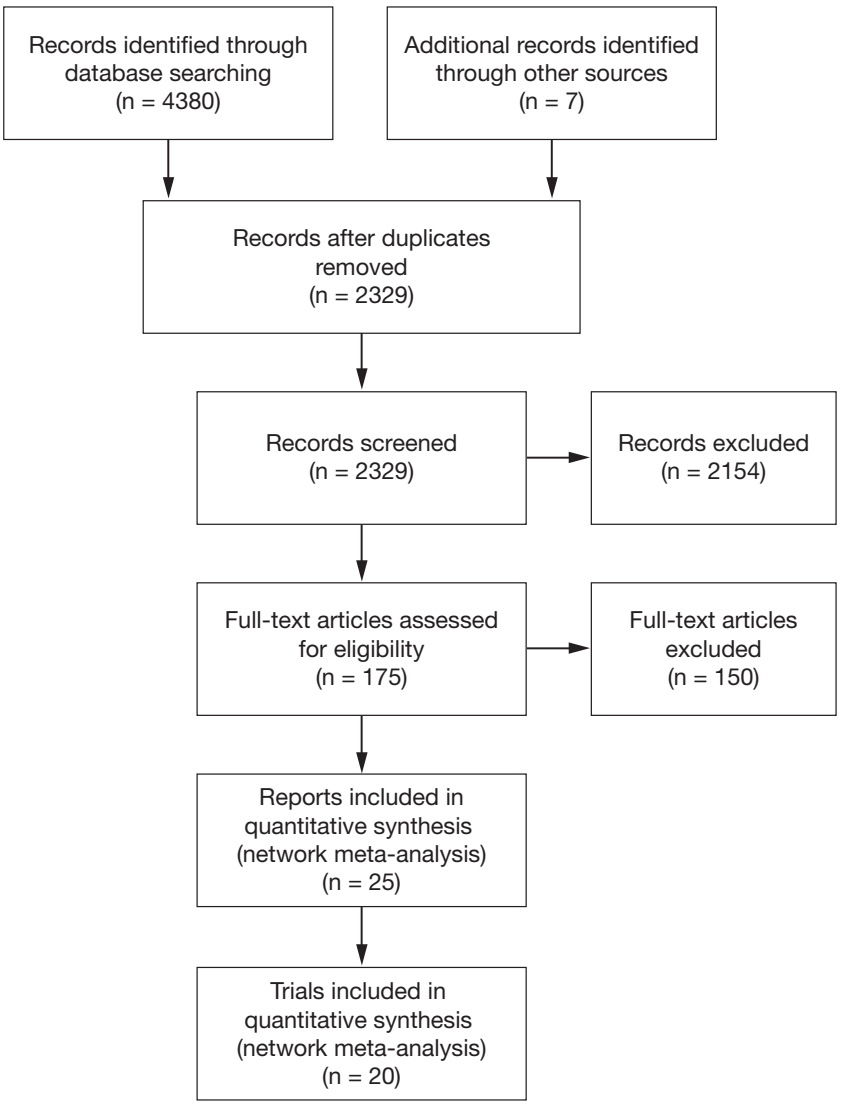


Fig. 1. Flow diagram of the study identification process.

estimated: five for PGB, three each for ESL, LCM, RTG and TGB, and two for ZNS.

From the CMA, all treatments led to a statistically significant higher withdrawal rate than placebo ($P = 0.041$ to $P < 0.0001$), with the exception of ESL ($P = 0.297$) (Fig. 4b).

Heterogeneity for the comparison of ESL versus placebo was moderate ($I^2 = 73.0\%$), whereas all other comparisons displayed low heterogeneity ($I^2 = 0\%$).

Based on the NMA, RTG was associated with a higher OR for overall withdrawals than ESL (OR [95% CrI]: 1.91 [1.18–2.89]), but was not associated with a markedly different withdrawal rate compared with other AEDs (Table 2).

3.4. Tolerability outcomes

3.4.1. Ataxia

Eight studies reported data for ataxia: four for PGB, two for RTG and one each for LCM and ZNS. All of these studies were evaluated in the CMA, but due to zero count data and subsequent problems with statistical convergence, ZNS was excluded from the NMA.

In the CMA, PGB, RTG and ZNS, but not LCM, were associated with statistically significant greater reporting of ataxia compared with placebo ($P = 0.047$ to $P < 0.001$) (Fig. 5a). It should be noted, however, that the ZNS and LCM comparisons each comprised only one study. Where estimable ($\geq$2 studies), low levels of heterogeneity were observed for all comparisons ($I^2 = 0\%$).

Based on the results of the NMA, RTG was not associated with a difference in the reporting of ataxia compared with other AEDs (Table 2).

3.4.2. Dizziness

Eighteen studies reported data on dizziness: five for PGB, three for ESL, LCM and RTG, and two for TGB and ZNS. The results from the CMA of dizziness were statistically significant for all drug comparisons versus placebo (ranging from $P = 0.003$ to $P < 0.0001$), that is, all AEDs were associated with greater reporting of dizziness compared with placebo (Fig. 5b). Low levels of heterogeneity were observed for all comparisons (I^2 values of 0% in the majority of comparisons). Based on the results of the NMA, RTG was not associated with a difference in the reporting of dizziness compared with the other AEDs (Table 2).

3.4.3. Fatigue

Seven studies reported data on fatigue: two for LCM and RTG, and one each for ESL, PGB and ZNS.

The results from the CMA of fatigue indicated that, of each of the AEDs analysed, only RTG was associated with a statistically significant higher incidence of fatigue compared with placebo

Table 1
Studies included in the meta-analyses.

Study	Population	Interventions and numbers randomized to placebo and treatment	Duration of intervention
Retigabine/ezogabine (RTG) studies			
Brodie (2010)[7]	Adults aged 18–75 y; localization-related epilepsy refractory to stable doses of 1–3 AEDs; ≥4 qualifying seizures per 28 d without a seizure-free period of >21 d during the baseline period	Placebo (n = 179) RTG 600 mg/d (n = 181) RTG 900 mg/d (n = 179)	Baseline period: 8 w Titration period: 4 w Maintenance period: 12 w Double-blind period: 16 w
French (2011)[8]	Adults aged 18–75 y; treatment-resistant focal epilepsy characterized by simple partial or complex partial-onset seizures, with/without secondary generalization; ≥4 partial seizures per 28 d over baseline period; receiving stable doses of 1–3 AEDs for ≥1 month prior to screening	Placebo (n = 152) RTG 1200 mg/d (n = 154)	Baseline period: 8 w Titration period: 6 w Maintenance period: 12 w Double-blind period: 18 w
Porter (2007)[9]	Adults aged 16–70 y; inadequately controlled partial-onset seizures (simple partial with an observable motor component or complex partial, with/without secondary generalization); ≥4 partial-onset seizures per month during baseline period, no 30-d seizure-free period; stable doses of 1–2 AEDs	Placebo (n = 96) RTG 600 mg/d (n = 100) RTG 900 mg/d (n = 95) RTG 1200 mg/d (n = 106)	Baseline period: 8 w Titration period: 8 w Maintenance period: 8 w Double-blind period: 16 w
Eslicarbazepine acetate (ESL) studies			
Ben-Menachem (2010)[10]	Adults aged ≥18 y; diagnosed with simple or complex partial-onset seizures, with/without secondary generalization, for ≥12 months prior to screening; ≥4 partial-onset seizures in the two 4-w periods prior to screening and during each of the two 4-w periods of the baseline phase; receiving stable doses of 1–3 concomitant AEDs for ≥2 months prior to screening	Placebo (n = 100) ESL 400 mg/d (n = 96) ESL 800 mg/d (n = 101) ESL 1200 mg/d (n = 98)	Baseline period: 8 w Titration period: 400/800 mg groups = start with full maintenance dose; 1200 mg group = 800 mg QID for 2 w, then full 1200 mg maintenance dose Maintenance period: ~12 to 14 w Double-blind period: 14 w
Elger (2009)[11]	Adults aged ≥18 y; simple or complex partial seizures with/without secondary generalization for ≥12 months prior to screening; ≥4 partial-onset seizures in the two 4-w periods of the baseline phase; no seizure-free interval >21 consecutive days; receiving stable doses of 1–2 AEDs for ≥2 months prior to screening	Placebo (n = 102) ESL 400 mg/d (n = 100) ESL 800 mg/d (n = 98) ESL 1200 mg/d (n = 102)	Baseline period: 8 w Titration period: 2 w (All patients started at 400 mg; 800 mg group = full dose by the end of week 1; 1200 mg group = full dose by end of week 2) Maintenance period: 12 w Double-blind period: 18 w including 4 w down-titration
Gil-Nagel (2009)[12]	Adults aged ≥18 y; simple or complex partial seizures (with/without secondary generalization) for ≥12 months prior to screening; ≥4 partial-onset seizures in the two 4-w periods prior to screening and during each of the two 4-w baseline periods; receiving stable doses of 1–2 concomitant AEDs for ≥2 months prior to screening	Placebo (n = 88) ESL 800 mg/d (n = 85) ESL 1200 mg/d (n = 80)	Baseline period: 8 w Titration period: 2 w Maintenance period: 12 w Double-blind period: 18 w including 4 w taper
Lacosamide (LCM) studies			
Ben-Menachem (2007)[13]	Adults aged 18–65 y; simple or complex partial-onset seizures, with/without secondary generalization; partial-onset seizures for at least the last 2 y despite therapy with ≥2 AEDs; during the baseline period, ≥4 partial-onset seizures per 28 d on average, no seizure-free period >21 d; receiving stable doses of 1–2 AEDs in the 4 w before enrolment and during the baseline period	Placebo (n = 97) LCM 200 mg/d (n = 107) LCM 400 mg/d (n = 108) LCM 600 mg/d (n = 106)	Baseline period: 8 w Titration period: 6 w (weekly increments of 100 mg/d) Maintenance period: 12 w Double-blind period: 18 w
Chung (2010)[14]	Adults aged 16–70 y; partial-onset seizures, with/without secondary generalization; ≥2-y history of partial onset seizures despite treatment with ≥2 AEDs (concurrently or sequentially); currently experiencing ≥4 partial-onset seizures per 28 d, with no seizure-free period >21 d during the 8 w prior to and during the baseline period; receiving stable doses of 1–3 AEDs in the 4 w prior to enrolment and during baseline	Placebo (n = 104) LCM 400 mg/d (n = 204) LCM 600 mg/d (n = 97)	Baseline period: 8 w Titration period: 6 w Maintenance period: 12 w Double-blind phase: 18 w

Table 1 (*Continued*)

Study	Population	Interventions and numbers randomized to placebo and treatment	Duration of intervention
Halasz (2009)[15]	Adults aged 16–70 y; partial-onset seizures for at least the preceding 2 y despite prior therapy with ≥2 AEDs; on average, ≥4 partial-onset seizures per 28 d, with no seizure-free period longer than 21 d during the 8-w period before enrolment and during the baseline period; stable doses of 1–3 AEDs in the 4 w prior to enrolment and during the baseline period	Placebo (n = 163) LCM 200 mg/d (n = 163) LCM 400 mg/d (n = 159)	Baseline period: 8 w Titration period: 4 w Maintenance period: 12 w Double-blind period: 18 w including 2 w taper
Pregabalin (PGB) studies			
Arroyo (2004)[22]	Adults aged ≥18 y; partial seizures (simple, complex, or secondarily generalized tonic–clonic) and failed ≥1 AED at the maximum tolerated dose; ≥3 partial seizures in the month before screening; ≥6 partial seizures and not seizure-free for any 4-w period during the 8-w period before randomization; receiving 1–3 AEDs at tolerated, clinically relevant doses; concurrent AED maintained at the same dose during the study	Placebo (n = 97) PGB 150 mg/d (n = 99) PGB 600 mg/d (n = 92)	Baseline period: 8 w Titration period: titrated to full dose by days 4 (placebo and 150 mg/d) and 8 (600 mg/d) Maintenance period: ~11 w Double-blind period: 12 w
Beydoun (2005)[23]	Adults aged ≥18 y; inadequately controlled partial-onset seizures; ≥6 partial-onset seizures during the baseline period, with no 28-d seizure-free period, while on stable doses of 1–3 AEDs; ≥2 AEDs at maximally tolerated doses failed	Placebo (n = 98) PGB 600 mg/d BID (n = 104) PGB 600 mg/d TID (n = 111)	Baseline period: 8 w Titration period: 1 w Maintenance period: 11 w Double-blind period: 12 w
Elger (2005)[24]	Adults aged ≥18 y; diagnosis of epilepsy with partial seizures; had not previously received PGB; ≥4 partial seizures during the baseline period with no 28-d seizure-free period; currently receiving 1–3 AEDs	Placebo (n = 73) PGB 600 mg/d (n = 131) PGB 150–600 mg/d (n = 137)	Baseline period: 6 w Titration period: placebo and 600 mg/d groups = none; PGB varied dose group = start on 150 mg/d (75 mg BID) for first 2 w, and increased to 300 mg/d for next 2 w (then 300–600 mg/d) Maintenance period: ≤12 w Double-blind period: 12 w
French (2003)[25]	Adults aged 12–70 y; ≥3 partial seizures in the month prior to screening and 6 partial seizures in the 8 w between screening and baseline; refractory to ≥2 AEDs at maximally tolerated doses; currently receiving 1–3 AEDs	Placebo (n = 100) (PGB 50, not evaluable in present report mg/d, n = 88) PGB 150 mg/d (n = 88) PGB 300 mg/d (n = 90) PGB 600 mg/d (n = 89)	Baseline period: 8 w Titration period: none (start on randomized dose) Maintenance period: 12 w Double-blind period: 12 w
Lee (2009)[26]	Adults ≥18 y; diagnosis of partial seizures (simple, complex or secondarily generalized tonic–clonic); ≥4 seizures that had occurred over ≥2 d during a 6-w baseline period; no 28-d seizure-free period; ≥1 AED at the maximally tolerable dose tried; taking 1–3 AEDs at a clinically relevant dose	Placebo (n = 59) PGB 600 mg/d (n = 119)	Baseline period: 6 w Titration period: 6 w Maintenance period: 6 w Double-blind period: 13 w (including 1 w taper)
Tiagabine (TGB) studies			
Kalviainen (1998)[16]	Adults aged 16–75 y; partial seizures (six in the previous 8 w); ≥8 partial seizures during the baseline period while on a stable regimen of 1–3 AEDs; no seizure-free interval of >4 w during the baseline period	Placebo (n = 77) TGB 30 mg/d (n = 77)	Baseline period: 12 w Titration period: 6 w Maintenance period: 12 w Double-blind period: 22 w including 4 w taper
Sachdeo (1997)[17]	Adults and teenagers aged 12–75 y; diagnosis of complex partial seizures with/without secondary generalization; ≥6 complex partial seizures during the 8-w period before screening and ≥1 complex partial seizure within each of the two 4-w segments within the 8-w period; treated with a stable regimen of 1–3 AEDs	Placebo (n = 107) TGB 32 mg/d BID (n = 106) TGB 32 mg/d QID (n = 105)	Baseline period: 8 w Titration period: 4 w Maintenance period: 8 w Double-blind period: 12 w
Uthman (1998)[18]	Patients aged 12–77 y; ≥6 complex partial seizures in the 8 w preceding the screening visit (each of the two 4-w segments containing ≥1 complex partial seizure); receiving a stable regimen of 1–3 hepatic enzyme-inducing AEDs	Placebo (n = 91) TGB 16 mg/d (n = 61) TGB 32 mg/d (n = 88) TGB 56 mg/d (n = 57)	Baseline period: 12 w Titration period: 4 w Maintenance period: 12 w Double-blind period: 20 w (including 4 w discontinuation)

Table 1 (*Continued*)

Study	Population	Interventions and numbers randomized to placebo and treatment	Duration of intervention
Zonisamide (ZNS) studies			
Brodie (2005)[19]	Patients aged ≥12 y; partial seizures, with/without secondary generalization unsatisfactorily controlled despite a stable regimen of 1–3 AEDs	Placebo (n = 120) ZNS 100 mg/d (n = 57) ZNS 300 mg/d (n = 56) ZNS 500 mg/d (n = 118)	Baseline period: 12 w Titration period: 6 w Maintenance period: 18 w Double-blind period: 24 w
Sackellares (2004)[20]	Adults aged 17–65 y; history of partial seizures refractory to current AED therapy; ≥4 complex partial seizures per month; no more than eight generalized tonic–clonic, or tonic–clonic seizures per month; receiving 1–2 of the following AEDs: phenytoin, carbamazepine, phenobarbital, primidone	Placebo (n = 74) ZNS 400–600 mg/d (n = 78)	Baseline period: 8–12 w Titration period: 4 w Maintenance period: 8 w Double-blind period: 12 w
Schmidt (1993)[21]	Adults aged 18–59 y; complex partial seizures; an average of ≥4 complex partial seizures per month during the 4 months preceding the baseline period, in spite of therapeutic plasma concentrations of standard AEDs	Placebo (n = 68) ZNS 6 mg/kg/d to achieve 20–30 μg/ml (n = 71)	Baseline period: 8–12 w Titration period: 4 w Maintenance period: 8 w Double-blind period: 12 w

All studies were randomized, double-blind placebo-controlled studies. AED, anti-epileptic drug; BID, twice daily; d, day; QID, once daily; TID; three times daily; w, weeks; y, years.

(OR [95% CI]: 3.78 [2.16–6.62], $P < 0.001$) (Fig. 5c). However, between-trial heterogeneity was observed for the RTG comparisons (I^2 = 72.6%). Based on the results of the NMA, RTG was not associated with a difference in the reporting of fatigue compared with other AEDs (Table 2).

3.4.4. Nausea

Eleven studies reported data on nausea: three for LCM and for RTG, two for ESL and ZNS and one for TGB.

The results from the CMA of nausea showed a statistically significant effect of ESL (P = 0.004) and LCM (P = 0.003) compared with placebo. No statistically significant effects were observed for other drug comparisons with placebo in the CMA (Fig. 5d). Where estimable (≥2 studies), low levels of heterogeneity were observed (I^2 values of 0–37.5%). Based on the results of the NMA, RTG was not associated with a difference in the reporting of nausea compared with other AEDs (Table 2).

3.4.5. Somnolence

Sixteen studies reported data on somnolence: five for PGB, three for ESL and RTG, two for LCM and ZNS, and one for TGB.

The results from the CMA of somnolence showed statistically significant effects of PGB ($P < 0.001$), RTG ($P < 0.001$) and ZNS (P = 0.003) compared with placebo. No other statistically significant effects were observed for comparisons in the CMA (Fig. 5e). Where estimable (≥2 studies), low levels of heterogeneity were observed (I^2 values of 0–41.4%). Based on the results of the NMA, RTG was not associated with a difference in the reporting of somnolence compared with other AEDs, with the exception of TGB, with RTG being associated with a greater reporting of somnolence (OR [95% CrI]: 2.38 [1.03–7.14]) (Table 2).

3.5. Comparison of data from the CMA and NMA

In the assessment of inconsistency between the CMA and NMA, all ORs for placebo comparisons from the NMA were within the 95% CIs of those from the CMA, indicating that the two analysis techniques were consistent.

4. Discussion

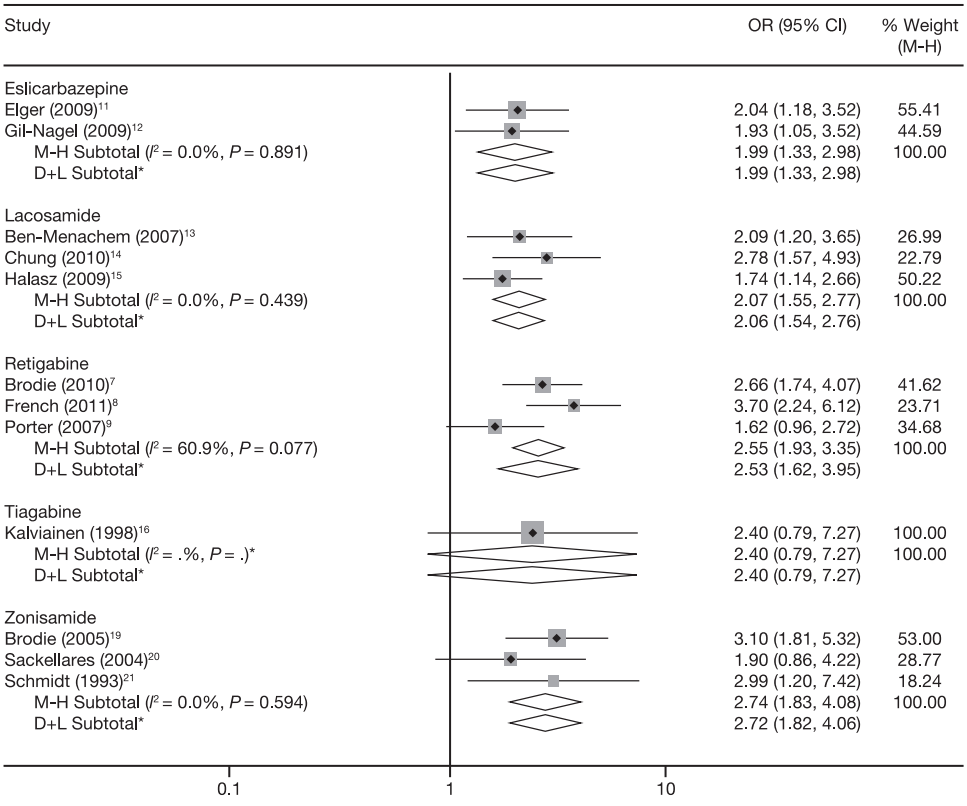
This analysis was undertaken to support submissions to reimbursement authorities, by providing data to facilitate comparison of the efficacy and tolerability of RTG with other selected AEDs that may be used in a similar position in the management pathway of adults with partial-onset seizures. A rigorously designed and conducted, systematic process was used to identify studies meeting the inclusion criteria for this review. As no

Table 2
Results of the network meta-analyses comparing retigabine with five comparator drugs (odds ratios and 95% credible intervals).

	Comparator drug				
Outcome	Eslicarbazepine acetate	Lacosamide	Pregabalin	Tiagabine	Zonisamide
50% responder rate – maintenance phase	1.34 (0.80–2.13)	1.28 (0.84–1.87)	NA	0.83 (0.29–3.23)	0.91 (0.58–1.52)
50% responder rate – double-blind phase	1.02 (0.57–1.67)	NA	**0.65 (0.41–0.96)**	0.63 (0.33–1.30)	NA
Seizure freedom – maintenance phase	1.13 (0.17–3.75)	1.09 (0.14–3.52)	NA	ND	NA
Seizure freedom – double-blind phase	ND	NA	2.59 (0.29–9.94)	ND	0.76 (0.20–6.25)
Withdrawals due to AEs	0.87 (0.38–1.67)	1.03 (0.53–1.83)	0.97 (0.51–1.66)	1.12 (0.60–2.38)	0.74 (0.34–1.82)
Withdrawals due to any reason	**1.91 (1.18–2.89)**	1.31 (0.79–2.02)	1.42 (0.91–2.13)	1.09 (0.65–1.89)	1.35 (0.79–2.44)
Ataxia	NA	1.30 (0.18–4.25)	1.01 (0.33–2.49)	NA	ND
Dizziness	1.12 (0.56–1.96)	1.07 (0.58–1.81)	0.98 (0.56–1.61)	1.45 (0.80–2.94)	0.88 (0.35–2.63)
Fatigue	3.92 (0.93–10.50)	2.11 (0.78–6.64)	2.25 (0.32–7.07)	NA	1.45 (0.55–5.00)
Nausea	0.41 (0.10–1.01)	0.69 (0.29–1.39)	NA	1.14 (0.42–4.35)	1.10 (0.47–3.23)
Somnolence	1.72 (0.92–2.90)	1.59 (0.69–3.07)	0.94 (0.55–1.52)	**2.38 (1.03–7.14)**	0.52 (0.21–1.54)

AEs, adverse events; NA, not available (data for comparison not available from studies reviewed); ND, non-determinable (problems with model convergence due to sparse data with zero count events in some treatment arms).
Data are presented as odds ratios (ORs) with 95% credible intervals (CrIs). The greater the observed OR, the greater the probability of the event occurring.
Numbers in bold type indicate notable differences between comparator drugs (95% CrIs do not cross 1).

a Fixed dose maintenance period



b Double-blind phase

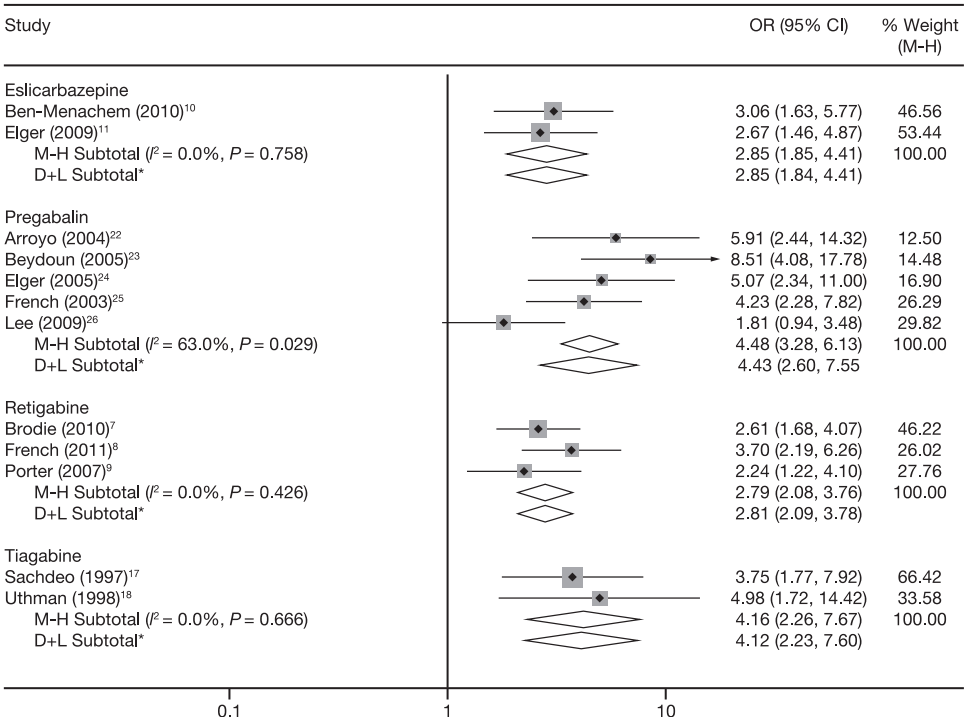


Fig. 2. Conventional meta-analysis forest plots for 50% responder rate. Plots indicate the observed I^2 values and associated P-value for heterogeneity from the conventional meta-analysis, along with the effect estimates and 95% CIs. Asterisks indicate an insufficient number of studies in the comparison to undertake heterogeneity testing. Diamond shape indicates overall treatment effect with 95% CIs. CI, confidence interval; OR, odds ratio; M–H, Mantel–Haenszel (fixed effects); D + L, DerSimonian and Laird (random effects).

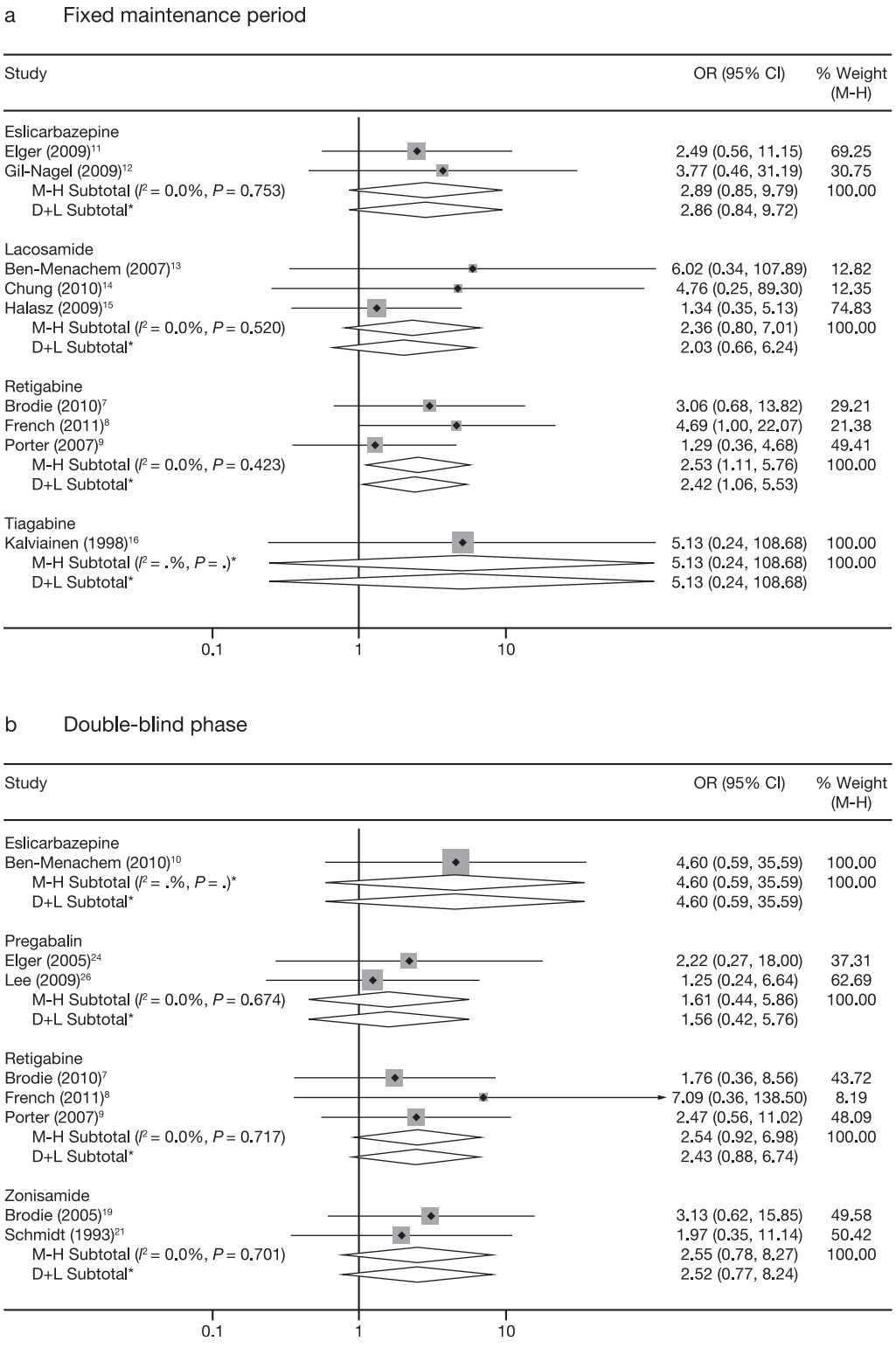


Fig. 3. Conventional meta-analysis forest plots for seizure freedom. Plots indicate the observed I^2 values and associated P-value for heterogeneity from the conventional meta-analysis, along with the effect estimates and 95% CIs. Asterisks indicate an insufficient number of studies in the comparison to undertake heterogeneity testing. Diamond shape indicates overall treatment effect with 95% CIs. CI, confidence interval; OR, odds ratio; M–H, Mantel–Haenszel (fixed effects); D + L, DerSimonian and Laird (random effects).

published trials compared AEDs directly, comparisons between drugs were conducted using indirect analyses of data from 20 eligible, placebo-controlled studies. For each AED included, the presented data represent the combined analysis of results pooled over the approved dose range, that is, the therapeutic range available to clinicians. From the analysis of pooled AED trials, the efficacy and tolerability of RTG appeared to be broadly comparable with the other selected AEDs.

In the absence of randomized controlled trials comparing AEDs directly, pooled effects from an NMA may provide useful information to inform treatment decisions.[27] In this review, results from individual placebo-controlled studies were pooled

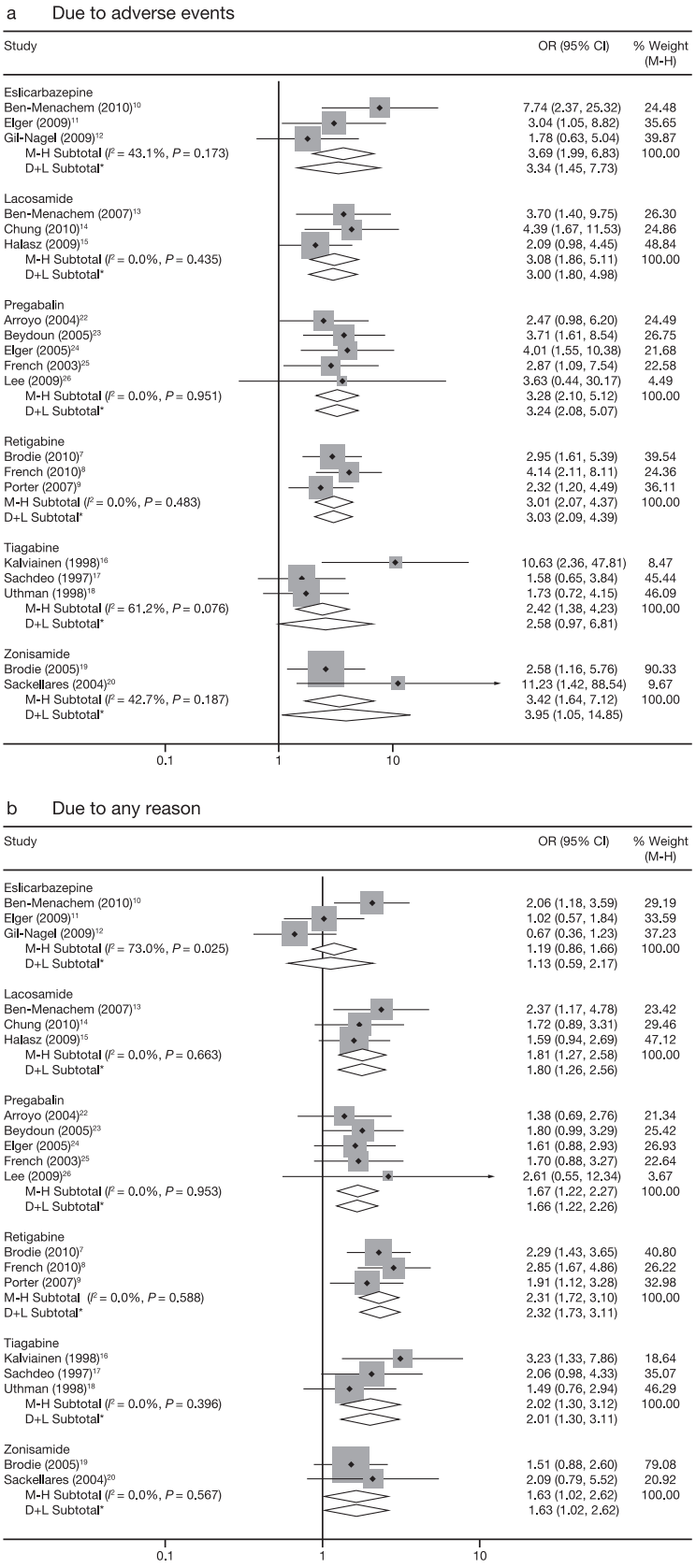


Fig. 4. Conventional meta-analysis forest plots for study withdrawals. Plots indicate the observed I^2 values and associated P-value for heterogeneity from the conventional meta-analysis, along with the effect estimates and 95% CIs. Asterisks indicate an insufficient number of studies in the comparison to undertake heterogeneity testing. Diamond shape indicates overall treatment effect with 95% CIs. CI, confidence interval; OR, odds ratio; M–H, Mantel–Haenszel (fixed effects); D + L, DerSimonian and Laird (random effects).

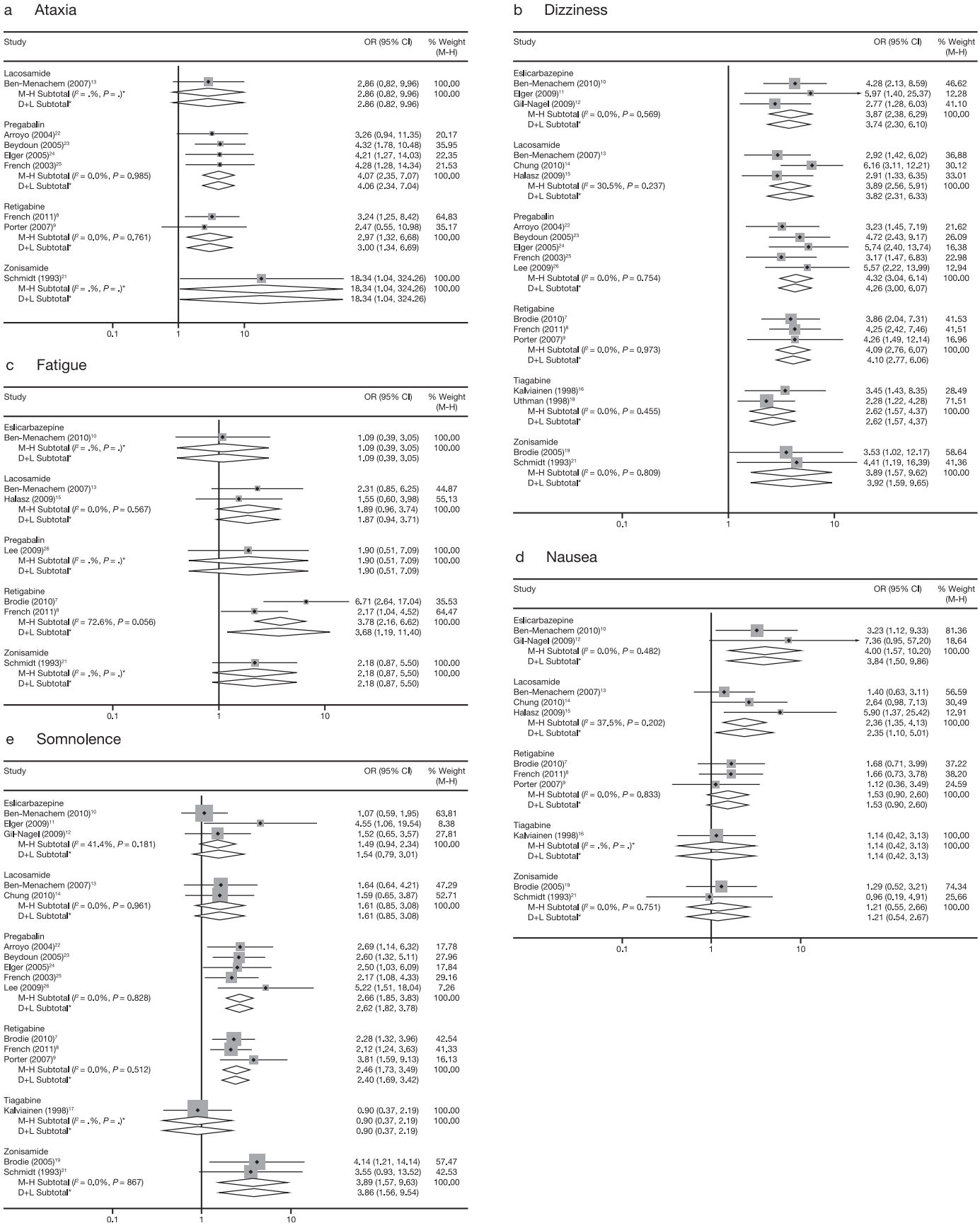


Fig. 5. Conventional meta-analysis forest plots for selected adverse events. Plots indicate the observed I^2 values and associated *P*-value for heterogeneity from the conventional meta-analysis, along with the effect estimates and 95% CIs. Asterisks indicate an insufficient number of studies in the comparison to undertake heterogeneity testing. Diamond shape indicates overall treatment effect with 95% CIs. CI, confidence interval; OR, odds ratio; M–H, Mantel–Haenszel (fixed effects); D + L, DerSimonian and Laird (random effects).

using a fixed-effect model in a CMA for each outcome of interest. By pooling multiple studies, meta-analysis can help to identify a common estimate of the effect size across the included studies. For the clinician, an NMA adds a further dimension to treatment comparisons. Rather than basing treatment decisions on trials that have evaluated the same treatment compared with placebo, an NMA allows comparisons of different treatments directly with each other using statistical inference. However, the estimates for ORs for active drug–placebo comparisons may differ between the CMA and NMA. The main reason for this is that the Bayesian estimate (NMA) is the mean of a simulated posterior distribution for the ORs; this distribution is skewed, so the mean is pulled away from the centre (median) of the distribution. In contrast with the Bayesian estimate, the Mantel–Haenszel estimate (CMA) is formed as the weighted mean of individual estimates of the OR from the component trials; each of these estimates corresponds to the centre (median) of what would be the Bayesian estimate for that trial. Both methods are statistically valid for estimating the location of a distribution, and they tend to differ more when the CIs are wide and when the ORs are far from 1. In the present analysis, no inconsistencies were observed between the NMA and CMA.

Although these statistical techniques are useful in providing comparative data, they also have recognized limitations that should be taken into consideration when interpreting results.[28,29] Results are susceptible to potential bias from a number of sources, including selective reporting and heterogeneity among included studies.[28] The analysis included unpublished data for RTG that were made available for this investigation by the study sponsor. For other AEDs, the analysis was limited to the data that could be extracted from published sources. It is therefore uncertain whether a publication bias may exist for these other AEDs. Whilst efforts were made to perform a meta-analysis on comparable studies, potential between-trial differences in design and patient characteristics cannot be discounted and should be taken into consideration when interpreting the results from this review. For example, studies evaluating flexible dosing (which is reflective of clinical practice) were identified for PGB, TGB and ZNS. In contrast, only fixed-dose studies (conducted for drug registration purposes) were identified for ESL, LCM and RTG. In addition, the speed of titration of an AED may impact on tolerability, with slower titration rates associated with better tolerability.[30] This may introduce bias in the comparison of tolerability outcomes for AEDs with different titration rates. Trials of the older agents (PGB, TGB and ZNS) generally included fewer patients, recruited from fewer centres, than the trials of the newer agents (RTG, ESL and LCM). The precision of the pooled effect estimates from these trials should also be considered when interpreting results. Factors such as participants' age, the proportion of men and women in the study, disease severity among participants, and concomitant treatments, are possible sources of clinical heterogeneity that should also be considered.

Moderate and high levels of between-trial heterogeneity were observed in some of the CMA comparisons for some AEDs. For the PGB studies reviewed for responder rate, the observed heterogeneity may be explained by the inclusion of one trial in which the time at target dose was shorter than in the other trials.[25] For the ESL studies reviewed for withdrawal rate, the observed heterogeneity may be partly explained by the inclusion of one trial, which reported a larger number of withdrawals due to protocol violation, compared with the other trials included in the analysis.[9] The moderate levels of heterogeneity that were observed among RTG studies measuring responder rate during the fixed-dose maintenance period may be explained by the contribution of one trial, which reported a high proportion of participant withdrawals, and in which the maintenance phase was shorter than in the other RTG trials.[8]

The methodological issues raised by indirect comparisons and their relevance for comparing AEDs in adjunctive therapy for partial epilepsy have been explored recently.[31] Variables that are also considered as factors influencing efficacy estimates include the treatment period used to calculate efficacy endpoints, the year in which the trial was conducted, and the method used to calculate responder rates.[31] The number of trials contributing to each outcome of interest for each AED should also be considered. It is recommended that the results from an NMA should also be interpreted alongside empirical observations.[27] Clinicians should consider these factors, in addition to those discussed previously, when interpreting results from an NMA. In the light of all available evidence, clinicians will need to decide whether one treatment can be considered a better option than another for the population or individual of interest.

In addition to the limitations of the techniques used, the findings from this review are also limited by the small number of eligible studies that were identified for each agent. Heterogeneity was therefore difficult to assess in some instances, and random-effect models proved difficult to fit in the NMA for some outcomes. The small number of included studies also resulted in large credible intervals for a number of outcomes/AEDs in the NMA. In addition, a few observations were not consistent with clinical experience. For example, ataxia was reported only in one of three LCM studies. Ataxia is not generally observed as an AE with this drug.[13–15] However, in the NMA, the frequency of ataxia appeared similar with LCM and PGB, which contrasts with the expectation that this AE would be reported more frequently with PGB.[22–26] The results for outcomes that were not reported by all of the trials evaluating a specific AED should therefore be interpreted with caution. The relatively short treatment periods that were evaluated in the included trials, coupled with variations in the characteristics of the patient populations recruited, also limits the generalizability of the findings from this review. Furthermore, the specified AEs evaluated in this review were central nervous system (CNS)-related events that are commonly related to AEDs as a class. Other, non-CNS-related AEs, including those that might be drug-specific, were not evaluated. The findings on comparative tolerability of the AEDs evaluated in this review must therefore be interpreted with caution.

The agents selected for comparison with RTG were chosen on the basis that they were the most recently launched agents licensed for adjunctive treatment but not monotherapy, and therefore had comparable positioning to RTG in the treatment pathway for partial-onset seizures. Although this strategy excluded some frequently used adjunctive AEDs, such as levetiracetam and topiramate, the AEDs included were those that reimbursement authorities were likely to require comparative data for when considering reimbursement for RTG. Although the performance of RTG was broadly comparable with the other selected AEDs, some differences were observed. Treatment with RTG was associated with a lower responder rate than PGB during the double-blind period (OR [95% CrI]: 0.65 [0.41–0.96]), and a higher rate of withdrawal due to any reason, compared with ESL (OR [95% CrI]: 1.91 [1.18–2.89]). RTG was also associated with higher reporting of somnolence than TGB (OR [95% CrI]: 2.38 [1.03–7.14]). Given that no adjustments for were made to correct for the occurrence of false positives that could emerge from evaluating multiple endpoints and treatment group comparisons, such differences might be expected. For the PGB and ESL studies reviewed for responder rate and withdrawals, respectively, in the NMA, moderate levels of between-study heterogeneity were observed (I^2 = 63% and 73%) in the CMA (possible explanations for this have been discussed earlier), whereas low heterogeneity was observed for the RTG studies (0%). This limits the validity of indirect comparisons for PGB and ESL with RTG within the NMA. For TGB, the outcome for

somnolence was based on one study only, so may not be representative of the wider patient population treated with this AED.

AEDs other than those evaluated in this review have been compared using indirect methods. Otoul et al. reported that levetiracetam was more effective in terms of responder rate than gabapentin and lamotrigine, and equally well tolerated.[32] The reviewers also observed that levetiracetam had a significantly lower withdrawal rate than topiramate and oxcarbazepine, with comparable efficacy.[32] The clinical comparability of oxcarbazepine, lamotrigine, topiramate, gabapentin, PGB, levetiracetam, TGB, ZNS, ESL and LCM in partial epilepsy has also been evaluated recently by Costa et al.[33] These reviewers observed that topiramate and levetiracetam were most effective in reducing seizure frequency, whereas gabapentin was less effective in comparison with the other AEDs evaluated. The reviewers also reported that tolerability, as indicated by higher withdrawal rates, was poorer with oxcarbazepine and topiramate, whereas gabapentin and levetiracetam were better tolerated than the other AEDs assessed but that, overall, the frequency of the most common AEs was comparable between the AEDs. These reviewers concluded that the relatively small magnitude of differences observed between AEDs did not allow a definitive conclusion to be reached about which AED(s) had superior clinical effectiveness. The limitations of indirect comparisons were considered to contribute to this uncertainty, and the authors suggested that clinical decision-making in partial epilepsy probably depends more on aspects such as individual patient characteristics and pharmacoeconomics than on available evidence from randomized controlled trials.

The limited number of eligible studies for some of the AEDs evaluated in this review, coupled with the uncertainty surrounding some of the efficacy and tolerability effect estimates, may explain why few differences were detected between RTG and other AEDs that have other mechanisms of action. Moreover, the lack of impact of mechanism of action on drug efficacy, and a common pattern of outcomes across different AEDs in clinical studies of refractory epilepsy, has been reported elsewhere.[34,35] It has been suggested that the introduction of AEDs with novel mechanisms of action has not substantially improved the efficacy of treatment, at least in part because the design of trials for regulatory purposes dictates that new agents are tested in patients with refractory seizures who are currently receiving one or more established AEDs.[34–36] Against this background of anti-seizure activity, potentially through multiple mechanisms of action, it is unlikely that adding a further AED will have a significant impact across the population studied, although each new AED is likely to have some impact in some patients.[37]

5. Conclusions

In conclusion, on the basis of the outcomes from the indirect comparisons, and considering the limitations and caveats outlined, our findings suggest that RTG provides similar risks and benefits as adjunctive therapy for patients with partial-onset seizures with or without secondary generalization compared with the other AEDs studied. On the basis of the data discussed here, RTG was recommended for use for this indication in adults aged 18 years and older with epilepsy in England and Wales by the National Institute for Health and Clinical Excellence (NICE) and in Scotland by the Scottish Medicines Consortium (SMC). The NICE recommendation is specifically for use when previous treatment with a defined list of AEDs has not provided an adequate response, or has not been tolerated, whereas the SMC recommendation is for use in patients with refractory epilepsy. Whilst these indirect comparisons should contribute to the total body of evidence available, it is recommended that they be considered in combination with direct evidence, and that randomized head-to-head studies be undertaken to permit a direct assessment of the comparative strengths and weaknesses of different AEDs in particular patient populations.

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Conflicts of interest

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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.2012.07.011.

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