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Pregabalin add-on for drug-resistant focal epilepsy (Review)

Panebianco M, Bresnahan R, Hemming K, Marson AG

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[Intervention Review]

Pregabalin add-on for drug-resistant focal epilepsy

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ABSTRACT

Background

Epilepsy is a common neurological disease that affects approximately 1% of the UK population. Approximately one-third of these people continue to have seizures despite drug treatment. Pregabalin is one of the newer antiepileptic drugs which have been developed to improve outcomes.

This is an updated version of the Cochrane Review published in Issue 3, 2014, and includes three new studies.

Objectives

To assess the efficacy and tolerability of pregabalin when used as an add-on treatment for drug-resistant focal epilepsy.

Search methods

For the latest update we searched the Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), on 5 July 2018, MEDLINE (Ovid, 1946 to 5 July 2018), ClinicalTrials.gov (5 July 2018), and the World Health Organization International Clinical Trials Registry Platform (ICTRP, 5 July 2018), and contacted Pfizer Ltd, manufacturer of pregabalin, to identify published, unpublished, and ongoing trials.

Selection criteria

We included randomised controlled trials comparing pregabalin with placebo or an alternative antiepileptic drug as an add-on for people of any age with drug-resistant focal epilepsy. Double-blind and single-blind trials were eligible for inclusion. The primary outcome was 50% or greater reduction in seizure frequency; secondary outcomes were seizure freedom, treatment withdrawal for any reason, treatment withdrawal due to adverse effects, and proportion of individuals experiencing adverse effects.

Data collection and analysis

Two review authors independently selected and assessed trials for eligibility and extracted data. Analyses were by intention-to-treat. We presented results as risk ratios (RR) and odds ratios (OR) with 95% confidence intervals (CIs). Two review authors assessed the included studies for risk of bias using the Cochrane 'Risk of bias' tool.

Main results

We included nine industry-sponsored randomised controlled trials (3327 participants) in the review. Seven trials compared pregabalin to placebo. For the primary outcome, participants randomised to pregabalin were significantly more likely to attain a 50% or greater reduction in seizure frequency compared to placebo (RR 2.28, 95% CI 1.52 to 3.42, 7 trials, 2193 participants, low-certainty evidence). The odds of response doubled with an increase in dose from 300 mg/day to 600 mg/day (OR 1.99, 95% CI 1.74 to 2.28), indicating a dose-response relationship. Pregabalin was significantly associated with seizure freedom (RR 3.94, 95% CI 1.50 to 10.37, 4 trials, 1125 participants, moderate-certainty evidence). Participants were significantly more likely to withdraw from pregabalin treatment than placebo for any reason (RR 1.35, 95% CI 1.11 to 1.65, 7 trials, 2193 participants, moderate-certainty evidence) and for adverse effects (RR 2.65, 95% CI 1.88 to 3.74, 7 trials, 2193 participants, moderate-certainty evidence).

Three trials compared pregabalin to three active-control drugs: lamotrigine, levetiracetam, and gabapentin. Participants allocated to pregabalin were significantly more likely to achieve a 50% or greater reduction in seizure frequency than those allocated to lamotrigine (RR 1.47, 95% CI 1.03 to 2.12, 1 trial, 293 participants) but not those allocated to levetiracetam (RR 0.94, 95% CI 0.80 to 1.11, 1 trial, 509 participants) or gabapentin (RR 0.96, 95% CI 0.82 to 1.12, 1 trial, 484 participants). We found no significant differences between pregabalin and lamotrigine (RR 1.39, 95% CI 0.40 to 4.83) for seizure freedom, however, significantly fewer participants achieved seizure freedom with add-on pregabalin compared to levetiracetam (RR 0.50, 95% CI 0.30 to 0.85). No data were reported for this outcome for pregabalin versus gabapentin. We found no significant differences between pregabalin and lamotrigine (RR 1.07, 95% CI 0.75 to 1.52), levetiracetam (RR 1.03, 95% CI 0.71 to 1.49), or gabapentin (RR 0.78, 95% CI 0.57 to 1.07) for treatment withdrawal due to any reason or due to adverse effects (pregabalin versus lamotrigine: RR 0.89, 95% CI 0.53 to 1.48; versus levetiracetam: RR 1.29, 95% CI 0.66 to 2.54; versus gabapentin: RR 1.07, 95% CI 0.54 to 2.11). Ataxia, dizziness, somnolence, weight gain, and fatigue were significantly associated with pregabalin.

We rated the overall risk of bias in the included studies as low or unclear due to the possibility of publication bias and lack of methodological details provided. We rated the certainty of the evidence as very low to moderate using the GRADE approach.

Authors' conclusions

Pregabalin, when used as an add-on drug for treatment-resistant focal epilepsy, is significantly more effective than placebo at producing a 50% or greater seizure reduction and seizure freedom. Results demonstrated efficacy for doses from 150 mg/day to 600 mg/day, with increasing effectiveness at 600 mg doses, however issues with tolerability were noted at higher doses. The trials included in this review were of short duration, and longer-term trials are needed to inform clinical decision making.

PLAIN LANGUAGE SUMMARY

Pregabalin add-on for drug-resistant focal epilepsy

Review question

This review aimed to assess the effectiveness and tolerability of pregabalin when used as an add-on antiepileptic drug in treatment-resistant focal epilepsy.

Background

Epilepsy is a common chronic neurological disease that affects approximately 1% of people in the UK. Approximately 1 in 400 people with epilepsy have seizures that continue despite antiepileptic drug treatment (drug-resistant epilepsy). A number of new antiepileptic drugs have been developed to treat epilepsy, of which pregabalin is one. Use of pregabalin in combination with other antiepileptic drugs can reduce the frequency of seizures, but has some adverse effects.

Study characteristics

This review examined data from 9 trials including a total of 3327 participants. Study participants were assigned using a random method to take pregabalin, placebo, or another antiepileptic drug in addition to their usual antiepileptic drugs.

Key results

Participants taking pregabalin were more than twice as likely to have their seizure frequency reduced by 50% or more during a 12-week treatment period compared to those taking placebo, and were nearly four times more likely to be completely free of seizures.

Pregabalin was shown to be effective across a range of doses (150 mg to 600 mg), with increasing effectiveness at higher doses. There was also an increased likelihood of treatment withdrawal with pregabalin. Side effects associated with pregabalin included ataxia, dizziness, fatigue, somnolence, and weight gain. When pregabalin was compared to three other antiepileptic drugs (lamotrigine, levetiracetam, and gabapentin), participants taking pregabalin were more likely to achieve a 50% reduction in seizure frequency than those taking lamotrigine. We found no significant differences between pregabalin and levetiracetam or gabapentin as add-on drugs.

Certainty of the evidence

We rated all included studies as at low or unclear in risk of bias due to missing information about the methods used to conduct the trial and a suspicion of publication bias. Publication bias can occur when studies that report non-significant findings are not published. We suspected publication bias because the majority of included studies showed significant findings and were sponsored by the same drug company. We assessed the certainty of the evidence for the primary outcome of reduction in seizure frequency as low, meaning that we cannot be certain that the finding reported is accurate. However, we rated the certainty of the evidence for the outcomes seizure freedom and treatment withdrawal as moderate, so we can be fairly confident that these results are accurate. There were no data regarding the longer-term effectiveness of pregabalin, which should be investigated in future studies.

The evidence is current to 5 July 2018.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Pregabalin compared to placebo for drug-resistant focal epilepsy

Patient or population: drug-resistant focal epilepsy
Setting: outpatient setting
Intervention: pregabalin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with pregabalin				
50% or greater reduction in seizure frequency - ITT analysis Follow-up: range 12 to 17 weeks	**Study population**		**RR 2.28** (1.52 to 3.42)	**2193** (7 RCTs)	⊕⊕◯◯ **LOW** [12356]	Pregabalin may increase the proportion of people achieving 50% or greater reduction in seizure frequency according to ITT analysis, but we are uncertain
	184 per 1000	420 per 1000 (280 to 631)				
50% or greater reduction in seizure frequency - best-case analysis Follow-up: range 12 to 17 weeks	**Study population**		**RR 3.57** (2.17 to 5.86)	**2193** (7 RCTs)	⊕◯◯◯ **VERY LOW** [1235]	Pregabalin may increase the proportion of people achieving 50% or greater reduction in seizure frequency according to best-case analysis, but we are very uncertain
	184 per 1000	658 per 1000 (400 to 1000)				
50% or greater reduction in seizure frequency - worst-case analysis Follow-up: range 12 to 17 weeks	**Study population**		**RR 1.15** (0.92 to 1.43)	**2193** (7 RCTs)	⊕◯◯◯ **VERY LOW** [12]	Pregabalin might have no effect on the proportion of people achieving 50% or greater reduction in seizure frequency ac-

						cording to worst-case analysis, however, we are very uncertain
	345 per 1000	397 per 1000 (318 to 494)				
Seizure freedom Follow-up: 12 weeks	**Study population**		**RR 3.94** (1.50 to 10.37)	**1125** (4 RCTs)	⊕⊕⊕◯ **MODERATE** [145]	Pregabalin likely increases the number of people achieving seizure freedom
	11 per 1000	42 per 1000 (16 to 112)				
Treatment withdrawal for any reason Follow-up: range 12 to 17 weeks	**Study population**		**RR 1.35** (1.11 to 1.65)	**2193** (7 RCTs)	⊕⊕⊕◯ **MODERATE** [1]	Pregabalin likely slightly increases the number of people who withdraw from treatment for any reason, however this effect may or may not be important
	161 per 1000	217 per 1000 (178 to 265)				
Treatment withdrawal due to adverse effects Follow-up: range 12 to 17 weeks	**Study population**		**RR 2.65** (1.88 to 3.74)	**2193** (7 RCTs)	⊕⊕⊕◯ **MODERATE** [145]	Pregabalin likely increases the number of people withdrawing from treatment due to adverse effects
	53 per 1000	141 per 1000 (100 to 199)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **ITT:** intention-to-treat; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded once for risk of bias: two studies did not confirm their method of randomisation; all studies failed to specify method of allocation concealment; three studies did not provide information on method of blinding; and two studies were judged to be at risk of other sources of bias.

[2]Downgraded twice for inconsistency: significant heterogeneity ($P < 0.05$) was detected within the data set.

[3]Downgraded once for publication bias: publication bias suspected.

[4]Downgraded once for imprecision: number of events reported (< 400) did not suffice the optimal information size.

[5]Upgraded once for large effect: risk ratio was greater than 2.00.

[6]Upgraded once for dose response: dose-response relationship was confirmed by regression model.

BACKGROUND

Description of the condition

Epilepsy is a common neurological chronic condition that affects approximately 1% of the UK population (Hauser 1990). A single antiepileptic drug (AED) (monotherapy) can induce remission for the majority of those diagnosed. However, up to 30% of people with epilepsy fail to respond to monotherapy (Cockerell 1995). Patients who have failed to respond to a minimum of two AEDs given as monotherapy are considered to be 'drug-resistant'. The majority of those who are drug-resistant have focal onset (also called focal- or localisation-related) seizures. During focal-onset seizures, abnormal electrical activity initiates in one part of the brain, and during the course of the seizure the abnormal electrical activity either remains localised or spreads to other parts of the brain (Ramaratnam 2016). For individuals with drug-resistant focal epilepsy, recurrent seizures can reduce quality of life, and may also lead to injuries, social isolation, and depression (Villeneuve 2004). Individuals with this neurological condition pose a significant therapeutic problem, which has led to the development of new AEDs as well as exploration of non-pharmacological treatment options, such as vagal nerve stimulation and epilepsy surgery (Panebianco 2015; West 2015). Over the past two decades, the introduction of several new antiepileptic drugs that often are better tolerated and more manageable than older AEDs has improved the ability to treat individuals with epilepsy. Recent studies have reported that 12% to 17% of treatment-resistant individuals become seizure-free with the addition of a previously untried, in most cases new-generation, antiepileptic drug (Granata 2009).

Description of the intervention

Since the 1990s, numerous new AEDs have become available that aim to provide more potent and better-tolerated treatments for epilepsy. Pregabalin is one of these new compounds with antiepileptic, analgesic, and anxiolytic (anxiety-reducing) properties. Pregabalin has favourable pharmacokinetics: it is not protein bound, is 90% bioavailable, and reaches peak plasma concentrations within 1.5 hours of administration of an oral dose. With repeated doses, a steady state is achieved within 24 to 48 hours. Furthermore, 90% of the drug is eliminated, unmetabolised, by the kidneys, and it has no known drug interactions (Brodie 2005). Pregabalin was launched in the UK market in 2004 as an add-on AED for focal-onset seizures, as well as a treatment for neuropathic pain, and as an anxiolytic in 2006.

How the intervention might work

Pregabalin is structurally related to both the neurotransmitter γ-aminobutyric acid (GABA), and the older antiepileptic drug, gabapentin. Similar to gabapentin, the primary mechanism underlying the pharmacological action of pregabalin does not appear to involve the GABA system. In particular, pregabalin does not bind to GABA-A, GABA-B, or benzodiazepine receptors. Pregabalin is neither metabolically converted to GABA or to a GABA agonist, nor does it have any effect on the uptake or degradation of GABA. In fact, the primary mode of action of pregabalin is via the inhibition of depolarisation-induced calcium influx at P-, Q-, and N-type voltage-gated calcium channels, located at the nerve terminals. At the molecular level, this action is achieved by pregabalin binding to the α-2-δ subunit of voltage-gated calcium channels (Ben-Menachem 2004). As a consequence of the reduced calcium influx, less excitatory neurotransmitter, such as glutamate, is released from the presynaptic nerve terminals.This action is thought to mediate its antiepileptic, anxiolytic, and analgesic properties. In addition, by acting on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, pregabalin indirectly reduces synaptic noradrenaline release (Fink 2002).

Notably, the mechanism of action of pregabalin does not appear to differ from that of gabapentin. The affinity of pregabalin for the α-2-δ modulatory site, however, is much greater than that of gabapentin. This explains why pregabalin is three- to six-fold more potent than gabapentin in animal models of seizures and epilepsy, and also in models of anxiety and neuropathic pain.

Why it is important to do this review

This review is an update of a previous Cochrane Review (Pulman 2014) and aims to summarise existing data regarding the effects of add-on pregabalin for people with drug-resistant focal-onset seizures. Clinical trials published on the antiepileptic properties of pregabalin have so far focused on people with drug-resistant focal-onset epilepsy. In these randomised placebo-controlled trials, study participants are randomised to have either pregabalin or placebo added to their existing AED treatment. This is in keeping with international guidelines on the development of AEDs (ILAE Commission 1989). Once a drug has confirmed efficacy and safety as an add-on therapy, it can be tested as monotherapy. The use of pregabalin as monotherapy has been addressed in a separate Cochrane Review by Zhou 2012.

OBJECTIVES

To assess the efficacy and tolerability of pregabalin when used as an add-on treatment for drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the review, studies had to meet the following criteria:

1. randomised controlled trials;
2. double-blind or single-blinded trials;
3. placebo controlled or active controlled;
4. parallel-group or cross-over studies.

Types of participants

People of any age with drug-resistant focal epilepsy (i.e. experiencing simple focal, complex focal, or secondary generalised tonic-clonic seizures).

Types of interventions

1. The active-treatment group received pregabalin in addition to an existing AED regimen taken at time of randomisation.
2. The control group received a matched placebo or an active comparator control in addition to an existing AED regimen taken at time of randomisation.

Types of outcome measures

Primary outcomes

50% or greater reduction in seizure frequency

We chose the proportion of people with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period as the primary outcome. We chose this because it is a commonly reported outcome, and can be calculated for studies that do not report this outcome provided that baseline seizure data were recorded.

Secondary outcomes

Seizure freedom

The proportion of participants with a complete cessation of seizures during the treatment period.

Treatment withdrawal

We used the proportion of participants having treatment withdrawn for any reason during the course of the treatment period as a measure of global effectiveness. Treatment is likely to be withdrawn due to adverse effects, lack of efficacy, or a combination of both, and this is an outcome to which the individual makes a direct contribution. In trials of short duration, it is likely that adverse effects will be the most common reason for withdrawal. We also assessed the proportion of participants having treatment withdrawn for adverse effects.

Adverse effects

1. The proportion of participants experiencing the following five adverse effects (we considered these adverse effects to be common and important adverse effects of AEDs):
   i) ataxia (co-ordination problems);
   ii) dizziness;
   iii) fatigue;
   iv) nausea;
   v) somnolence (unusual drowsiness).
2. The proportion of participants experiencing the five most common adverse effects mentioned in the included trials if these differed from those listed in (1) above.

Search methods for identification of studies

Electronic searches

We ran searches for the original review in 2007, and subsequent searches in March 2010, September 2011, May 2012, January 2014, September 2015, and September 2016. For the latest update we searched the following.

1. Cochrane Register of Studies (CRS Web, 5 July 2018), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), using the search strategy outlined in Appendix 1.
2. MEDLINE (Ovid, 1946 to 5 July 2018) using the search strategy outlined in Appendix 2.
3. ClinicalTrials.gov (5 July 2018) using the search strategy outlined in Appendix 3.
4. World Health Organization International Clinical Trials Registry Platform (ICTRP, 5 July 2018) using the search strategy outlined in Appendix 4.

We did not impose any language restrictions.

Searching other resources

We reviewed the reference lists of retrieved studies to check for additional reports of relevant studies. We also contacted Pfizer Ltd (manufacturer of pregabalin) and colleagues in the field.

Data collection and analysis

Selection of studies

For the update, two review authors (RB and MP) independently assessed trials for inclusion. Any disagreements were resolved by discussion with a third review author (AM). Two review authors (RB and MP) extracted data and assessed risk of bias; again, disagreements were resolved by discussion.

Data extraction and management

The same two review authors extracted the following information from the included trials. Any disagreements were resolved by mutual discussion.

Methodological/trial design

1. Method of randomisation and concealment.
2. Method of double-blinding.
3. Whether any participants had been excluded from the reported analyses.
4. Duration of baseline period.
5. Duration of treatment period.
6. Dose(s) of pregabalin tested.

Participant/demographic information

1. Total number of participants allocated to each treatment group.
2. Age/sex.
3. Number with focal/generalised epilepsy.
4. Seizure types.
5. Seizure frequency during the baseline period.
6. Number of background drugs.

For all trials sponsored by Pfizer Ltd, confirmation of the following information

1. Method of randomisation.
2. Total number randomised to each group.
3. Number of participants in each group achieving a 50% or greater reduction in seizure frequency.
4. Number of participants in each group having treatment withdrawn postrandomisation.
5. For excluded participants:
   i) the reason for exclusion;
   ii) whether any of those excluded completed the treatment phase;
   iii) whether any of those excluded had a 50% or greater reduction in seizure frequency during the treatment phase.

Outcomes

We recorded the number of participants experiencing each outcome (see Types of outcome measures) per randomised group.

Assessment of risk of bias in included studies

For the update, two review authors (RB and MP) independently assessed risk of bias for each trial using the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were discussed and resolved. We judged each included study to be at low, high, or unclear risk of bias for the six domains applicable to randomised controlled trials: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

We presented the primary outcome of seizure reduction as a risk ratio. We also presented the secondary outcomes, including seizure freedom, treatment withdrawal, and adverse effects, as risk ratios.

Unit of analysis issues

The inclusion of cross-over studies in meta-analyses introduces unit of analysis issues because each patient contributes data to both treatment groups. We had planned to extract data from the first treatment period of any eligible cross-over studies, had any been identified for inclusion. Essentially, we would have regarded the first treatment period as a parallel study, thus preventing data from the same patient being considered twice whilst simultaneously avoiding any issues of carry-over effect. We did not include any cross-over studies in this current review update, hence there were no unit of analysis issues to consider.

Dealing with missing data

We sought any missing data from the study authors. We carried out intention-to-treat (ITT), best-case, and worst-case analysis on the primary outcome to account for any missing data. All analyses are presented in the main report.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors amongst trials (e.g. age, seizure type, duration of epilepsy, number of antiepileptic drugs taken at the time of randomisation) and trial factors (e.g. allocation concealment, blinding, losses to follow-up). We examined statistical heterogeneity using a Chi^2 test and the I^2 statistic for heterogeneity and, providing no significant heterogeneity was present ($P > 0.10$), we employed a fixed-effect model. In the event that we found heterogeneity ($P < 0.10$), we planned to use a random-effects model analysis employing the inverse-variance method.

Assessment of reporting biases

We requested protocols from study authors to enable a comparison of outcomes of interest. We investigated outcome reporting bias using the Outcome Reporting Bias in Trials (ORBIT I) matrix system for benefit outcomes, Kirkham 2010, and ORBIT II matrix system for harm outcomes (Saini 2014). We examined the asymmetry of funnel plots to detect any publication bias.

Data synthesis

We employed a fixed-effect model meta-analysis to synthesise the data. Comparisons we expected to carry out included:

1. pregabalin intervention group versus placebo control group;
2. pregabalin intervention group versus active-comparator control group.

We planned to stratify each comparison by study characteristics, such as dose of pregabalin used, during subgroup analysis to ensure the appropriate combination of study data.

Our preferred estimator was the Mantel-Haenszel risk ratio (RR). For the outcomes 50% or greater reduction in seizure frequency and treatment withdrawal, we used 95% confidence intervals (CIs). For individual adverse effects, we used 99% CIs to make an allowance for multiple testing.

Our analyses included all participants in the treatment group to which they had been allocated. For the efficacy outcome (50% or greater reduction in seizure frequency), we undertook three analyses:

1. Primary (ITT) analysis: participants not completing follow-up or with inadequate seizure data were assumed to be non-responders. Analysis by ITT was reported by all of the included studies.
2. Worst-case analysis: participants not completing follow-up or with inadequate seizure data were assumed to be non-responders in the intervention group, and responders in the placebo group.
3. Best-case analysis: participants not completing follow-up or with inadequate seizure data were assumed to be responders in the intervention group, and non-responders in the placebo group.

The purpose of the best-case and worst-case analyses is to test the whether the assumption that all participants not completing follow-up or with inadequate seizure data are non-responders, made during ITT analysis, affects the estimated effect size.

Dose regression analysis

Dose-response analysis was evaluated using a generalised linear mixed model (i.e. a model including both fixed and random effects) with the logit link function, as described in Turner 2000, and estimated using the command xtmelogit in STATA SE version 14 (Stata statistical software 2015). Study and dose were included as fixed effects within the mixed model whilst treatment was included as a random-effect within the mixed model (no random-effect was included for the constant term of the mixed model). Dose was standardised by its standard deviation (245 mg). This method estimated an odds ratio (OR) as opposed to a RR.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analysis for all of the outcomes included in this review. For the comparison pregabalin versus placebo, subgroup analysis was stratified by dose of pregabalin. Dose of pregabalin was chosen because it was the most striking clinical difference identified between the included studies and was thus anticipated to be the cause of any observed heterogeneity. For the comparison pregabalin versus active comparator, subgroup analysis was stratified by active comparator in order to determine whether pregabalin might be advantageous or disadvantageous compared to a specific alternative AED. If deemed appropriate, we intended to investigate heterogeneity using sensitivity analysis.

Sensitivity analysis

We also intended to carry out sensitivity analysis if peculiarities were found between study quality, characteristics of participants, interventions, and outcomes. We did not find any peculiarities between the studies, therefore no sensitivity analyses were conducted.

Summarising and interpreting results

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to interpret findings, and GRADEpro GDT software (which imports data from Review Manager 5 software (GRADEpro GDT 2015)), to create a 'Summary of findings' table for both comparisons: pregabalin versus placebo and pregabalin versus active comparator. We GRADE-assessed the following outcomes, deemed to be the most important: 50% of greater reduction in seizure frequency (intention-to-treat, best-case, and worst-case analysis), seizure freedom, treatment withdrawal for any reason and treatment withdrawal due to adverse effects. We assessed the evidence across eight criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding factors, and dose-response gradient) to determine its certainty.

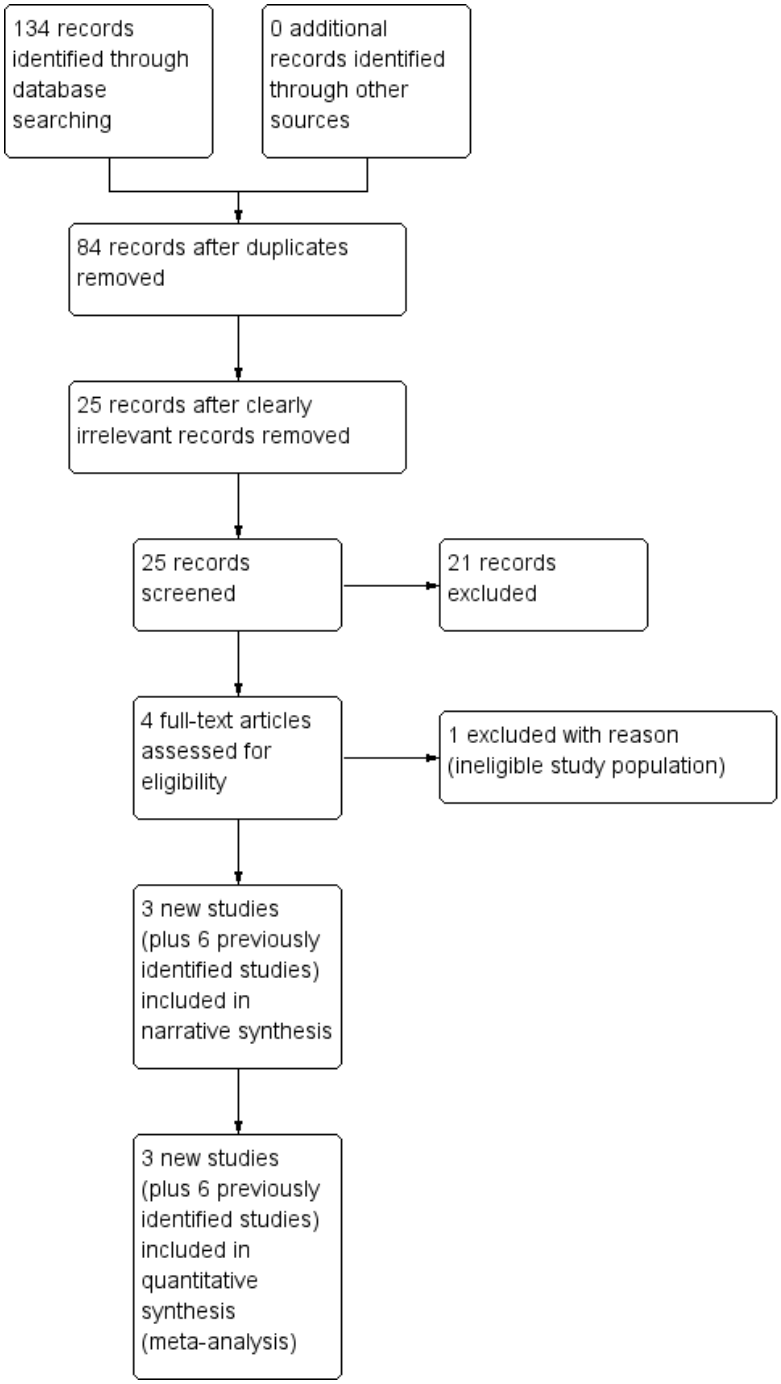
RESULTS

Description of studies

Results of the search

The searches conducted (September 2015, September 2016 and July 2018), subsequent to the previously published search in January 2014, retrieved a total of 134 new records (see Figure 1). We removed 50 duplicates and 59 obviously irrelevant records, prior to any screening. This left 25 records to be evaluated based on title and abstract. We removed 21 records, based on their title and abstract, and subsequently assessed four records as full-text articles. We excluded one record that was ineligible for inclusion (Taghdiri 2015). The other three studies (French 2014, French 2016 and Zaccara 2014), however, satisfied all inclusion criteria and were therefore included in the review.

Figure 1. Study flow diagram showing the screening results from the searches conducted in: September 2015, September 2016, and July 2018.



Included studies

We included nine randomised controlled trials (3327 participants) with parallel-group design in the review, all of which were sponsored by the drug manufacturer Pfizer Ltd. All nine of the included studies recruited participants with drug-resistant focal-onset seizures. Participants were taking between one and four AEDs and had at least three, four, or six focal seizures per month in the pre-randomisation baseline period. Further details are given below and are summarised in the Characteristics of included studies tables.

Arroyo and colleagues published a multicentre (45 sites in Europe, Australia, and Africa) trial in 2004 that included 288 participants (Arroyo 2004). Inclusion criteria were defined as people aged 18 years or older with focal-onset seizures. As an electroencephalogram (EEG) was not required to confirm the diagnosis, some of the 18 participants who were stated as having "generalised seizures", rather than secondary generalised, may have had primary generalised epilepsy. Participants were randomised to either 50 mg pregabalin three times daily (n = 99); 200 mg pregabalin three times daily (n = 92); or placebo three times daily (n = 97). After a baseline assessment of eight weeks, the treatment period was conducted over 12 weeks (including a titration period of four and eight days). During the treatment period, participants were assessed weekly for the first two weeks and fortnightly thereafter. Median follow-up was 12 weeks (range one day to 12 weeks). Three time points were reported in the study, each at four-weekly intervals.

Baulac and colleagues conducted a multicentre (97 sites in Europe, Canada, and Australia) trial, comprising 434 participants (Baulac 2010). Randomised participants were between 16 and 82 years of age and had undergone an EEG within two years prior to randomisation. Treatment arms were 150 mg to 300 mg pregabalin twice daily (n = 152); 150 mg to 200 mg lamotrigine twice daily (n = 141); and placebo (n = 141). Following a six-week baseline period, there was a 17-week double-blind treatment period comprising two phases. The first phase (phase I) spanned 11 weeks and included an up-titration period (one week for pregabalin and five weeks for lamotrigine). During phase I, participants randomised to pregabalin and lamotrigine were both up-titrated to 300 mg/d of their respective treatment drugs and were then maintained on this dose. Participants who were seizure-free for the duration of phase I continued to be maintained on 300 mg/d active treatment for the duration of phase II (six weeks). Participants randomised to pregabalin who continued to have seizures were further up-titrated to 600 mg/d pregabalin during phase II, whereas participants randomised to lamotrigine who continued to have seizures were up-titrated to 400 mg/d lamotrigine for the remaining six weeks of the treatment period. Participant review time points and follow-up were not reported.

Beydoun and colleagues randomised 313 participants, aged 17 to 82 years, from 43 US and Canadian centres in a randomised placebo-controlled trial (Beydoun 2005). Treatment groups included 200 mg pregabalin three times daily (n = 111); 300 mg pregabalin twice daily (n = 104); and placebo (n = 98). After a baseline assessment of eight weeks, the treatment period was conducted over 12 weeks (including a one-week titration period). Follow-up occurred on weeks two, four, eight, and 12. Median follow-up was 12 weeks (range not reported). During the trial an interim analysis was carried out on 129 participants, which led to an alteration of the subsequent statistical analysis.

Elger and colleagues reported a multicentre (53 sites in Canada and Europe) trial of 341 participants, aged 17 to 78 years (Elger 2005). Treatment arms were 150 mg to 600 mg pregabalin (n = 131), titrated with respect to clinical response and adverse effects in 150 mg daily increments; fixed-dose pregabalin of 300 mg twice daily (n = 137); and placebo (n = 73). Participants were randomised to one of the three treatments using a 2:2:1 ratio, respectively. The treatment period ran over 12 weeks and followed a six-week baseline period. Participants were reviewed at two, four, eight, and 12 weeks into the study. Median follow-up was 12 weeks, and over 58% of participants completed the study in each arm. The range of follow-up was not reported.

French and colleagues published a multicentre (76 sites in US and Canada) trial that included 455 participants (French 2003). Randomised participants were between 12 and 70 years of age, but not all had EEG and imaging data. Those with absence seizures and Lennox-Gastaut syndrome were excluded; however, the inclusion of some patients with primary generalised epilepsy could not be ruled out. Participants were randomised into one of five treatment arms: 50 mg/day (n = 88), 150 mg/day (n = 88), 300 mg/day (n = 90), and 600 mg/day (n = 89) pregabalin in a twice-daily regimen, and placebo (n = 100). Baseline assessment occurred over eight weeks, and treatment duration was 12 weeks with no titration period. Follow-up occurred on weeks two, four, eight, and 12. Median follow-up was 12 weeks (range one day to 12 weeks). Around 83% of participants completed the study.

French and colleagues published a multicentre (66 centres in the USA, Europe, and Asia) trial that included 325 participants, aged 18 to 75 years (French 2014). Participants were randomised 1:1:1 to controlled-release pregabalin 165 mg (n = 101), 330 mg (n = 114), or placebo (n = 110). The trial ran over 23 weeks including an eight-week baseline phase, a two-week double-blind dose escalation, a 12-week double-blind maintenance phase, and a one-week taper. The mean overall compliance was 99.2% for all three treatment arms, as demonstrated by participant-completed diaries.

French and colleagues conducted a multicentre (56 centres in Eastern and Western Europe, Asia, South and Central America) trial

that included 484 participants between 18 and 80 years of age (French 2016). Participants were randomised 1:1 to pregabalin 450 mg/d (n = 241) or gabapentin 1500 mg/d (n = 241). The trial included a six-week baseline phase (screening), a nine-week double-blind dose escalation (titration) phase, and a 12-week double-blind maintenance phase (21-week treatment phase overall). The primary endpoint was the percentage change from baseline in 28-day seizure rate to the treatment phase. Around 74% of participants completed the study.

Lee and colleagues conducted a multicentre (nine sites in Korea) trial consisting of two treatment arms (Lee 2009). A total of 178 participants, aged 18 years and above, were randomised to either 75 mg to 300 mg pregabalin twice daily (n = 119) or placebo (n = 59) using a 2:1 ratio. Following a six-week baseline period, treatment was conducted over 12 weeks with a one-week taper period at the end. Participants were assessed at weeks two, four, six, eight, and 12 with a follow-up visit at week 13. Eighty-eight per cent of randomised participants completed the study.

Zaccara and colleagues randomised 509 participants aged ≥ 18 from 71 centres in Europe, the USA, and Asia to one of two groups: pregabalin (n= 254; median dose 450 mg) or levetiracetam (n = 255; median dose 2000 mg) (Zaccara 2014). The trial included a six-week baseline phase, a four-week dose escalation phase, and a 12-week maintenance phase. During the trial an interim analysis was carried out after approximately 50% of participants had completed the maintenance phase. The trial continued as planned.

Excluded studies

From the searches conducted since the previous review update, it was clear that one previously ongoing trial (Bali 2012), has since been published (Taghdiri 2015). This study was, however, excluded due to the ineligibility regarding the study population. Further details are provided in the Characteristics of excluded studies table.

Studies awaiting classification

We assessed two studies as awaiting classification (see Characteristics of studies awaiting classification table), as we have obtained no additional information regarding either study since the publication of the previous review (Russi 2006; Tata 2007).

Risk of bias in included studies

We assessed all nine included studies for risk of bias based on the six domains of the Cochrane 'Risk of bias' tool. See Characteristics of included studies tables for each study for further details and Figure 2 for 'Risk of bias' graph and Figure 3 for 'Risk of bias' summary.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

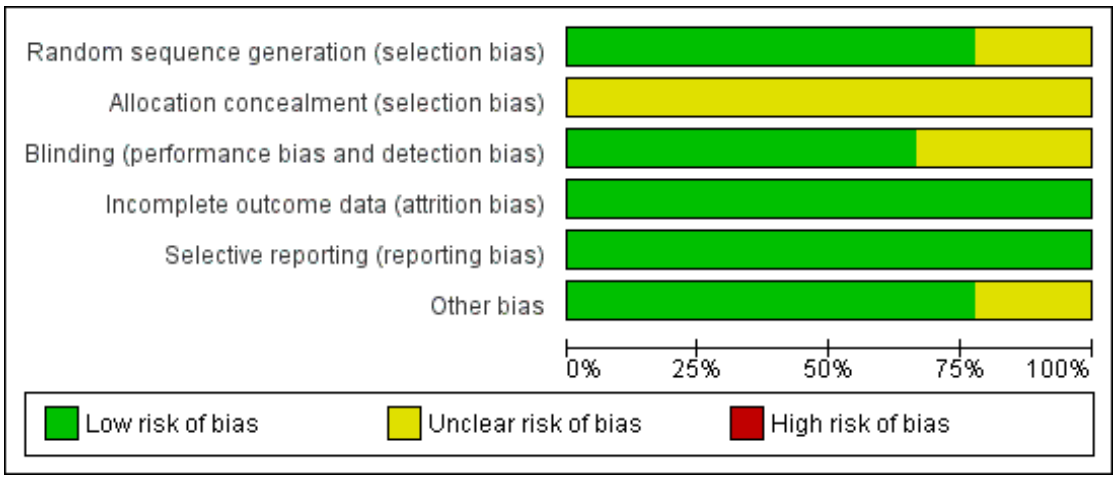
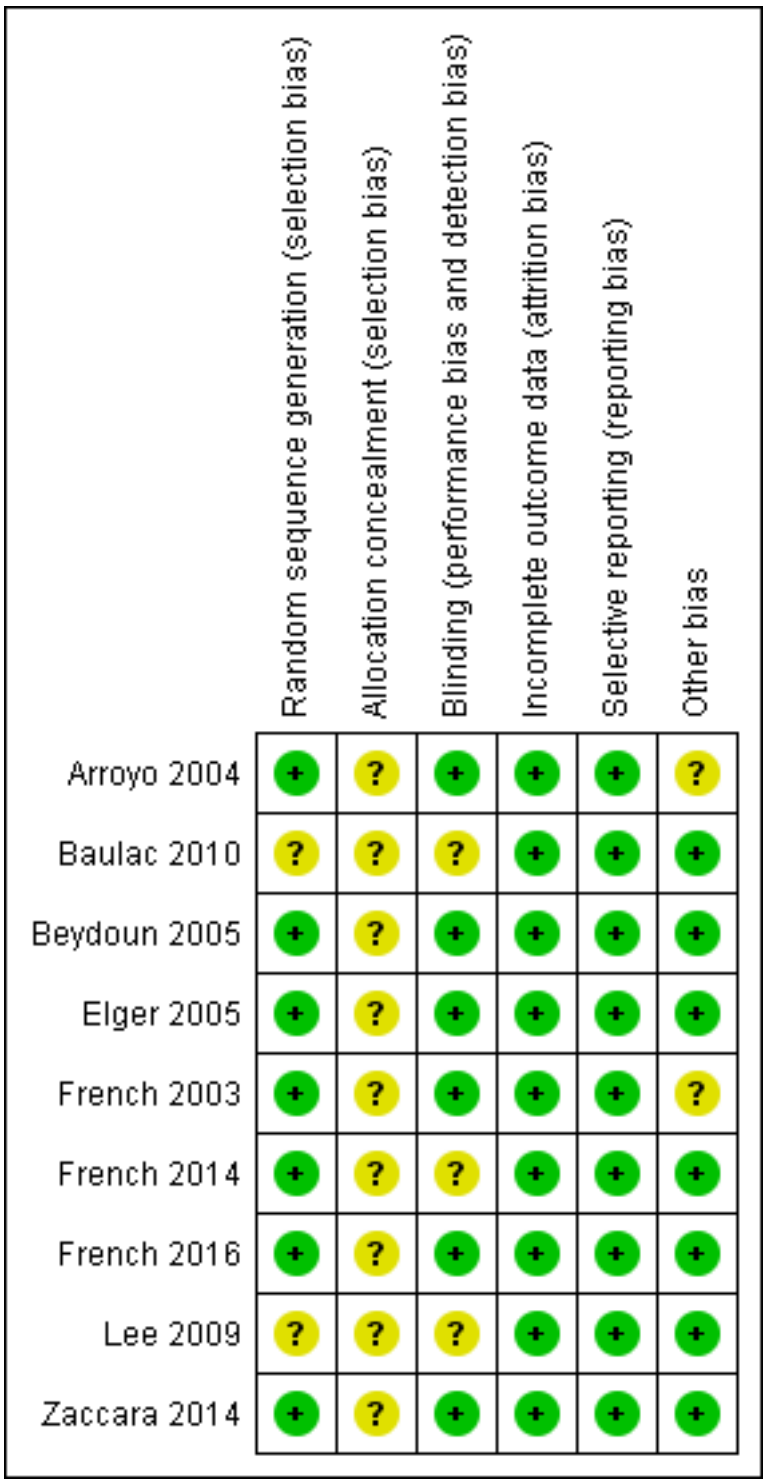


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Seven of the nine included studies employed an adequate method of sequence generation by using computer-generated identification numbers and block sizes of five or six (Arroyo 2004; Beydoun 2005; Elger 2005; French 2003; French 2014; French 2016; Zaccara 2014), therefore we assessed them as being at low risk of selection bias with regard to random sequence generation. Two of the studies did not provide details regarding method of randomisation and were judged as at unclear risk of bias (Baulac 2010; Lee 2009). None of the studies reported methods employed to prevent foreknowledge of group assignment (allocation concealment), and were therefore assessed as at unclear risk of bias for selection bias with regard to allocation concealment.

Blinding

Six studies were reported as double-blinded with the use of identical tablets with identical packaging for all treatment groups (Arroyo 2004; Beydoun 2005; Elger 2005; French 2003; French 2016; Zaccara 2014); we assessed these studies as at low risk of performance and detection bias. Two studies were reported as double-blinded, but no further details were provided (French 2014; Lee 2009). Another study stated that the same number of capsules per day were administered to each study group, however the study did not specify whether the tablets were identical in appearance (Baulac 2010). As a result, it was not clear whether blinding was effectively maintained. We therefore assessed these three studies as at unclear risk of performance and detection bias (Baulac 2010; French 2014; Lee 2009).

Incomplete outcome data

All studies reported study attrition rates, and all studies used an ITT analysis on randomised participants who took at least one dose of medication, using the 'last observation carried forward' approach (Arroyo 2004; Baulac 2010; Beydoun 2005; Elger 2005; French 2003; French 2014; French 2016; Lee 2009), that is for participants failing to complete follow-up, seizure-frequency data were extrapolated from the last participant observation point for the whole treatment period, whilst for participants with no seizure data during the treatment period, baseline data were extrapolated. In the trial reports a total of six participants were excluded from analyses; these participants have been included in the denominator as non-responders for the primary analysis.

Selective reporting

Most of the included studies distinguished between the primary and secondary outcome variables. No trial protocols were available for examination to compare reported outcomes, however all studies reported the primary/secondary outcomes stated in the methods section in the results section of the articles. Notably, all expected outcomes with respect to this review were reported, therefore we had no suspicions or concerns about any purposefully withheld data.

Further to this, we also completed an outcome matrix (Figure 4) according to the ORBIT I and ORBIT II matrix system to investigate the potential for outcome reporting bias (Kirkham 2010; Saini 2014). Four included studies did not report seizure freedom (Arroyo 2004; French 2003; French 2014; French 2016), however we did not find this to be concerning. All of the participants in the included studies had drug-resistant epilepsy, meaning that their epilepsy is refractory despite treatment with currently available antiepileptic medication. As a result, it is unlikely that many patients will achieve seizure freedom. Instead, 50% or greater reduction in seizure frequency is a more clinically relevant efficacy outcome for these patients. Consequently, it would be much more concerning and suspicious if any of the included studies failed to report the primary outcome, 50% or greater reduction in seizure frequency.

Figure 4. ORBIT matrix for review outcomes.

Study ID (author, date of publication)	Review primary outcomes	Review secondary outcomes (ORBIT I Classification: A-I)			Review harm outcomes (ORBIT I Classification: P1-V)							
	50% or greater reduction in seizure frequency	Seizure freedom	Treatment withdrawal for any reason	Treatment withdrawal due to adverse events	Ataxia	Dizziness	Fatigue	Nausea	Somnolence	Headache	Weight gain	Weight gain
Arroyo 2004	✓	✗ (G)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Baulac 2010	✓	✓	✓	✓	✓	✓	✓	✗ (T1)	✓	✓	✓	✓
Beydoun 2005	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗ (T1)	✓	✓
Elger 2005	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
French 2003	✓	✗ (G)	✓	✓	✓	✓	✓	✗ (T1)	✓	✓	✓	✓
French 2014	✓	✗ (G)	✓	✓	✗ (T1)	✓	✓	✓	✓	✗ (T1)	✓	✓
French 2016	✓	✗ (G)	✓	✓	✗ (T1)	✓	✗ (T1)	✗ (T1)	✓	✓	✓	✓
Lee 2009	✓	✓	✓	✓	✓	✓	✓	✗ (T1)	✓	✓	✓	✓
Zaccara 2014	✓	✓	✓	✓	✗ (T1)	✓	✗ (T1)	✓	✓	✓	✓	✓

✗ Outcome not reported

○ Outcome partially reported

✓ Outcome fully reported

✱ Outcome not measured

G: Not mentioned but clinical judgment says likely to have been measured and analysed but not reported.

T1: Specific harm not mentioned but all other specific harms fully reported.

In addition, we noted that several of the included studies did not report all of the adverse effects investigated as part of this review. However, because the majority of other harms were fully reported, we did not find this to be suspicious. The studies specified that they only reported the most common adverse events, for example only those reported by more than 5% of the study population, thus further justifying the absence of some data.

We consequently rated all nine included studies as at low risk of reporting bias.

Other potential sources of bias

In two included studies (Arroyo 2004; French 2003), individuals with primary generalised epilepsy may have been included in the trials, possibly leading to bias within the results, thus we assessed these studies as at unclear risk of other bias. We detected no other potential sources of bias for the remaining seven studies (Baulac 2010; Beydoun 2005; Elger 2005; French 2014; French 2016; Lee 2009; Zaccara 2014), resulting in a judgement of low risk of other bias for these studies.

Effects of interventions

See: **Summary of findings for the main comparison** Pregabalin compared to placebo for drug-resistant focal epilepsy; **Summary of findings 2** Pregabalin compared to active comparators for drug-resistant focal epilepsy

See Summary of findings for the main comparison for the main comparison 'pregabalin versus placebo for refractory epilepsy'.

Pregabalin versus placebo control

Six included studies involving a total of 1868 randomised participants compared immediate-release pregabalin versus placebo (Arroyo 2004; Baulac 2010; Beydoun 2005; Elger 2005; French 2003; Lee 2009). Another study (French 2014), including 325 participants, compared controlled-release pregabalin versus placebo. We included these seven trials in the analysis for the comparison 'pregabalin versus placebo'.

50% or greater reduction in seizure frequency

Seven included studies (2193 participants) reported this outcome (Arroyo 2004; Baulac 2010; Beydoun 2005; Elger 2005; French 2003; French 2014; Lee 2009). An ITT analysis pooling all doses (50 mg to 600 mg/day immediate- and controlled-release pregabalin) showed evidence of heterogeneity (I^2 = 80%), therefore we employed a random-effects model. Participants allocated to pregabalin were significantly more likely to achieve a 50% or greater

reduction in seizure frequency than those allocated to placebo (risk ratio (RR) 2.28, 95% confidence interval (CI) 1.52 to 3.42; Analysis 1.1). Subgroup analyses assessing the effect of individual doses showed no significant effect for 50 mg/d immediate-release pregabalin (RR 1.06, 95% CI 0.52 to 2.12; Analysis 2.1). Higher doses of immediate-release pregabalin were associated with a significantly higher proportion of participants achieving a 50% or greater reduction in seizure frequency compared to placebo (150 mg/d: RR 2.22, 95% CI 1.36 to 3.63; 300 mg/d: RR 2.86, 95% CI 1.65 to 4.94; 600 mg/d: RR 4.62, 95% CI 3.34 to 6.39; titrated 150 mg/d to 600 mg/d: RR 1.76, 95% CI 1.35 to 2.30; Analysis 2.1). Notably, during subgroup analysis, the effect size appeared to increase as the daily dose of pregabalin increased. Neither dose of controlled-release pregabalin, 165 mg/d or 330 mg/d, was associated with a significantly higher proportion of participants achieving a 50% or greater reduction in seizure frequency than placebo (165 mg/d: RR 1.03, 95% CI 0.72 to 1.48; 330 mg: RR 1.26, 95% CI 0.91 to 1.75; Analysis 2.1). Although the effect size did vary between subgroups, the direction of the effect (pregabalin being advantageous compared to placebo) was consistent amongst all subgroups, even those showing the smallest and statistically insignificant risk ratios.

Best-case and worst-case analyses

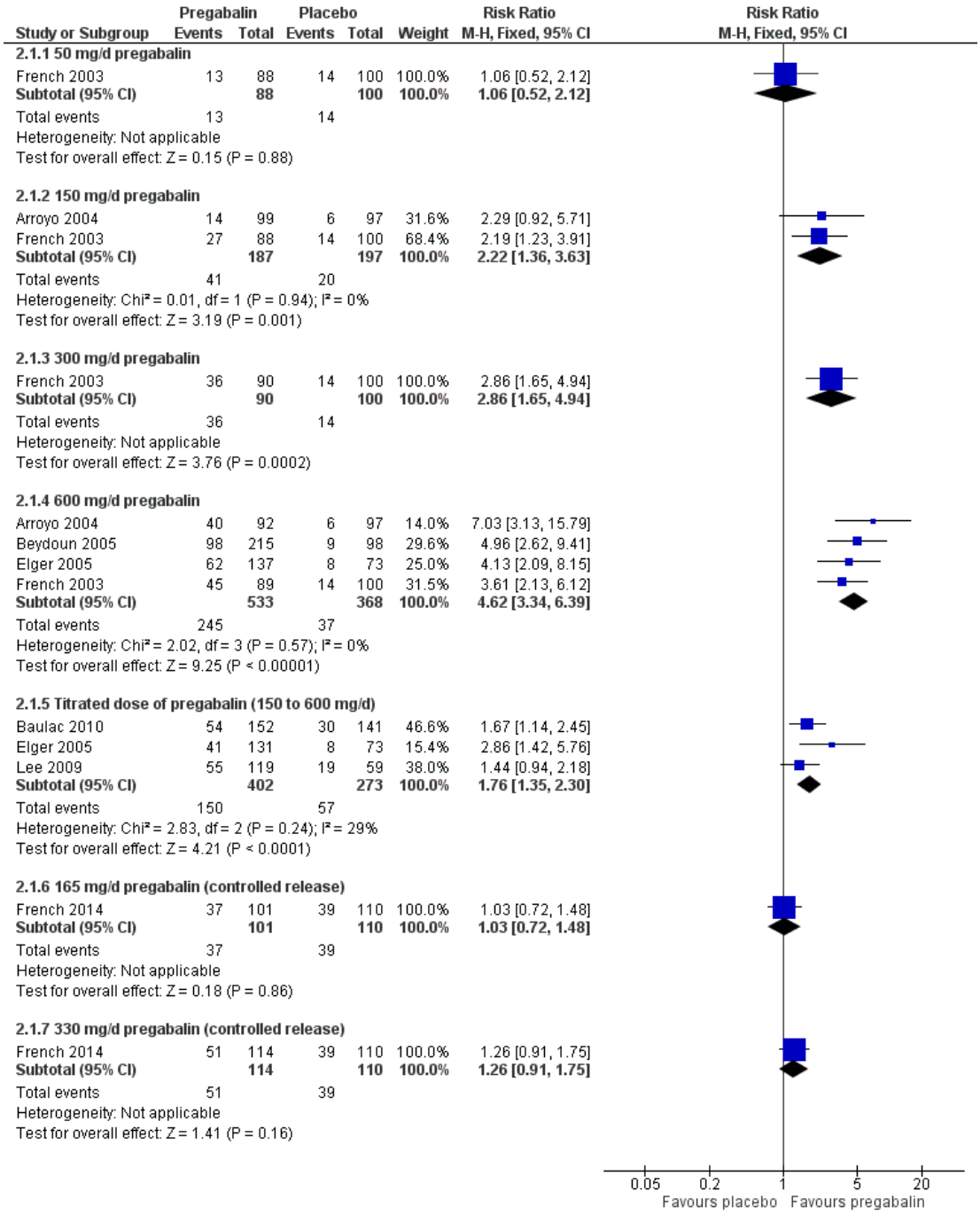
A best-case analysis (all treatment withdrawals in the treatment group assumed to be responders), pooling all doses (50 mg to 600 mg/day immediate- and controlled-release pregabalin), again showed that participants allocated to pregabalin were significantly more likely to achieve a 50% or greater reduction in seizure frequency compared to placebo (RR 3.57, 95% CI 2.17 to 5.86; Analysis 1.2). Again, we detected significant heterogeneity within the data set (I^2 = 88%) and so employed a random-effects model followed by a subgroup analysis according to dose to investigate dose as a potential source of heterogeneity (Analysis 2.2). Subgroup analyses assessing the effect of individual doses showed significant effects for all pregabalin doses, including 330 mg/d controlled-release pregabalin (50 mg/d: RR 1.87, 95% CI 1.03 to 3.40; 150 mg/d: RR 3.18, 95% CI 2.00 to 5.06; 300 mg/d: RR 4.37, 95% CI 2.61 to 7.29; 600 mg/d: RR 7.72, 95% CI 5.64 to 10.57; titrated 150 mg/d to 600 mg/d: RR 2.86, 95% CI 2.24 to 3.65; 330 mg/d controlled-release: RR 1.63, 95% CI 1.21 to 2.20), with the exception of 165 mg/d controlled-release pregabalin (RR 1.28, 95% CI 0.92 to 1.79), for which the effect size remained insignificant, even during best-case analysis (Analysis 2.2).

In contrast, a worst-case analysis (all dropouts from the control group assumed to be responders) pooling all doses of pregabalin (50 mg/d to 600 mg/d and including controlled-release pregabalin) showed no significant difference between pregabalin and placebo for the outcome 50% or greater seizure reduction (RR 1.15, 95% CI 0.92 to 1.43; Analysis 1.3). The analysis did, however, continue to show significant heterogeneity within the data set (I^2 = 66%). Subgroup analyses by dose indicated that one dose (50 mg/d) was associated with significantly fewer participants achieving a 50% or greater seizure reduction in the pregabalin group compared to the placebo group during worst-case analysis (RR 0.55, 95% CI 0.30 to 0.99). In contrast, 600 mg/d pregabalin continued to demonstrate a significant advantage over placebo with respect to the number of participants who achieved a 50% or greater reduction in seizure frequency (RR 1.72, 95% CI 1.42 to 2.09). There were no significant differences between the other pregabalin dose groups and placebo for the outcome during worst-case analysis (150 mg/d: RR 0.96, 95% CI 0.66 to 1.38; 300 mg/d: RR 1.48, 95% CI 0.98 to 2.23; titrated 150 mg/d to 600 mg/d: RR 0.92, 95% CI 0.76 to 1.12; 165 mg/d controlled-release: RR 0.79, 95% CI 0.57 to 1.09; 330 mg/d controlled-release: RR 0.96, 95% CI 0.72 to 1.28; Analysis 2.3).

Dose regression analysis for 50% response

We fitted a generalised linear mixed model to the data from Analysis 2.1 (Figure 5) to estimate the effect of dose on the primary outcome, 50% or greater reduction in seizure frequency (details in Data synthesis). This method estimates an odds ratio (OR) as opposed to an RR. Dose was standardised by its standard deviation (245 mg). The odds of response (50% reduction in seizure frequency) approximately doubled (OR 1.99, 95% CI 1.74 to 2.28) with estimated between-study standard deviation of 0.17 (standard error 0.13) for each 245 mg increase in dose of pregabalin. This translates into an estimated doubling of odds of response with an increase in dose of 245 mg (e.g. a doubling of odds from approximately 300 mg to 600 mg).

Figure 5. Forest plot of comparison: 1 Pregabalin versus placebo: 50% seizure reduction - intention-to-treat analysis, outcome: 2.1 50% or greater reduction in seizure frequency, intention-to-treat.



Seizure freedom

Four included studies involving a total of 1125 participants reported seizure freedom (Baulac 2010; Beydoun 2005; Elger 2005; Lee 2009). Specifically, these studies reported the number of participants who had complete cessation of their seizures over the entire treatment period. In contrast, the study by Arroyo 2004 recorded the number of participants who were seizure-free during the last 28 days of their treatment. This definition of seizure freedom was not consistent with the definition used by the other studies, therefore we excluded the data extracted from Arroyo 2004 from the analysis.

The pooled analysis, consisting of all doses, showed evidence of no heterogeneity (I^2 = 11%), therefore we continued to employ a fixed-effect model. The analysis demonstrated that participants allocated to pregabalin were significantly more likely to attain seizure freedom than those allocated to placebo (RR 3.94, 95% CI 1.50 to 10.37; Analysis 1.4).

Although we detected no important heterogeneity, we continued to use subgroup analysis to investigate whether there was any potentially undetected heterogeneity due to experimental dose of pregabalin. Two subgroups were included in the analysis, 600 mg/d pregabalin and 150 mg/d to 600 mg/d titrated dose of pregabalin. Subgroup analysis highlighted that a significantly greater number of participants randomised to 600 mg/d pregabalin attained seizure freedom compared to those randomised to placebo (RR 6.92, 95% CI 1.31 to 36.70; Analysis 2.4). There was no significant difference in the proportion of participants who achieved seizure freedom between participants allocated to 150 mg/d to 600 mg/d titrated dose of pregabalin compared to placebo (RR 2.39, 95% CI 0.83 to 6.89; Analysis 2.4).

Treatment withdrawal for any reason

An analysis pooling all doses (50 mg/d to 600 mg/d immediate- and controlled-release pregabalin) showed no evidence of heterogeneity (I^2 = 0%), therefore we used a fixed-effect model. Participants allocated to pregabalin were significantly more likely to have withdrawn from treatment compared to those allocated to placebo (RR 1.35, 95% CI 1.11 to 1.65; Analysis 1.5). Subgroup analysis assessing the individual doses showed no significant effect for 50 mg/d (RR 0.87, 95% CI 0.40 to 1.89); 150 mg/d (RR 0.72, 95% CI 0.41 to 1.28); 300 mg/d (RR 1.62, 95% CI 0.85 to 3.10); or 150 mg/d to 600 mg/d titrated dose of immediate-release pregabalin (RR 1.20, 95% CI 0.89 to 1.62) compared to placebo. Similarly, neither dose of controlled-release pregabalin displayed a significant effect on the rate of treatment withdrawal (165 mg/d controlled-release: RR 0.82, 95% CI 0.36 to 1.86; 330 mg/d controlled-release: RR 1.21, 95% CI 0.59 to 2.46). The only dose of pregabalin associated with a significantly higher treatment withdrawal rate for any reason compared to placebo was 600 mg/d (RR 1.84, 95% CI 1.42 to 2.40; Analysis 2.5). In fact, the two lowest doses of immediate-release pregabalin (50 mg/d and 150 mg/d) and lowest dose of controlled-release pregabalin (165 mg/d) both actually estimated risk ratios of less than one (50 mg/d: RR 0.87, 95% CI 0.40 to 1.89; 150 mg/d: RR 0.72, 95% CI 0.41 to 1.28; 165 mg/d controlled-release: RR 0.82, 95% CI 0.36 to 1.86), meaning that fewer people randomised to low doses of pregabalin withdrew from treatment compared to those randomised to placebo.

Treatment withdrawal due to adverse effects

An analysis pooling all doses (50 mg/d to 600 mg/d immediate- and controlled-release pregabalin) showed no evidence of heterogeneity (I^2 = 0%), thus we used a fixed-effect model for the analysis. Participants allocated to pregabalin were significantly more likely to withdraw from treatment due to adverse effects (RR 2.65, 95% CI 1.88 to 3.74; Analysis 1.6). Subgroup analyses assessing treatment withdrawal with differing doses suggested that a higher withdrawal rate was associated with higher doses of pregabalin (50 mg/d: RR 1.36, 95% CI 0.43 to 4.31; 150 mg/d: RR 1.02, 95% CI 0.45 to 2.32; 300 mg/d: RR 2.89, 95% CI 1.07 to 7.78; 600 mg/d: RR 3.78, 95% CI 2.47 to 5.81; Analysis 2.6). Specifically, participants randomised to 300 mg/d, 600 mg/d, or a titrated dose of pregabalin of 150 mg/d to 600 mg/d (RR 2.26, 95% CI 1.30 to 3.95) were all significantly more likely to withdraw from treatment due to adverse effects than were participants randomised to placebo. Neither dose of controlled-release pregabalin was associated with a significantly different treatment withdrawal rate due to adverse effects compared to placebo (165 mg/d controlled-release: RR 1.09, 95% CI 0.22 to 5.27; 330 mg/d controlled-release: RR 2.57, 95% CI 0.70 to 9.45).

Adverse effects

In addition to the five prespecified adverse effects, weight gain and headache were amongst the most common adverse effects reported. Analyses pooling across doses (50 mg/d to 600 mg/d immediate- and controlled-release pregabalin) indicated that ataxia (RR 3.90, 99% CI 2.05 to 7.42; Analysis 1.7); dizziness (RR 3.15, 99% CI 2.23 to 4.44; Analysis 1.8); fatigue (RR 1.34, 99% CI 0.93 to 1.94; Analysis 1.9); somnolence (RR 2.15, 99% CI 1.50 to 3.09; Analysis 1.12); and weight gain (RR 5.02, 99% CI 2.49 to 10.10; Analysis 1.13) were all significantly more prevalent in participants randomised to pregabalin compared to placebo. Nausea incidence did not differ significantly between pregabalin and placebo groups (RR 1.20, 99% CI 0.56 to 2.58; Analysis 1.11). In

contrast, participants randomised to pregabalin were significantly less likely to experience headache compared to those randomised to placebo (RR 0.63, 99% CI 0.42 to 0.93; Analysis 1.10). We detected no significant heterogeneity for any of the adverse effects analysed (all: I^2 = 0%).

Subgroup analysis according to dose of pregabalin revealed that the highest dose, 600 mg/d pregabalin, was consistently associated with a significantly greater likelihood of participants experiencing adverse effects compared to placebo. Specifically, participants receiving 600 mg/d were more likely to experience the following adverse effects than participants receiving placebo: ataxia (RR 4.49, 99% CI 2.25 to 8.95; Analysis 2.7); dizziness (RR 3.72, 99% CI 2.42 to 5.69; Analysis 2.8); somnolence (RR 2.57, 99% CI 1.64 to 4.03; Analysis 2.12); and weight gain (RR 5.88, 99% CI 2.52 to 13.73; Analysis 2.13). Similarly, a titrated dose of 150 mg/d to 600 mg/d pregabalin was associated with a significantly increased incidence rate of ataxia (RR 4.46, 99% CI 1.28 to 15.48; Analysis 2.7); dizziness (RR 3.08, 99% CI 1.80 to 5.28; Analysis 2.8); somnolence (RR 2.35, 99% CI 1.31 to 4.19; Analysis 2.12); and weight gain (RR 3.64, 99% CI 1.49 to 8.87; Analysis 2.13). In contrast, none of the other dose subgroups were consistently associated with an increased likelihood of the individual adverse effects. Interestingly, all of the dose groups, with the exception of 50 mg/d pregabalin (RR 1.01, 99% CI 0.31 to 3.33), were, however, associated with the an increased incidence of dizziness compared to placebo (Analysis 2.8). Furthermore, all of the dose subgroups had a risk ratio suggesting that there was a decreased likelihood of participants experiencing headache when receiving pregabalin compared to those receiving placebo, however the difference was only significant for one subgroup, 150 mg/d pregabalin (RR 0.53, 99% CI 0.24 to 1.17; Analysis 2.10).

Pregabalin versus active comparator

Three included studies involving a total of 1286 participants compared pregabalin to other existing AEDs as active comparators. One study included 293 randomised participants and compared pregabalin with lamotrigine as the active control drug (Baulac 2010). Another trial included 509 randomised participants and compared pregabalin with levetiracetam as the active control drug (Zaccara 2014). The remaining study, French 2016, involved 484 participants and compared pregabalin with gabapentin as the active control drug.

50% or greater reduction in seizure frequency

All three included studies (1286 participants) reported this outcome. We detected significant heterogeneity within the data set (I^2 = 61%), therefore we used a random-effects model. The likelihood of participants achieving a 50% or greater reduction in seizure frequency was not significantly different based on whether participants were randomised to pregabalin or an alternative active-comparator AED (RR 1.03, 95% CI 0.85 to 1.25; Analysis 3.1). Interestingly, subgroup analysis according to active-comparator control group revealed that participants receiving pregabalin were significantly more likely to achieve a 50% or greater reduction in seizure frequency compared to those receiving the active comparator lamotrigine (RR 1.47, 95% CI 1.03 to 2.12; Analysis 4.1), however there was no significant difference between pregabalin and either levetiracetam (RR 0.94, 95% CI 0.80 to 1.11) or gabapentin (RR 0.96, 95% CI 0.82 to 1.12). The test for subgroup differences did not highlight a significant subgroup effect (P = 0.07; Analysis 4.1).

Best-case and worst-case analyses

We subsequently conducted a best-case analysis (all dropouts assumed to be responders to treatment). This revealed a significant increase in the proportion of participants who achieved a 50% or greater seizure reduction in favour of the pregabalin group compared to active comparators (RR 1.60, 95% CI 1.17 to 2.19; Analysis 3.2). However, a worst-case analysis (all dropouts assumed to be responders to control) revealed a significant increase in the proportion of participants who achieved a 50% or greater seizure reduction in favour of the control group (RR 0.67, 95% CI 0.62 to 0.74; Analysis 3.3).

This was similarly the case when best-case and worst-case analysis was performed for each of the individual active comparators during subgroup analysis. Pregabalin appeared to be more efficacious than lamotrigine (RR 2.73, 95% CI 1.99 to 3.74); levetiracetam (RR 1.27, 95% CI 1.11 to 1.46); and gabapentin (RR 1.34, 95% CI 1.18 to 1.52) during best-case analysis (Analysis 4.2), but was shown to perform significantly worse than the active comparators during worst-case analysis (pregabalin versus lamotrigine: RR 0.68, 95% CI 0.52 to 0.88; pregabalin versus levetiracetam: RR 0.71, 95% CI 0.62 to 0.82; pregabalin versus gabapentin: RR 0.64, 95% CI 0.57 to 0.73; Analysis 4.3). The test for subgroup differences detected significantly different effect sizes between the subgroups during best-case scenario analysis (P < 0.001; Analysis 4.2), but not during worst-case analysis (P = 0.57; Analysis 4.3).

Seizure freedom

Only two included studies involving a total of 802 participants reported this outcome (Baulac 2010; Zaccara 2014). French 2016 reported no data regarding seizure freedom for this comparison. Participants randomised to pregabalin were significantly less likely to attain seizure freedom than participants randomised to an active comparator (RR 0.59, 95% CI 0.37 to 0.95; Analysis 3.4). When analysed separately during subgroup analysis according to active-comparator control group , the proportion of participants attaining seizure freedom was not significantly different for those receiving pregabalin compared to those receiving the active comparator lamotrigine (RR 1.39, 95% CI 0.40 to 4.83; Analysis 4.4).

However, the seizure freedom rate was significantly lower in participants receiving pregabalin than in those receiving levetiracetam (RR 0.50, 95% CI 0.30 to 0.85; Analysis 4.4). Despite this, the test for subgroup differences did not reveal any significant differences between the effect size estimated by the two active-comparator control groups (P = 0.14; Analysis 4.4).

Treatment withdrawal for any reason

Three included studies involving a total of 1286 randomised participants reported this outcome (Baulac 2010; French 2016; Zaccara 2014). We found no significant difference in the rate of treatment withdrawal for any reason between pregabalin and active comparators (RR 0.93, 95% CI 0.76 to 1.13; Analysis 3.5). Similarly, during subgroup analysis according to active comparator, pregabalin was not shown to have a significantly different rate of treatment withdrawal for any reason compared to any of the individual active comparators: lamotrigine (RR 1.07, 95% CI 0.75 to 1.52); levetiracetam (RR 1.03, 95% CI 0.71 to 1.49); and gabapentin (RR 0.78, 95% CI 0.57 to 1.07) (Analysis 4.5). Furthermore, the test for subgroup differences was not statistically significant (P = 0.36).

Treatment withdrawal due to adverse effects

Three included studies involving a total of 1286 randomised participants also reported treatment withdrawal due specifically to adverse effects experienced (Baulac 2010; French 2016; Zaccara 2014). Again, there was no significant difference in the proportion of participants who withdrew from treatment due to adverse effects between those randomised to pregabalin compared to an active comparator (RR 1.04, 95% CI 0.73 to 1.48; Analysis 3.6). According to the subgroup analysis, pregabalin did not demonstrate a significantly different treatment withdrawal rate due to adverse effects compared to any of the individual active comparators: lamotrigine (RR 0.89, 95% CI 0.53 to 1.48); levetiracetam (RR 1.29, 95% CI 0.66 to 2.54); or gabapentin (RR 1.07, 95% CI 0.54 to 2.11) (Analysis 4.6). Again, the test for subgroup difference was statistically insignificant (P = 0.69).

Adverse effects

Although the three included studies involving a total of 1286 participants documented and reported adverse effects, they did not report all of the adverse effects we were investigating in this review (Baulac 2010; French 2016; Zaccara 2014). Notably, for some adverse effects, data were only supplied by one study, namely for ataxia, fatigue, and nausea. Furthermore, we detected significant heterogeneity within the data sets for the following adverse effects: dizziness (I^2 = 65%), headache (I^2 = 64%), and weight gain (I^2 = 60%). We therefore used a random-effects model for the analysis of these adverse effects.

More participants randomised to pregabalin compared to those randomised to active comparators experienced dizziness (RR 1.64, 99% CI 0.85 to 3.16; Analysis 3.8) and weight gain (RR 2.87, 99% CI 0.94 to 8.75; Analysis 3.13). In contrast, significantly fewer participants randomised to pregabalin compared to those randomised to active comparators experienced nausea (RR 0.20, 99% CI 0.04 to 1.01; Analysis 3.11). Importantly, however, only one study, Zaccara 2014, provided data for this outcome, so it is difficult to draw any conclusions from this result. The occurrence of ataxia (RR 1.72, 99% CI 0.54 to 5.55; Analysis 3.7); fatigue (RR 1.72, 99% CI 0.77 to 3.83; Analysis 3.9); headache (RR 0.83, 99% CI 0.41 to 1.65; Analysis 3.10); and somnolence (RR 1.16, 99% CI 0.88 to 1.53; Analysis 3.12) did not differ significantly between pregabalin and active-comparator treatment groups.

Subgroup analysis according to active-comparator control group revealed that pregabalin was associated with a higher incidence rate for some of the adverse effects investigated compared to two of the active-comparator controls, lamotrigine and levetiracetam. Specifically, participants receiving pregabalin were more likely than those receiving the active comparator lamotrigine to experience the following adverse effects: dizziness (RR 2.94, 99% CI 1.32 to 6.52; Analysis 4.7); somnolence (RR 1.99, 99% CI 0.91 to 4.33; Analysis 4.10); and weight gain (RR 4.33, 99% CI 0.86 to 21.68; Analysis 4.11). Similarly, participants receiving pregabalin were more likely than those receiving the active comparator levetiracetam to experience dizziness (RR 1.44, 99% CI 0.89 to 2.34; Analysis 4.7) and weight gain (RR 4.82, 99% CI 1.39 to 16.74; Analysis 4.11). Interestingly, the incidence rate of adverse effects for pregabalin and gabapentin was not significantly different. Notably, however, pregabalin was associated with a significantly lower rate of headache compared to lamotrigine (RR 0.52, 99% CI 0.26 to 1.05; Analysis 4.8), as well as a significantly lower rate of nausea compared to levetiracetam (RR 0.20, 99% CI 0.04 to 1.01; Analysis 4.9), as alluded to earlier. Importantly, only one study provided data to each of the subgroups included in the subgroup analysis. Interestingly, the test for subgroup differences for each of the individual adverse effects indicated that there was not a significant subgroup effect dependent on active-comparator control (dizziness: P = 0.06; headache: P = 0.06; somnolence: P = 0.15; weight gain: P = 0.08).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Pregabalin compared to active comparator for drug-resistant focal epilepsy

Patient or population: drug-resistant focal epilepsy
Setting: outpaitent setting
Intervention: pregabalin
Comparison: active comparator (gabapentin, lamotrigine and levetiracetam)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with active comparator	Risk with Pregabalin				
50% or greater reduction in seizure frequency Follow-up: range 16 to 21 weeks	**Study population**		**RR 1.03** (0.85 to 1.25)	**1286** (3 RCTs)	⊕⊕◯◯ **LOW** [12]	According to ITT analysis, pregabalin does not appear to affect the proportion of people achieving a 50% or greater reduction in seizure frequency compared to other active comparators. We are, however, uncertain about this finding
	491 per 1,000	505 per 1,000 (417 to 613)				
50% or greater reduction in seizure frequency - best-case analysis Follow-up: range 16 to 21 weeks	**Study population**		**RR 1.60** (1.17 to 2.19)	**1286** (3 RCTs)	⊕◯◯◯ **VERY LOW** [13]	According to best-case analysis, pregabalin may increase the proportion of participants achieving a 50% or greater reduction in seizure frequency, however, we are very uncertain about this finding

	491 per 1,000	785 per 1,000 (574 to 1,000)				
50% or greater reduction in seizure frequency - worst-case analysis Follow-up: range 16 to 21 weeks	**Study population**		**RR 0.67** (0.62 to 0.74)	**1286** (3 RCTs)	⊕⊕⊕◯ **MODERATE** [1]	According to worst-case analysis, pregabalin may decrease the proportion of participants achieving a 50% or greater reduction in seizure frequency. We are moderately certain about this finding
	732 per 1,000	490 per 1,000 (454 to 542)				
Seizure freedom Follow-up: range 16 to 17 weeks	**Study population**		**RR 0.59** (0.37 to 0.95)	**802** (2 RCTs)	⊕◯◯◯ **VERY LOW** [14]	Pregabalin may reduce the number of people achieving seizure freedom, but we are very uncertain
	106 per 1,000	63 per 1,000 (39 to 101)				
Treatment withdrawal for any reason Follow-up: range 16 to 21 weeks	**Study population**		**RR 0.93** (0.76 to 1.13)	**1286** (3 RCTs)	⊕⊕◯◯ **LOW** [15]	Pregabalin does not appear to affect the number of participants withdrawing from treatment for any reason, however, we are uncertain
	241 per 1,000	224 per 1,000 (183 to 273)				
Treatment withdrawal for adverse events Follow-up: range 16 to 21 weeks	**Study population**		**RR 1.04** (0.73 to 1.48)	**1286** (3 RCTs)	⊕⊕◯◯ **LOW** [15]	Pregabalin does not appear to affect the number of participants withdrawing from treatment for adverse effects, but we are uncertain
	85 per 1,000	88 per 1,000 (62 to 125)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **ITT:** intention-to-treat; **RCT:** randomised controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once for risk of bias: one study did not confirm the method of randomisation; all studies failed to specify their method of allocation concealment; one study did not provide information on the method of blinding.
[2] Downgraded once for inconsistency: significant heterogeneity ($P < 0.10$) was detected within the data set.
[3] Downgraded twice for inconsistency: very significant heterogeneity ($P < 0.05$) was detected within the data set.
[4] Downgraded twice for imprecision: very low number of events (< 100) which did not suffice the optimal information size.
[5] Downgraded once for imprecision: very low number of events (< 400) which did not suffice the optimal information size.

DISCUSSION

Summary of main results

We identified six randomised placebo-controlled parallel trials (Arroyo 2004; Beydoun 2005; Elger 2005; French 2003; French 2014; Lee 2009), two active-comparator-controlled parallel trials (French 2016; Zaccara 2014), and one trial that included both an active-drug group and a placebo control group (Baulac 2010). All nine studies were industry-sponsored (Pfizer Ltd). Summary trial data were taken from the relevant publications, and individual patient data were not obtained. We attempted to retrieve the respective trial protocols but were unsuccessful. All studies appeared to be of good methodological quality overall. Most were randomised using suitable sequence generation methods, however none of the studies reported their methods for concealing allocation. All included studies were reported to be double-blind, but only six studies provided adequate details of how blinding was achieved and maintained. Few participants were lost to follow-up, however overall attrition rates were high for certain studies, especially those that included higher doses of pregabalin.

The included studies tested doses of pregabalin ranging from 50 mg/d to 600 mg/d, including both immediate- and controlled-release pregabalin. The results showed that pregabalin, when used as an add-on treatment, can reduce seizure frequency in individuals with drug-resistant focal epilepsy. In the main analysis, when all doses of pregabalin were pooled, the RR for a 50% or greater reduction in seizure frequency was 2.28 (95% CI 1.52 to 3.42), thus demonstrating that out of 100 people with refractory epilepsy, 42 are likely to have their seizures reduced when taking pregabalin, compared to 18 out of 100 people taking placebo. A summary of the main findings for the pooled analysis of all doses of pregabalin versus placebo can be found in the Summary of findings for the main comparison.

We detected significant heterogeneity within the data set for the outcome 50% or greater reduction in seizure frequency. Whilst all doses of immediate-release pregabalin above 50 mg/d were observed to significantly increase 50% responder rate (the proportion of participants achieving 50% or greater seizure reduction) during ITT analysis, only 600 mg/d pregabalin consistently showed a significant therapeutic effect compared to placebo during ITT, best-case, and worst-case analysis. This suggests that the effect noted at 600 mg/d is a true effect, whereas it is possible that the therapeutic effect reported at the lower doses of pregabalin could be as a result of treatment withdrawals and may, therefore, not be accurate of the true efficacy of pregabalin. Furthermore, the significant therapeutic effect (an increased proportion of participants achieving 50% or greater seizure reduction) observed during pooled analysis was not consistently detected. Specifically, it was not reported during worst-case analysis. This raises doubts about the validity of the pooled effect described, and suggests that the therapeutic effect may be dose-dependent and might only be observed at the higher doses of pregabalin, rather than being a feature of all doses of pregabalin, generally.

The alternative efficacy outcome, seizure freedom, again emphasised the therapeutic potential of pregabalin. Participants allocated to pregabalin were significantly more likely to attain seizure freedom. However, data for this outcome were only provided by four studies, which accounted for two subgroups, 600 mg/d pregabalin and titrated dose of 150 mg/d to 600 mg/d. Consequently, we have no data specifically for the lower doses of pregabalin that were included in the previous efficacy analyses for 50% or greater seizure reduction. This potentially explains the lack of heterogeneity present in the seizure freedom data set compared to that revealed for the primary efficacy outcome. Again, the subgroup analysis indicated a high risk ratio for 600 mg/d (RR 6.92, 95% CI 1.31 to 36.70), emphasising a large treatment effect at this dose. In this scenario, it is estimated that if 1000 people were to receive pregabalin, 41 would likely achieve complete cessation of seizures, compared to 6 people if 1000 people were to receive placebo. Notably, other than 50% or greater reduction in seizure frequency, none of the other outcomes for the comparison pregabalin versus placebo displayed significant heterogeneity.

Although both efficacy outcomes recognised 600 mg/d pregabalin as a highly efficacious dose, it is important to acknowledge that 600 mg/d pregabalin was also associated with tolerability issues. This was the only dose to display a significantly higher withdrawal rate for any reason compared to placebo during subgroup analysis, and was one of only three doses to display a significantly higher treatment withdrawal rate due specifically to adverse effects. Notably, 600 mg/d pregabalin demonstrated the greatest risk ratio (RR 3.78, 95% CI 2.47 to 5.81) for treatment withdrawal due to adverse effects, indicating a very large effect size. Accordingly, 600 mg/d pregabalin was repeatedly associated with an increased incidence rate for the majority of the adverse effects investigated, namely ataxia, dizziness, fatigue, somnolence, and weight gain.

When pregabalin was compared to other AEDs, rather than placebo, it did not show a significant therapeutic advantage with regard to 50% responder rate during pooled analysis. During subgroup analysis, however, pregabalin was associated with a significantly higher responder rate compared to lamotrigine, but not when compared to levetiracetam or gabapentin. Surprisingly, the pooled analysis for the alternative efficacy outcome showed that participants randomised to pregabalin were significantly less likely to attain seizure freedom. Although we did not detect statistical heterogeneity in the data set, the two studies (each contributing to one subgroup) indicated opposing effects. The study comparing pregabalin to lamotrigine estimated an insignificant therapeutic effect (RR 1.39, 95% CI 0.40 to 4.83), whereas the study comparing pregabalin to levetiracetam indicated a diminished seixure freedom rate for participants randomised to pregabalin (RR 0.50, 95% CI 0.30 to 0.85). We detected no significant differences in treatment withdrawal rate for any reason or due to adverse effects, specifically, during either pooled analysis or subgroup analysis.

The majority of the adverse effects investigated, namely ataxia, fatigue, headache, and somnolence, were no more prevalent in participants randomised to pregabalin than in those randomised to active control. Participants receiving pregabalin did appear to be much more likely to experience weight gain compared to participants receiving active control. Specifically, during subgroup analysis large effect sizes were recognised for pregabalin versus both lamotrigine and levetiracetam. Notably, however, subgroup analysis did not reveal any differences in incidence rates of individual adverse effects between pregabalin and gabapentin. This is not surprising given that pregabalin and gabapentin are structurally related. Both drugs are structural analogues of γ-aminobutyric acid (GABA) and both bind with high affinity to the α-2-δ subunit of voltage-gated calcium channels (Bockbrader 2010).

Overall completeness and applicability of evidence

Heterogeneity was a serious issue for the outcome 50% or greater reduction in seizure frequency for both comparisons, pregabalin versus placebo and pregabalin versus active comparator. As a result, the treatment effect described and estimated for each pooled analysis may only be minimally informative. For the comparison pregabalin versus placebo, a large range of doses, including a titrated dose regimen, were combined into a single meta-analysis. It is less clear what dose individual participants were actually receiving during a titrated dose regimen. Data for many of these participants could have likely been entered into specific dose subgroups (i.e. 150 mg/d, 300 mg/d, or 600 mg/d), if the stratified data to enable this had been available in the relevant trial publications. This further complicates the meta-analysis.

Additionally, the pooled analysis for the comparison pregabalin versus placebo included both immediate-release and controlled-release pregabalin, which have very different pharmacokinetics. This explains the difference in effect size calculated and the apparent heterogeneity between subgroups. For the other comparison, pregabalin versus active comparator, it is possible that the other AEDs equally have very different mechanisms of actions and potencies, therefore, it is difficult to combine them into a meta-analysis. As a result, for both comparisons, the pooled effect is unlikely to be representative of what will occur at every dose of pregabalin, or to reflect what the anticipated effect size of pregabalin is compared to another AED.

For this reason, the effect sizes reported from the subgroup analyses should be considered more informative than the effect size reported from the pooled analysis for the outcome 50% or greater reduction in seizure frequency. The variation in the effect reported thus limits our ability to sufficiently answer the question of whether pregabalin is more efficacious than placebo when used as an add-on treatment for drug-resistant focal epilepsy. The overall consensus appears to be that higher doses of immediate-release pregabalin, specifically 150 mg/d and greater, are more efficacious than placebo with regard to the 50% responder rate, however, pregabalin does not appear to offer a competitive advantage over other AEDs.

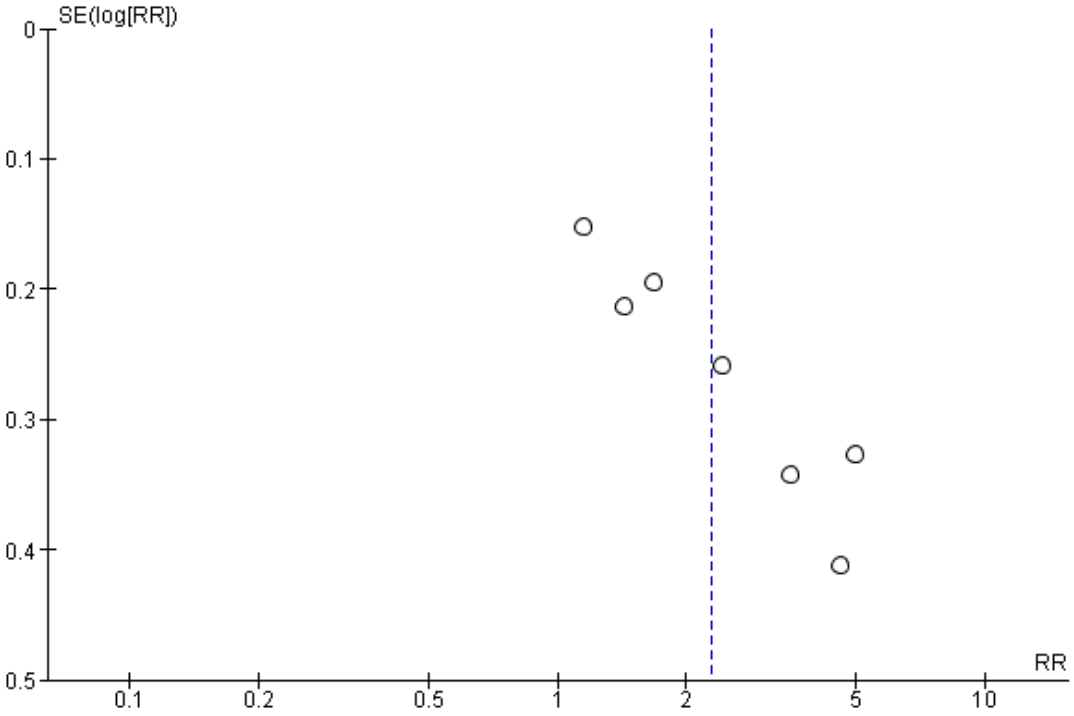
With further regard to subgroup analysis, it is important to recognise that for each active-comparator subgroup (i.e. pregabalin versus lamotrigine, pregabalin versus levetiracetam, and pregabalin versus gabapentin) for the comparison pregabalin versus active comparator, data were only supplied by one study, therefore were very limited. Similarly, for the comparison pregabalin versus placebo, data were only provided by one study for four of the subgroups: 50 mg/d, 300 mg/d, 165 mg/d controlled-release, and 330 mg/d controlled-release pregabalin. As a result, multiple subgroups may have been underpowered and therefore any conclusions reached must be interpreted cautiously.

An additional issue is that the data included in this review were mainly derived from adult study populations (patients aged 16 years and above). Only one study included a subset of younger patients (French 2003). Their inclusion criteria specified that people aged 12 and above were eligible for the study. As a result, teenagers were included in the study, however children remained excluded. Consequently, the findings reported in this review are only applicable to adults and are not informative of the effects of pregabalin in children.

Quality of the evidence

We assessed the certainty of the evidence for the primary and secondary outcomes for the comparison pregabalin versus placebo using the GRADE approach. The GRADE assessment is presented and summarised in Summary of findings for the main comparison. Overall, we rated the evidence as very low to moderate in certainty. We downgraded all outcomes once due to the unclear risk of bias across studies, mainly because all of the included studies failed to describe how allocation was concealed. Three of these studies also did not provide details about either the generation of the randomisation sequence or how blinding was effectively achieved. We further downgraded the certainty of evidence for all three analyses, ITT, best-case, and worst-case analysis, for the outcome 50% or greater reduction in seizure frequency due to the significant statistical heterogeneity detected. As explained above, statistical heterogeneity greatly affected our ability to answer our hypothesis and impacted the validity of our conclusion. Furthermore, the ITT and best-case analyses had to been downgraded once more because we strongly suspected publication bias, as demonstrated by the funnel plot generated (Figure 6). It is clear from the funnel plot that the larger studies are predicting a much smaller effect size than the smaller studies. Ideally, we would expect the data points to produce a funnel shape, with the risk ratios estimated by the individual studies evenly distributed either side of the estimated pooled effect. Instead, the data points plotted from the individual study effects look more similar to a linear regression, suggesting publication bias.

Figure 6. Funnel plot of comparison: 1 Pregabalin versus placebo, outcome: 1.1 50% or greater reduction in seizure frequency - intention-to-treat analysis.



Both outcomes concerning treatment withdrawal and the other efficacy outcome, seizure freedom, were not affected by either heterogeneity or suspected publication bias. Both seizure freedom and treatment withdrawal due to adverse effects were, however, rarer events compared to the outcome 50% or greater reduction in seizure frequency, and therefore, the number of events reported did not satisfy the optimal information size necessary for a robust meta-analysis. As a consequence, we downgraded the certainty of the evidence to low. Nevertheless, we were able to then upgrade the certainty of the evidence back to moderate for the outcomes seizure freedom and treatment withdrawal due to adverse effects because of the large effect size noted for each (RR > 2.00). We also upgraded the certainty of the evidence for the outcome 50% or greater reduction in seizure frequency for both the ITT and best-case analysis, under the same principle. We further upgraded the certainty of the evidence for the ITT analysis as a result of the dose-response relationship detected by the regression analysis. This produced an overall judgement of low certainty of evidence for the primary efficacy outcome.

The low certainty of evidence for the outcome 50% or greater reduction in seizure frequency means that we are uncertain whether the effect size estimated is accurate of the true efficacy of pregabalin. In contrast, the rating of moderate certainty of evidence for the other three outcomes, seizure freedom and treatment withdrawal for any reason and due to adverse effects, means that we are fairly certain that the effect size reported is an accurate estimate of the true effect size.

Potential biases in the review process

The approach to analysis for all of the included trials used the 'last observation carried forward' method. For participants failing to complete follow-up, seizure frequency data were extrapolated to the whole treatment period, whereas for participants with no seizure data during the treatment period, baseline data were extrapolated. Whilst this approach may help minimise bias due to

losses to follow-up (and is preferred by drug regulatory authorities), its use must be taken into consideration when interpreting the results of this systematic review, especially due to the high attrition rate noted in certain studies.

Importantly, the 'last observation carried forward' method assumes that a participant's response does not alter after treatment withdrawal. Specifically, the method does not consider any fluctuations in a participant's response or incorporate any imputation uncertainty. Consequently, the method likely predicts narrower confidence intervals than would normally be observed and, as a result, the effect size estimate is more likely to be statistically significant. Care must therefore be taken when considering the significance of the results presented.

Agreements and disagreements with other studies or reviews

We were able to identify two other systematic reviews that investigated pregabalin as an add-on therapy for drug-resistant focal epilepsy. Neither review included a meta-analysis, but both emphasised the therapeutic potential of pregabalin compared to placebo. Specifically, both reviews reported the outcome 50% or greater reduction in seizure frequency as evidence of pregabalin's antiepileptic effect. One review reported a responder rate (the proportion of participants achieving a 50% or greater reduction in seizure frequency) of 31% to 51% (Hamandi 2006), whilst the other reported a responder rate of 14% to 51% (Ryvlin 2008). Notably, both reviews collected data from studies included in this review, namely Arroyo 2004, Beydoun 2005, Elger 2005, and French 2003. Although both studies are in overall agreement with our current review, our current review provides novel information compared to the currently available reviews due to the meta-analysis conducted and the additional studies included.

The latter review by Ryvlin 2008 also discussed the long-term effectiveness of pregabalin after reviewing data collected from four open-label extension studies. Collectively, the data suggested that there was no loss of efficacy with the long-term use of pregabalin. For patients who entered long-term extension studies, 3.7% of patients remained seizure-free during the last year of the respective studies. Likewise, a long-term observational study that followed 105 patients (aged 16 to 81 years) over a one-year period revealed that 5.7% of patients reported that they had been seizure-free for the previous 4 weeks when contacted at 12 months, and 17.1% of patients reported that they had a 50% or greater reduction in seizure frequency over the 12-month period (Brandt 2009). Although all of the studies included in our review were of short duration (treatment periods varied from 12 to 14 weeks for all outcomes), these observations suggest that there should be no decline in efficacy over longer time periods. However, this hypothesis remains to be investigated and demonstrated by randomised controlled trials of longer durations.

Another review specifically compared the efficacy of pregabalin and gabapentin by conducting a meta-analysis and by performing an indirect comparison method (Delahoy 2010). The review reported that pregabalin was more efficacious than gabapentin. Specifically, at the highest doses of both drugs, 600 mg pregabalin versus 1800 mg gabapentin, Delahoy 2010 reported an odds ratio of 2.52 (95% CI 1.21 to 5.27) for the outcome 50% or greater reduction in seizure frequency, in favour of pregabalin.

The findings of the review by Delahoy 2010 are in contrast to those of the randomised controlled trial conducted by French 2016 that we included in this review, and which directly compared pregabalin and gabapentin. French 2016 demonstrated no significant difference in efficacy between the two drugs for the outcome 50% or greater reduction in seizure frequency (RR 0.96, 95% CI 0.82 to 1.12). Furthermore, French 2016 reported that participants randomised to either of the two treatment groups (median dose 450 mg/d pregabalin and median dose 1500 mg/d gabapentin) experienced comparable percentage reductions in seizure frequency (58.7% and 57.4% median per cent reduction in seizure frequency, respectively).

Notably, the review by Delahoy 2010 has the advantage of including data from multiple sources and, as a result, includes a larger sample size. This should, in theory, provide a more accurate estimate of the effect of the two drugs. The study by French 2016, however, has the benefit of being a direct comparison between the two drugs which provides more convincing evidence than an indirect comparison. Specifically, the randomised controlled trial would be expected to have a more even distribution of patient characteristics at baseline and would have used a more standardised approach to compare the two drugs than the review. More randomised controlled trials directly comparing the two drugs would be necessary to appropriately compare their effectiveness and to enable conclusive findings to be reached.

With regard to the adverse event profile of pregabalin, the two reviews discussed earlier, Hamandi 2006 and Ryvlin 2008, both reported somnolence, dizziness, ataxia, and fatigue as the most commonly reported adverse effects, in keeping with the findings in this review. Ryvlin 2008 also specified that most adverse effects were mild to moderate in severity. Additionally, Ryvlin 2008 observed a dose-response relationship in the reporting of adverse effects. Weight gain was also a common adverse effect, with Ryvlin 2008 reporting that 24% of participants experienced weight gain whilst receiving pregabalin. In actuality, weight gain was the most reported adverse effect for patients who participated in the observational study by Brandt 2009, followed by tiredness and cognitive disturbances.

In another meta-analysis specifically focused on investigating the adverse event profile of pregabalin (Zaccara 2012), it was shown that vestibulo-cerebellar and central nervous system adverse events, including ataxia and somnolence, were more commonly reported when pregabalin was used in those with focal epilepsy than when used for its other clinical indications, including anxiety disorders and pain disorders. It was suggested that these adverse events may

not necessarily be attributable to pregabalin, but could instead be associated with patient's concomitant AEDs or could actually be a symptom of focal epilepsy itself.

In contrast, Ryvlin 2008 appeared to consider the adverse effects reported by people with epilepsy to be a true representation of the adverse event profile of pregabalin. Ryvlin 2008 suggested that tolerability amongst people with epilepsy can instead be improved by individualising the dose of pregabalin, namely by using a titration and dose adjustment protocol, to limit adverse effects. Specifically, Ryvlin 2008 recognised that 24% of participants withdrew from trials during the first week of treatment in studies that utilised a fixed dose of pregabalin. This was compared to a withdrawal rate of only 3% in studies that used an individualised flexible-dose regimen. In studies of short duration, adverse effects are the most common reason for treatment withdrawal. Although this trend was not recognised in our current review, this outcome, that is treatment withdrawal within a given time period, may be of interest for future review updates as it would be informative for clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

In the short term (12 to 14 weeks), 150 mg/d to 600 mg/d of immediate-release pregabalin, given in a twice- or three-times-daily regimen, can significantly reduce seizure frequency in adults with treatment-resistant focal epilepsy. A dose of 600 mg/d immediate-release pregabalin can also significantly increase seizure freedom rates amongst people with treatment-resistant focal epilepsy, but is associated with a significantly higher treatment withdrawal rate compared to placebo. Pregabalin was significantly associated with the following adverse effects: ataxia, dizziness, fatigue, somnolence, and weight gain. The evidence suggests that there is no significant difference in efficacy and harms between pregabalin and some of the other currently available antiepileptic drugs, namely gabapentin, levetiracetam, and lamotrigine. There are currently no data regarding the longer-term effectiveness of pregabalin versus placebo or the effects of pregabalin in children.

Implications for research

To improve clinical decisions, further clinical trials are required in adults and children with drug-refractory focal epilepsy. These trials should:

1. compare the efficacy and tolerability of pregabalin with other adjunctive treatments;

2. be of long-term duration (at least 12 months);

3. assess seizure freedom rates, quality of life, and health economic outcomes;

4. establish cost-effectiveness and compare it with that of other antiepileptic drugs.

Further data regarding pregnancy outcomes are also needed, which will require the recruitment of women taking pregabalin to ongoing pregnancy registries.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arroyo 2004

Methods	Randomised, double-blind, PBO-controlled, parallel, multicentre (45 in Europe, Australia, and South Africa) trial 3 treatment arms: 1 PBO, 2 PGB. Participants randomised in blocks of 6, each allocated unique ID number. All participants received 2 capsules 3 times a day, but 2 capsule sizes were used (no further information available) Duration of baseline period: 8 weeks. 12-week treatment period included 4- to 8-day titration period
Participants	Adults aged 17 to 73 years (mean 37 years), 50.5% male, all with drug-resistant focal epilepsy. Participants were on 1 to 4 baseline AEDs 344 patients screened, 288 participants randomised: 97 participants to PBO (mean baseline 28-day seizure frequency: 23.5); 99 participants to 50 mg/d PGB 3 times a day (mean baseline 28-day seizure frequency: 26.2); and 92 participants to 200 mg/d PGB 3 times a day (mean baseline 28-day seizure frequency: 19.3)
Interventions	Group 1: Placebo Group 2: PGB 50 mg 3 times a day (150 mg/d; 4-day titration phase) Group 3: PGB 200 mg 3 times a day (600 mg/d; 8-day titration phase)
Outcomes	Primary outcome: reduction in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, seizure freedom, change in seizure frequency, adverse effects
Notes	Study used capsules of 2 sizes, containing 25 mg PGB or PBO (size 1# = small capsules) and 100 mg PGB or PBO (size 4# = large capsules). It is stated that participants received 2 capsules 3 times a day. 1 patient excluded from ITT in PBO arm, as failed to take study drugs Study was sponsored by Pfizer Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random computer-generated code used stratified by centre using block size of 6
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Medication presented in identical capsules.

Arroyo 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results, however there was no protocol available to check a priori outcomes
Other bias	Unclear risk	As an EEG was not required to confirm the above, some of the 18 patients included who were stated as having "generalised seizures", rather than secondary generalised, may have had primary generalised epilepsy

Baulac 2010

Methods	Randomised, double-blind, PBO- and active-drug-controlled, parallel, multicentre (97 in Europe, Canada, and Australia) trial 3 treatment arms: 1 PBO, 1 PGB, and 1 LTG. Participants randomised to 1 of 3 treatment arms (no further information available) Duration of baseline period: 6 weeks. 17-week treatment period with 2 phases in addition to a titration phase (1 week of titration for PGB and 5 weeks of titration for LTG). (Phase I: 11 weeks treatment including 1 week titration for PGB and 5 weeks titration for LTG; Phase II: 6 weeks treatment)
Participants	Adults aged 16 to 82 years (mean 39.4 years), 48.5% male, all with treatment-resistant focal epilepsy confirmed by history and recent EEG. Participants were on 1 to 3 baseline AEDs 546 patients screened, 434 participants randomised: 141 participants to PBO (mean baseline 28-day seizure frequency: 16.38); 152 participants to 150 mg to 300 mg PGB twice daily (mean baseline 28-day seizure frequency: 21.32); and 141 participants to 150 mg to 300 mg LTG twice daily (mean baseline 28-day seizure frequency: 21.80)
Interventions	Group 1: Placebo Group 2: PGB 150 mg to 300 mg twice daily (300 to 600 mg/d; 1-week titration phase) Group 3: LTG 150 mg to 300 mg twice daily (300 to 600 mg/d; 5-week titration phase)
Outcomes	Primary outcome: change in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, seizure freedom, adverse effects
Notes	One participant randomised to the PBO group failed to take > 1 dose of medication and was therefore excluded from ITT analysis. No information provided on methods of randomisation, concealment, or blinding Study was sponsored by Pfizer Inc.
Risk of bias	

Baulac 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of method of randomisation.
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Same number of capsules administered per study day per group. No further details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis employed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results, however there was no protocol available to check a priori outcomes
Other bias	Low risk	None detected.

Beydoun 2005

Methods	Randomised, double-blind, PBO-controlled, parallel, multicentre (43 in USA and Canada) trial 3 treatment arms: 1 PBO, 2 PGB. Participants randomised in blocks of 6, each allocated unique ID number. All participants received 3-times-daily regimen of blinded capsules (no further information available) Duration of baseline period: 8 weeks. 12-week treatment period with 1-week titration period
Participants	Adults aged 17 to 82 years (mean 39.1 years), 50.2% male, all with treatment-resistant focal epilepsy confirmed by history and recent EEG. Participants were on 1 to 4 baseline AEDs 378 patients screened, 313 participants randomised: 98 participants to PBO (mean baseline 28-day seizure frequency: 25.1); 104 participants to 300 mg PGB twice daily (mean baseline 28-day seizure frequency: 21.5); and 111 participants to 200 mg PGB 3 times a day (mean baseline 28-day seizure frequency: 21.3)
Interventions	Group 1: Placebo Group 2: 300 mg PGB twice daily (600 mg/d; 1-week titration phase) Group 3: 200 mg PGB 3 times a day (600 mg/d; 1-week titration phase)
Outcomes	Primary outcome: reduction in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, median percentage change in seizure frequency

Beydoun 2005 (*Continued*)

Notes	1 participant randomised to the 300 mg twice-daily group failed to take tablets and was therefore excluded from ITT analysis. Blinding was broken with 1 participant in the PBO arm when she became pregnant Study was sponsored by Pfizer Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised in blocks of 6 and allocated unique ID number
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	All participants received identical capsules.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis employed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results, however there was no protocol available to check a priori outcomes
Other bias	Low risk	None detected.

Elger 2005

Methods	Randomised, double-blind, PBO-controlled, parallel, multicentre (53 in Europe and Canada) trial 3 treatment arms: 1 PBO, 2 PGB. Participants randomised in blocks of 5, each allocated unique ID number. All regimens mimicked control group using identical capsules (no further information available) Duration of baseline period: 6 weeks. 12-week treatment period
Participants	Adults aged 18 to 78 years (mean 40.5 years), 49.9% male, all with treatment-resistant focal epilepsy confirmed by personal and family history as well as recent EEG Participants were on 1 to 5 baseline AEDs. 400 patients screened, 341 participants randomised: 73 participants to PBO (median baseline 28-day seizure frequency: 8.7) ; 137 participants to 300 mg PGB twice daily fixed (median baseline 28-day seizure frequency: 10); and 131 participants to PGB flexible dosing (median baseline 28-day seizure frequency: 9.33)
Interventions	Group 1: Placebo Group 2: 300 mg PGB twice-daily fixed dose (600 mg/d)

Elger 2005 (*Continued*)

	Group 3: 75 mg to 300 mg PGB twice-daily flexible titration at physician's discretion (150 to 600 mg/d)
Outcomes	Primary outcome: reduction in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, median percentage change in seizure frequency and reduction of GTCS in those completing the study, adverse effects
Notes	In PGB titration and PBO groups, patients were included with seizure frequency of over 120 a day. Documenting seizures at this frequency is difficult and may be unreliable. Medium length of follow-up not reported Study was sponsored by Pfizer Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomised using a 1:2:2 ratio and block sizes of 5
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study medication presented in identical capsules.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis employed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results, however there was no protocol available to check a priori outcomes
Other bias	Low risk	None detected.

French 2003

Methods	Randomised, double-blind, PBO-controlled, parallel, multicentre (71 in the USA and 5 in Canada) trial 5 treatment arms: 1 PBO, 4 PGB. Participants randomised in blocks of 5, each allocated unique ID number. Capsule sizes varied (no further information available) Duration of baseline period: 8 weeks. There was no titration; 12-week treatment period
Participants	Patients 12 years and above (range 12 to 75 years, mean 38.4 years), 48.1% male, all with treatment-resistant focal epilepsy. Participants were on 1 to 4 baseline AEDs 586 patients screened, 455 participants randomised: 100 participants to PBO (mean baseline seizure frequency: 22.3); 88 participants to 50 mg PGB (mean baseline seizure frequency: 27.4); 88 participants to 150 mg PGB (mean baseline 28-day seizure fre-

	quency: 23.1); 90 participants to 300 mg PGB (mean baseline 28-day seizure frequency: 19.1); and 89 participants to 600 mg PGB (mean baseline 28-day seizure frequency: 18.6)
Interventions	Group 1: Placebo Group 2: 50 mg/d PGB (twice daily) Group 3: 150 mg/d PGB (twice daily) Group 4: 300 mg/d PGB (twice daily) Group 5: 600 mg/d PGB (twice daily)
Outcomes	Primary outcome: reduction in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, pairwise comparisons with PBO, adverse effects
Notes	Blinding broken for interim analysis (data obtained were only known to committee who were not involved in further running of study) and for 1 participant who developed visual field defect. 2 participants were excluded from ITT analysis (1 withdrew consent, 1 had AEDs changed during baseline period). Seizure frequency and responder rate were calculated from data collected from seizure diaries and mean calculated over a 4-week period Study was sponsored by Pfizer Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used a computer-generated randomised schedule using block sizes of 5
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study medication presented in identical capsules.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis employed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results, however there was no protocol available to check a priori outcomes
Other bias	Unclear risk	Possibility of the inclusion of individuals with primary generalised epilepsy

French 2014

Methods	Randomised, double-blind, placebo-controlled, parallel, multicentre (18 countries) trial assessing the efficacy and tolerability of controlled-release PGB 3 treatment arms: 1 PBO, 2 PGB Randomised 1:1:1 to PGB 165 mg/d or PGB 330 mg/d or placebo using a computer-generated randomisation system Duration of baseline period: 8 weeks. 14-week double-blind treatment period with 2-week double-blind dose escalation (titration phase); 1-week taper
Participants	Adults aged 18 to 75 years, 47.7% male, all with focal epilepsy. Participants were on 1 to 3 baseline AEDs 400 patients screened, 325 participants randomised: 110 participants to placebo (mean baseline 28-day seizure frequency: 17.8); 101 participants to PGB 165 mg (mean baseline 28-day seizure frequency: 13.0); 114 participants to PGB 330 mg (mean baseline 28-day seizure frequency: 17.0)
Interventions	Group 1: Placebo Group 2: PGB 165 mg/d controlled release Group 3: PGB 330 mg/d controlled release
Outcomes	Primary outcomes: reduction in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, adverse effects
Notes	Clinical trials: NCT01262677 Study sponsored by Pfizer Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation system.
Allocation concealment (selection bias)	Unclear risk	Allocate participants to each of the 3 treatment groups in a 1:1:1 manner. No further details provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details regarding blinding of participants and personnel provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT efficacy analysis performed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results There was no protocol available to check a priori outcomes.

French 2014 (*Continued*)

Other bias	Low risk	None detected.

French 2016

Methods	Randomised, double-blind, parallel, multicentre (56 centres in Eastern and Western Europe, Asia, South and Central America) trial assessing the efficacy and safety of PGB and GPN 2 treatment arms: PGB and GPN Randomised 1:1 to PGB 242 or GPN 242 using a computer-generated randomisation system Duration of baseline period: 6 weeks. 21-week double-blind phase (9 weeks of double-blind dose escalation and 12 weeks of double-blind maintenance phase)
Participants	Adults aged 18 to 80 years, 53.3% male, all with drug-resistant focal epilepsy (inadequately controlled with ≥ 2 to < 5 prior AEDs). All participants were on 1 to 2 baseline AEDs 561 patients screened, 484 participants randomised: 242 participants to PGB 450 mg median dose (mean baseline 28-day seizure frequency: 14.1); 242 participants to GPN 1500 mg median dose (mean baseline 28-day seizure frequency: 13.1)
Interventions	Group 1: PGB (150, 300, 450, and 600 mg/d during the 9-week dose escalation phase) Group 2: GPN (300, 600, 1200, 1500, and 1800 mg/d during the 9-week dose escalation phase)
Outcomes	Primary outcome: reduction in seizure frequency (50% or more reduction of seizures and 75% or more reduction of seizures) Secondary outcomes: seizure freedom for maintenance phase (last 28-day seizure-free rates), adverse effects
Notes	Clinical trials: NCT00537940 Study was sponsored by Pfizer Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation system.
Allocation concealment (selection bias)	Unclear risk	Allocate participants to each of the 2 treatment groups in a 1:1 manner. No further details provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Medication presented in identical tablets. Identical analysis of results

French 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT efficacy analysis performed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results There was no protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

Lee 2009

Methods	Randomised, double-blind, PBO-controlled, parallel, multicentre (9 in Korea) trial 2 treatment arms: 1 PBO, 1 PGB Participants randomised to 1 of 2 treatment arms (no further information available) Duration of baseline period: 6 weeks. 12-week treatment period (no further details provided)
Participants	Participants 18 years and above (mean 34.2 years), 48.3% male, all with treatment-resistant focal epilepsy. Participants were on 1 to 3 baseline AEDs 209 patients screened, 178 participants randomised: 59 participants to PBO (mean baseline 28-day seizure frequency: 13.2) and 119 participants to 150 mg to 600 mg PGB (mean baseline 28-day seizure frequency 13.2)
Interventions	Group 1: Placebo Group 2: 75 mg to 300 mg PGB twice daily (150 to 600 mg/d)
Outcomes	Primary outcome: change in seizure frequency (response ratio) Secondary outcomes: responder rate, seizure freedom, anxiety/depression, sleep, quality of life, adverse effects
Notes	All randomised participants included in ITT analysis. No information provided on methods of randomisation, concealment, or blinding Study was sponsored by Pfizer Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants randomised using 2:1 ratio. No further information given
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.

Lee 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis employed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results, however there was no protocol available to check a priori outcomes
Other bias	Low risk	None detected.

Zaccara 2014

Methods	Randomised, double-blind, flexible-dose, parallel, multicentre (71 centres in Western and Eastern Europe, South and Central America, Asia) trial 2 treatment arms: PGB and LEV Randomised 1:1 to either PGB or LEV using a computer-generated randomisation system Duration of baseline phase: 6 weeks; 4-week double-blind dose escalation (titration phase); 12-week double-blind maintenance phase
Participants	Adults aged 18 to 65 years (mean 37 years), all with drug-resistant focal epilepsy (inadequately controlled with at least 2, but no more than 5 AEDs). Participants were on 1 to 2 baseline AEDs 633 patients were screened, 509 participants were randomised: 254 participants to PGB (mean baseline 28-day seizure frequency: 16.2) and 255 participants to LEV (mean baseline 28-day seizure frequency: 13.9)
Interventions	Group 1: PGB twice daily (150, 300, 450, and 600 mg/d) Group 2: LEV twice daily (1000, 2000, and 3000 mg/d)
Outcomes	Primary outcome: reduction in seizure frequency (50% or more reduction of seizures) Secondary outcomes: seizure freedom for maintenance phase, adverse effects
Notes	Clinical trials: NCT00537238 Study was sponsored by Pfizer Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation system.
Allocation concealment (selection bias)	Unclear risk	Allocate participants to each of the 2 treatment group in a 1:1 ratio. No further details provided

Zaccara 2014 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Details are not provided, however it is likely that blinding of participants and personnel was maintained due to the methods used Medication presented in identical tablets. Identical analysis of results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT efficacy analysis performed.
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods section of paper were reported in the results No protocol available to check a priori outcomes.
Other bias	Low risk	None detected.

AED: antiepileptic drug; EEG: electroencephalogram; GPN: gabapentin; GTCS: generalised tonic-clonic seizures; ITT: intention-to-treat; LEV: levetiracetam; LTG: lamotrigine; PBO: placebo; PGB: pregabalin.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Taghdiri 2015	This previously ongoing study, Bali 2012, was published and excluded from the current review as the participant sample (including participants with a diagnosis of primary generalised epilepsy) did not meet our inclusion criteria

Characteristics of studies awaiting assessment *[ordered by study ID]*

Russi 2006

Methods	Randomised observational controlled study. 4 treatment arms: 1 LEV fast-rate, 2 LEV slow-rate, 3 PGB fast-rate, 4 PGB slow-rate dosage
Participants	128 patients with refractory focal epilepsy (32 in each treatment arm)
Interventions	Group 1: starting dose of 1000 mg twice daily LEV fast rate with weekly increments of 500 mg Group 2: starting dose of 500 mg twice daily LEV slow rate with weekly increments of 250 mg Group 3: starting dose of 300 mg twice daily PGB fast rate with weekly increments of 150 mg Group 4: starting dose of 150 mg twice daily PGB slow rate with weekly increments of 75 mg
Outcomes	Rate of withdrawals and continuation to maximum dose Incidence of adverse effects

Russi 2006 (*Continued*)

Notes	Study reported in abstract form only. Further details of study are unavailable

Tata 2007

Methods	Randomised cross-over trial consisting of 2 treatment arms: 1 PGB, 2 LEV. Participants randomised to groups using 1:1 ratio. Study was open-label. Long-term study duration of minimum 6 months
Participants	28 adults aged 19 to 62 years, 54% male. Participants currently taking different AED without maintaining good seizure control, stabilised to therapeutic association of valproate and lamotrigine
Interventions	Group 1: starting dose of 150 mg to target dose of 600 mg PGB Group 2: starting dose of 1000 mg to target dose of 3000 mg LEV
Outcomes	Seizure freedom Seizure reduction Withdrawals Adverse effects
Notes	Study reported in abstract only. Further details of study are unavailable

AED: antiepileptic drug; LEV: levetiracetam; PGB: pregabalin

DATA AND ANALYSES

Comparison 1. Pregabalin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency - ITT	7	2193	Risk Ratio (IV, Random, 95% CI)	2.28 [1.52, 3.42]
2 50% or greater reduction in seizure frequency - best-case analysis	7	2193	Risk Ratio (IV, Random, 95% CI)	3.57 [2.17, 5.86]
3 50% or greater reduction in seizure frequency - worst-case analysis	7	2193	Risk Ratio (IV, Random, 95% CI)	1.15 [0.92, 1.43]
4 Seizure freedom	4	1125	Risk Ratio (M-H, Fixed, 95% CI)	3.94 [1.50, 10.37]
5 Treatment withdrawal for any reason	7	2193	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.11, 1.65]
6 Treatment withdrawal due to adverse effects	7	2193	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [1.88, 3.74]
7 Ataxia	6	1868	Risk Ratio (M-H, Fixed, 99% CI)	3.90 [2.05, 7.42]
8 Dizziness	7	2193	Risk Ratio (M-H, Fixed, 99% CI)	3.15 [2.23, 4.44]
9 Fatigue	7	2193	Risk Ratio (M-H, Fixed, 99% CI)	1.34 [0.93, 1.94]
10 Headache	5	1555	Risk Ratio (M-H, Fixed, 99% CI)	0.63 [0.42, 0.93]
11 Nausea	4	1267	Risk Ratio (M-H, Fixed, 99% CI)	1.20 [0.56, 2.58]
12 Somnolence	7	2193	Risk Ratio (M-H, Fixed, 99% CI)	2.15 [1.50, 3.09]
13 Weight gain	7	2193	Risk Ratio (M-H, Fixed, 99% CI)	5.02 [2.49, 10.10]

Comparison 2. Pregabalin versus placebo - subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency - ITT	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.52, 2.12]
1.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.36, 3.63]
1.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [1.65, 4.94]
1.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [3.34, 6.39]
1.5 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.35, 2.30]
1.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.72, 1.48]
1.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.91, 1.75]

2 50% or greater reduction in seizure frequency - best-case analysis	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.03, 3.40]
2.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	3.18 [2.00, 5.06]
2.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	4.37 [2.61, 7.29]
2.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 95% CI)	7.72 [5.64, 10.57]
2.5 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [2.24, 3.65]
2.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.92, 1.79]
2.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.21, 2.20]
3 50% or greater reduction in seizure frequency - worst-case analysis	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.30, 0.99]
3.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.38]
3.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.98, 2.23]
3.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.42, 2.09]
3.5 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.76, 1.12]
3.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.09]
3.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.28]
4 Seizure freedom	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 600 mg/d	2	523	Risk Ratio (M-H, Fixed, 95% CI)	6.92 [1.31, 36.70]
4.2 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.83, 6.89]
5 Treatment withdrawal for any reason	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.40, 1.89]
5.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.41, 1.28]
5.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.85, 3.10]
5.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [1.42, 2.40]
5.5 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.62]
5.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.36, 1.86]
5.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.59, 2.46]
6 Treatment withdrawal due to adverse effects	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.43, 4.31]
6.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.45, 2.32]
6.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [1.07, 7.78]
6.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 95% CI)	3.78 [2.47, 5.81]
6.5 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.30, 3.95]

6.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.22, 5.27]
6.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.70, 9.45]
7 Ataxia	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
7.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	1.14 [0.14, 9.00]
7.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	1.98 [0.56, 7.01]
7.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	3.33 [0.62, 17.81]
7.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 99% CI)	4.49 [2.25, 8.95]
7.5 Titrated dose pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 99% CI)	4.46 [1.28, 15.48]
8 Dizziness	7		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
8.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	1.01 [0.31, 3.33]
8.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	2.04 [0.99, 4.22]
8.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	3.46 [1.39, 8.62]
8.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 99% CI)	3.72 [2.42, 5.69]
8.5 Titrated dose of pregabalin (150 to 600 mg/d pregabalin)	3	675	Risk Ratio (M-H, Fixed, 99% CI)	3.08 [1.80, 5.28]
8.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 99% CI)	5.99 [0.85, 42.02]
8.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 99% CI)	5.31 [0.76, 37.30]
9 Fatigue	7		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
9.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	0.71 [0.17, 2.94]
9.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	1.09 [0.50, 2.39]
9.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	1.53 [0.49, 4.76]
9.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 99% CI)	1.50 [0.89, 2.52]
9.5 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 99% CI)	1.15 [0.69, 1.91]
9.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 99% CI)	3.27 [0.17, 62.62]
9.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 99% CI)	5.79 [0.37, 91.55]
10 Headache	5		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
10.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	0.52 [0.16, 1.77]
10.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	0.53 [0.24, 1.17]
10.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	0.43 [0.12, 1.57]
10.4 600 mg/d pregabalin	3	588	Risk Ratio (M-H, Fixed, 99% CI)	0.63 [0.33, 1.19]
10.5 Titrated dose of pregabalin (150 to 600 mg/d)	3	675	Risk Ratio (M-H, Fixed, 99% CI)	0.74 [0.44, 1.25]
11 Nausea	4		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
11.1 150 mg/d pregabalin	1	196	Risk Ratio (M-H, Fixed, 99% CI)	1.31 [0.34, 5.00]
11.2 600 mg/d pregabalin	3	712	Risk Ratio (M-H, Fixed, 99% CI)	1.18 [0.51, 2.75]
11.3 Titrated dose of pregabalin (150 to 600 mg/d)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	1.11 [0.12, 10.05]
11.4 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 99% CI)	3.27 [0.17, 62.62]
11.5 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 99% CI)	0.96 [0.03, 36.26]
12 Somnolence	7		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
12.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	0.93 [0.31, 2.78]
12.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	1.26 [0.58, 2.74]

12.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	1.62 [0.63, 4.12]
12.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 99% CI)	2.57 [1.64, 4.03]
12.5 Titrated dose of pregabalin	3	675	Risk Ratio (M-H, Fixed, 99% CI)	2.35 [1.31, 4.19]
12.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 99% CI)	2.18 [0.24, 19.70]
12.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 99% CI)	2.89 [0.36, 23.05]
13 Weight gain	7		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
13.1 50 mg/d pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	3.40 [0.05, 224.69]
13.2 150 mg/d pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	3.85 [0.64, 23.35]
13.3 300 mg/d pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	14.43 [0.34, 620.87]
13.4 600 mg/d pregabalin	4	901	Risk Ratio (M-H, Fixed, 99% CI)	5.88 [2.52, 13.73]
13.5 Titrated dose of pregabalin (150 to 600 mg/d pregabalin)	3	675	Risk Ratio (M-H, Fixed, 99% CI)	3.64 [1.49, 8.87]
13.6 165 mg/d pregabalin (controlled release)	1	211	Risk Ratio (M-H, Fixed, 99% CI)	3.26 [0.05, 215.86]
13.7 330 mg/d pregabalin (controlled release)	1	224	Risk Ratio (M-H, Fixed, 99% CI)	14.48 [0.34, 613.54]

Comparison 3. Pregabalin versus active comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency	3	1286	Risk Ratio (IV, Random, 95% CI)	1.03 [0.85, 1.25]
2 50% or greater reduction in seizure frequency - best-case analysis	3	1286	Risk Ratio (IV, Random, 95% CI)	1.60 [1.17, 2.19]
3 50% or greater reduction in seizure frequency - worst-case analysis	3	1286	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.62, 0.74]
4 Seizure freedom	2	802	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.95]
5 Treatment withdrawal for any reason	3	1286	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.76, 1.13]
6 Treatment withdrawal due to adverse effects	3	1286	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.73, 1.48]
7 Ataxia	1	293	Risk Ratio (M-H, Fixed, 99% CI)	1.72 [0.54, 5.55]
8 Dizziness	3	1286	Risk Ratio (IV, Random, 99% CI)	1.64 [0.85, 3.16]
9 Fatigue	1	293	Risk Ratio (M-H, Fixed, 99% CI)	1.72 [0.77, 3.83]
10 Headache	3	1286	Risk Ratio (IV, Random, 99% CI)	0.83 [0.41, 1.65]
11 Nausea	1	509	Risk Ratio (M-H, Fixed, 99% CI)	0.20 [0.04, 1.01]
12 Somnolence	3	1286	Risk Ratio (M-H, Fixed, 99% CI)	1.16 [0.88, 1.53]
13 Weight gain	3	1286	Risk Ratio (IV, Random, 99% CI)	2.87 [0.94, 8.75]

Comparison 4. Pregabalin versus active comparator - subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.03, 2.12]
1.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.11]
1.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.12]
2 50% or greater reduction in seizure frequency - best-case analysis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.99, 3.74]
2.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.11, 1.46]
2.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.18, 1.52]
3 50% or greater reduction in seizure frequency - worst-case analysis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.52, 0.88]
3.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.62, 0.82]
3.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.57, 0.73]
4 Seizure freedom	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.40, 4.83]
4.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.85]
5 Treatment withdrawal for any reason	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.75, 1.52]
5.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.49]
5.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.57, 1.07]
6 Treatment withdrawal due to adverse effects	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.53, 1.48]
6.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.66, 2.54]

6.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.54, 2.11]
7 Dizziness	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
7.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 99% CI)	2.94 [1.32, 6.52]
7.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 99% CI)	1.44 [0.89, 2.34]
7.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 99% CI)	1.1 [0.51, 2.35]
8 Headache	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
8.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 99% CI)	0.52 [0.26, 1.05]
8.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 99% CI)	1.25 [0.64, 2.45]
8.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 99% CI)	0.85 [0.38, 1.92]
9 Nausea	1		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
9.1 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 99% CI)	0.20 [0.04, 1.01]
10 Somnolence	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
10.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 99% CI)	1.99 [0.91, 4.33]
10.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 99% CI)	1.09 [0.77, 1.54]
10.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 99% CI)	1.0 [0.56, 1.78]
11 Weight gain	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
11.1 Pregabalin versus lamotrigine	1	293	Risk Ratio (M-H, Fixed, 99% CI)	4.33 [0.86, 21.68]
11.2 Pregabalin versus levetiracetam	1	509	Risk Ratio (M-H, Fixed, 99% CI)	4.82 [1.39, 16.74]
11.3 Pregabalin versus gabapentin	1	484	Risk Ratio (M-H, Fixed, 99% CI)	1.46 [0.60, 3.58]

Analysis 1.1. Comparison 1 Pregabalin versus placebo, Outcome 1 50% or greater reduction in seizure frequency - ITT.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 1 50% or greater reduction in seizure frequency - ITT

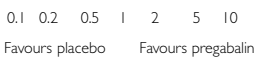
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Arroyo 2004	54/191	6/97		10.9 %	4.57 [2.04, 10.25]
Baulac 2010	54/152	30/141		16.2 %	1.67 [1.14, 2.45]
Beydoun 2005	98/215	9/98		12.9 %	4.96 [2.62, 9.41]
Elger 2005	103/268	8/73		12.5 %	3.51 [1.79, 6.86]
French 2003	121/355	14/100		14.6 %	2.43 [1.47, 4.04]
French 2014	88/215	39/110		17.2 %	1.15 [0.86, 1.56]
Lee 2009	55/119	19/59		15.8 %	1.44 [0.94, 2.18]
Total (95% CI)	**1515**	**678**		**100.0 %**	**2.28 [1.52, 3.42]**

Total events: 573 (Pregabalin), 125 (Placebo)

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 29.69$, df = 6 (P = 0.00004); $I^2 = 80\%$

Test for overall effect: Z = 3.96 (P = 0.000076)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Pregabalin versus placebo, Outcome 2 50% or greater reduction in seizure frequency - best-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 2 50% or greater reduction in seizure frequency - best-case analysis

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Arroyo 2004	88/191	6/97		11.9 %	7.45 [3.38, 16.41]
Baulac 2010	100/152	30/141		15.8 %	3.09 [2.21, 4.33]
Beydoun 2005	157/215	9/98		13.4 %	7.95 [4.24, 14.90]
Elger 2005	191/268	8/73		13.1 %	6.50 [3.37, 12.56]
French 2003	185/355	14/100		14.5 %	3.72 [2.27, 6.11]
French 2014	112/215	39/110		16.1 %	1.47 [1.11, 1.95]
Lee 2009	65/119	19/59		15.3 %	1.70 [1.13, 2.54]
Total (95% CI)	**1515**	**678**		**100.0 %**	**3.57 [2.17, 5.86]**

Total events: 898 (Pregabalin), 125 (Placebo)

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 49.38$, df = 6 (P<0.00001); $I^2 = 88\%$

Test for overall effect: Z = 5.02 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Pregabalin versus placebo, Outcome 3 50% or greater reduction in seizure frequency - worst-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 3 50% or greater reduction in seizure frequency - worst-case analysis

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Arroyo 2004	54/191	19/97		11.2 %	1.44 [0.91, 2.29]
Baulac 2010	54/152	65/141		16.4 %	0.77 [0.58, 1.02]
Beydoun 2005	98/215	26/98		13.9 %	1.72 [1.20, 2.46]
Elger 2005	103/268	25/73		14.2 %	1.12 [0.79, 1.60]
French 2003	121/355	27/100		14.2 %	1.26 [0.89, 1.80]
French 2014	88/215	51/110		17.1 %	0.88 [0.68, 1.14]
Lee 2009	55/119	21/59		13.0 %	1.30 [0.88, 1.93]
Total (95% CI)	**1515**	**678**		**100.0 %**	**1.15 [0.92, 1.43]**

Total events: 573 (Pregabalin), 234 (Placebo)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 17.51$, df = 6 (P = 0.01); $I^2 = 66\%$

Test for overall effect: Z = 1.21 (P = 0.23)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Pregabalin versus placebo, Outcome 4 Seizure freedom.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 4 Seizure freedom

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Beydoun 2005	17/215	0/98		11.5 %	16.04 [0.97, 264.07]
Baulac 2010	6/152	1/141		17.4 %	5.57 [0.68, 45.66]
Elger 2005	8/268	1/73		26.3 %	2.18 [0.28, 17.14]
Lee 2009	5/119	2/59		44.8 %	1.24 [0.25, 6.20]
Total (95% CI)	**754**	**371**		**100.0 %**	**3.94 [1.50, 10.37]**

Total events: 36 (Pregabalin), 4 (Placebo)

Heterogeneity: $Chi^2 = 3.37$, df = 3 (P = 0.34); $I^2 = 11\%$

Test for overall effect: Z = 2.78 (P = 0.0055)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Pregabalin versus placebo, Outcome 5 Treatment withdrawal for any reason.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 5 Treatment withdrawal for any reason

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Arroyo 2004	34/191	13/97		12.1 %	1.33 [0.74, 2.40]
Baulac 2010	46/152	35/141		25.5 %	1.22 [0.84, 1.77]
Beydoun 2005	59/215	17/98		16.4 %	1.58 [0.98, 2.57]
Elger 2005	88/268	17/73		18.8 %	1.41 [0.90, 2.21]
French 2003	64/355	13/100		14.2 %	1.39 [0.80, 2.41]
French 2014	24/215	12/110		11.1 %	1.02 [0.53, 1.97]
Lee 2009	10/119	2/59		1.9 %	2.48 [0.56, 10.95]
Total (95% CI)	**1515**	**678**		**100.0 %**	**1.35 [1.11, 1.65]**

Total events: 325 (Pregabalin), 109 (Placebo)

Heterogeneity: Chi^2 = 2.08, df = 6 (P = 0.91); I^2 =0.0%

Test for overall effect: Z = 2.97 (P = 0.0030)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Pregabalin versus placebo, Outcome 6 Treatment withdrawal due to adverse effects.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 6 Treatment withdrawal due to adverse effects

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Arroyo 2004	27/191	6/97		16.5 %	2.29 [0.98, 5.35]
Baulac 2010	24/152	10/141		21.5 %	2.23 [1.10, 4.49]
Beydoun 2005	48/215	7/98		19.9 %	3.13 [1.47, 6.66]
Elger 2005	61/268	5/73		16.3 %	3.32 [1.39, 7.97]
French 2003	41/355	5/100		16.2 %	2.31 [0.94, 5.69]
French 2014	11/215	3/110		8.2 %	1.88 [0.53, 6.59]
Lee 2009	7/119	0/59		1.4 %	7.50 [0.44, 129.13]
Total (95% CI)	**1515**	**678**		**100.0 %**	**2.65 [1.88, 3.74]**

Total events: 219 (Pregabalin), 36 (Placebo)

Heterogeneity: $Chi^2 = 1.69$, df = 6 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 5.55 (P < 0.00001)

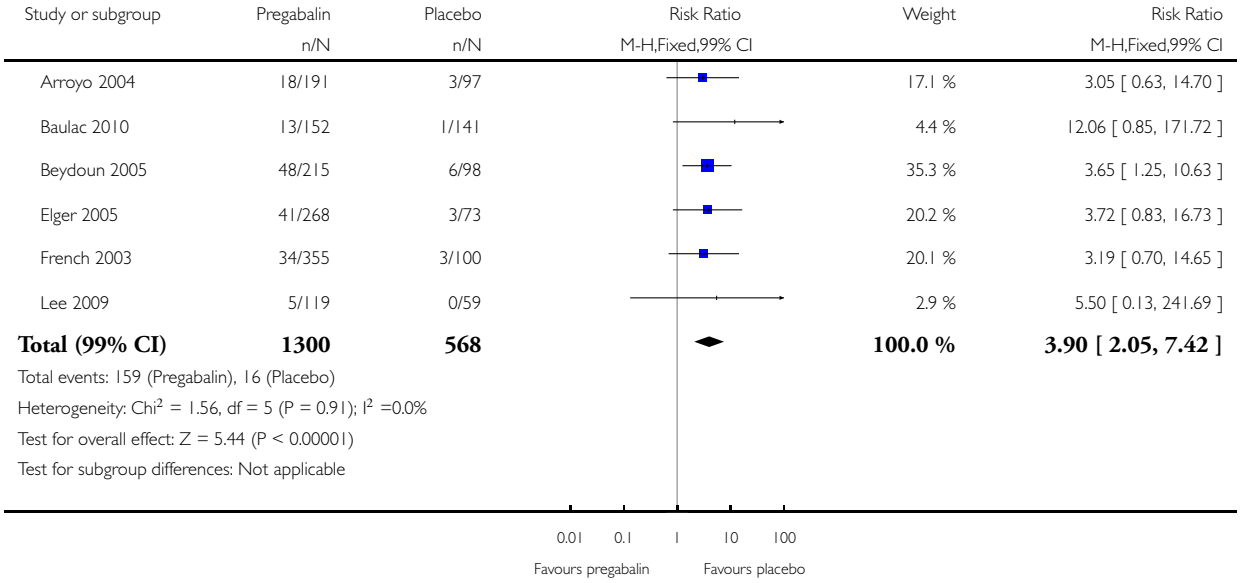
Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Pregabalin versus placebo, Outcome 7 Ataxia.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 7 Ataxia



Analysis 1.8. Comparison 1 Pregabalin versus placebo, Outcome 8 Dizziness.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 8 Dizziness

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Arroyo 2004	43/191	8/97		13.7 %	2.73 [1.07, 6.98]
Baulac 2010	38/152	13/141		17.4 %	2.71 [1.25, 5.86]
Beydoun 2005	88/215	14/98		24.8 %	2.87 [1.46, 5.61]
Elger 2005	91/268	6/73		12.2 %	4.13 [1.47, 11.58]
French 2003	88/355	9/100		18.1 %	2.75 [1.17, 6.46]
French 2014	22/215	2/110		3.4 %	5.63 [0.86, 36.82]
Lee 2009	46/119	6/59		10.4 %	3.80 [1.34, 10.76]
Total (99% CI)	**1515**	**678**		**100.0 %**	**3.15 [2.23, 4.44]**

Total events: 416 (Pregabalin), 58 (Placebo)

Heterogeneity: $Chi^2 = 2.01$, $df = 6$ ($P = 0.92$); $I^2 = 0.0\%$

Test for overall effect: $Z = 8.59$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Pregabalin versus placebo, Outcome 9 Fatigue.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 9 Fatigue

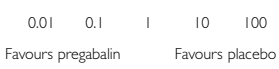
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Arroyo 2004	26/191	11/97		18.3 %	1.20 [0.50, 2.86]
Baulac 2010	26/152	24/141		31.2 %	1.00 [0.52, 1.95]
Beydoun 2005	27/215	5/98		8.6 %	2.46 [0.73, 8.29]
Elger 2005	47/268	10/73		19.7 %	1.28 [0.56, 2.94]
French 2003	32/355	8/100		15.6 %	1.13 [0.42, 2.99]
French 2014	9/215	1/110		1.7 %	4.60 [0.31, 68.40]
Lee 2009	11/119	3/59		5.0 %	1.82 [0.36, 9.25]
Total (99% CI)	**1515**	**678**		**100.0 %**	**1.34 [0.93, 1.94]**

Total events: 178 (Pregabalin), 62 (Placebo)

Heterogeneity: $Chi^2 = 4.87$, df = 6 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 2.04 (P = 0.041)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 Pregabalin versus placebo, Outcome 10 Headache.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 10 Headache

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Arroyo 2004	17/191	15/97		21.8 %	0.58 [0.25, 1.35]
Baulac 2010	18/152	28/141		31.9 %	0.60 [0.29, 1.22]
Elger 2005	28/268	8/73		13.8 %	0.95 [0.36, 2.53]
French 2003	24/355	13/100		22.3 %	0.52 [0.23, 1.20]
Lee 2009	9/119	7/59		10.3 %	0.64 [0.19, 2.18]
Total (99% CI)	**1085**	**470**		**100.0 %**	**0.63 [0.42, 0.93]**

Total events: 96 (Pregabalin), 71 (Placebo)

Heterogeneity: $Chi^2 = 1.66$, df = 4 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 3.05 (P = 0.0023)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Pregabalin versus placebo, Outcome 11 Nausea.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 11 Nausea

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Arroyo 2004	13/191	6/97		38.5 %	1.10 [0.32, 3.76]
Beydoun 2005	11/215	6/98		39.9 %	0.84 [0.23, 2.97]
Elger 2005	15/268	2/73		15.2 %	2.04 [0.30, 13.78]
French 2014	4/215	1/110		6.4 %	2.05 [0.12, 35.88]
Total (99% CI)	**889**	**378**		**100.0 %**	**1.20 [0.56, 2.58]**

Total events: 43 (Pregabalin), 15 (Placebo)

Heterogeneity: $Chi^2 = 1.32$, df = 3 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Pregabalin versus placebo, Outcome 12 Somnolence.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 12 Somnolence

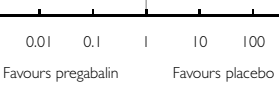
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Arroyo 2004	33/191	7/97		12.4 %	2.39 [0.86, 6.66]
Baulac 2010	30/152	15/141		20.9 %	1.86 [0.87, 3.95]
Beydoun 2005	57/215	12/98		22.1 %	2.17 [1.02, 4.61]
Elger 2005	49/268	6/73		12.6 %	2.22 [0.77, 6.43]
French 2003	65/355	11/100		23.0 %	1.66 [0.76, 3.66]
French 2014	10/215	2/110		3.5 %	2.56 [0.36, 18.38]
Lee 2009	26/119	3/59		5.4 %	4.30 [0.94, 19.57]
Total (99% CI)	**1515**	**678**		**100.0 %**	**2.15 [1.50, 3.09]**

Total events: 270 (Pregabalin), 56 (Placebo)

Heterogeneity: $Chi^2 = 2.47$, df = 6 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 5.45 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Pregabalin versus placebo, Outcome 13 Weight gain.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 1 Pregabalin versus placebo

Outcome: 13 Weight gain

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Arroyo 2004	20/191	2/97		13.6 %	5.08 [0.77, 33.39]
Baulac 2010	14/152	2/141		10.7 %	6.49 [0.95, 44.46]
Beydoun 2005	38/215	2/98		14.1 %	8.66 [1.37, 54.65]
Elger 2005	53/268	5/73		40.4 %	2.89 [0.91, 9.17]
French 2003	20/355	0/100		4.0 %	11.63 [0.29, 459.09]
French 2014	8/215	0/110		3.4 %	8.74 [0.21, 366.41]
Lee 2009	14/119	2/59		13.8 %	3.47 [0.52, 23.28]
Total (99% CI)	**1515**	**678**		**100.0 %**	**5.02 [2.49, 10.10]**

Total events: 167 (Pregabalin), 13 (Placebo)

Heterogeneity: $Chi^2 = 2.96$, df = 6 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 5.94 (P < 0.00001)

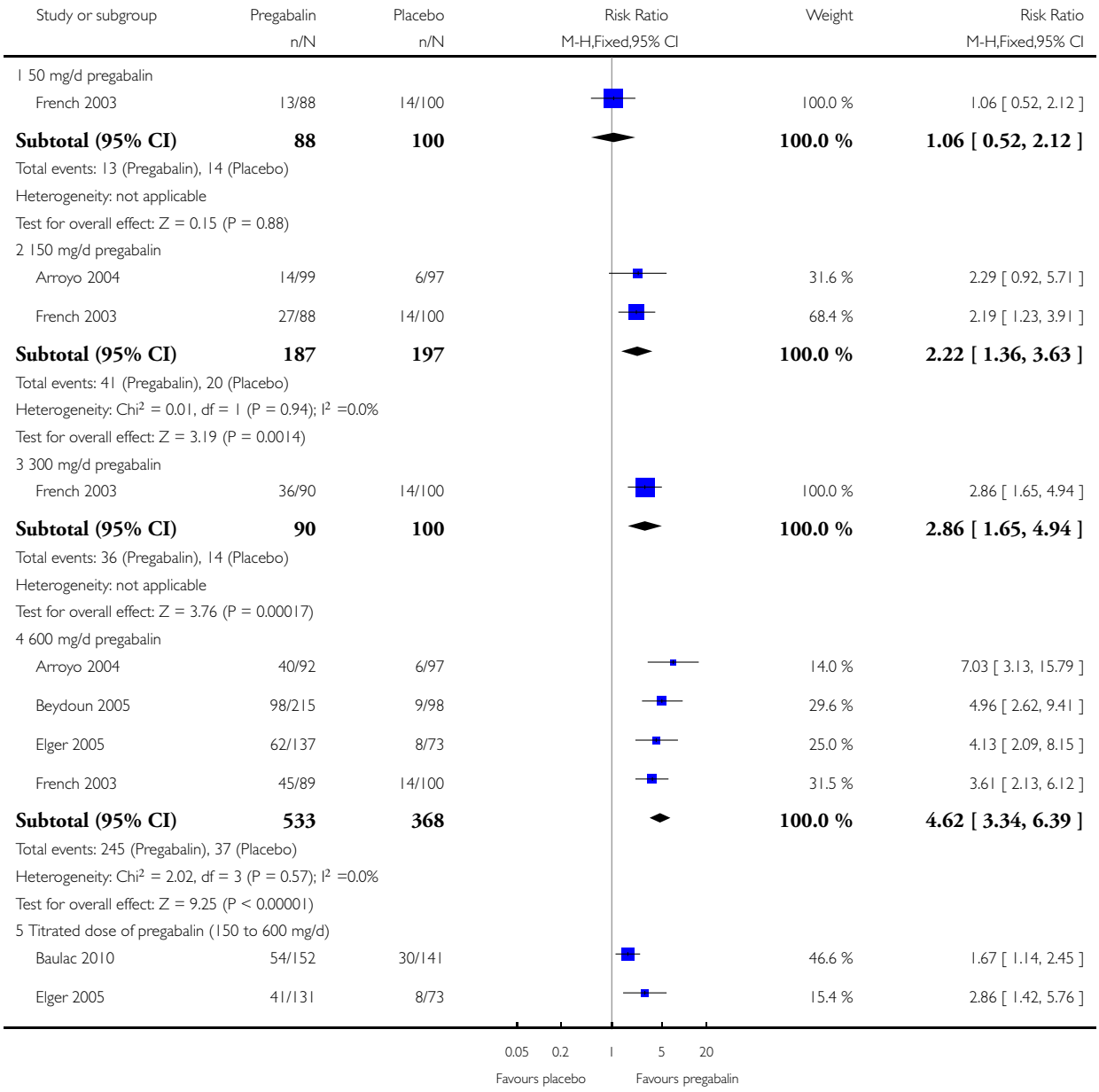
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 1 50% or greater reduction in seizure frequency - ITT.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 1 50% or greater reduction in seizure frequency - ITT



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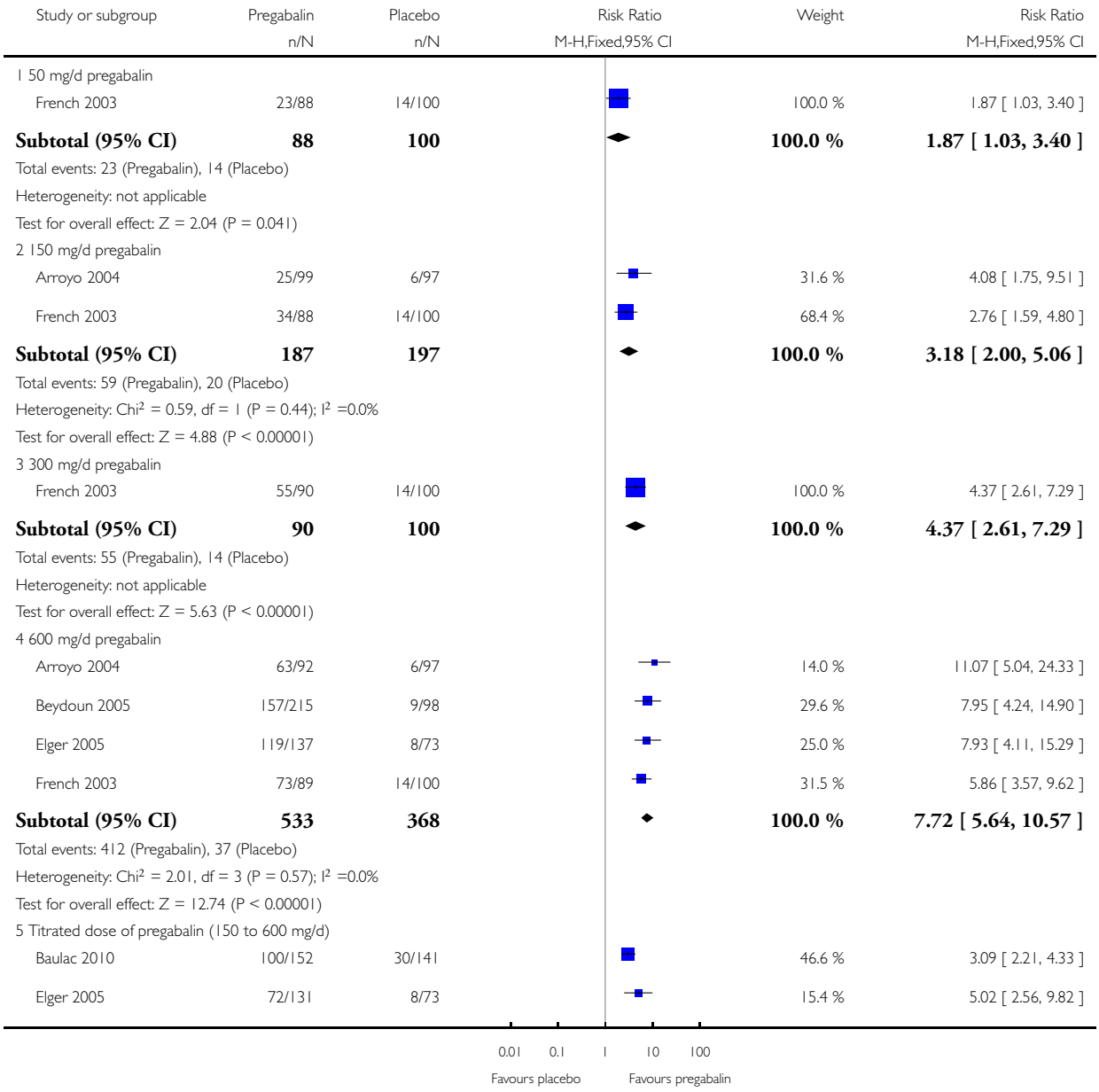
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lee 2009	55/119	19/59		38.0 %	1.44 [0.94, 2.18]
Subtotal (95% CI)	**402**	**273**		**100.0 %**	**1.76 [1.35, 2.30]**
Total events: 150 (Pregabalin), 57 (Placebo)					
Heterogeneity: Chi^2 = 2.83, df = 2 (P = 0.24); I^2 =29%					
Test for overall effect: Z = 4.21 (P = 0.000025)					
6 165 mg/d pregabalin (controlled release)					
French 2014	37/101	39/110		100.0 %	1.03 [0.72, 1.48]
Subtotal (95% CI)	**101**	**110**		**100.0 %**	**1.03 [0.72, 1.48]**
Total events: 37 (Pregabalin), 39 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.86)					
7 330 mg/d pregabalin (controlled release)					
French 2014	51/114	39/110		100.0 %	1.26 [0.91, 1.75]
Subtotal (95% CI)	**114**	**110**		**100.0 %**	**1.26 [0.91, 1.75]**
Total events: 51 (Pregabalin), 39 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					

Analysis 2.2. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 2 50% or greater reduction in seizure frequency - best-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 2 50% or greater reduction in seizure frequency - best-case analysis



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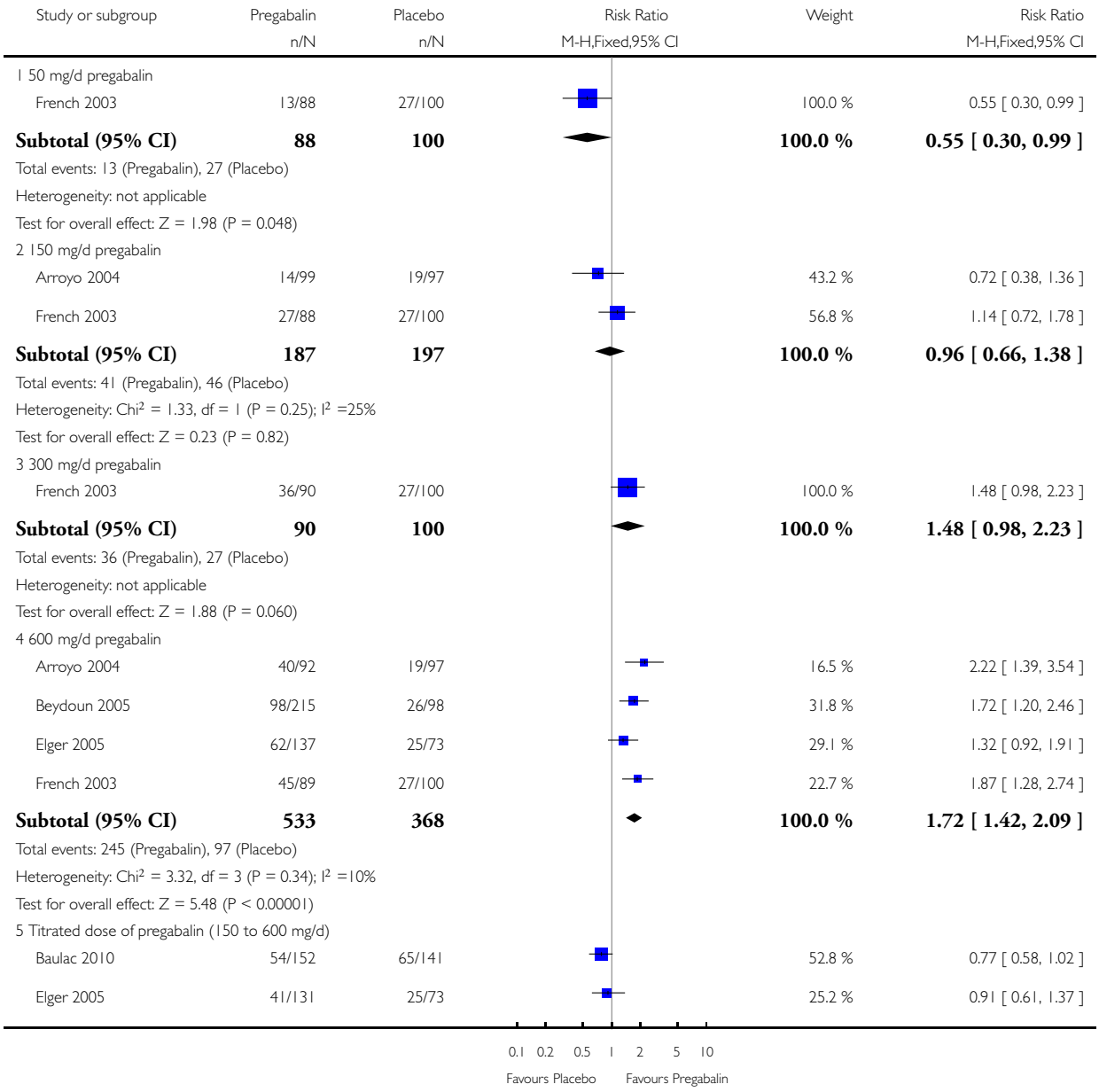
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lee 2009	65/119	19/59		38.0 %	1.70 [1.13, 2.54]
Subtotal (95% CI)	**402**	**273**		**100.0 %**	**2.86 [2.24, 3.65]**
Total events: 237 (Pregabalin), 57 (Placebo)					
Heterogeneity: Chi^2 = 9.28, df = 2 (P = 0.01); I^2 =78%					
Test for overall effect: Z = 8.43 (P < 0.00001)					
6 165 mg/d pregabalin (controlled release)					
French 2014	46/101	39/110		100.0 %	1.28 [0.92, 1.79]
Subtotal (95% CI)	**101**	**110**		**100.0 %**	**1.28 [0.92, 1.79]**
Total events: 46 (Pregabalin), 39 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					
7 330 mg/d pregabalin (controlled release)					
French 2014	66/114	39/110		100.0 %	1.63 [1.21, 2.20]
Subtotal (95% CI)	**114**	**110**		**100.0 %**	**1.63 [1.21, 2.20]**
Total events: 66 (Pregabalin), 39 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.24 (P = 0.0012)					

Analysis 2.3. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 3 50% or greater reduction in seizure frequency - worst-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 3 50% or greater reduction in seizure frequency - worst-case analysis



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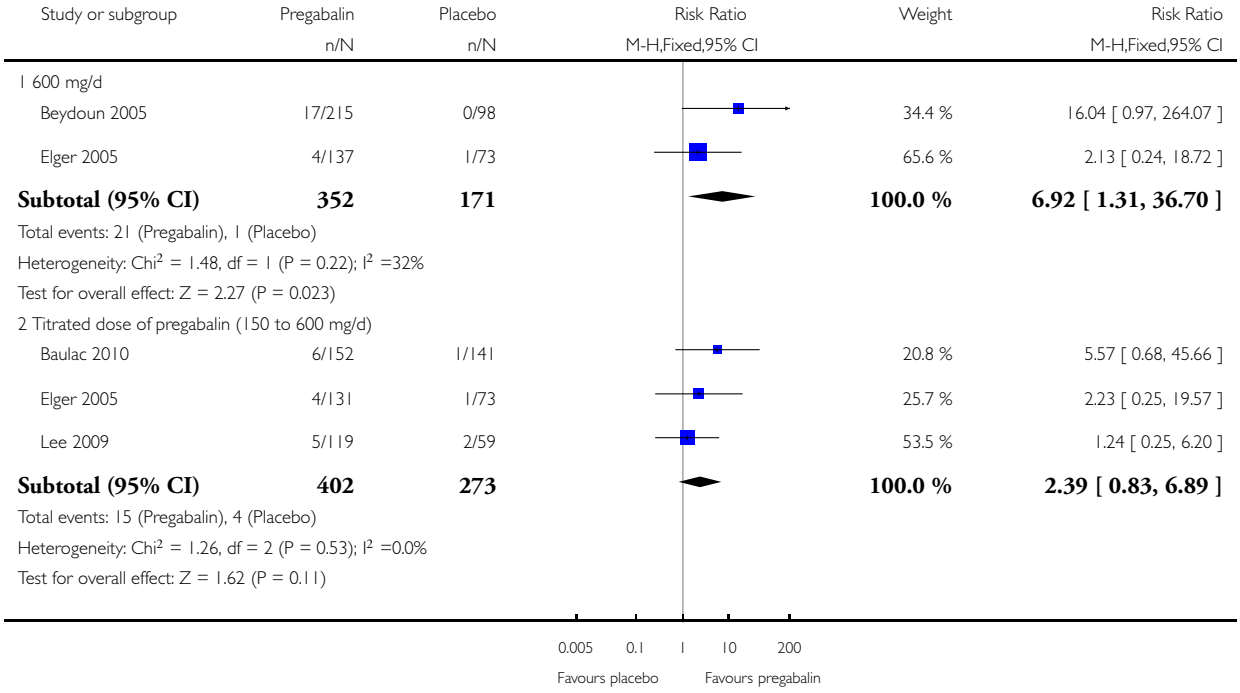
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lee 2009	55/119	21/59		22.0 %	1.30 [0.88, 1.93]
Subtotal (95% CI)	**402**	**273**		**100.0 %**	**0.92 [0.76, 1.12]**
Total events: 150 (Pregabalin), 111 (Placebo)					
Heterogeneity: Chi^2 = 4.49, df = 2 (P = 0.11); I^2 =55%					
Test for overall effect: Z = 0.80 (P = 0.43)					
6 165 mg/d pregabalin (controlled release)					
French 2014	37/101	51/110		100.0 %	0.79 [0.57, 1.09]
Subtotal (95% CI)	**101**	**110**		**100.0 %**	**0.79 [0.57, 1.09]**
Total events: 37 (Pregabalin), 51 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
7 330 mg/d pregabalin (controlled release)					
French 2014	51/114	51/110		100.0 %	0.96 [0.72, 1.28]
Subtotal (95% CI)	**114**	**110**		**100.0 %**	**0.96 [0.72, 1.28]**
Total events: 51 (Pregabalin), 51 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24 (P = 0.81)					

Analysis 2.4. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 4 Seizure freedom.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 4 Seizure freedom

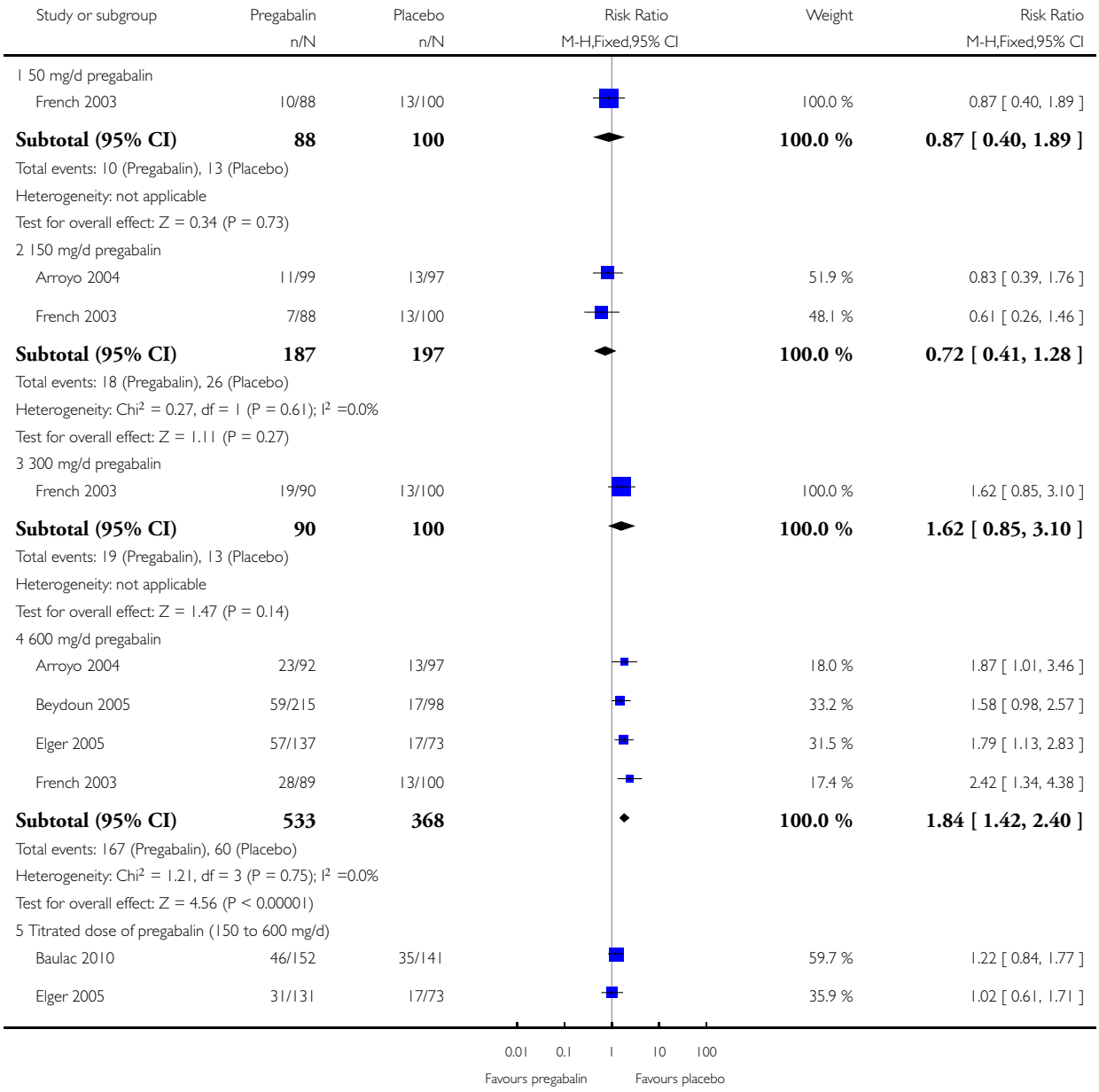


Analysis 2.5. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 5 Treatment withdrawal for any reason.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 5 Treatment withdrawal for any reason



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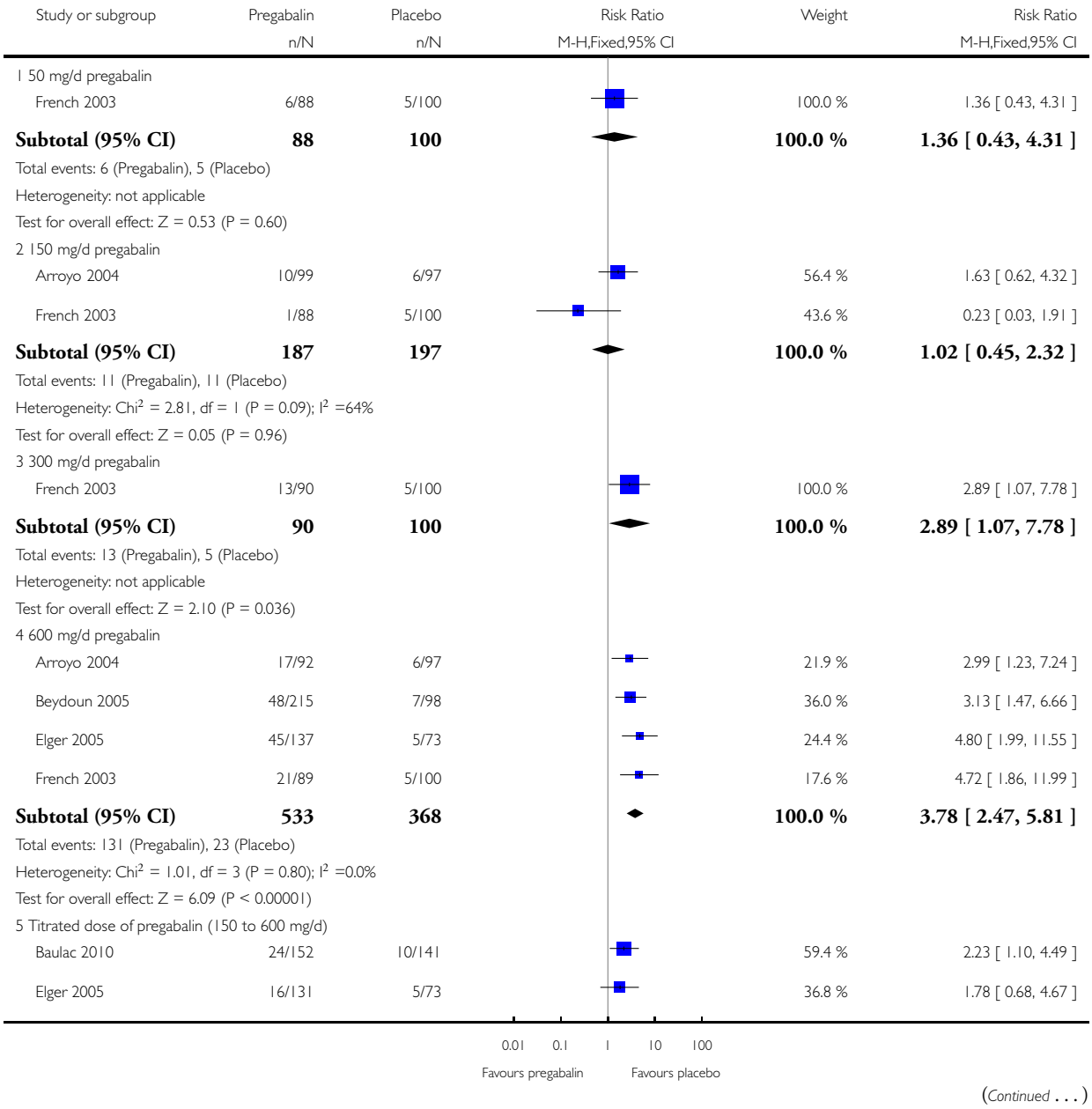
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lee 2009	10/119	2/59		4.4 %	2.48 [0.56, 10.95]
Subtotal (95% CI)	**402**	**273**		**100.0 %**	**1.20 [0.89, 1.62]**
Total events: 87 (Pregabalin), 54 (Placebo)					
Heterogeneity: Chi^2 = 1.32, df = 2 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 1.21 (P = 0.23)					
6 165 mg/d pregabalin (controlled release)					
French 2014	9/101	12/110		100.0 %	0.82 [0.36, 1.86]
Subtotal (95% CI)	**101**	**110**		**100.0 %**	**0.82 [0.36, 1.86]**
Total events: 9 (Pregabalin), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
7 330 mg/d pregabalin (controlled release)					
French 2014	15/114	12/110		100.0 %	1.21 [0.59, 2.46]
Subtotal (95% CI)	**114**	**110**		**100.0 %**	**1.21 [0.59, 2.46]**
Total events: 15 (Pregabalin), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.61)					

Analysis 2.6. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 6 Treatment withdrawal due to adverse effects.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 6 Treatment withdrawal due to adverse effects



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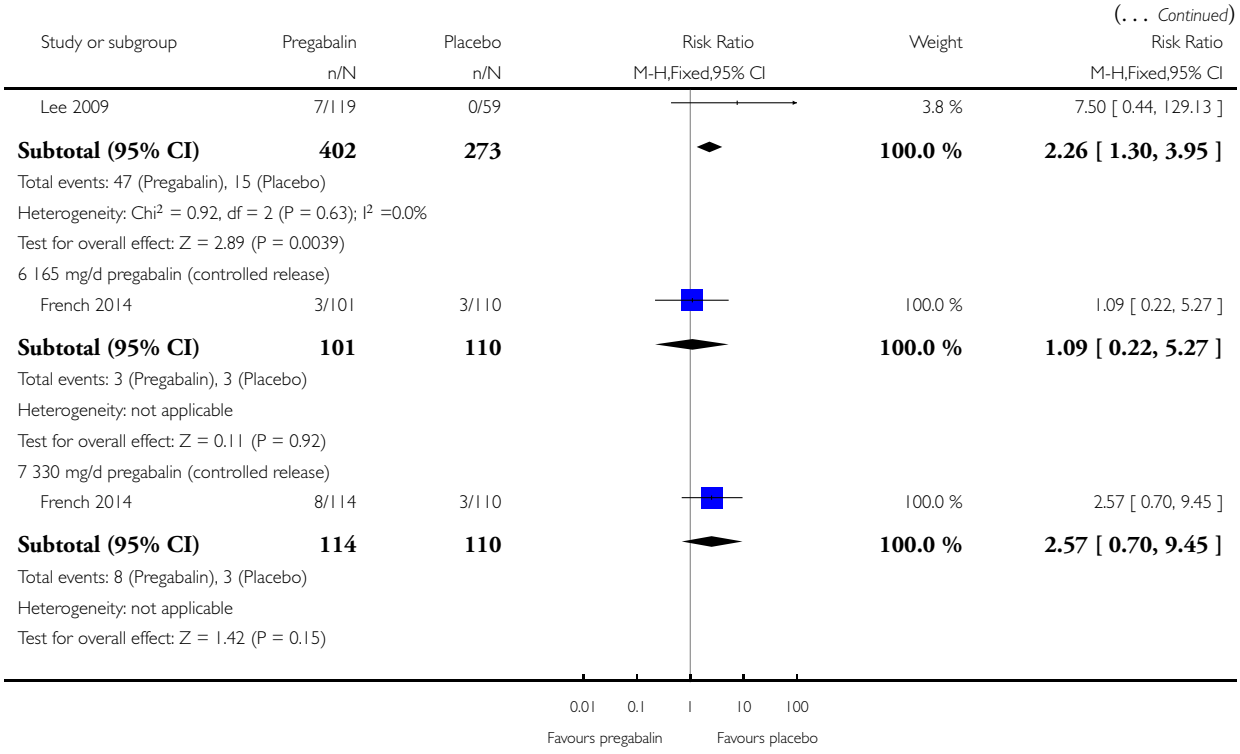
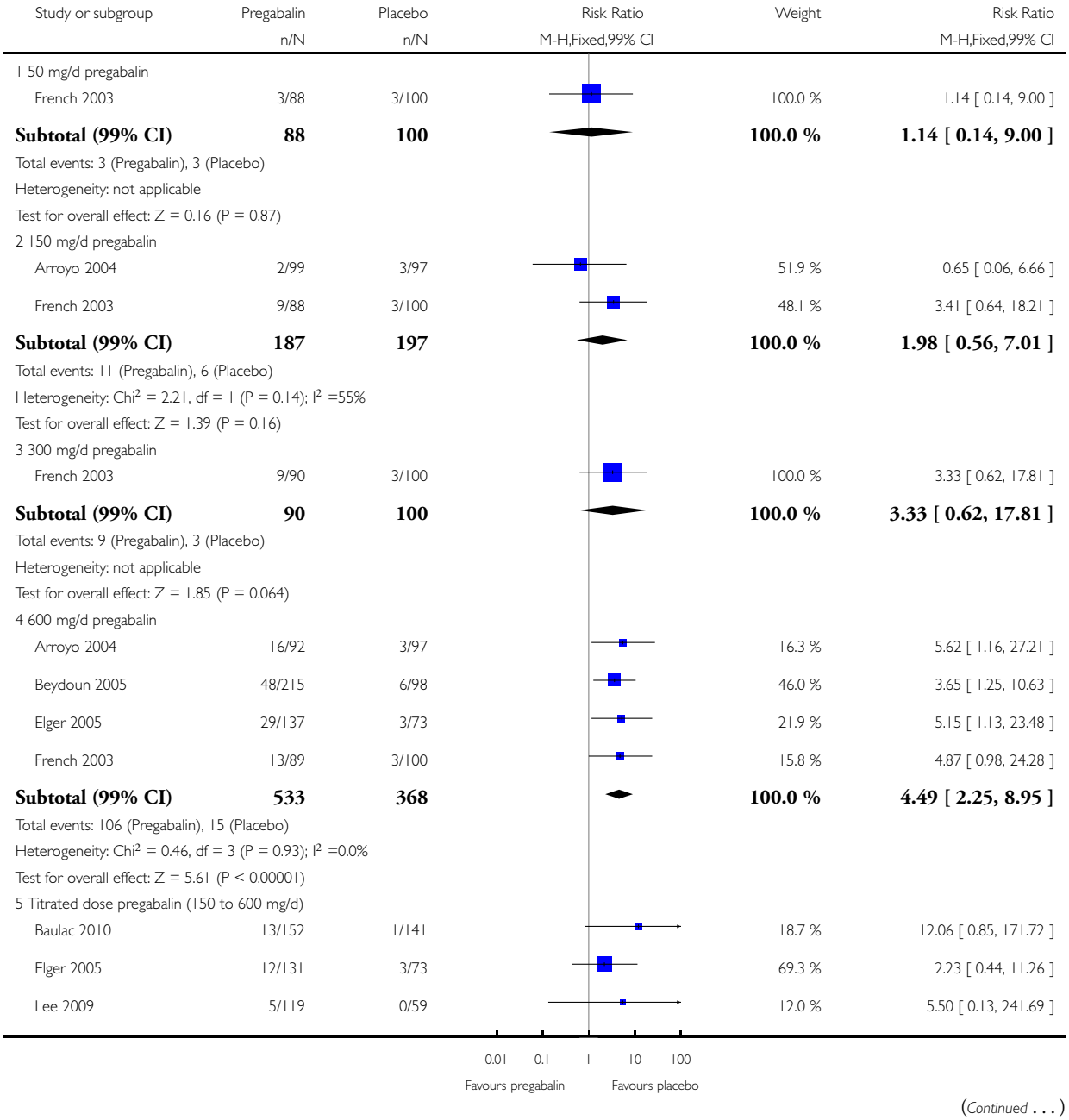


Analysis 2.7. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 7 Ataxia.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 7 Ataxia



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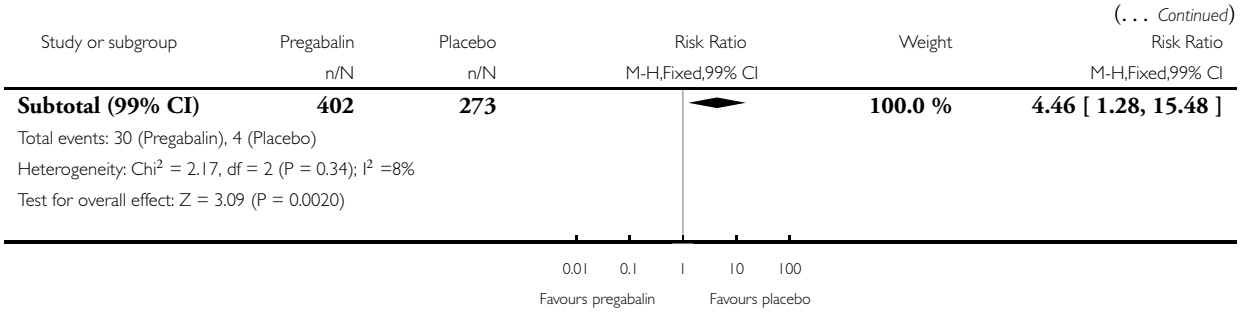
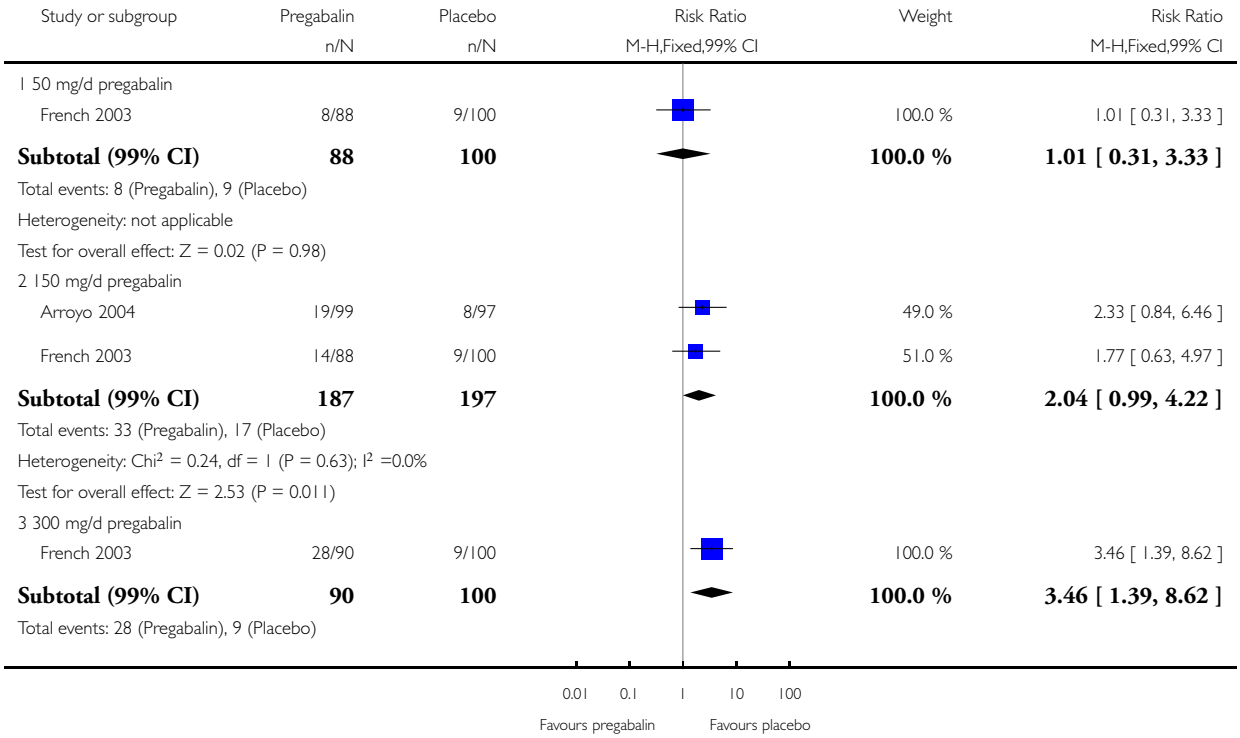


Analysis 2.8. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 8 Dizziness.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 8 Dizziness



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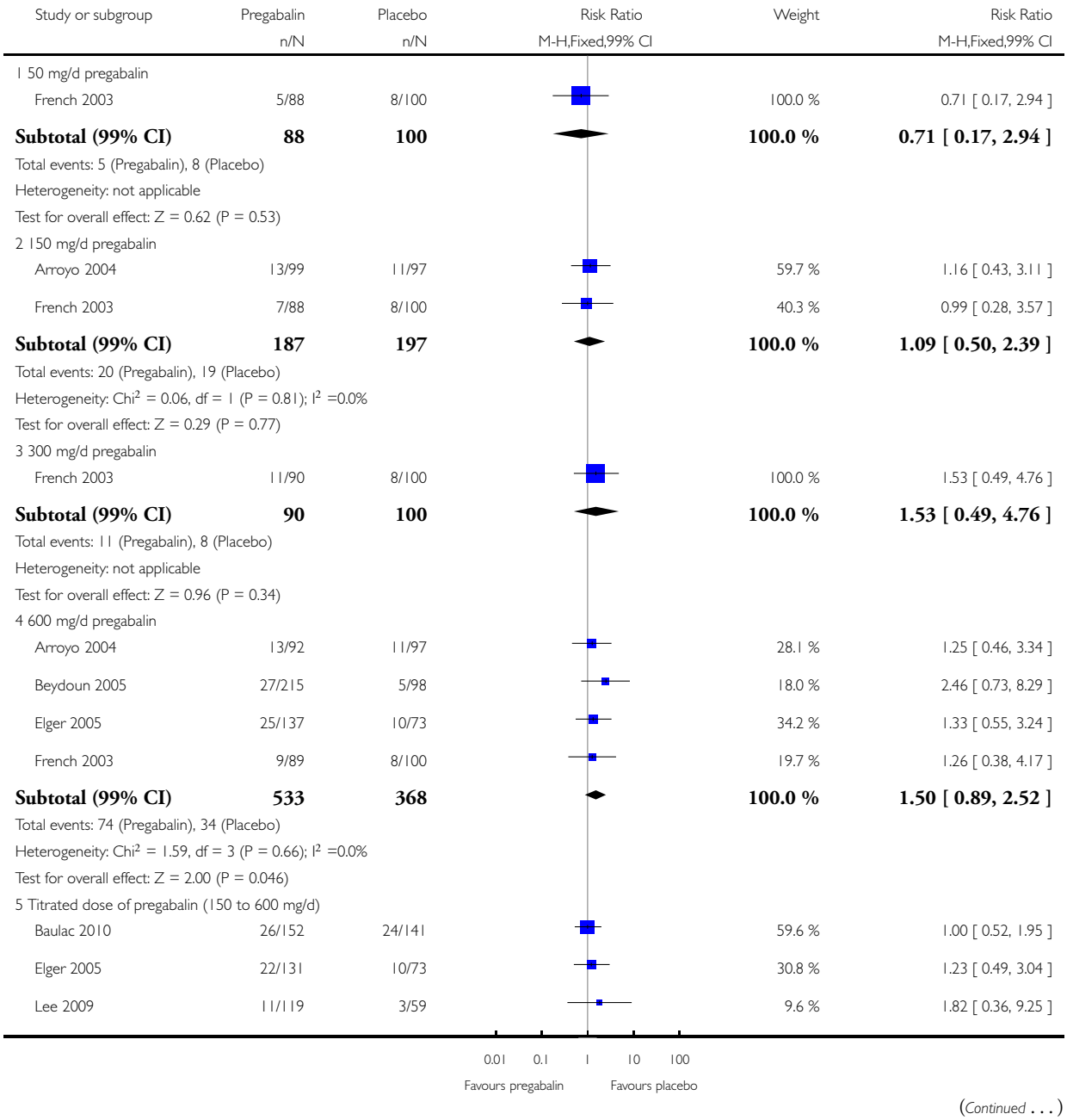
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 3.50 (P = 0.00047)					
4 600 mg/d pregabalin					
Arroyo 2004	24/92	8/97		18.0 %	3.16 [1.18, 8.45]
Beydoun 2005	88/215	14/98		44.4 %	2.87 [1.46, 5.61]
Elger 2005	59/137	6/73		18.1 %	5.24 [1.85, 14.81]
French 2003	38/89	9/100		19.6 %	4.74 [1.97, 11.41]
Subtotal (99% CI)	**533**	**368**		**100.0 %**	**3.72 [2.42, 5.69]**
Total events: 209 (Pregabalin), 37 (Placebo)					
Heterogeneity: Chi^2 = 2.41, df = 3 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 7.92 (P < 0.00001)					
5 Titrated dose of pregabalin (150 to 600 mg/d pregabalin)					
Baulac 2010	38/152	13/141		46.2 %	2.71 [1.25, 5.86]
Elger 2005	32/131	6/73		26.4 %	2.97 [1.01, 8.77]
Lee 2009	46/119	6/59		27.5 %	3.80 [1.34, 10.76]
Subtotal (99% CI)	**402**	**273**		**100.0 %**	**3.08 [1.80, 5.28]**
Total events: 116 (Pregabalin), 25 (Placebo)					
Heterogeneity: Chi^2 = 0.46, df = 2 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 5.37 (P < 0.00001)					
6 165 mg/d pregabalin (controlled release)					
French 2014	11/101	2/110		100.0 %	5.99 [0.85, 42.02]
Subtotal (99% CI)	**101**	**110**		**100.0 %**	**5.99 [0.85, 42.02]**
Total events: 11 (Pregabalin), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.37 (P = 0.018)					
7 330 mg/d pregabalin (controlled release)					
French 2014	11/114	2/110		100.0 %	5.31 [0.76, 37.30]
Subtotal (99% CI)	**114**	**110**		**100.0 %**	**5.31 [0.76, 37.30]**
Total events: 11 (Pregabalin), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.20 (P = 0.027)					

Analysis 2.9. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 9 Fatigue.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 9 Fatigue



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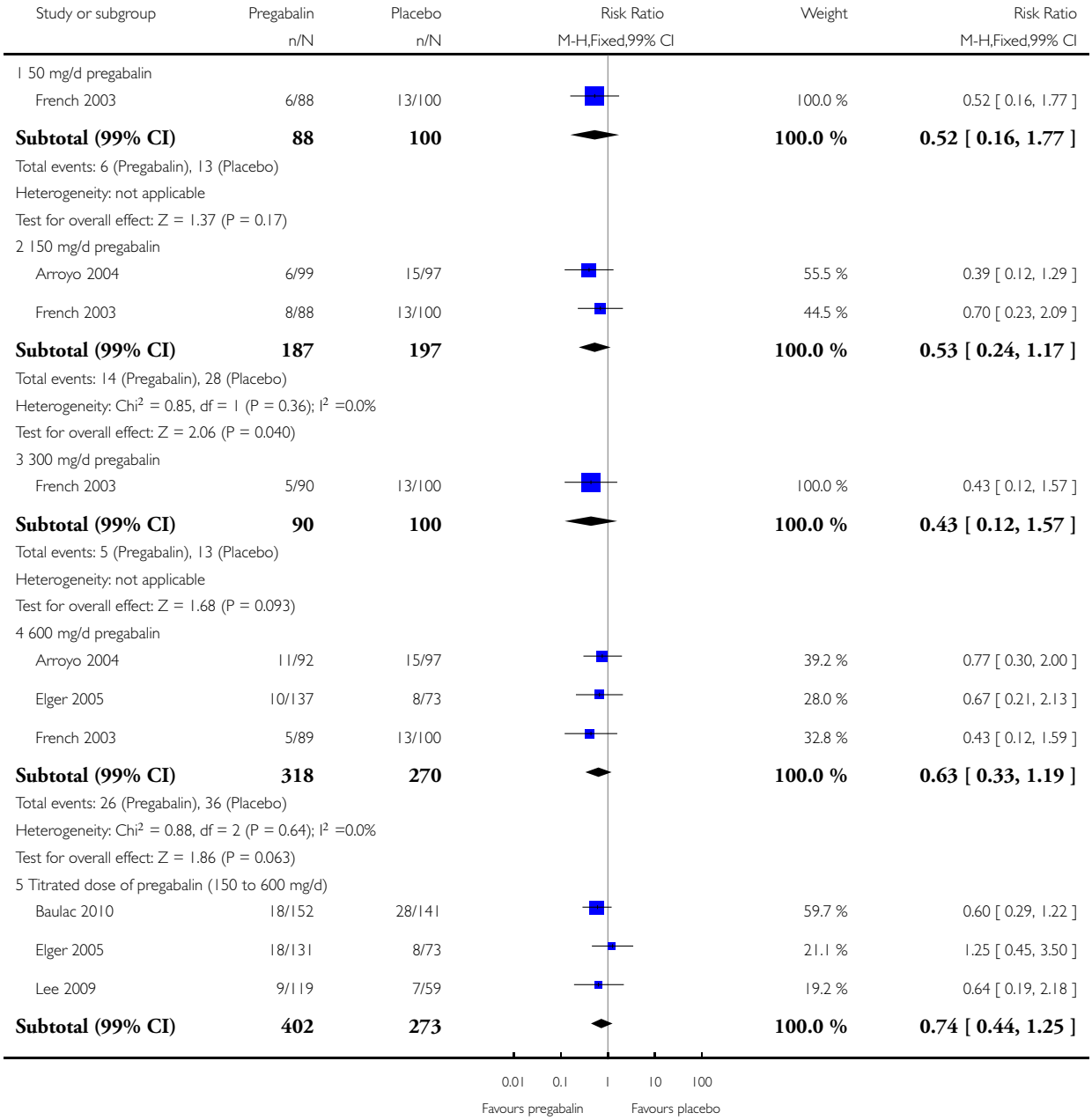
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Subtotal (99% CI)	**402**	**273**		**100.0 %**	**1.15 [0.69, 1.91]**
Total events: 59 (Pregabalin), 37 (Placebo)					
Heterogeneity: Chi^2 = 0.83, df = 2 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 0.71 (P = 0.48)					
6 165 mg/d pregabalin (controlled release)					
French 2014	3/101	1/110		100.0 %	3.27 [0.17, 62.62]
Subtotal (99% CI)	**101**	**110**		**100.0 %**	**3.27 [0.17, 62.62]**
Total events: 3 (Pregabalin), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
7 330 mg/d pregabalin (controlled release)					
French 2014	6/114	1/110		100.0 %	5.79 [0.37, 91.55]
Subtotal (99% CI)	**114**	**110**		**100.0 %**	**5.79 [0.37, 91.55]**
Total events: 6 (Pregabalin), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					

Analysis 2.10. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 10 Headache.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 10 Headache



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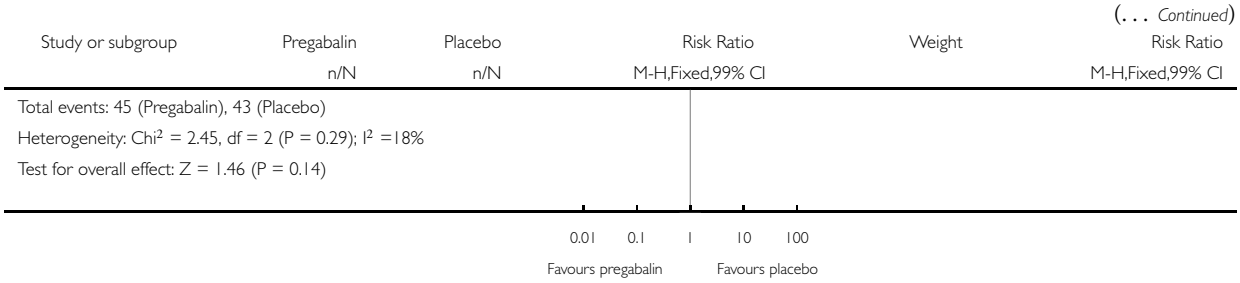
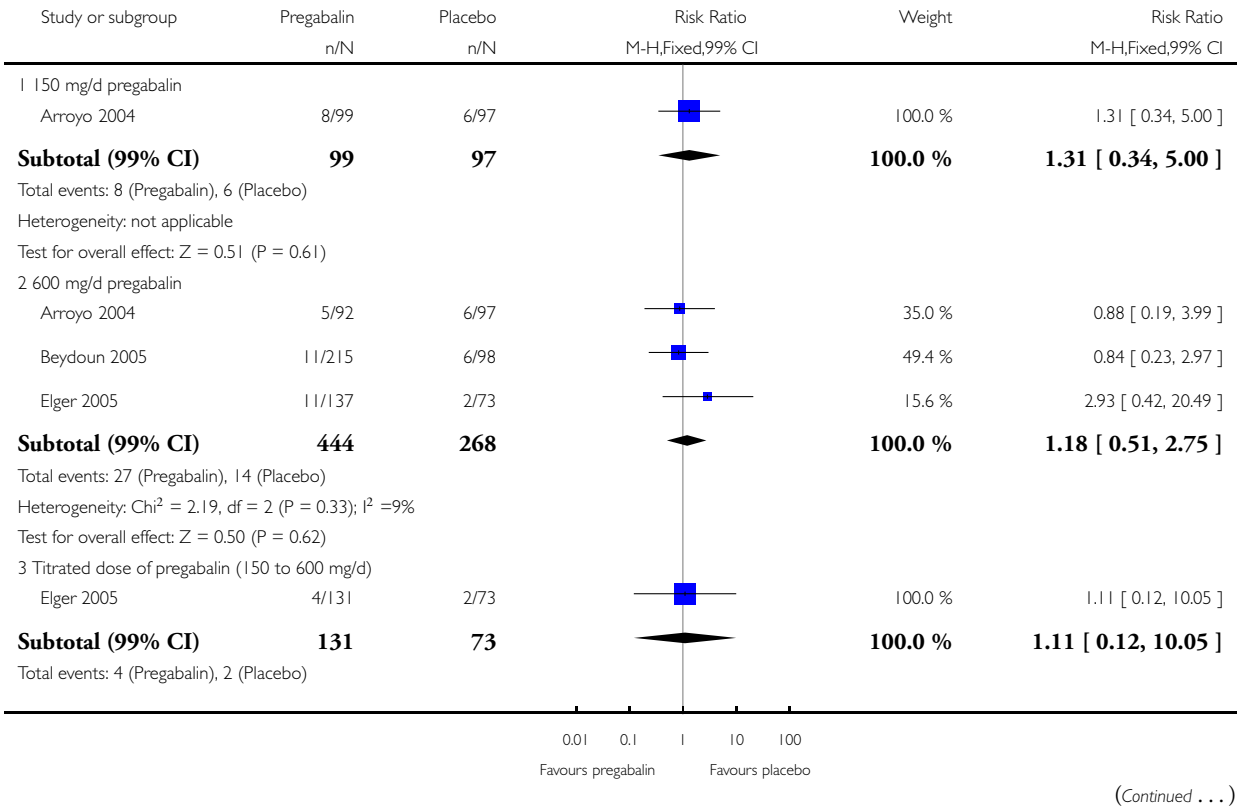


Analysis 2.11. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 11 Nausea.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 11 Nausea



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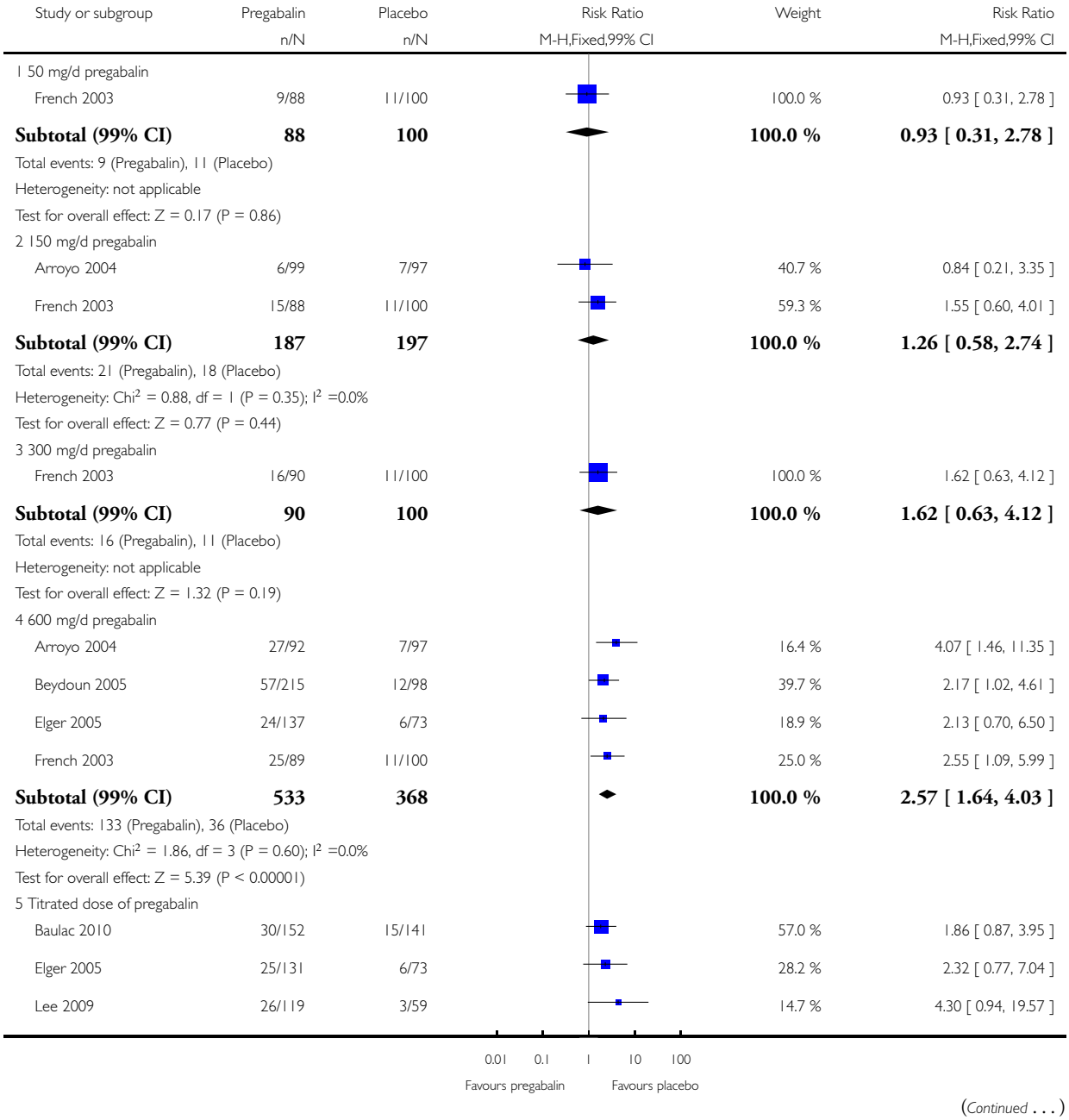
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.13 (P = 0.90)					
4 165 mg/d pregabalin (controlled release)					
French 2014	3/101	1/110		100.0 %	3.27 [0.17, 62.62]
Subtotal (99% CI)	**101**	**110**		**100.0 %**	**3.27 [0.17, 62.62]**
Total events: 3 (Pregabalin), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
5 330 mg/d pregabalin (controlled release)					
French 2014	1/114	1/110		100.0 %	0.96 [0.03, 36.26]
Subtotal (99% CI)	**114**	**110**		**100.0 %**	**0.96 [0.03, 36.26]**
Total events: 1 (Pregabalin), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					

Analysis 2.12. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 12 Somnolence.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 12 Somnolence



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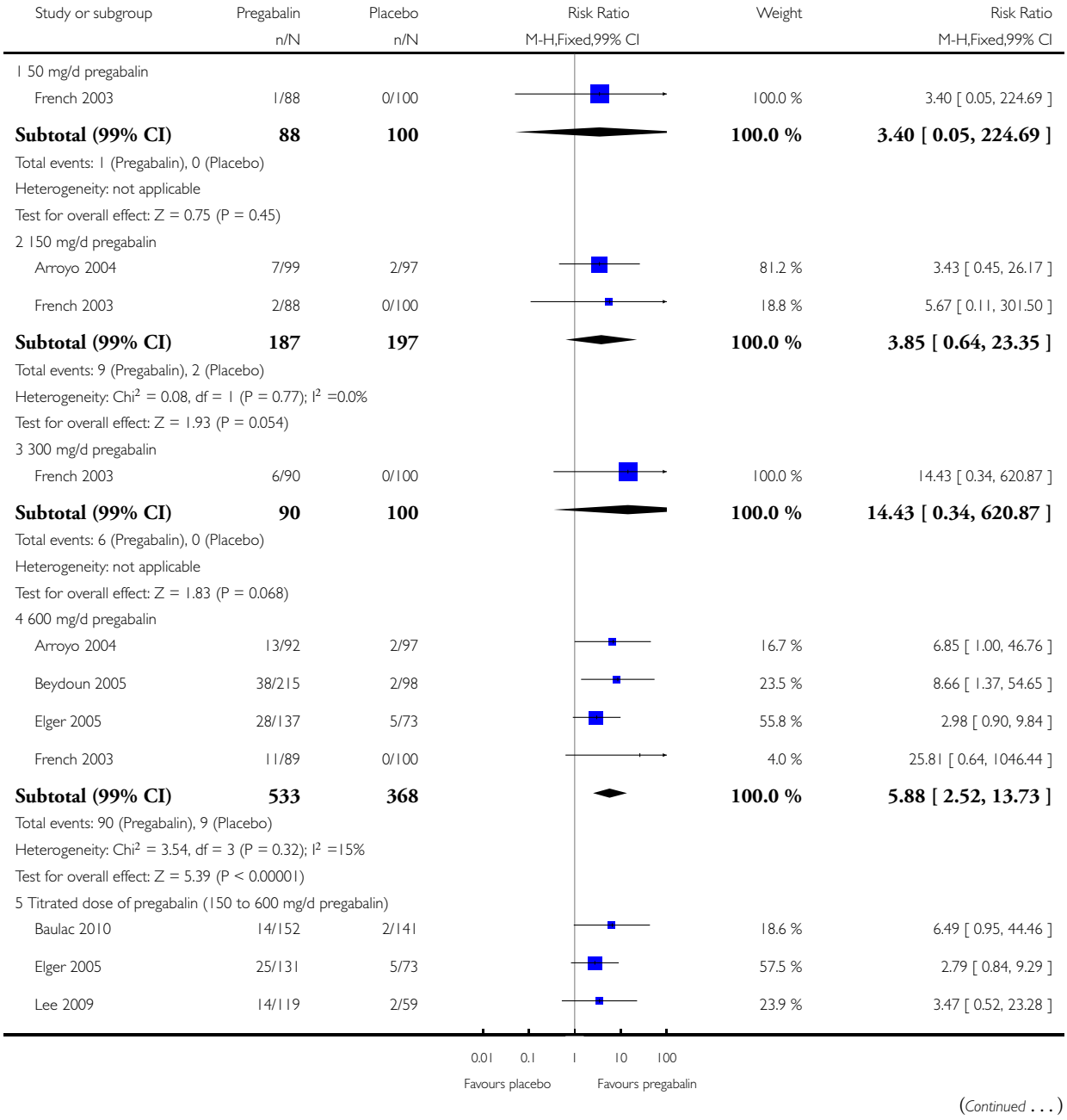
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Subtotal (99% CI)	**402**	**273**		**100.0 %**	**2.35 [1.31, 4.19]**
Total events: 81 (Pregabalin), 24 (Placebo)					
Heterogeneity: Chi^2 = 1.70, df = 2 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 3.79 (P = 0.00015)					
6 165 mg/d pregabalin (controlled release)					
French 2014	4/101	2/110		100.0 %	2.18 [0.24, 19.70]
Subtotal (99% CI)	**101**	**110**		**100.0 %**	**2.18 [0.24, 19.70]**
Total events: 4 (Pregabalin), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.36)					
7 330 mg/d pregabalin (controlled release)					
French 2014	6/114	2/110		100.0 %	2.89 [0.36, 23.05]
Subtotal (99% CI)	**114**	**110**		**100.0 %**	**2.89 [0.36, 23.05]**
Total events: 6 (Pregabalin), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					

Analysis 2.13. Comparison 2 Pregabalin versus placebo - subgroup analysis, Outcome 13 Weight gain.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 2 Pregabalin versus placebo - subgroup analysis

Outcome: 13 Weight gain



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Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Subtotal (99% CI)	**402**	**273**		**100.0 %**	**3.64 [1.49, 8.87]**
Total events: 53 (Pregabalin), 9 (Placebo)					
Heterogeneity: Chi^2 = 0.93, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 3.74 (P = 0.00019)					
6 165 mg/d pregabalin (controlled release)					
French 2014	1/101	0/110		100.0 %	3.26 [0.05, 215.86]
Subtotal (99% CI)	**101**	**110**		**100.0 %**	**3.26 [0.05, 215.86]**
Total events: 1 (Pregabalin), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					
7 330 mg/d pregabalin (controlled release)					
French 2014	7/114	0/110		100.0 %	14.48 [0.34, 613.54]
Subtotal (99% CI)	**114**	**110**		**100.0 %**	**14.48 [0.34, 613.54]**
Total events: 7 (Pregabalin), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.066)					

Analysis 3.1. Comparison 3 Pregabalin versus active comparator, Outcome 1 50% or greater reduction in seizure frequency.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 1 50% or greater reduction in seizure frequency

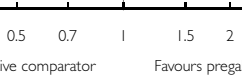
Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Baulac 2010	54/152	34/141		18.7 %	1.47 [1.03, 2.12]
French 2016	134/242	140/242		41.2 %	0.96 [0.82, 1.12]
Zaccara 2014	130/254	139/255		40.1 %	0.94 [0.80, 1.11]
Total (95% CI)	**648**	**638**		**100.0 %**	**1.03 [0.85, 1.25]**

Total events: 318 (Pregabalin), 313 (Active comparator)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.19$, df = 2 (P = 0.07); $I^2 = 61\%$

Test for overall effect: Z = 0.30 (P = 0.77)

Test for subgroup differences: Not applicable



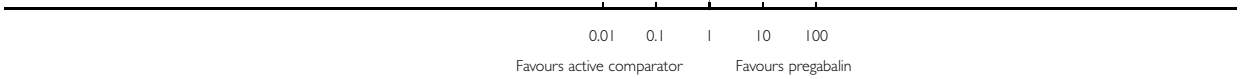
Analysis 3.2. Comparison 3 Pregabalin versus active comparator, Outcome 2 50% or greater reduction in seizure frequency - best-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 2 50% or greater reduction in seizure frequency - best-case analysis

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Baulac 2010	100/152	34/141		27.7 %	2.73 [1.99, 3.74]
French 2016	188/242	140/242		36.4 %	1.34 [1.18, 1.52]
Zaccara 2014	176/254	139/255		35.9 %	1.27 [1.11, 1.46]
Total (95% CI)	**648**	**638**		**100.0 %**	**1.60 [1.17, 2.19]**
Total events: 464 (Pregabalin), 313 (Active comparator)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 19.54$, df = 2 (P = 0.00006); $I^2 = 90\%$					
Test for overall effect: Z = 2.98 (P = 0.0029)					
Test for subgroup differences: Not applicable					



Analysis 3.3. Comparison 3 Pregabalin versus active comparator, Outcome 3 50% or greater reduction in seizure frequency - worst-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 3 50% or greater reduction in seizure frequency - worst-case analysis

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baulac 2010	54/152	74/141		16.4 %	0.68 [0.52, 0.88]
French 2016	134/242	209/242		44.5 %	0.64 [0.57, 0.73]
Zaccara 2014	130/254	184/255		39.1 %	0.71 [0.62, 0.82]
Total (95% CI)	**648**	**638**		**100.0 %**	**0.67 [0.62, 0.74]**

Total events: 318 (Pregabalin), 467 (Active comparator)

Heterogeneity: Chi^2 = 1.12, df = 2 (P = 0.57); I^2 =0.0%

Test for overall effect: Z = 8.63 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Pregabalin versus active comparator, Outcome 4 Seizure freedom.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 4 Seizure freedom

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baulac 2010	6/152	4/141		9.9 %	1.39 [0.40, 4.83]
Zaccara 2014	19/254	38/255		90.1 %	0.50 [0.30, 0.85]
Total (95% CI)	**406**	**396**		**100.0 %**	**0.59 [0.37, 0.95]**

Total events: 25 (Pregabalin), 42 (Active comparator)

Heterogeneity: Chi^2 = 2.19, df = 1 (P = 0.14); I^2 =54%

Test for overall effect: Z = 2.19 (P = 0.029)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Pregabalin versus active comparator, Outcome 5 Treatment withdrawal for any reason.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 5 Treatment withdrawal for any reason

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baulac 2010	46/152	40/141		26.7 %	1.07 [0.75, 1.52]
French 2016	54/242	69/242		44.4 %	0.78 [0.57, 1.07]
Zaccara 2014	46/254	45/255		28.9 %	1.03 [0.71, 1.49]
Total (95% CI)	**648**	**638**		**100.0 %**	**0.93 [0.76, 1.13]**

Total events: 146 (Pregabalin), 154 (Active comparator)

Heterogeneity: Chi^2 = 2.04, df = 2 (P = 0.36); I^2 =2%

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable

Analysis 3.6. Comparison 3 Pregabalin versus active comparator, Outcome 6 Treatment withdrawal due to adverse effects.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 6 Treatment withdrawal due to adverse effects

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baulac 2010	24/152	25/141		47.2 %	0.89 [0.53, 1.48]
French 2016	16/242	15/242		27.3 %	1.07 [0.54, 2.11]
Zaccara 2014	18/254	14/255		25.4 %	1.29 [0.66, 2.54]
Total (95% CI)	**648**	**638**		**100.0 %**	**1.04 [0.73, 1.48]**

Total events: 58 (Pregabalin), 54 (Active comparator)

Heterogeneity: $Chi^2 = 0.75$, df = 2 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 0.22 (P = 0.82)

Test for subgroup differences: Not applicable

Analysis 3.7. Comparison 3 Pregabalin versus active comparator, Outcome 7 Ataxia.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 7 Ataxia

Study or subgroup	Pregabalin n/N	Active Comparator n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Baulac 2010	13/152	7/141		100.0 %	1.72 [0.54, 5.55]
Total (99% CI)	**152**	**141**		**100.0 %**	**1.72 [0.54, 5.55]**

Total events: 13 (Pregabalin), 7 (Active Comparator)

Heterogeneity: not applicable

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable

Analysis 3.8. Comparison 3 Pregabalin versus active comparator, Outcome 8 Dizziness.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 8 Dizziness

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio IV,Random,99% CI	Weight	Risk Ratio IV,Random,99% CI
Baulac 2010	38/152	12/141		29.3 %	2.94 [1.32, 6.52]
French 2016	22/242	20/242		30.5 %	1.10 [0.51, 2.35]
Zaccara 2014	56/254	39/255		40.2 %	1.44 [0.89, 2.34]
Total (99% CI)	**648**	**638**		**100.0 %**	**1.64 [0.85, 3.16]**

Total events: 116 (Pregabalin), 71 (Active comparator)

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 5.75$, df = 2 (P = 0.06); $I^2 = 65\%$

Test for overall effect: Z = 1.92 (P = 0.055)

Test for subgroup differences: Not applicable

Analysis 3.9. Comparison 3 Pregabalin versus active comparator, Outcome 9 Fatigue.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 9 Fatigue

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
Baulac 2010	26/152	14/141		100.0 %	1.72 [0.77, 3.83]
Total (99% CI)	**152**	**141**		**100.0 %**	**1.72 [0.77, 3.83]**

Total events: 26 (Pregabalin), 14 (Active comparator)
Heterogeneity: not applicable
Test for overall effect: Z = 1.75 (P = 0.080)
Test for subgroup differences: Not applicable

Analysis 3.10. Comparison 3 Pregabalin versus active comparator, Outcome 10 Headache.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 10 Headache

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio IV,Random,99% CI	Weight	Risk Ratio IV,Random,99% CI
Baulac 2010	18/152	32/141		34.3 %	0.52 [0.26, 1.05]
French 2016	17/242	20/242		30.4 %	0.85 [0.38, 1.92]
Zaccara 2014	30/254	24/255		35.3 %	1.25 [0.64, 2.45]
Total (99% CI)	**648**	**638**		**100.0 %**	**0.83 [0.41, 1.65]**

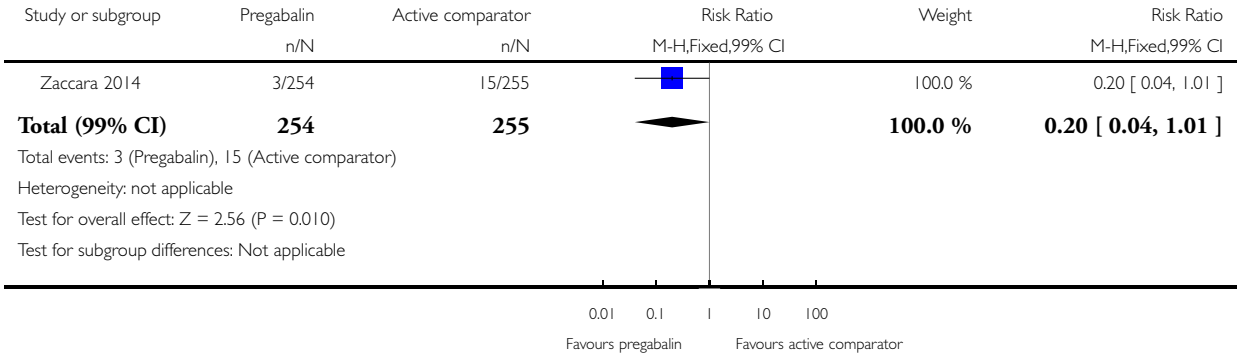
Total events: 65 (Pregabalin), 76 (Active comparator)
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 5.50$, df = 2 (P = 0.06); $I^2 = 64\%$
Test for overall effect: Z = 0.71 (P = 0.47)
Test for subgroup differences: Not applicable

Analysis 3.11. Comparison 3 Pregabalin versus active comparator, Outcome 11 Nausea.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 11 Nausea

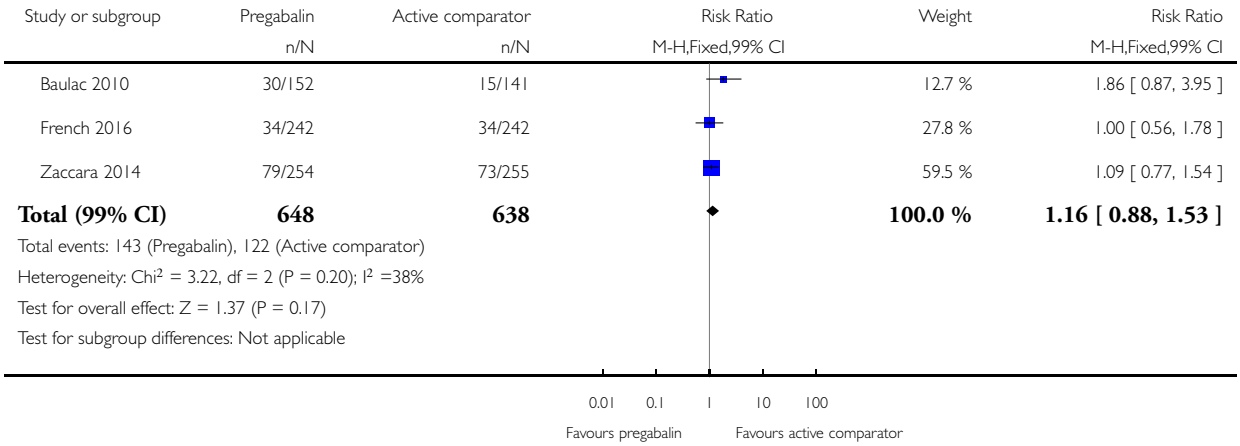


Analysis 3.12. Comparison 3 Pregabalin versus active comparator, Outcome 12 Somnolence.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 12 Somnolence



Analysis 3.13. Comparison 3 Pregabalin versus active comparator, Outcome 13 Weight gain.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 3 Pregabalin versus active comparator

Outcome: 13 Weight gain

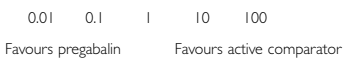
Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio IV,Random,99% CI	Weight	Risk Ratio IV,Random,99% CI
Baulac 2010	14/152	3/141		25.8 %	4.33 [0.86, 21.68]
French 2016	19/242	13/242		41.1 %	1.46 [0.60, 3.58]
Zaccara 2014	24/254	5/255		33.0 %	4.82 [1.39, 16.74]
Total (99% CI)	**648**	**638**		**100.0 %**	**2.87 [0.94, 8.75]**

Total events: 57 (Pregabalin), 21 (Active comparator)

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 4.99$, df = 2 (P = 0.08); $I^2 = 60\%$

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable



Analysis 4.1. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 1 50% or greater reduction in seizure frequency.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 1 50% or greater reduction in seizure frequency

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pregabalin versus lamotrigine					
Baulac 2010	54/152	34/141		100.0 %	1.47 [1.03, 2.12]
Subtotal (95% CI)	**152**	**141**		**100.0 %**	**1.47 [1.03, 2.12]**
Total events: 54 (Pregabalin), 34 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.09 (P = 0.036)					
2 Pregabalin versus levetiracetam					
Zaccara 2014	130/254	139/255		100.0 %	0.94 [0.80, 1.11]
Subtotal (95% CI)	**254**	**255**		**100.0 %**	**0.94 [0.80, 1.11]**
Total events: 130 (Pregabalin), 139 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					
3 Pregabalin versus gabapentin					
French 2016	134/242	140/242		100.0 %	0.96 [0.82, 1.12]
Subtotal (95% CI)	**242**	**242**		**100.0 %**	**0.96 [0.82, 1.12]**
Total events: 134 (Pregabalin), 140 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					
Test for subgroup differences: Chi^2 = 5.19, df = 2 (P = 0.07), I^2 =61%					

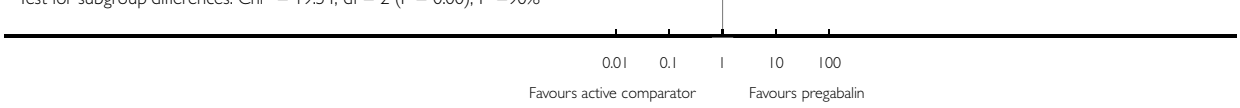
Analysis 4.2. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 2 50% or greater reduction in seizure frequency - best-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 2 50% or greater reduction in seizure frequency - best-case analysis

Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pregabalin versus lamotrigine					
Baulac 2010	100/152	34/141		100.0 %	2.73 [1.99, 3.74]
Subtotal (95% CI)	**152**	**141**		**100.0 %**	**2.73 [1.99, 3.74]**
Total events: 100 (Pregabalin), 34 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.26 (P < 0.00001)					
2 Pregabalin versus levetiracetam					
Zaccara 2014	176/254	139/255		100.0 %	1.27 [1.11, 1.46]
Subtotal (95% CI)	**254**	**255**		**100.0 %**	**1.27 [1.11, 1.46]**
Total events: 176 (Pregabalin), 139 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.39 (P = 0.00071)					
3 Pregabalin versus gabapentin					
French 2016	188/242	140/242		100.0 %	1.34 [1.18, 1.52]
Subtotal (95% CI)	**242**	**242**		**100.0 %**	**1.34 [1.18, 1.52]**
Total events: 188 (Pregabalin), 140 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.55 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 19.54, df = 2 (P = 0.00), I^2 =90%					



Analysis 4.3. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 3 50% or greater reduction in seizure frequency - worst-case analysis.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 3 50% or greater reduction in seizure frequency - worst-case analysis

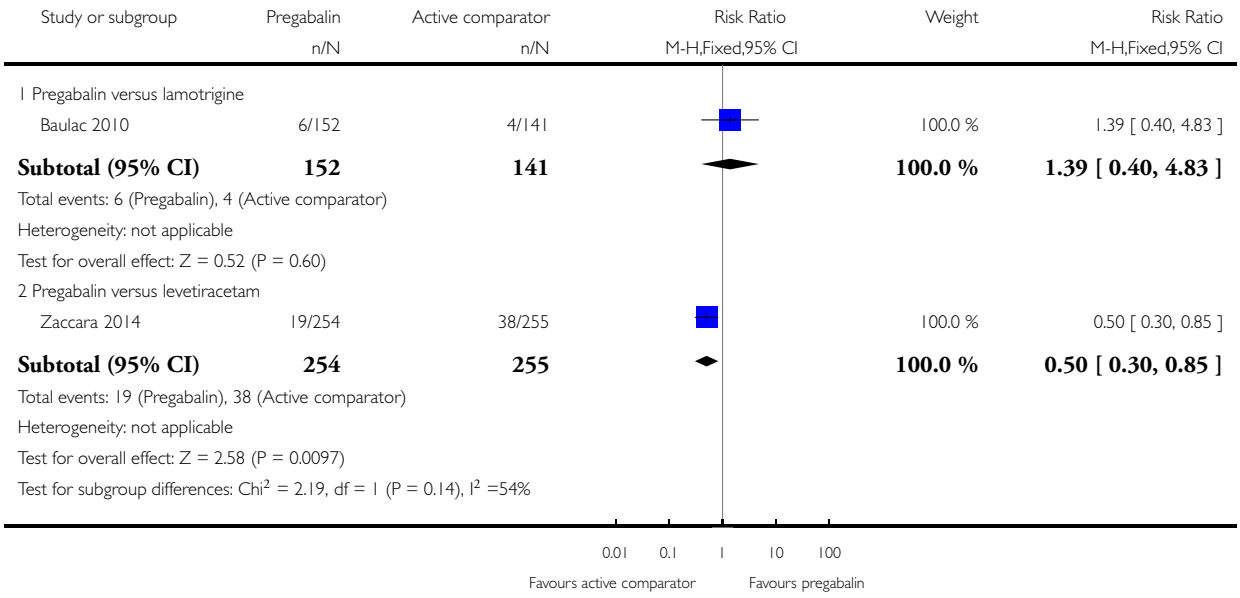
Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pregabalin versus lamotrigine					
Baulac 2010	54/152	74/141		100.0 %	0.68 [0.52, 0.88]
Subtotal (95% CI)	**152**	**141**		**100.0 %**	**0.68 [0.52, 0.88]**
Total events: 54 (Pregabalin), 74 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.88 (P = 0.0040)					
2 Pregabalin versus levetiracetam					
Zaccara 2014	130/254	184/255		100.0 %	0.71 [0.62, 0.82]
Subtotal (95% CI)	**254**	**255**		**100.0 %**	**0.71 [0.62, 0.82]**
Total events: 130 (Pregabalin), 184 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.73 (P < 0.00001)					
3 Pregabalin versus gabapentin					
French 2016	134/242	209/242		100.0 %	0.64 [0.57, 0.73]
Subtotal (95% CI)	**242**	**242**		**100.0 %**	**0.64 [0.57, 0.73]**
Total events: 134 (Pregabalin), 209 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.04 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.11, df = 2 (P = 0.57), I^2 =0.0%					

Analysis 4.4. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 4 Seizure freedom.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 4 Seizure freedom

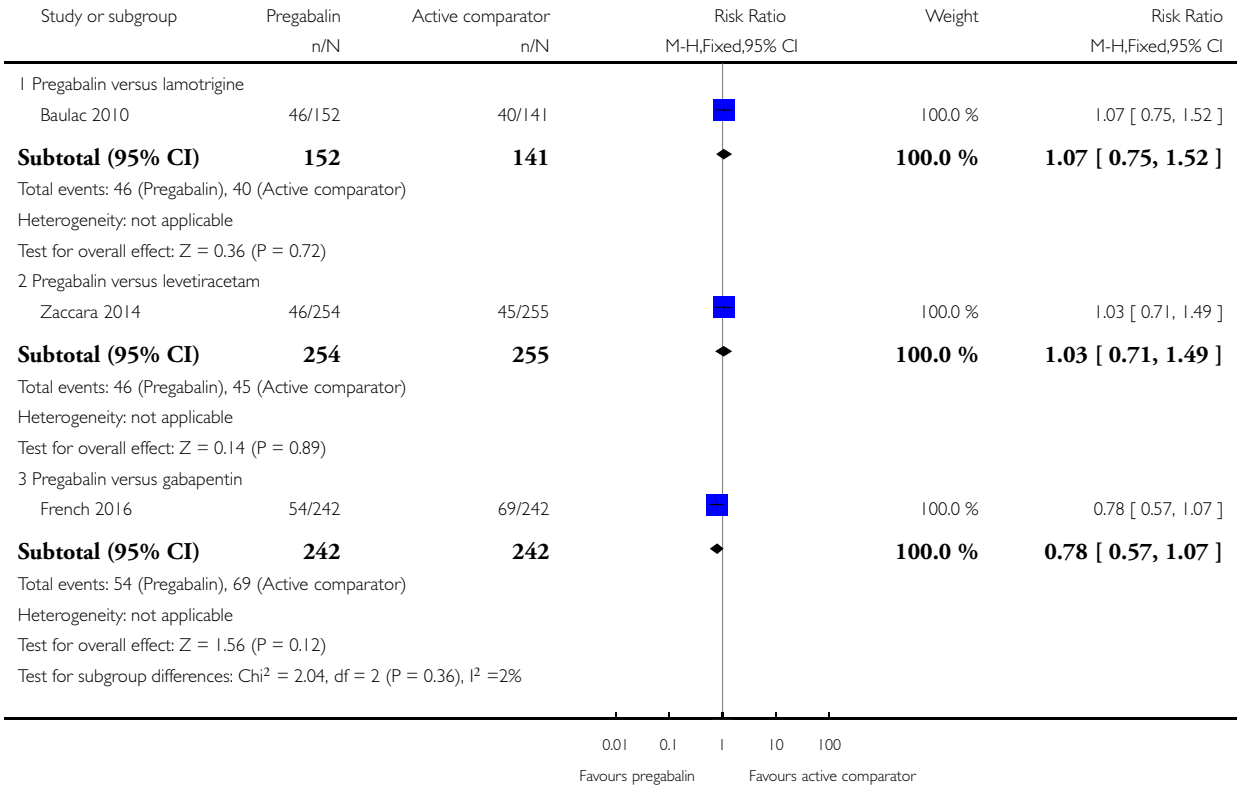


Analysis 4.5. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 5 Treatment withdrawal for any reason.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 5 Treatment withdrawal for any reason

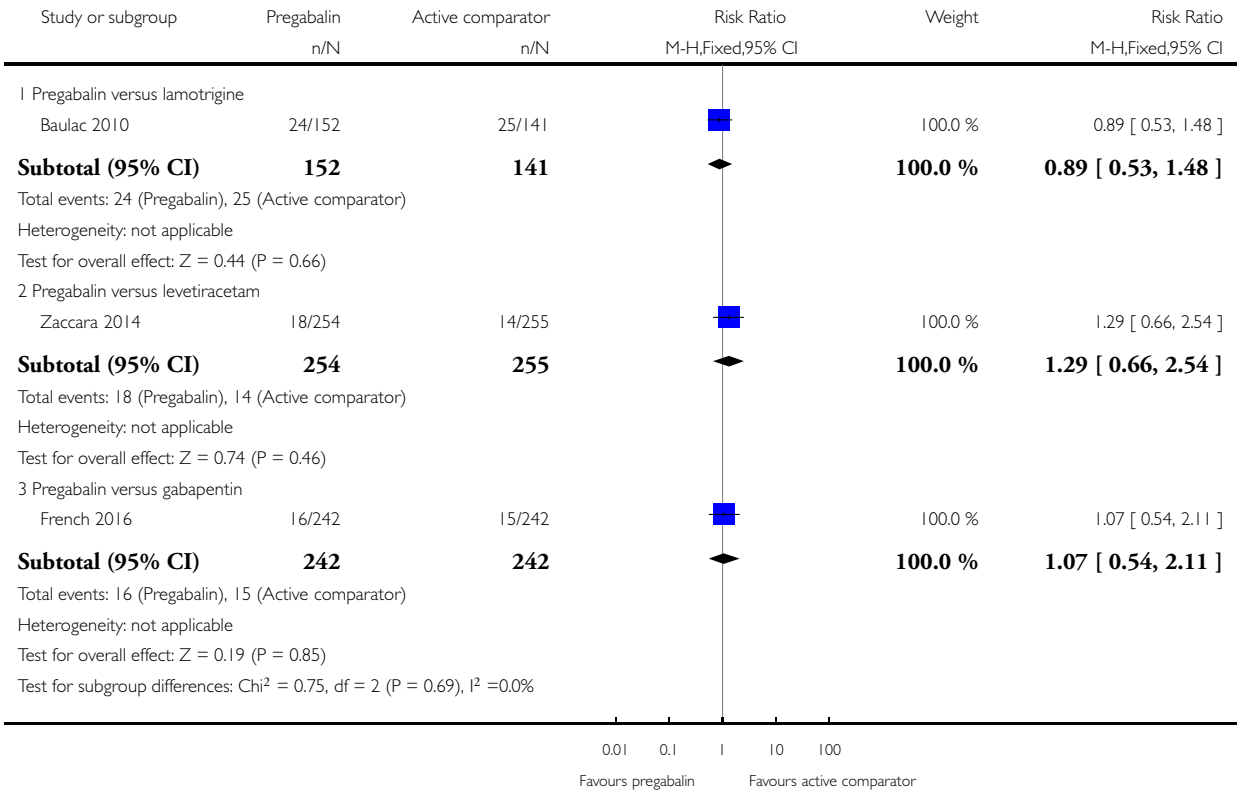


Analysis 4.6. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 6 Treatment withdrawal due to adverse effects.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 6 Treatment withdrawal due to adverse effects

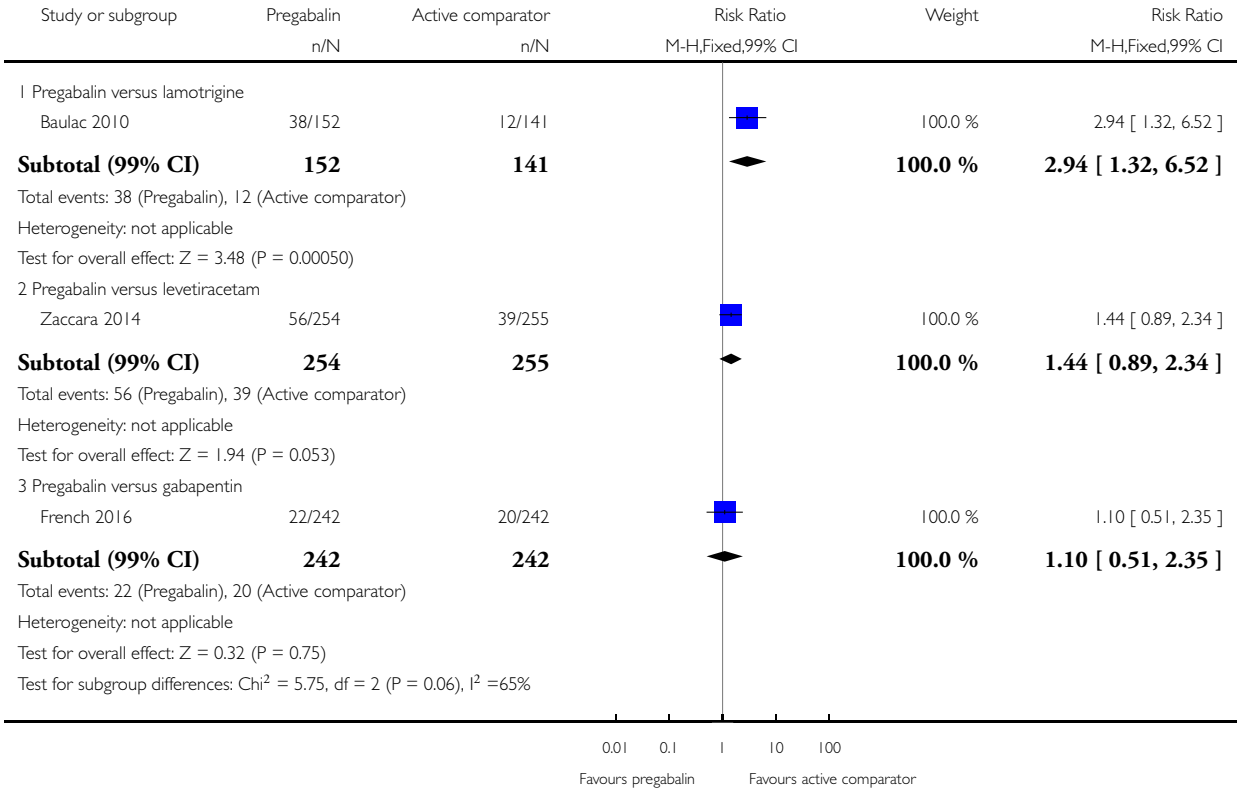


Analysis 4.7. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 7 Dizziness.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 7 Dizziness

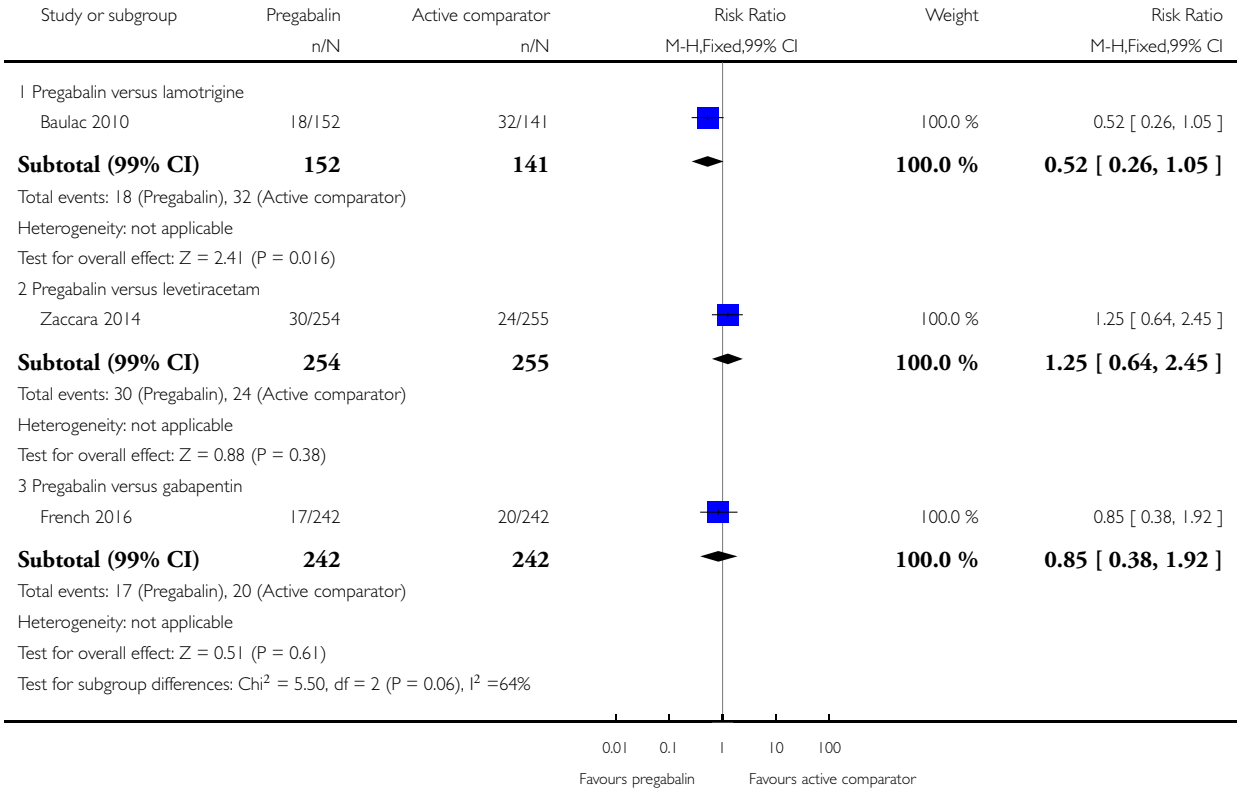


Analysis 4.8. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 8 Headache.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 8 Headache



Analysis 4.9. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 9 Nausea.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 9 Nausea

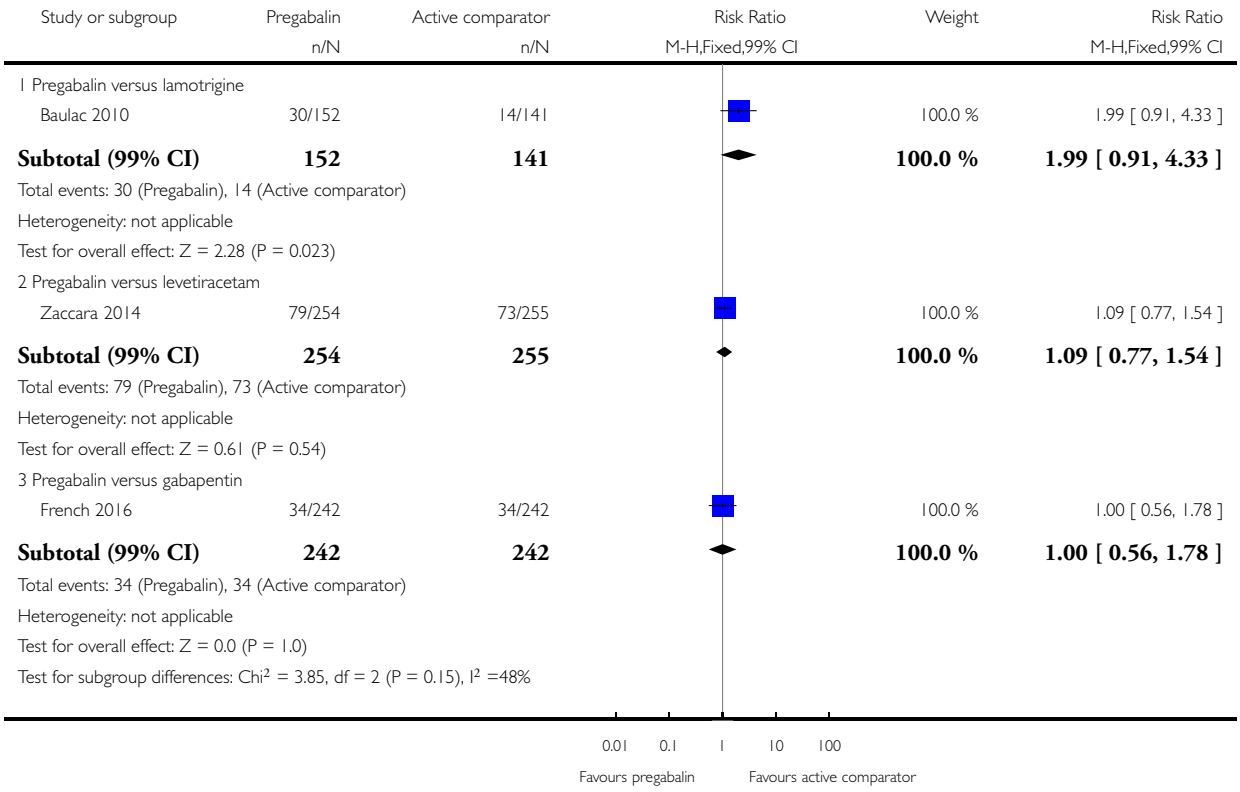
Study or subgroup	Pregabalin n/N	Active comparator n/N	Risk Ratio M-H,Fixed,99% CI	Weight	Risk Ratio M-H,Fixed,99% CI
1 Pregabalin versus levetiracetam					
Zaccara 2014	3/254	15/255		100.0 %	0.20 [0.04, 1.01]
Subtotal (99% CI)	**254**	**255**		**100.0 %**	**0.20 [0.04, 1.01]**
Total events: 3 (Pregabalin), 15 (Active comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					
Test for subgroup differences: Not applicable					

Analysis 4.10. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 10 Somnolence.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 10 Somnolence

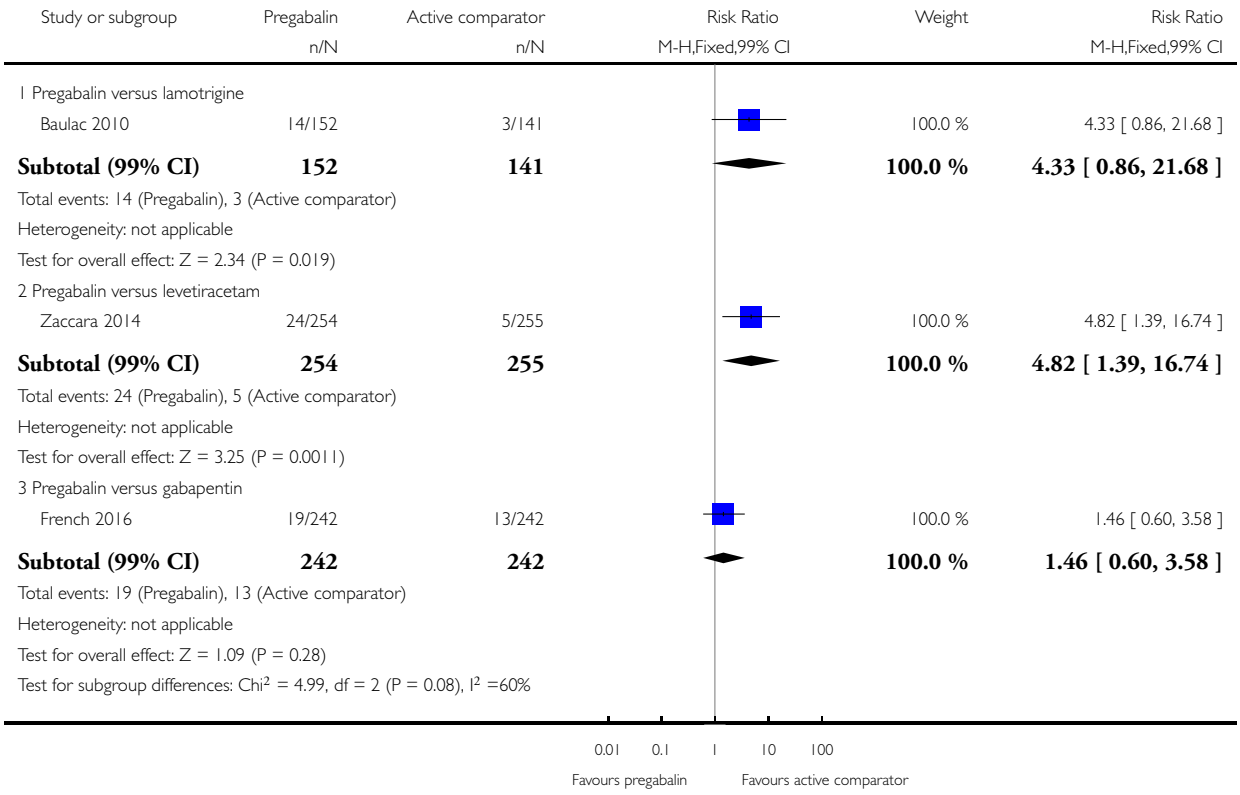


Analysis 4.11. Comparison 4 Pregabalin versus active comparator - subgroup analysis, Outcome 11 Weight gain.

Review: Pregabalin add-on for drug-resistant focal epilepsy

Comparison: 4 Pregabalin versus active comparator - subgroup analysis

Outcome: 11 Weight gain



APPENDICES

Appendix 1. Cochrane Register of Studies (CRS Web) search strategy

1. MESH DESCRIPTOR Pregabalin EXPLODE ALL AND CENTRAL:TARGET
2. (lyrica OR pregabalin*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
3. #1 OR #2
4. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET
5. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET
6. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
7. #4 OR #5 OR #6 AND CENTRAL:TARGET
8. #3 AND #7
9. (monotherap* NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)):TI AND CENTRAL:TARGET
10. #8 NOT #9
11. >06/09/2016:CRSINCENTRAL AND CENTRAL:TARGET
12. #10 AND #11

Appendix 2. MEDLINE (Ovid) search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials, published in Lefebvre 2011.
1. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
2. clinical trials as topic.sh.
3. trial.ti.
4. 1 or 2 or 3
5. exp animals/ not humans.sh.
6. 4 not 5
7. exp Epilepsy/
8. exp Seizures/
9. (epilep$ or seizure$ or convuls$).tw.
10. 7 or 8 or 9
11. exp Pregabalin/ or (pregabalin$ or lyrica).tw.
12. 6 and 10 and 11
13. (monotherap$ not (adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$)).ti.
14. 12 not 13
15. limit 14 to ed=20160906-20180705
16. 14 not (1$ or 2$).ed.
17. 16 and (2016$ or 2017$ or 2018$).dt.
18. 15 or 17
19. remove duplicates from 18

Appendix 3. ClinicalTrials.gov search strategy

Interventional Studies | Epilepsies, Partial | Pregabalin

Appendix 4. WHO ICTRP search strategy

Condition: Partial epilepsy OR Focal epilepsy
Intervention: Lyrica OR Pregabalin
Phases: 2, 3, 4

WHAT'S NEW

Date	Event	Description
5 July 2018	New citation required but conclusions have not changed	Conclusions remain the same.
5 July 2018	New search has been performed	Searches updated 5 July 2018; three new studies (French 2014, French 2016 and Zaccara 2014) have been added to the review. The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017) .

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 1, 2008

Date	Event	Description
9 January 2014	New search has been performed	Searches updated 9 January 2014; one previously ongoing study, Bali 2012, has been added to excluded studies (Taghdiri 2015).
9 January 2014	New citation required but conclusions have not changed	Conclusions remain the same.
12 June 2012	New search has been performed	Two new studies were included in this update of the original review
7 August 2009	Amended	Copy edits made at editorial base.
16 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MP and RB carried out and completed the update of this review. MP and RB assessed trials for eligibility and completed data extraction. RB and MP both contributed to the writing of the review and the data analysis. KH conducted the dose regression analysis. AM provided supervision throughout the review process.

DECLARATIONS OF INTEREST

MP: none known.

RB: none known.

KH: acted as expert witness as a statistician in a number of legal cases including antiepileptic drug cases.

AM: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is part funded by National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol was amended for the previous review to include interventions comparing pregabalin to other antiepileptic drugs.

The method of analysis for examining dose regression was changed for the previous version of the review due to advances in techniques for analysis binary data. Specifically, a generalised linear mixed model using the software package STATA SE version 14 (Stata statistical software 2015) was employed as opposed to a generalised linear model. We continued to use a generalised linear mixed model in the current review update.

The title of the review has been changed from “Pregabalin add-on for drug-resistant partial epilepsy” to “Pregabalin add-on for drug-resistant focal epilepsy” in accordance with the latest classification of epilepsies released by the International League Against Epilepsy (ILAE) (Scheffer 2017). Likewise, any previous mention of “partial epilepsy” or “refractory epilepsy” throughout this review was changed to “focal epilepsy” and “drug-resistant epilepsy”, respectively.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects; *therapeutic use]; Drug Resistance; Epilepsies, Partial [*drug therapy]; Pregabalin; Randomized Controlled Trials as Topic; gamma-Aminobutyric Acid [adverse effects; *analogs & derivatives; therapeutic use]

MeSH check words

Humans