Pregabalin add-on for drug-resistant partial epilepsy

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Abstract

Background—Epilepsy is a common chronic neurological disease with an estimated prevalence of 1% in the UK. Approximately one third of these people continue to have seizures despite drug treatment. In order to try to improve outcomes a number of new antiepileptic drugs have been developed and pregabalin is one of these. This review is an update of a previous Cochrane review (Lozsadi 2008).

Objectives—To summarise evidence from randomised controlled trials regarding the efficacy and tolerability of pregabalin when used as an add-on antiepileptic drug in treatment-resistant partial epilepsy.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
Protocol for last up-to-date review was amended for this review to include interventions comparing pregabalin to other active AEDs. The method of analysis for examining dose-regression has been changed for this review due to advances in techniques for analysis binary data. A generalised linear mixed model using the software package STATA SE version 11 was employed as opposed to the generalised linear model using Splus.

Search methods—We searched the Cochrane Epilepsy Group Specialized Register (May 2012), CENTRAL (the Cochrane Central Register of Controlled Trials issue 5 of 12, *The Cochrane Library* 2012), MEDLINE (Ovid, 1946 to May week 4 2012) and contacted Pfizer Ltd. (the manufacturers of pregabalin) to identify published, unpublished and ongoing trials.

Selection criteria—We included randomised controlled double-blind trials comparing pregabalin with placebo for people with drug-refractory partial epilepsy. Outcomes included 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal for any reason, treatment withdrawal for adverse events and nature of adverse events.

Data collection and analysis—Two review authors (JP and AGM) independently selected and assessed suitable trials and extracted data. Primary analyses were by intention-to-treat (ITT). Results are presented as risk ratios (RR) with 95% confidence intervals (CI).

Main results—Six suitable industry-sponsored trials (2009 participants) were identified and included in the analysis. Trials tested doses of pregabalin ranging from 50 mg/day to 600 mg/day. For the primary outcome, 50% or higher seizure reduction was significantly more likely in patients randomised to pregabalin than to placebo (RR 2.61; 95% CI 1.70 to 4.01). A dose-response analysis suggested increasing effect with increasing dose. Pregabalin was significantly associated with seizure freedom (RR 2.59; 95% CI 1.05 to 6.36). Patients were significantly more likely to have withdrawn from pregabalin treatment than placebo treatment for any reason (RR 1.39; 95% CI 1.13 to 1.72) or for adverse effects (RR 2.69; 95% CI 1.88 to 3.86). Ataxia, dizziness, somnolence and weight gain were significantly associated with pregabalin. The odds of response doubled with an increase in dose from 300 mg/day to 600 mg/day (OR 2.12; 95% CI 1.76 to 2.54).

Authors' conclusions—Pregabalin, when used as an add-on drug for treatment-resistant partial epilepsy, is significantly more effective than placebo at achieving a 50% or greater seizure reduction and significantly increasing seizure freedom. Results demonstrate efficacy for doses from 150 mg/day to 600 mg/day, with increasing effectiveness at 600 mg doses. The trials included in this review were of short duration and longer-term trials are needed to inform clinical decision making better.

Medical Subject Headings (MesH)

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

MeSH check words

Humans

BACKGROUND

Epilepsy is a common neurological chronic condition affecting up to 1% of the UK population (Hauser 1990). A single antiepileptic drug (AED) (monotherapy) will induce remission for the majority of those diagnosed. However, up to 30% of patients will fail to respond to monotherapy (Cockerell 1995). Their continuing attacks will result in reduced quality of life, and may also lead to injuries, social isolation and depression (Villeneuve

2004). This group poses a significant therapeutic problem, leading to the development of new AEDs as well as exploration of non-pharmacological treatment options, such as vagal nerve stimulation and epilepsy surgery.

Since the 1990s numerous new AEDs have become available, raising hope for more potent and better tolerated treatment of epilepsy. Pregabalin is one of these new compounds with antiepileptic, analgesic and anxiolytic (anxiety reducing) properties. It acts through binding to an auxiliary protein (alpha 2 delta) of the voltagegated calcium channels. It has been shown to reduce calcium influx into nerve terminals resulting in reduced presynaptic release of glutamate. In addition, by acting on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors it indirectly reduces synaptic noradrenaline release (Fink 2002). These actions are thought to mediate its antiepileptic, anxiolytic and analgesic 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 drug interactions (Brodie 2005). Pregabalin was launched onto the UK market in 2004 as an add-on AED for partial-onset seizures, as well as a treatment for neuropathic pain, and more recently (2006) as an anxiolytic.

Clinical trials published on the antiepileptic properties of pregabalin so far have focused on patients with refractory partialonset epilepsy. In these randomised placebo-controlled trials, patients 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 will be the subject of a future Cochrane review.

This review is an update of a previous Cochrane review and aims to summarise existing data regarding the effects of add-on pregabalin for patients with refractory partial-onset seizures. This review is one in a series in which the efficacy and tolerability of seven new AEDs (gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, zonisamide and pregabalin) are investigated in patients with drug-resistant partial epilepsy. Findings from the previous review showed significant seizure reduction in users of pregabalin compared to controls. Seizure freedom was not significantly associated with pregabalin. Pregabalin users were more likely to withdraw from the study than controls and significant adverse events associated with pregabalin were ataxia, dizziness, somnolence and weight gain.

OBJECTIVES

Our review aims to identify and evaluate data on the anticonvulsant effects and tolerability of add-on pregabalin in patients with drug-resistant partial epilepsy. The definitions of drug resistance used will be those employed by the authors of the included trials.

METHODS

Criteria for considering studies for this review

Types of studies—To be included in our review, studies had to meet all of the following criteria:

1. randomised controlled trials, in which an adequate method of randomisation and allocation concealment was used;

2. double-blind trials, in which both participant and clinician treating or assessing outcome were blinded to the treatment allocated;

3. placebo controlled; or

4. active controlled;

5. parallel group or cross-over studies.

Types of participants—People of any age with drug-resistant partial epilepsy (i.e. experiencing simple partial, complex partial 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 in addition to an existing AED regimen taken at time of randomisation.

3. The control group received an active 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: The proportion of people with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period was chosen as the primary outcome. It was chosen 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 patients with a complete cessation of seizures during the treatment period.

Treatment withdrawal: The proportion of people having treatment withdrawn for any reason during the course of the treatment period was used 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 have also assessed the proportion of people having treatment withdrawn for adverse effects.

Adverse effects

1. The proportion of individuals experiencing the following five adverse effects:

   - ataxia (co-ordination problems),

   - dizziness,

   - fatigue,

   - nausea,

   - somnolence (unusual drowsiness).

   These adverse effects were chosen as we considered them to be common and important adverse effects of AEDs.

2. The proportion of individuals 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 searched:

1. The Cochrane Epilepsy Group's Specialized Register (31 May 2012) using the search term 'pregabalin OR Lyrica'

2. the Cochrane Central Register of Controlled Trials (CENTRAL issue 5 of 12, *The Cochrane Library*, 2012) using the search strategy outlined in Appendix 1;

3. MEDLINE (Ovid, 1946 to May week 4, 2012) using the search strategy outlined in Appendix 2.

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. (manufacturers of pregabalin), and colleagues in the field.

Data collection and analysis

Two review authors (JP and AGM) independently assessed trials for inclusion. Any disagreements were resolved by mutual discussion.

The same two review authors extracted the following information from included trials. Again 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 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 partial/generalised epilepsy.

4. Seizure types.

5. Seizure frequency during the baseline period.

6. Number of background drugs.

For all trials sponsored by Pfizer Ltd. the following information was confirmed

1. The method of randomisation.

2. The total number randomised to each group.

3. The number of participants in each group achieving a 50% or greater reduction in seizure frequency per treatment group.

4. The number of participants having treatment withdrawn post randomisation per treatment group.

5. For those excluded:

    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—The number of participants experiencing each outcome (see Types of outcome measures) was recorded per randomised group.

Analysis—Initial analyses were undertaken using RevMan, the Cochrane Collaboration software package (RevMan 2011). Statistical heterogeneity was assessed using the I^2 statistic with an I^2 greater than 70% indicating heterogeneity. A Chi^2 test for heterogeneity was also used with a P value < 0.10 providing evidence of heterogeneity. Provided no significant statistical heterogeneity was present, the analyses used a fixed-effect model using the Mantel-Haenszel method. Where statistical heterogeneity was present then randomeffects models are presented using Mantel-Haenszel methods. Results are presented as risk ratios (RR) with 95% confidence intervals (95% CI). For individual adverse effects 99% CI is quoted to make allowance for multiple testing.

All analyses included all participants in the treatment groups to which they had been allocated. For the efficacy outcome (50% or greater reduction in seizure frequency) three analyses were planned.

1. Primary (intention-to-treat) analysis - where participants not completing follow-up or with inadequate seizure data were assumed to be non-responders.

2. Worst case - where participants not completing follow-up or with inadequate seizure data were assumed to be non-responders in the pregabalin group and responders in the placebo group.

3. Best case - where participants not completing follow-up or with inadequate seizure data were assumed to be responders in the pregabalin group and non-responders in the placebo group.

Dose regression analysis—Dose-response analysis was evaluated using a generalised linear mixed model with the logit link function xtmelogit in STATA SE version 11. Study and dose were included as fixed effects and a random effect was included for the treatment (no random effect for the constant term) as described in Turner 2000. Dose was standardised by its standard deviation (277 mg). This method estimates an odds ratio (OR) as opposed to RR.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of studies awaiting classification.

Six randomised, controlled, parallel trials were identified; these had been sponsored by the company Pfizer Ltd. A total of 2009 participants were randomised into these studies. All six of the included studies recruited participants with treatment-resistant partial seizures. Participants were taking between one and four AEDs and had at least three partial seizures per month in the pre-randomisation baseline period. Further details are given below and in the table of included studies.

Arroyo et al (Arroyo 2004) published a multicentre (45 sites in Europe, Australia and Africa) parallel trial in 2004 on 288 patients. Inclusion criteria were defined as patients 18 years or older with partial seizures. As an electroencephalogram (EEG) was not required to confirm the above, some of the 18 patients included who were stated to have 'generalised seizures' rather than secondary generalised, may have had primary generalised epilepsy. Treatment arms included 99 patients on 50 mg pregabalin three times daily (TDS) and 92 patients on 200 mg pregabalin TDS, while 97 patients were randomised to placebo. After a baseline assessment of eight weeks the trial was conducted over 12 weeks (including titration period of four and eight days). During the trial period patients 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. For further details see Characteristics of included studies as well as text below.

Baulac et al (Baulac 2010) conducted a multicentre (97 sites in Europe, Canada and Australia) parallel trial on 434 patients. Randomised patients 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 (BD) (n = 152), 150 mg to 300 mg lamotrigine BD (n = 141) and 141 patients were randomised to the placebo arm. Following a six-week baseline period, treatment was conducted over 12 weeks following a five-week titration phase (one week for pregabalin and five weeks for lamotrigine). The lamotrigine titration phase started four weeks prior to the pregabalin titration phase so all patients were started the treatment phase on the same dose. Patient review time points and follow-up were not reported.

Beydoun et al (Beydoun 2005) randomised three-hundred and thirteen patients aged 17 to 82 years from 43 US and Canadian centres. Parallel groups included 111 individuals on 200 mg pregabalin TDS, 104 on 300 mg pregabalin BD and 98 on placebo. After a baseline assessment of eight weeks the trial was conducted over 12 weeks (including a one-week titration period). Follow-up occurred on weeks 2, 4, 8 and 12. Median follow-up was 12 weeks (range not reported). During the trial an interim analysis was carried out on 129 patients. This led to alteration of the statistical analysis.

Elger et al (Elger 2005) reported a multicentre (53 sites in Canada and Europe) parallel trial of 341 patients aged 17 to 78 years. Treatment arms were 150 to 600 mg pregabalin (n = 131) titrated to clinical response and adverse effects in 150 mg daily increments and fixed-dose pregabalin of 300 mg DB (n = 137). A total of 73 people received placebo. Patients were randomised to one of the three treatments using a 1:2:2 ratio. The trial ran over 12 weeks and followed a six-week baseline period. Patients were reviewed at 2, 4, 8 and 12 weeks into the study. Median follow-up was 12 weeks and over 58% of patients completed the study in each arm. Range of follow-up was not reported.

French et al (French 2003) published a multicentre (76 sites in US and Canada) parallel trial including 455 patients. Randomised patients 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 DB regimen, and 100 patients were in the placebo group. Baseline assessment occurred over eight weeks and trial duration was 12 weeks with no titration period. Follow-up occurred on weeks 2, 4, 8 and 12. Median follow-up was 12 weeks (range one day to 12 weeks). Around 83% of patients completed the study.

Lee et al (Lee 2009) conducted a multicentre (9 sites in Korea) parallel trial consisting of two treatment arms. A total of 178 patients, aged 18 years and above, were randomised to either 75 mg to 300 mg pregabalin BD (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. Patients were assessed at weeks 2, 4, 6, 8 and 12 with a follow-up visit at week 13. Eighty-eight per cent of patients randomised completed the study.

Risk of bias in included studies

All six included studies were subject to an assessment of bias on six domains. See 'Risk of bias' tables for each study for further details.

Randomisation: four of the six studies used an adequate method of allocation concealment by using computer-generated identification numbers and block sizes of five or six. Two of the studies did not provide details of method of randomisation (Baulac 2010; Lee 2009).

Concealment: methods employed to prevent foreknowledge of group assignment were not reported in any of the studies.

Blinding: all studies reported to be double blind and used identical tablets with identical packaging for all treatment groups. Further information regarding the blinding of key study personnel, participants and outcome assessors was not provided for all studies.

Missing data: all studies reported study attrition rates and all studies used an intention-to-treat analysis on randomised patients who took at least one dose of medication and using the last-observation-carried-forwards approach. That is, for participants failing to complete follow-up, seizure-frequency data were extrapolated from the last patient observation point for the whole treatment period, while for participants with no seizure data during the treatment period, baseline data were extrapolated. In the trial reports, a total of four patients were excluded from analyses, but these patients have been included in the denominator as non-responders for calculations in this review.

Outcome reporting: most of the included studies distinguished between the primary and secondary outcome variables. All studies reported their primary/secondary outcomes within the articles; however, no trial protocols were available for examination in order to compare reported outcomes.

Other bias: in two of the studies, patients with primary generalised epilepsy may have been included in the trials possibly leading to bias within the results (Arroyo 2004; French 2003). All studies were sponsored by the same pharmaceutical company indicating the possibility of reporting bias.

See Figure 1 for 'Risk of bias' graph.

Effects of interventions

See: Summary of findings for the main comparison. Pregabalin versus placebo: 50% seizure reduction - ITT for drug-resistant partial epilepsy

Intention-to-treat analysis—As mentioned above, the six trials included a total of four patients who were randomised (one to placebo and three to treatment) but not included in the analysis, as neither took first dose of trial medication. In our primary intention-to-treat analysis, these participants are included in the denominator and assumed to be non-responders.

Pregabalin versus placebo control

Primary outcome measure: 50% seizure reduction: An intention-to-treat analysis pooling across doses (50 mg to 600 mg/day) (Analysis 1.1) shows evidence of heterogeneity (I^2 74%). A sensitivity analysis showed two studies contributing largely to the heterogeneity (Baulac 2010; Lee 2009) therefore a random effects model was employed for this outcome. See Discussion for further details. Those participants allocated pregabalin were significantly more likely to achieve a 50% or greater reduction in seizure frequency (RR 2.61; 95% CI 1.70 to 4.01) (Figure 2; Figure 3). Subgroup analyses assessing the effect of individual doses show no significant effect for 50 mg pregabalin (RR 1.06; 95% CI 0.52 to 2.12). Higher doses of pregabalin were significantly associated with 50% or greater reduction in seizure frequency (150 mg: RR 2.22; 95% CI 1.36 to 3.63; 300 mg: RR 2.86; 95% CI 1.65 to 4.94; 600 mg: RR 2.86; 95% CI 2.32 to 3.54; titrated 150 to 600mg: RR 2.86; 95% CI 1.42 to 5.76) (Analysis 1.1; Analysis 1.2; Summary of findings for the main comparison).

A best-case analysis (all drop-outs assumed to be responders to treatment) pooling across doses (50 mg to 600 mg/day) showed participants allocated to pregabalin were significantly more likely to achieve a 50% or greater reduction in seizure frequency (RR 3.58; 95% CI 2.38 to 5.39) (Analysis 1.3; Analysis 1.4). Subgroup analyses assessing the effect of individual doses show significant effects for all pregabalin doses (50 mg: RR 1.87; 95% CI 1.03 to 3.40; 150 mg: RR 2.61; 95% CI 1.63 to 4.19; 300 mg: RR 4.37; 95% CI 2.61 to 7.29; 600 mg: RR 4.32; 95% CI 2.60 to 7.17; titrated 105 to 600mg: RR 5.02; 95% CI 2.56 to 9.82).

A worst-case analysis (all drop-outs assumed to be responders to control) pooling across doses (50 mg to 600 mg/day) showed no significant differences between pregabalin and placebo (RR 1.40; 95% CI 0.65 to 3.00) (Analysis 1.5). Subgroup analyses by dose showed one dose (50 mg) to be significantly associated with seizure reduction in the placebo group compared to pregabalin (RR 0.55; 95% CI 0.30 to 0.99). There were no significant differences between group for all other doses (150 mg: RR 1.32; 95% CI 0.88 to 1.96; 300 mg: RR 1.48; 95% CI 0.98 to 2.23; 600 mg: RR 1.64; 95% CI 0.78 to 3.44; titrated 150 to 600mg: RR 0.35; 95% CI 0.27 to 0.46).

Dose regression analysis for 50% response: We fitted a generalised linear mixed model (logit link) to estimate the effect of dose (details in Methods). This method estimates an OR as opposed to an RR. Dose was standardised by its standard deviation (277 mg). The odds of response (50% reduction in seizure frequency) more than doubled (OR 2.12; 95% CI 1.76 to 2.54 with estimated between-study standard deviation of 0.49 (standard error (SE) 0.22)) for each 279 mg increase in dose of pregabalin. This translates into an estimated doubling of odds of response with an increase in dose from 300 mg to 600 mg.

Secondary outcome measures

Seizure freedom: Three trials (Arroyo 2004; Beydoun 2005; French 2003) gave data for the proportion of patients free of seizures for the last eight weeks of the treatment phase, while a fourth trial (Elger 2005) gave the number free of seizures for the last 12 weeks. Baulac 2010 provided percentages of patients free of seizures over the 17-week study period and Lee

2009 gave proportions over the 12-week double-blind period and any 28-day period. An analysis pooling across doses (50 mg/day to 600 mg/day) showed no evidence of heterogeneity (I^2 0%). Pregabalin was significantly associated with freedom from seizures (RR 2.59; 95% CI 1.05 to 6.36; Analysis 2.1).

Treatment withdrawal for any reason: An analysis pooling across doses (50 mg/day to 600 mg/day) showed no evidence of heterogeneity (I^2 0%). Participants allocated pregabalin were significantly more likely to have withdrawn from treatment (RR 1.39; 95% CI 1.13 to 1.72; Analysis 3.1). Subgroup analyses assessing the individual doses showed no significant effect for 50 mg/day pregabalin (RR 0.87; 95% CI 0.40 to 1.89), 150 mg/day pregabalin (RR 0.72; 95% CI 0.41 to 1.28), 300 mg/day daily dose (RR 1.62; 95% CI 0.85 to 3.10) and 150 to 600 mg titrated dose of pregabalin (RR 1.02; 95% CI 0.61 to 1.71). The only dose associated with significant withdrawal for all reasons was 600 mg/day (RR 1.65; 95% CI 1.33 to 2.04) (Analysis 3.1).

Treatment withdrawal due to adverse effects: An analysis pooling across doses (50 mg/day to 600 mg/day) showed no evidence of heterogeneity (I^2 0%). Participants allocated pregabalin were significantly more likely to withdraw from treatment for adverse effects (RR 2.69; 95% CI 1.88 to 3.86; Analysis 4.1). Subgroup analyses assessing treatment withdrawal with differing doses of pregabalin showed a higher withdrawal rate with higher doses (50 mg/day: RR 1.36; 95% CI 0.43 to 4.31; 150 mg/day: RR 1.02; 95% CI 0.45 to 2.32; 300 mg/day: RR 2.89; 95% CI 1.07 to 7.78; 600 mg/day: RR 3.39; 95% CI 2.36 to 4.87; Analysis 4.1). In Elger 2005, one treatment group had the dose titrated up to 150/day to 600 mg/day according to clinical response. The RR for withdrawal for this group was 1.78 (95% CI 0.68 to 4.67; Analysis 4.1).

Adverse events: In addition to the five pre-specified adverse effects, weight gain and headache were among the most common adverse effects reported. Analyses pooling across doses (50 mg/day to 600 mg/day) indicated that ataxia (RR 3.90; 99% CI 2.05 to 7.42; Analysis 5.1), dizziness (RR 3.06; 99% CI 2.16 to 4.34; Analysis 5.3), somnolence (RR 2.08; 99% CI 1.45 to 2.99; Analysis 5.5) and weight gain (RR 4.92; 99% CI 2.41 to 10.03; Analysis 5.6) were significantly associated with pregabalin, while fatigue (RR 1.28; 99% CI 0.88 to 1.86; Analysis 5.2), headache (RR 0.75; 99% CI 0.52 to 1.08; Analysis 5.7) and nausea (RR 1.14; 99% CI 0.51 to 2.53; Analysis 5.4) were not.

Pregabalin versus lamotrigine—Only one included study (Baulac 2010) compared pregabalin with an active control drug (lamotrigine), therefore the pooling of data could not be undertaken for this comparison.

Primary outcome measure: 50% seizure reduction: Within this study, participants allocated to pregabalin were significantly more likely to achieve a 50% or greater reduction in seizure frequency (RR 1.47; 95% CI 1.03 to 2.12) than those allocated lamotrigine (Analysis 6.1). A best-case analysis (all drop-outs assumed to be responders to treatment) revealed a significant increase in seizure reduction in favour of the pregabalin group (RR 2.73; 95% CI 1.99 to 3.74). A worst-case analysis (all drop-outs assumed to be responders to

control) revealed a significant increase in seizure reduction in favour of the control group (RR 0.68; 95% CI 0.52 to 0.88) (Analysis 6.6).

Secondary outcome measures

Seizure freedom: No significant differences were found between pregabalin and lamotrigine for seizure frequency (RR 1.39; 95% CI 0.40 to 4.83; Analysis 6.2).

Treatment withdrawal for any reason: No significant differences were found between pregabalin and lamotrigine for withdrawal from the study due to any reason (RR 1.07; 95% CI 0.75 to 1.52; Analysis 6.3).

Treatment withdrawal due to adverse effects: No significant differences were found between pregabalin and lamotrigine for withdrawal from the study due to adverse events (RR 0.96; 95% CI 0.57 to 1.60; Analysis 6.4).

Adverse events: Within this study, patients allocated to pregabalin were significantly more likely to experience dizziness (RR 2.94; 99% CI 1.32 to 6.52) than patients allocated lamotrigine (Analysis 6.5). No other differences were found for the remaining adverse events between pregabalin and lamotrigine (ataxia: RR 1.72; 99% CI 0.54 to 5.55; fatigue: RR 1.72; 99% CI 0.77 to 3.83; somnolence: RR 1.99; 99% CI 0.91 to 4.33; weight gain: RR 4.33; 99% CI 0.86 to 21.68; headache: RR 0.52; 99% CI 0.26 to 1.05; (Analysis 6.5)).

DISCUSSION

This systematic review is one in a series of reviews analysing effects of new AEDs on treatment-resistant localisation-related epilepsy. We identified six industry-sponsored (Pfizer Ltd.) randomised placebo-controlled parallel trials. All studies were of good methodological quality and most were randomised using suitable sequence generation methods; all studies did not report methods of concealing allocation; all were reported to be double blinded and had few patients lost to follow-up. Summary trial data were taken from the relevant publications and individual patient data were not obtained. The approach to analysis for all of the included trials used the last-observation-carried-forwards approach. For participants failing to complete follow-up, seizure frequency data were extrapolated to the whole treatment period, while for participants with no seizure data during the treatment period, baseline data were extrapolated. While 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.

The included studies tested doses ranging from 50 mg/day to 600 mg/day. The results showed that pregabalin, when used as add-on treatment, can reduce seizure frequency in individuals with treatment-resistant localisation-related epilepsy. In the analysis, when all doses of pregabalin were pooled, the RR for a 50% or greater reduction in seizure frequency was 2.61 (95% CI 1.70 to 4.01), thus demonstrating that out of 100 people with refractory epilepsy 40 are likely to have their seizures reduced when taking pregabalin compared to 15 out of 100 people not taking pregabalin. The large heterogeneity statistic associated with this result led to a sensitivity analysis that revealed two studies to be contributing largely. There

were three main reasons for this: one study Lee 2009 was conducted in Korea and used a non-Western population sample and two studies, Baulac 2010 and Lee 2009, were conducted at later times and therefore treatment regimens may have been different from earlier therapies. Both of these trials had the 150 mg/day to 300 mg/dayTD and 75 mg/day to 300 mg/day TD treatment arms, therefore heterogeneity could also be due to the range of doses administered within the studies. Heterogeneity between studies was not found for any of the other outcomes.

A generalised linear mixed-model analysis showed evidence of a dose effect, suggesting that using pregabalin as an add-on treatment at 600 mg dose doubles the odds of reducing seizures compared to 300 mg. Participants taking pregabalin were also found to be more likely to be free of seizures than controls.

Participants were more likely to withdraw for any reason or because of adverse effects from pregabalin than from placebo. In both cases, treatment withdrawal was more likely on higher doses. Although the assessment of adverse events showed that ataxia, dizziness, somnolence and weight gain were significantly associated with pregabalin, these adverse events were not documented using a checklist or other systematic approach, but required physician reporting, so event rates may have been underestimated.

The one study (Baulac 2010) that examined the effectiveness of pregabalin in comparison to another add-on drug (lamotrigine) showed that pregabalin was more effective in reducing seizure frequency than lamotrigine. Participants taking pregabalin were no more likely to be free of seizures than participants taking lamotrigine. Participants taking pregabalin were not more likely to withdraw from the study than participants taking lamotrigine. This was found for both any reason for withdrawal and due to adverse events. Only dizziness was found to be significantly more prevalent when taking pregabalin.

In summary, pregabalin (150 mg/day to 600 mg/day) as an add-on drug can effectively reduce seizures by 50% or more in people with partial epilepsy. However, the addition of pregabalin doubled seizure freedomhad four significant adverse effects, ataxia, dizziness, somnolence and weight gain.

AUTHORS' CONCLUSIONS

Implications for practice

In the short term (12 weeks) 150 mg/day to 600 mg/day of pregabalin given in a three times regimen can significantly reduce seizure frequency and significantly increase seizure freedom rates in people with treatment-resistant partial epilepsy. Adverse events significantly associated with pregabalin were ataxia, dizziness, somnolence and weight gain. There are currently no data regarding cost-effectiveness, longer-term effectiveness of pregabalin versus placebo and, more importantly, versus other adjunctive treatments.

Implications for research

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

1. compare 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 AEDs.

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

Acknowledgments

Appendix 1. CENTRAL search strategy

#1 (pregabalin or Lyrica)

#2 MeSH descriptor Epilepsy explode all trees

#3 MeSH descriptor Seizures explode all trees

#4 epilep* or seizure* or convulsion*

#5 (#2 OR #3 OR #4)

#6 (#1 AND #5)

Appendix 2. MEDLINE search strategy

The most recent version of this review used the following search strategy, which is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011).

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp animals/not humans.sh.

10. 8 not 9

11. exp Epilepsy/

12. exp Seizures/

13. (epilep$ or seizure$ or convuls$).tw.

14. 11 or 12 or 13

15. (pregabalin or lyrica).tw.

16. 10 and 14 and 15

Earlier versions of this review employed the following search strategy. It was based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE as described in Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0, updated March 2011) (Higgins 2011).

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. exp Randomized Controlled Trials/

4. exp Random Allocation/

5. exp Double-Blind Method/

6. exp Single-Blind Method/

7. 1 or 2 or 3 or 4 or 5 or 6

8. (animals not humans).sh.

9. 7 not 8

10. clinical trial.pt.

11. Clinical Trial/

12. (clin$ adj trial$).ab,ti.

13. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ab,ti.

14. exp PLACEBOS/

15. placebo$.ab,ti.

16. random$.ab,ti.

17. exp Research Design/

18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. (animals not humans).sh.

20. 18 not 19

21. 9 or 20

22. epilep$.tw.

23. exp EPILEPSY/

24. seizure$.tw.

25. exp SEIZURES/

26. convulsion$.tw.

27. 22 or 23 or 24 or 25 or 26

28. Lyrica.tw.

29. pregabalin.tw.

30. 28 or 29

31. 21 and 27 and 30

CHARACTERISTICS OF STUDIES

Characteristics of included studies

[ordered by study ID]

Arroyo 2004

Methods	Randomised double-blind placebo (PCB) controlled parallel multicentre (45 in Europe, Australia and South Africa) trial. 3 treatment arms: 1 PCB, 2 PGB. Patients randomised in blocks of 6, each allocated unique ID number. All patients received 2 capsules TDS 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 treatment-resistant partial epilepsy. Patients were on 1 to 4 baseline AEDs. 344 patients screened, 288 patients randomised: 97 patients to PCB (mean baseline 28-day seizure frequency: 23. 5), 99 patients to 50 mg/day PGB TDS (mean baseline 28-day seizure frequency: 26.2) and 92 patients to 200 mg/day PGB TDS (mean baseline 28-day seizure frequency: 19. 3)
Interventions	Group 1: PCB Group 2: PGB 50 mg TDS (4-day titration phase) Group 3: PGB 200 mg TDS (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, ad verse events
Notes	Study used capsules of 2 sizes, containing 25 mg PGB or PCB (size 1# = small capsules) ; and 100 mg PGB or PCB (size 4# = large capsules). It is stated that patients received 2 capsules TDS. One patient excluded from ITT in PCB arm, as failed to take study drugs

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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis performed

| Selective reporting (reporting bias) | Unclear 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 | High risk | As an EEG was not required to confirm the above, some of the 18 patients included who were stated to have 'generalised seizures' rather than secondary generalised, may have had primary generalised epilepsy
Sponsored by the same pharmaceutical company (Pfizer Ltd.) as with all the other included trials |

Baulac 2010

Methods	Randomised double-blind PCB and active drug controlled parallel multicentre (97 in Europe, Canada and Australia) trial. 3 treatment arms: 1 PCB, 1 PGB and 1 LTG. Patients randomised to 1 of 3 treatment arms (no further information available). Duration of baseline period: 6 weeks. 12-week treatment period with 5-week titration phase before treatment (1 week of titration for PGB and 5 weeks of titration for LTG)
Participants	Adults aged 16 to 82 years (mean 39.4 years), 48.5% male, all with treatment-resistant partial epilepsy confirmed by history and recent EEG. Patients were on 1 to 3 baseline AEDs. 546 patients screened, 434 patients randomised: 141 patients to PCB (mean baseline 28-day seizure frequency: 16.38), 152 patients to 150 mg to 300 mg PGB BD (mean baseline 28-day seizure frequency: 21.32), and 141 patients to 150 mg to 300 mg LTG BD (mean baseline 28-day seizure frequency: 21.80)
Interventions	Group 1: PCB Group 2: PGB 150 mg to 300 mg BD (1-week titration phase) Group 3: LTG 150 mg to 300 mg BD (5-week titration phase)
Outcomes	Primary outcome: change in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, seizure freedom, adverse events
Notes	One patient randomised to the PCB group failed to take > 1 dose of medication, and therefore was excluded from ITT analysis. No information provided on methods of randomisation, concealment or blinding

Risk of bias

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 concealment of allocation
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)	Unclear 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	High risk	Sponsored by same pharmaceutical company (Pfizer Ltd.) as with all the other included trials

Beydoun 2005

Methods	Randomised double-blind PCB controlled parallel multicentre (43 in USA and Canada) trial. 3 treatment arms: 1 PCB, 2 PGB. Patients randomised in blocks of 6, each allocated unique ID number. All patients received TDS regimen of blinded capsules (no further information available). Duration of baseline period: 8 weeks. 1-week titration period and 11-week treatment period
Participants	Adults aged 17 to 82 years (mean 39.1 years), 50.2% male, all with treatment-resistant partial epilepsy confirmed by history and recent EEG. Patients were on 1 to 4 baseline AEDs. 378 patients screened, 313 patients randomised: 98 patients to PCB (mean baseline 28-day seizure frequency: 25.1), 104 patients to 300 mg PGB BD (mean baseline 28-day seizure frequency: 21.5), and 111 patients to 200 mg PGB TDS (mean baseline 28-day seizure frequency: 21.3)
Interventions	Group 1: PCB Group 2: 300 mg PGB BD (1-week titration phase) Group 3: 200 mg PGB TDS (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
Notes	One patient randomised to the 300 mg BD group failed to take tablets, and therefore was excluded from ITT analysis. Blinding was broken with 1 patient in the PCB arm when she became pregnant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomised in blocks of 6 and al located unique ID number
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	Low risk	All patients received identical capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis employed
Selective reporting (reporting bias)	Unclear 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	High risk	Sponsored by same pharmaceutical company (Pfizer Ltd.) as with all the other included trials

Elger 2005

Methods	Randomised double-blind PCB controlled parallel multicentre (53 in Europe and Canada) trial. 3 treatment arms: 1 PCB, 2 PGB. Patients 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 partial epilepsy confirmed by personal and family history as well as recent EEG. Patients were on 1 to 5 baseline AEDs. 400 patients screened, 341 patients randomised: 73 patients to PCB (median baseline 28-day seizure frequency: 8.7), 137 patients to 300 mg PGB BD fixed (median baseline 28-day seizure frequency: 10), and 131 patients to PGB flexible dosing (median baseline 28-day seizure frequency: 9.33)
Interventions	Group 1: PCB Group 2: 300 mg PGB DB fixed dose Group 3: 75 mg to 300 mg PGB BD flexible titration at physician's discretion

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 events
Notes	In PGB titration and PCB 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients 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)	Unclear 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	High risk	Sponsored by same pharmaceutical company as with all the other included trials

French 2003

Methods	Randomised double-blind PCB-controlled parallel multicentre (71 in the USA and 5 in Canada) trial. 5 treatment arms: 1 PCB, 4 PGB. Patients 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 partial epilepsy. Patients were on 1 to 4 baseline AEDs. 586 patients screened, 455 patients randomised: 100 patients to PCB (mean baseline seizure frequency: 22.3); 88 patients to 50 mg PGB (mean baseline seizure frequency: 27.4); 88 patients to 150 mg PGB (mean baseline 28-day seizure frequency: 23.1); 90 patients to 300 mg PGB (mean baseline 28-day seizure frequency: 19.1) and 89 patients to 600 mg PGB (mean baseline 28-day seizure frequency: 18.6)
Interventions	Group 1: PCB Group 2: 50 mg PGB daily Group 3: 150 mg PGB Group 4: 300 mg PGB Group 5: 600 mg PGB daily
Outcomes	Primary outcome: reduction in seizure frequency compared to baseline (response ratio) Secondary outcomes: responder rate, pairwise comparisons with PCB, adverse events
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 patients who developed visual field defect. 2 patients 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence	Low risk	Used a computer-generated randomised schedule using block sizes of 5

generation (selection bias)		
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear 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)	Unclear 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	High risk	Possibility of the inclusion of patients with primary generalised epilepsy Sponsored by same pharmaceutical company as with all the other included trials

Lee 2009

Methods	Randomised double-blind PCB-controlled parallel multicentre (9 in Korea) trial. 2 treatment arms: 1 PCB, 1 PGB. Patients 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	Patients 18 years and above (mean 34.2 years), 48.3% male, all with treatment-resistant partial epilepsy. Patients were on 1 to 3 baseline AEDs. 209 patients screened, 178 patients randomised: 59 patients to PCB (mean baseline 28-day seizure frequency: 13. 2) and 119 patients to 150 mg to 600 mg PGB (mean baseline 28-day seizure frequency 13.2)
Interventions	Group 1: PCB Group 2: 150 mg/day to 600 mg/day
Outcomes	Primary outcome: change in seizure frequency (response ratio) Secondary outcomes: responder rate, seizure freedom, anxiety/depression, sleep, quality of life, adverse events
Notes	All randomised patients included in ITT analysis. No information provided on methods of randomisation, concealment or blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients 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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported. ITT analysis employed

Selective reporting (reporting bias)	Unclear 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	High risk	Sponsored by same pharmaceutical company (Pfizer Ltd.) as with all the other included trials

AED: antiepileptic drug; BD: twice daily; EEG: electroencephalogram; GTCS: generalised tonic-clonic seizures; ITT: intention-to- treat analysis; LEV: levetiracetam; LTG: lamotrigine; PCB: placebo; PGB: pregabalin; TDS: three times a day

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 partial epilepsy (32 in each treatment arm)
Interventions	Group 1: starting dose of 1000 mg BD LEV fast rate with weekly increments of 500 mg Group 2: starting dose of 500 mg BD LEV slow rate with weekly increments of 250 mg Group 3: starting dose of 300 mg BD PGB fast rate with weekly increments of 150 mg Group 4: starting dose of 150 mg BD PGB slow rate with weekly increments of 75 mg
Outcomes	Rate of withdrawals and continuation to maximum dose Incidence of adverse events
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. Patients 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. Patients 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 events
Notes	Study reported in abstract only. Further details of study are unavailable

LEV: levetiracetam

DATA AND ANALYSES

Comparison 1
Pregabalin versus placebo: 50% seizure reduction - ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% responders, ITT	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.52, 2.12]
1.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.36, 3.63]
1.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [1.65, 4.94]
1.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [2.32, 3.54]
1.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [1.42, 5.76]
1.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [2.06, 3.16]
2 50% responders (random effects)	6	1868	Risk Ratio (M-H, Random, 95% CI)	2.61 [1.70, 4.01]
3 50% responders, Best Case Analysis	6	4206	Risk Ratio (M-H, Fixed, 95% CI)	3.72 [3.27, 4.23]
3.1 50mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.03, 3.40]
3.2 150mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [1.63, 4.19]
3.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	4.37 [2.61, 7.29]
3.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 95% CI)	4.09 [3.34, 5.01]
3.5 Titrated dose of pregabalin (150-600mg)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	5.02 [2.56, 9.82]
3.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 95% CI)	3.60 [2.93, 4.43]
4 50% responders, Best Case Analysis Random Effects	6	3240	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.92, 2.45]
4.1 600 mg pregabalin	6	1372	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.78, 3.44]
4.2 Any dose pregabalin	6	1868	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.65, 3.00]
5 50% responders, Worst Case Analysis	6	4206	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.14]
5.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.30, 0.99]
5.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.88, 1.96]
5.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.98, 2.23]
5.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.08, 1.43]
5.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.27, 0.46]
5.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.94, 1.23]

Comparison 2

Pregabalin versus placebo: seizure freedom - ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure freedom post titration	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	3.40 [0.14, 82.52]
1.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.92]
1.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 600 mg pregabalin	6	1880	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [1.02, 5.91]
1.5 Titrated dose of pregabalin (150-600mg)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	5.05 [0.28, 92.42]
1.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.05, 6.36]

Comparison 3

Pregabalin versus placebo: treatment withdrawal (any reason) - ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment withdrawal any reason	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.40, 1.89]
1.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.41, 1.28]
1.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.85, 3.10]
1.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.33, 2.04]
1.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.61, 1.71]
1.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.13, 1.72]

Comparison 4
Pregabalin versus placebo: treatment withdrawal
(adverse events) - ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment withdrawal for adverse events	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.43, 4.31]
1.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.45, 2.32]
1.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [1.07, 7.78]
1.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 95% CI)	3.39 [2.36, 4.87]
1.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.68, 4.67]
1.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.88, 3.86]

Comparison 5
Pregabalin versus placebo: adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ataxia	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
1.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	1.14 [0.14, 9.00]
1.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	1.98 [0.56, 7.01]
1.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	3.33 [0.62, 17.81]
1.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 99% CI)	4.93 [2.56, 9.48]
1.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	2.23 [0.44, 11.26]
1.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 99% CI)	3.90 [2.05, 7.42]
2 Fatigue	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
2.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	0.71 [0.17, 2.94]
2.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	1.09 [0.50, 2.39]
2.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	1.53 [0.49, 4.76]
2.4 600 mg pregabalin	6	1503	Risk Ratio (M-H, Fixed, 99% CI)	1.32 [0.89, 1.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	1.23 [0.49, 3.04]
2.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 99% CI)	1.28 [0.88, 1.86]
3 Dizziness	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
3.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	1.01 [0.31, 3.33]
3.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	2.04 [0.99, 4.22]
3.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	3.46 [1.39, 8.62]
3.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 99% CI)	3.57 [2.50, 5.09]
3.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	2.97 [1.01, 8.77]
3.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 99% CI)	3.06 [2.16, 4.34]
4 Nausea	3		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
4.1 150 mg pregabalin	1	196	Risk Ratio (M-H, Fixed, 99% CI)	1.31 [0.34, 5.00]
4.2 600 mg pregabalin	3	712	Risk Ratio (M-H, Fixed, 99% CI)	1.18 [0.51, 2.75]
4.3 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	1.11 [0.12, 10.05]
4.4 Any dose pregabalin	3	942	Risk Ratio (M-H, Fixed, 99% CI)	1.14 [0.51, 2.53]
5 Somnolence	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
5.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	0.93 [0.31, 2.78]
5.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	1.26 [0.58, 2.74]
5.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	1.62 [0.63, 4.12]
5.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 99% CI)	2.42 [1.68, 3.50]
5.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	2.32 [0.77, 7.04]
5.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 99% CI)	2.08 [1.45, 2.99]
6 Weight gain	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
6.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	3.40 [0.05, 224.69]
6.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	3.85 [0.64, 23.35]
6.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	14.43 [0.34, 620.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 99% CI)	5.61 [2.74, 11.47]
6.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	2.79 [0.84, 9.29]
6.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 99% CI)	4.92 [2.41, 10.03]
7 Headache	6		Risk Ratio (M-H, Fixed, 99% CI)	Subtotals only
7.1 50 mg pregabalin	1	188	Risk Ratio (M-H, Fixed, 99% CI)	0.52 [0.16, 1.77]
7.2 150 mg pregabalin	2	384	Risk Ratio (M-H, Fixed, 99% CI)	0.53 [0.24, 1.17]
7.3 300 mg pregabalin	1	190	Risk Ratio (M-H, Fixed, 99% CI)	0.43 [0.12, 1.57]
7.4 600 mg pregabalin	6	1372	Risk Ratio (M-H, Fixed, 99% CI)	0.77 [0.51, 1.15]
7.5 Titrated dose of pregabalin (150-600 mg)	1	204	Risk Ratio (M-H, Fixed, 99% CI)	1.25 [0.45, 3.50]
7.6 Any dose pregabalin	6	1868	Risk Ratio (M-H, Fixed, 99% CI)	0.75 [0.52, 1.08]

Comparison 6
Pregabalin versus Lamotrigine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% responders, ITT	1	293	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.03, 2.12]
2 Seizure freedom	1	293	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.40, 4.83]
3 Treatment withdrawal (any reason)	1	293	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.75, 1.52]
4 Treatment withdrawal (adverse events)	1	304	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.57, 1.60]
5 Adverse events	1	1758	Risk Ratio (M-H, Fixed, 99% CI)	1.57 [1.12, 2.20]
5.1 Ataxia	1	293	Risk Ratio (M-H, Fixed, 99% CI)	1.72 [0.54, 5.55]
5.2 Fatigue	1	293	Risk Ratio (M-H, Fixed, 99% CI)	1.72 [0.77, 3.83]
5.3 Dizziness	1	293	Risk Ratio (M-H, Fixed, 99% CI)	2.94 [1.32, 6.52]
5.4 Somnolence	1	293	Risk Ratio (M-H, Fixed, 99% CI)	1.99 [0.91,4.33]
5.5 Weight gain	1	293	Risk Ratio (M-H, Fixed, 99% CI)	4.33 [0.86, 21.68]
5.6 Headache	1	293	Risk Ratio (M-H, Fixed, 99% CI)	0.52 [0.26, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 50% responders, Best and Worst Case Analysis	1	586	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.09, 1.60]
6.1 Best Case	1	293	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.99, 3.74]
6.2 Worst Case	1	293	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.52, 0.88]

WHAT'S NEW

Last assessed as up-to-date: 12 June 2012.

Date	Event	Description
12 June 2012	New search has been performed	Two new studies were included in this update of the original review

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 1, 2008

Date	Event	Description
7 August 2009	Amended	Copyedits made at editorial base.
16 September 2008	Amended	Converted to new review format.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Pregabalin versus placebo: 50% seizure reduction - ITT for drug-resistant partial epilepsy

Patient or population: patients with drug-resistant partial epilepsy

Settings:

Intervention: Pregabalin versus placebo: 50% seizure reduction - ITT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Pre-gabalin versus placebo: 50% seizure reduction - ITT**				

Patient or population: patients with drug-resistant partial epilepsy					
Settings:					
Intervention: Pregabalin versus placebo: 50% seizure reduction - ITT					
50% responders, ITT - any dose pregabalin	**15 per 100**	**40 per 100** (26 to 61)	**RR 2.61** (1.7 to 4.01)	1868 (6 studies)	⊕⊕⊕◯ **moderate** *1,1*

CI: Confidence interval;

RR: Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

*
The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

1
High heterogeneity statistic.

2
All studies sponsored by the same pharmaceutical company all reporting significant findings.

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* Indicates the major publication for the study

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PLAIN LANGUAGE SUMMARY

Pregabalin add-on for drug-resistant partial epilepsy

Use of pregabalin in combination with other antiepileptic drugs can reduce the frequency of seizures, but has some adverse effects.

Approximately one in 400 people have epileptic seizures that continue despite antiepileptic drug treatment. This review summarises data from six trials that included a total of 2009 participants. In addition to their usual antiepileptic drugs, participants were randomised to take pregabalin (an antiepileptic drug) or control drug. Results showed that patients taking pregabalin were two to three times more likely to reduce their seizure frequency by more than 50% than those taking placebo and two to three times more likely to increase seizure freedom over a 12-week interval. Pregabalin was shown to be effective across a range of doses (150 mg to 600 mg) with increasing effectiveness at higher doses. Side effects associated with pregabalin included co-ordination problems, dizziness, sleepiness, and weight gain. There are no data regarding the longer-term effectiveness of pregabalin; this should be investigated in future studies.
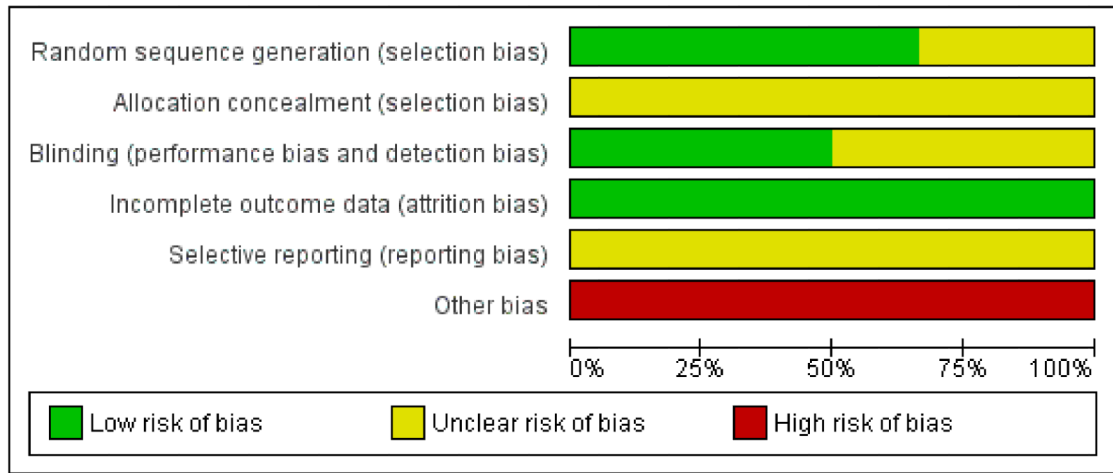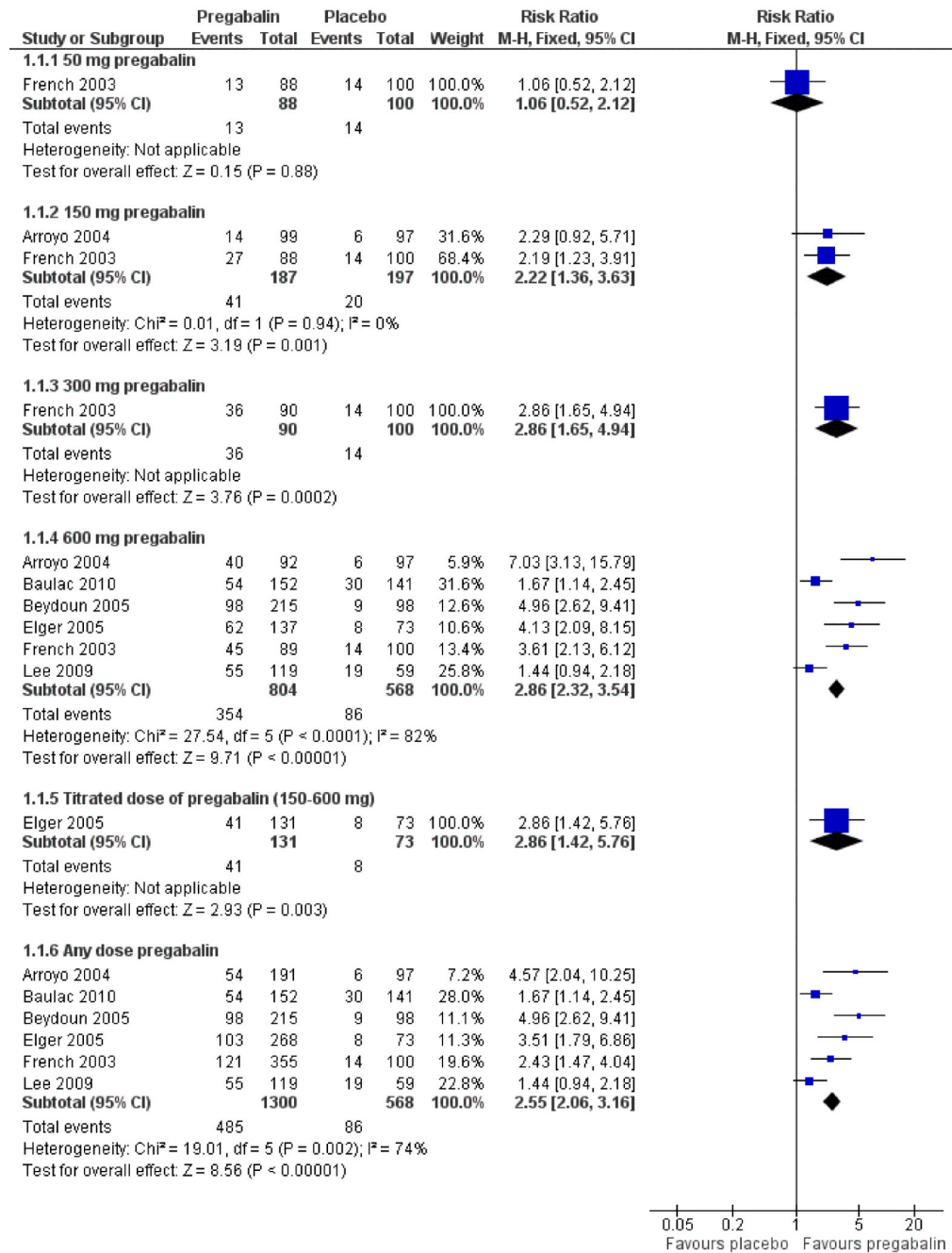
Figure 1.

Figure 2. Forest plot of comparison: 1 Pregabalin versus placebo: 50% seizure reduction - ITT, outcome: 1.1 50% responders, ITT
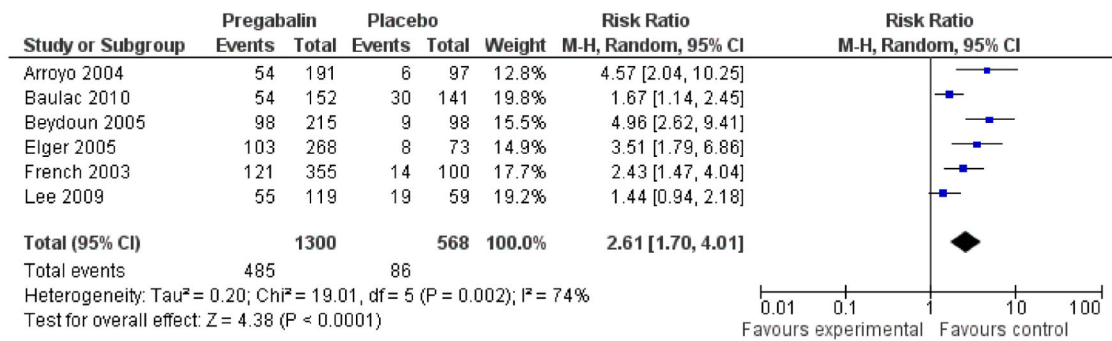
Figure 3. Forest plot of comparison: 1 Pregabalin versus placebo: 50% seizure reduction - ITT, outcome: 1.2 50% responders (random effects)