Topiramate add-on therapy for drug-resistant focal epilepsy

Review information

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Dates

Assessed as Up-to-date:	2 July 2018
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What's new

Date	Event	Description
2 July 2018	New citation: conclusions not changed	Conclusions are unchanged.
2 July 2018	Updated	Searches updated 2 July 2018; one new study has been included (Chung 2014).

History

Date	Event	Description
18 June 2013	New citation: conclusions not changed	One new study added to the review; authors of review changed.
18 June 2013	Updated	Search re-run to include head-to-head trials; new 'Summary of findings' table; methods sections updated.
31 August 2012	New citation: conclusions not changed	Updated search, added additional study and re-ran analyses including additional side effect analyses. Additional figure to better demonstrate the dose-response analysis. Completed 'Risk of bias' assessment for all included studies. Completed 'Summary of findings' table. Studies added to excluded studies. MEDLINE search strategy included.
24 October 2008	Amended	Search strategy amended to comply with RevMan 5 format.
24 April 2008	Amended	Converted to new review format.
24 April 2008	Updated	We re-ran our searches on 10 May 2007 – several potentially relevant studies were found.
24 April 2008	New citation: conclusions not changed	New studies have been added to the 'included', 'excluded' and 'ongoing assessment' sections. Analysis has been re-run and the text of the study has been updated to take into account the newly included studies.
22 April 2002	New citation: conclusions changed	Substantive amendment.

Abstract

Background

The majority of people with epilepsy have a good prognosis and their seizures are controlled by a single antiepileptic drug. However, up to 20% of patients from population-based studies, and up to 30% from clinical series (not population-based), develop drug-resistant epilepsy, especially those with focal-onset seizures. In this review, we summarise the current evidence regarding topiramate, an antiepileptic drug first marketed in 1996, when used as an add-on treatment for drug-resistant focal epilepsy.

This is an update of a Cochrane Review first published in 1999, and last updated in 2014.

Objectives

To evaluate the efficacy and tolerability of topiramate when used as an add-on treatment for people with drug-resistant focal epilepsy.

Search methods

For the latest update of this review we searched the following databases on 2 July 2018: Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (Ovid, 1946–); ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). We imposed no language restrictions. We also contacted the manufacturers of topiramate and researchers in the field to identify any ongoing or unpublished studies.

Selection criteria

Randomised, placebo-controlled add-on trials of topiramate, recruiting people with drug-resistant focal epilepsy.

Data collection and analysis

Two review authors independently selected trials for inclusion and extracted the relevant data. We assessed the following outcomes: (1) 50% or greater reduction in seizure frequency; (2) seizure freedom; (3) treatment withdrawal (any reason); (4) adverse effects. Primary analyses were intention-to-treat (ITT), and summary risk ratios (RRs) with 95% confidence intervals (95% CIs) are presented. We evaluated dose–response in regression models. We carried out a 'Risk of bias' assessment for each included study using the Cochrane 'Risk of bias' tool and assessed the overall certainty of evidence using the GRADE approach.

Main results

We included 12 trials, representing 1650 participants. Baseline phases ranged from four to 12 weeks and double-blind phases ranged from 11 to 19 weeks. The RR for a 50% or greater reduction in seizure frequency with add-on topiramate compared to placebo was 2.71 (95% CI 2.05 to 3.59; 12 studies; high-certainty evidence). Dose regression analysis showed increasing effect with increasing topiramate dose demonstrated by an odds ratio (OR) of 1.45 (95% CI 1.28 to 1.64; $P < 0.001$) per 200 mg/d increase in topiramate dosage. The proportion of participants achieving seizure freedom was also significantly increased with add-on topiramate compared to placebo (RR 3.67, 95% CI 1.79 to 7.54; 8 studies; moderate-certainty evidence). Treatment withdrawal was significantly higher for add-on topiramate compared to placebo (RR 2.37, 95% CI 1.66 to 3.37; 12 studies; high-certainty evidence). The RRs for the following adverse effects indicate that they are significantly more prevalent with topiramate, compared to placebo: ataxia 2.29 (99% CI 1.10 to 4.77; 4 studies); concentration difficulties 7.81 (99% CI 2.08 to 29.29; 6 studies; moderate-certainty evidence); dizziness 1.52 (99% CI 1.07 to 2.16; 8 studies); fatigue 2.08 (99% CI 1.37 to 3.15; 10 studies); paraesthesia 3.65 (99% CI 1.58 to 8.39; 7 studies; moderate-certainty evidence); somnolence 2.44 (99% CI 1.61 to 3.68; 9 studies); 'thinking abnormally' 5.70 (99% CI 2.26 to 14.38; 4 studies; high-certainty evidence); and weight loss 3.99 (99% CI 1.82 to 8.72; 9 studies; low-certainty evidence). Evidence of publication bias for the primary outcome was found (Egger test, $P = 0.001$). We rated all studies included in the review as having either low or unclear risk of bias. Overall, we assessed the evidence as moderate to high certainty due to the evidence of publication bias, statistical heterogeneity and imprecision, which was partially compensated for by large effect sizes.

Authors' conclusions

Topiramate has efficacy as an add-on treatment for drug-resistant focal epilepsy as it is almost three times more effective compared to a placebo in reducing seizures. The trials reviewed were of relatively short duration and provided no evidence for the long-term efficacy of topiramate. Short-term use of add-on topiramate was shown to be associated with several adverse events. The results of this review should only be applied to adult populations as only one study included children. Future research should consider further examining the effect of dose.

Plain language summary

Topiramate add-on for drug-resistant focal epilepsy

Background

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges from the brain. Most seizures can be controlled by a single antiepileptic drug. Unfortunately, some people require more than one antiepileptic medication to control their seizures, especially if these originate from one area of the brain (focal epilepsy), instead of affecting the entire brain (generalised epilepsy). These people are said to have drug-resistant epilepsy. Topiramate can be used in addition to other antiepileptic drugs, called an add-on treatment, to try to control drug-resistant epilepsy.

Aim of this review

This review investigated the effectiveness and tolerability of topiramate when used as an add-on treatment for people with drug-resistant focal epilepsy.

Results

We found 12 trials that investigated topiramate as an add-on treatment. They included a total of 1650 people with drug-resistant focal epilepsy. These trials compared the antiepileptic drug topiramate to a placebo drug (an inactive, dummy drug which should not show any effect) for a period of up to 18 weeks. Taking all the evidence of the trials into account, the review found that topiramate is almost three times more effective, when used with other drugs, at reducing the number of seizures in drug-resistant focal epilepsy than placebo. Adding topiramate to people's usual treatment was, however, associated with an increase in adverse effects such as problems with co-ordination (ataxia), concentration, dizziness, drowsiness (somnolence), fatigue, 'thinking abnormally', tickling or numbness of the skin (paraesthesia) and weight loss. People taking add-on topiramate were also more than twice as likely to withdraw from treatment than those taking placebo, most likely due to adverse effects.

Certainty of the evidence

We assessed the trials with regards to potential bias and certainty. Overall, we rated the certainty of the evidence as moderate to high which means that we are fairly certain that the findings that we have reported are accurate. The trials included in this review did not examine the long-term effects of topiramate as an add-on treatment

and only one study investigated the use of add-on topiramate in children. The findings should, therefore, only be applied to adults with drug-resistant focal epilepsy. Future research should test which dose is most effective.

The evidence is current to July 2018.

Background

This is an update of a Cochrane Review first published in 1999 (Jette 1999b), and last updated in 2014 (Pulman 2014). The purpose of this update is to synthesise the current data in order to understand the role of topiramate as an add-on treatment in drug-resistant focal epilepsy. For the purpose of this review, people with drug-resistant focal epilepsy have been defined as having focal-onset seizures (simple focal and/or complex focal seizures and/or secondary generalised tonic-clonic seizures) that have failed to respond to at least one monotherapy treatment with a standard antiepileptic drug.

Description of the condition

The majority of people given a diagnosis of epilepsy have a good prognosis and their seizures are controlled by treatment with a single antiepileptic drug (Kwan 2000; Reynolds 1981), but up to 20% of patients from population-based studies, and up to 30% from clinical (non population-based) series, will develop drug-resistant epilepsy (Cockerell 1995; Kwan 2000), often requiring treatment with combinations of antiepileptic drugs. This presents a significant therapeutic problem when approximately 1% of the general population will suffer from epilepsy at some point in their lifetime (Fiest 2017).

Description of the intervention

Over the past decade, there has been renewed interest in the development of newer antiepileptic drugs. This is largely because several of the standard antiepileptic drugs are not always successful at controlling seizures, and because some have been associated with certain adverse effects. In the first instance, new antiepileptic drugs are tested as an add-on treatment for people with drug-resistant focal epilepsy in randomised controlled trials (RCTs). Having demonstrated a therapeutic effect in these trials, new antiepileptic drugs tend to be licensed for add-on use before monotherapy trials have been undertaken, in which new antiepileptic drugs are compared with standard ones.

How the intervention might work

There are an ever increasing number of licensed antiepileptic drugs from which to choose from, for people with drug-resistant focal epilepsy. This review focuses upon the effects of topiramate, a drug whose mechanisms of action include a modulatory effect on voltage-dependent sodium conductance (Coulter 1993), enhancement of gamma-aminobutyric acid-A (GABAA)-mediated chloride flux (Brown 1993), antagonism of kainate receptor-mediated excitatory currents (Gryder 2003), and inhibition of carbonic anhydrase, an enzyme necessary for GABAergic neurotransmission (Herrero 2002). Topiramate was licensed for add-on use in the UK in 1996.

Why it is important to do this review

In this review, we summarise evidence from RCTs which have investigated the effects of topiramate in people with drug-resistant focal epilepsy in order to aid clinical decision-making when prescribing antiepileptic drug treatments within this population.

Objectives

To evaluate the efficacy and tolerability of topiramate when used as an add-on treatment for people with drug-resistant focal epilepsy.

Methods

Criteria for considering studies for this review

Types of studies

Studies had to meet all of the following criteria.

1. RCTs
2. Double- or single-blinded trials
3. Placebo-controlled
4. Parallel-group or cross-over studies
5. Minimum treatment period of eight weeks

Types of participants

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

Types of interventions

1. The active treatment group received treatment with topiramate in addition to conventional antiepileptic drug treatment.

2. The control group received a matched placebo or an alternative dose of topiramate in addition to conventional antiepileptic drug treatment.

Types of outcome measures

Primary outcomes

50% or greater reduction in seizure frequency

The primary outcome is the proportion of people with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period. This outcome was chosen as it is commonly reported in this type of study. Furthermore, this outcome can also be calculated for studies which report baseline and follow-up seizure frequencies.

Secondary outcomes

Seizure freedom

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

Treatment withdrawal

The proportion of people having treatment withdrawn 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 participants make a direct contribution. In trials of short duration, it is likely that adverse effects will be the most common reason for withdrawal.

Adverse effects

The proportion of people experiencing:

1. ataxia;
2. dizziness;
3. headache;
4. nausea/vomiting;
5. paraesthesias;
6. weight loss/decrease;
7. fatigue;
8. somnolence;
9. concentration impairment;
0. speech difficulty;
1. thinking abnormally.

We chose these adverse effects as we considered them to be common and important adverse effects of antiepileptic drugs.

Search methods for identification of studies

Electronic searches

We ran searches for the original review on 18 June 2013, and subsequent searches in August 2016 and November 2016. For the latest update, we searched the following databases on 2 July 2018.

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

There were no language restrictions.

Previously we also searched SCOPUS (1823 to 18 June 2013) as an alternative to Embase, using the strategy outlined in Appendix 5. This is no longer necessary, because randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL, so the SCOPUS search has not been updated.

Searching other resources

We reviewed reference lists of included studies to search for additional reports of relevant studies and contacted Johnson and Johnson for information about any unpublished or ongoing studies.

Data collection and analysis

Selection of studies

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

Data extraction and management

We extracted the following information for each trial using a data extraction form.

Methodological/trial design

1. Method of randomisation and allocation concealment
2. Method of blinding
3. Whether any participants had been excluded from reported analyses
4. Length of baseline period
5. Length of treatment period
6. Dose(s) of topiramate tested

Patient/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

Most of the trials found were sponsored by Johnson and Johnson who were asked to confirm 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 per treatment group
4. Number of participants having treatment withdrawn post-randomisation per treatment group
5. For those excluded:
   a. the reason for exclusion;
   b. whether any of those excluded completed the treatment phase;
   c. whether any of those excluded had a 50% or greater reduction in seizure frequency during the treatment phase.

Outcomes

We recorded the number of people experiencing each outcome (see Types of outcome measures) per randomised group. We contacted authors of trials for any missing information.

Assessment of risk of bias in included studies

Two review authors (RB and JH) independently made an assessment of the 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). We discussed and resolved any disagreements. We rated the included studies as high risk, low risk or unclear risk for the six domains applicable to RCTs: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting and other sources of bias.

We created 'Summary of findings' tables, and employed the GRADE approach for assessing certainty of evidence.

Measures of treatment effect

We presented the primary outcome, 50% or greater reduction in seizure frequency, and the secondary outcomes, seizure freedom and treatment withdrawal, as risk ratios (RRs) with 95% confidence intervals (CIs). For the reporting of the individual adverse effects, we again presented the results as RRs, but instead quoted 99% CIs to compensate for multiple testing. By contrast, we reported the results from the dose regression model as odds ratios (ORs) with 95% CIs.

Unit of analysis issues

There were no unit of analysis issues.

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 individual participant factors among trials (for example, age, seizure type, duration of epilepsy, number of antiepileptic drugs taken at the time of randomisation) and trial factors (for example, randomisation 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 heterogeneity was present ($P > 0.10$), we employed a fixed-effect model. In the event that heterogeneity was found, we planned to use a random-effects model analysis using the inverse-variance method.

Assessment of reporting biases

We requested all protocols from study authors to enable a comparison of outcomes of interest. Outcome

reporting bias was to be investigated using the ORBIT matrix system (Kirkham 2010). We also undertook visual examination of funnel plots as well as the Egger test, a statistical test to determine publication bias in meta-analyses, to establish any publication bias.

Data synthesis

We employed a fixed-effect model meta-analysis to synthesise the data for the comparison, topiramate versus placebo, for the outcomes:

1. 50% or greater reduction in seizure frequency;
2. seizure freedom;
3. treatment withdrawal;
4. adverse effects.

Each outcome was to be stratified by study characteristics to ensure the appropriate combination of study data.

Our preferred estimator was the Mantel-Haenszel RR. For the outcomes 50% or greater reduction in seizure frequency and treatment withdrawal, we used 95% 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, two of which were sensitivity analyses:

1. Primary (ITT) analysis: participants from both treatment groups not completing follow-up or with inadequate seizure data were assumed to be non-responders.
   a. Worst-case analysis (sensitivity analysis): participants not completing follow-up or with inadequate seizure data were assumed to be non-responders in the intervention (topiramate) group, but were assumed to be responders in the placebo group.
   b. Best-case analysis (sensitivity analysis): participants not completing follow-up or with inadequate seizure data were assumed to be responders in the intervention (topiramate) group, but were assumed to be non-responders in the placebo group.

The best-case and worst-case analyses served to determine whether the assumption made during ITT analysis (i.e. that all participants not completing follow-up or with inadequate seizure data are non-responders) grossly affected the estimated effect size.

Dose regression analysis

For the primary outcome, we examined the dose-response relationship using a generalised linear mixed model with the xtmelogit in STATA SE version 14. The binary outcome was defined with the value '0' for patients who did not achieve a 50% or greater reduction in seizure frequency and was defined as the value '1' for patients who did. Study and dose were included as a fixed-effect 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 (351.9 mg/d). This method estimated an OR as opposed to a RR. We then used the command, meqrlogit, to predict the probabilities for the following: (i) the percentage of patients having a 50% response at differing doses; (ii) the difference in the percentage of patients responding to each dose compared to placebo.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analysis for adverse effects. We intended to investigate heterogeneity using sensitivity analysis if deemed appropriate.

Sensitivity analysis

We conducted five forms of sensitivity analyses in total during the data synthesis. Two such sensitivity analyses were highlighted and explained earlier, best- and worst-case analysis (see Data synthesis). We also intended to carry out sensitivity analysis if peculiarities were found between study quality, characteristics of participants, interventions and outcomes. Specifically, we detected heterogeneity in the outcome, 50% or greater reduction in seizure frequency, and, therefore, we applied the following sensitivity analysis according to: study quality (we excluded studies with either high or unclear risk of bias) and age (we excluded one study because it included paediatric participants). Finally, we conducted a sensitivity according to dosage. We excluded three studies because all three only assessed dose of 200 mg/d topiramate.

Summarising and interpreting results using GRADE

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence and to interpret findings. We used GRADEpro GDT software (GRADEpro GDT 2015), which imports data from Review Manager 5 software (Review Manager 2014), to create a 'Summary of findings' table for the following outcomes: 50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal, weight loss/decrease, paraesthesia, thinking abnormally, and difficulty with concentration.

Results

Description of studies

Results of the search

The search revealed 1346 records identified from the databases, outlined in Electronic searches. After removing 541 duplicates, 805 records remained and we screened all for inclusion in the review. We excluded 758 records at this point due to irrelevance, leaving 46 records to be assessed for eligibility at the full-text stage of screening. Following this, we excluded five studies, linked to seven individual records (see Figure 1 and Characteristics of excluded studies for reasons of exclusion). We included a total of 12 studies (linked to 37 individual records) in the review, all of which we included in meta-analyses. We identified two abstracts (two records) as studies awaiting classification and contacted the authors of these studies for more information. At the time of publication, no correspondence had been received.

Included studies

The 12 RCTs identified by the screening process recruited a total of 1650 participants and between them tested doses of 200 mg, 300 mg, 400 mg, 600 mg, 800 mg and 1000 mg topiramate per day. For further information on each trial, see Characteristics of included studies.

Overall, there were 10 randomised controlled trials (RCTs) which compared topiramate to placebo in adults aged 18 to 75 years (Ben-Menachem 1996; Chung 2014; Faught 1996; Guberman 2002; Korean Topiramate Study Group 1999; Privitera 1996; Rosenfeld 1996; Sharief 1996; Tassinari 1996; Yen 2000), one RCT which examined topiramate versus a placebo in children (Elterman 1999), and one other RCT which examined the same comparison within the elderly (Zhang 2011). Eight of these trials were sponsored by Johnson and Johnson. In all of the trials, participants were eligible to take part in the double-blind part of the trials if they were found to experience a minimum number of focal seizures (range 3 to 12 seizures) and were currently taking one to two or one to three antiepileptic drug treatments. See Table 1 for comparison of study characteristics.

One multicentre, parallel trial had a pre-randomisation period of eight weeks and a treatment period of 13 weeks (Ben-Menachem 1996), randomising 56 adults to one of two treatment arms: 800 mg of topiramate (n = 28) or placebo (n = 28). The study medication was administered twice daily or to the maximal tolerated dose.

Similarly, a multicentre, parallel trial had a pre-randomisation baseline period of eight weeks (Chung 2014). This trial featured a shorter treatment period of 11 weeks and consisted of two treatment arms. Two hundred and forty-nine participants were randomised to either placebo (n = 125) or 200 mg/d topiramate (n = 124).

The Elterman 1999 multicentre (USA, Costa Rica), parallel trial, randomised 41 children aged one to 16 years to topiramate and 45 to placebo. Participants were eligible if they experienced six or more seizures during baseline and were taking one or two antiepileptic drugs. The baseline period was eight weeks in duration with a treatment period of 16 weeks.

Another parallel trial from the USA had three different treatment arms and a placebo arm (Faught 1996). Forty-five adults aged 18 to 65 years were randomised to 200 mg per day of topiramate, 45 mg to 400 mg per day topiramate or 46 mg to 600 mg per day topiramate and 45 were randomised to the placebo group. This trial had a baseline period of 12 weeks and a treatment period of 16 weeks.

A further multicentre, parallel trial (Guberman 2002), randomised adults to one of three treatment arms: topiramate escalated weekly by 25 mg to 200 mg per day (n = 85), topiramate escalated weekly by 50 mg to 200 mg per day (n = 83), and placebo (n = 91). This trial had a baseline period of four weeks and a titration period of eight weeks for the 25 mg group or four weeks for the 50 mg group. The double-blind treatment phase was 12 weeks in duration.

The parallel trial run by the Korean Topiramate Study Group (Korean Topiramate Study Group 1999), investigated adults only and consisted of two main treatment arms including 600 mg topiramate (n = 91) and placebo (n = 86). The baseline period was 12 weeks in duration followed by a titration period of 10 weeks and then a stabilisation period of eight weeks.

A multicentre, parallel trial had a 12-week baseline period followed by an 18-week double-blind treatment period (Privitera 1996). Within this phase was a six-week titration period and 12-week stabilisation period. Adults were randomised to one of four treatment arms: 48 mg to 600 mg per day topiramate, 48 mg to 800 mg per day topiramate, 47 mg to 1000 mg per day topiramate and 47 were randomised to placebo.

Another multicentre, parallel trial had an eight-week baseline period and a 19-week treatment period (Rosenfeld 1996). Two hundred and nine adults were randomised to one of two treatment arms in a ratio of 1:3, resulting in 42 patients being randomised to placebo and 167 patients being randomised to 1000 mg per day topiramate.

Another multicentre, parallel trial had a pre-randomisation period of eight weeks and a treatment period of 11 weeks (Sharief 1996), where 23 adults were randomised to 400 mg per day topiramate and 24 were randomised to placebo. At the target dose, medication was administered twice daily.

The parallel trial by Tassinari 1996 was a multicentre trial in which adults were randomised to one of two treatments arms: 600 mg topiramate (n = 30) and placebo (n = 30). The baseline period was eight weeks followed by a treatment period of 12 weeks.

One single-centre, parallel trial in China had a baseline period of eight weeks and a treatment period of 14 weeks (Yen 2000), and randomised 23 adults to 300 mg per day topiramate and 23 to placebo.

One study included elderly patients (aged over 65) only and had two treatment arms (Zhang 2011): 200 mg per day topiramate (n = 46) or placebo (n = 40). The baseline period for this study was eight weeks in duration followed by a titration phase of eight weeks and then a treatment period of 12 weeks.

Excluded studies

We excluded five RCTs for the following reasons: two studies had no placebo control group (Christensen 2003; Ramsay 2008), one study was an active comparator-controlled trial (Chung 2009), one study had a baseline period of 48 hours (Novotny 2010), and one study did not investigate any of the outcomes under review (Coles 1999). For further information regarding exclusion, see Characteristics of excluded studies.

Studies awaiting classification

We were unable to include a further two studies in the review as we unsure about their eligibility for inclusion (Aranguiz 1991; Kazibutowska 2000). We attempted to contact the authors for additional information to allow for the classification of the studies, but no correspondence had been received at the time of publication. For details regarding these studies, see Characteristics of studies awaiting classification.

Risk of bias in included studies

We allocated each study a rating for each risk of bias domain. All studies included in the review were rated as having either low risk of bias or unclear risk of bias across all domains. Below, the specific domain ratings are explained.

See 'Risk of bias' tables within the Characteristics of included studies tables for further details. See Figure 2 for a summary of the risk of bias in each included study and Figure 3 for a summary of each domain across studies.

Allocation (selection bias)

For the domain of random sequence generation, we rated 11 studies as low risk of bias due to the use of a computer-generated randomisation schedule or the use of random number tables/random permuted blocks (Ben-Menachem 1996; Chung 2014; Elterman 1999; Faught 1996; Korean Topiramate Study Group 1999; Privitera 1996; Rosenfeld 1996; Sharief 1996; Tassinari 1996; Yen 2000; Zhang 2011). We rated one study as unclear due to a lack of detail provided regarding the methods used (Guberman 2002).

In addition, we rated the methods by which allocation was concealed in 10 of the included studies as low risk of bias (Ben-Menachem 1996; Chung 2014; Elterman 1999; Faught 1996; Korean Topiramate Study Group 1999; Privitera 1996; Rosenfeld 1996; Sharief 1996; Tassinari 1996; Yen 2000). Nine of the studies used sealed, numbered packages, allocated sequentially, to conceal allocation (Ben-Menachem 1996; Elterman 1999; Faught 1996; Korean Topiramate Study Group 1999; Privitera 1996; Rosenfeld 1996; Sharief 1996; Tassinari 1996; Yen 2000), and one more recent trial used an interactive voice response system (Chung 2014). Two trials did not provide clear methods and we thus rated them as having unclear risk of bias for this domain (Guberman 2002; Zhang 2011).

Blinding (performance bias and detection bias)

In all but one study, successful blinding of participants was achieved by using identical medication within the topiramate and placebo groups (Ben-Menachem 1996; Chung 2014; Elterman 1999; Faught 1996; Guberman 2002; Korean Topiramate Study Group 1999; Privitera 1996; Rosenfeld 1996; Sharief 1996; Tassinari 1996; Yen 2000); we judged these 11 studies at low risk of performance bias. There were no details reported by Zhang 2011, and so we rated this study as having unclear risk of bias. The blinding of the outcome assessor was difficult to judge due to the lack of detail in 10 of the publications (Ben-Menachem 1996; Chung 2014; Elterman 1999; Faught 1996; Guberman 2002; Korean Topiramate Study Group 1999; Privitera 1996; Rosenfeld 1996; Tassinari 1996; Zhang 2011) and, therefore, we rated these studies as having unclear detection bias. We rated the other two studies at low risk of bias for this particular domain (Sharief 1996; Yen 2000), as the two studies specified that outcome assessors remained blinded.

Incomplete outcome data (attrition bias)

We rated all studies at low risk of bias for this domain due to the ITT analyses undertaken by the study authors.

Selective reporting (reporting bias)

We requested the protocols for all included studies to compare a priori methods and outcomes to the published report but the majority of these were unavailable. We rated all included studies as low risk of bias for this domain as there was no suspicion of selective outcome reporting bias; all expected outcomes were reported in each of the publications.

Other potential sources of bias

We rated all studies at low risk of bias for this domain as we did not detect any further bias in any of the included studies.

Effects of interventions

See Summary of findings table 1 for a summary and GRADE assessment of the primary and secondary outcomes.

50% or greater reduction in seizure frequency

Intention-to-treat (ITT) analysis

Data from all 12 studies and including 1650 participants contributed to this outcome. A Chi² test for heterogeneity in a response to topiramate showed significant heterogeneity between trials (Chi² = 18.29, df = 11, P = 0.07, I² = 40%), therefore we employed a random-effects model. The overall risk ratio (RR) for a response to topiramate compared to placebo using the random-effects model was 2.71 (95% confidence interval (CI) 2.05 to 3.59; 12 studies, 1650 participants; high-certainty evidence; Analysis 1.2), indicating that participants receiving add-on topiramate were nearly three times more likely to have a 50% or greater reduction in seizure frequency than those receiving add-on placebo.

As a result of the significant heterogeneity detected, we conducted three separate sensitivity analyses. Firstly, we noted that the studies included in the analysis for this outcome varied with regards to the overall risk of bias awarded. We thus completed a sensitivity analysis by study quality by only including studies associated with low risk of bias overall. Following this sensitivity analysis, the RR increased to 4.36 (95% CI 2.24 to 8.50) and there was no longer any detectable statistical heterogeneity (Chi² = 0.13, df = 2, P = 0.94, I² = 0%; Analysis 1.1). We similarly conducted a sensitivity analysis according to patient characteristics. For this, we excluded one study from the analysis because it studied a paediatric study population and all other studies were conducted in adults (Elterman 1999). The exclusion of this study did not resolve the detected heterogeneity (Chi² = 17.94, df = 10, P = 0.06, I² = 44%) and did not greatly impact the estimated RR (RR 2.85, 95% CI 2.09 to 3.88; Analysis 1.3). Finally, we conducted a sensitivity analysis according to intervention, during which we excluded three studies (Chung 2014; Guberman 2002; Zhang 2011). The three excluded studies only assessed the lowest dosage of topiramate (200 mg/d). Again, heterogeneity was no longer detected amongst the data set (Chi² = 7.29, df = 8, P = 0.51, I² = 0%), however, the effect estimate remained statistically significant and was unsurprisingly slightly higher than that detected when all studies were included (RR 3.32, 95% CI 2.51 to 4.38; Analysis 1.4). We did not conduct a sensitivity analysis according to outcome as this was not deemed appropriate.

Best- and worst-case scenarios

We again used a random-effects model for both the best-case and worst-case analyses due to the significant heterogeneity detected (Chi² = 20.93, df = 11, P = 0.03, I² = 47%; Analysis 1.5; and Chi² = 18.97, df = 11, P = 0.06, I² = 42%; Analysis 1.6, respectively). The overall best-case RR scenario for a response to topiramate was RR 3.54 (95% CI 2.67 to 4.69), whilst the worst-case RR scenario was 1.96 (95% CI 1.54 to 2.50). Importantly, all three analyses for the outcome, 50% or greater seizure reduction, suggest a significant treatment effect for add-on topiramate compared to add-on placebo (P < 0.00001).

Dose-response regression

We fitted a generalised linear mixed model to the data provided in Analysis 1.2 to estimate the effect of dose on the primary outcome, 50% or greater reduction in seizure frequency (details in Data synthesis). To include the data extracted from the study by Elterman 1999, which only recruited children, the daily dose was approximated by assuming an average adult weight of 75 kg, multiplied by the study dose of 6 mg/kg/day, to give 450 mg/day topiramate. It was not necessary to conduct any more dose adjustments for the other included studies. The study by Zhang 2011 only recruited elderly patients, above 65 years of age, and the remaining studies all recruited patients from adult populations. Doses ranged between 200 mg/day and 1000 mg/day topiramate. In order to use this model, the dose was standardised by its standard deviation (352 mg). Importantly, the method used estimated an OR as opposed to a RR.

The OR for a 50% or greater reduction in seizure frequency per 200 mg/d increase in topiramate dose was 1.45 (95% CI 1.28 to 1.64; P < 0.001), with estimated between-study standard deviation of 0.54 (standard error (SE) 0.16), thus revealing that patients were significantly more likely to attain a 50% or greater seizure reduction if their dose was increased by 200 mg/d (P < 0.001). Notably, the odds of a patient achieving a 50% or greater reduction in seizure frequency were nearly doubled (OR 1.92, 95% CI 1.54 to 2.40; P < 0.001) when their dose of topiramate was increased by 350 mg/d, the standard deviation of the included doses (P < 0.001).

The estimated response rate (the percentage of participants achieving a 50% or greater reduction in seizure frequency) per dose, as well as the estimated increase in response rate compared to placebo for each dose are given in Table 2. The estimated response rate on placebo was 17.8% (95% CI 6.3% to 29.4%), whereas the estimated response rate for topiramate ranged from 37.6% to 51.1%, dependent on dose (Table 2). Accordingly, the estimated response rate per dose compared to placebo ranged from 19.7% for participants randomised to 200 mg/day topiramate up to 33.3% for participants randomised to 1000 mg/day. Both the estimated fitted response rate and the difference in response rate compared to placebo generally increased with dosage, as would be expected from the dose-response relationship demonstrated.

Seizure freedom

A Chi² test for heterogeneity showed no significant heterogeneity between trials (Chi² = 1.84, df = 6, P = 0.93, I² = 0%). The overall RR for seizure freedom was 3.67 (95% CI 1.79 to 7.54; 8 studies, 1177 participants; moderate-certainty evidence; Analysis 1.7), indicating that participants randomised to add-on topiramate were over three times more likely to attain seizure freedom than participants randomised to add-on placebo.

Treatment withdrawal

Data from 12 studies, consisting of 1650 participants, contributed to this outcome. A Chi² test for heterogeneity demonstrated no significant statistical heterogeneity (Chi² = 8.76, df = 10, P = 0.55, I² = 0%). The overall RR (95% CI) for withdrawal for any reason was 2.37 (95% CI 1.66 to 3.37; 12 studies, 1650 participants; high-certainty evidence; Analysis 1.8), thus highlighting that participants were significantly more likely to withdraw from topiramate than placebo.

Adverse effects

The RRs for adverse effects were as follows (Analysis 1.9).

1. Ataxia: 2.29 (99% CI 1.10 to 4.77; 4 studies; 757 participants)
2. Concentration difficulties: 7.81 (99% CI 2.08 to 29.29; 6 studies; 702 participants)
3. Dizziness: 1.52 (99% CI 1.07 to 2.16; 8 studies; 1385 participants)
4. Fatigue: 2.08 (99% CI 1.37 to 3.15; 9 studies; 1092 participants)
5. Headache: 0.96 (99% CI 0.67 to 1.39; 10 studies; 1427 participants
6. Nausea/vomiting: 1.50 (99% CI 0.71 to 3.15; 4 studies; 492 participants)
7. Paraesthesia: 3.65 (99% CI 1.58 to 8.39; 7 studies; 1071 participants)
8. Somnolence: 2.44 (99% CI 1.61 to 3.68; 9 studies; 1462 participants)
9. Speech difficulty: 3.37 (99% CI 0.80 to 14.13; 3 studies; 310 participants)
10. Thinking abnormally: 5.70 (99% CI 2.26 to 14.38; 4 studies; 640 participants)
11. Weight loss/decrease: 3.99 (99% CI 1.82 to 8.72; 9 studies; 1070 participants)

Collectively, the results imply that receiving add-on topiramate is associated with a higher incidence rate for many adverse effects compared to add-on placebo. Specifically, add-on topiramate was associated with a significantly higher incidence rate for the following adverse effects: ataxia (P = 0.003), concentration difficulties (P < 0.001), dizziness (P = 0.002), fatigue (P < 0.001) , paraesthesia (P < 0.001), somnolence (P < 0.001), speech difficulty (P = 0.03), 'thinking abnormally' (P < 0.001), and weight loss (P < 0.001), although to differing degrees of effect. For example, the incidence rate for dizziness was increased by a modest 50% when receiving add-on topiramate, whereas the incidence rate for 'thinking abnormally' was almost six times greater with add-on topiramate than with placebo. Notably, however, add-on topiramate did not incur a statistically significant increase in the risk of experiencing headache (RR 0.96, 99% CI 0.67 to 1.39; 9 studies; 1092 participants; P = 0.79) or nausea (RR 1.50, 99% CI 0.71 to 3.15; 4 studies; 492 participants; P = 0.16) compared to placebo.

Discussion

Summary of main results

The 12 trials included in this review were all double-blinded and the majority expressly used adequate methods of allocation concealment. All analyses were by intention-to-treat (ITT). Results from the overall efficacy analysis show that topiramate is effective in reducing seizure frequency by at least 50% when used as an add-on drug for people with drug-resistant focal epilepsy. Topiramate was found to be almost three times more effective than a placebo drug. Even the lowest dose, 200 mg per day, results in nearly 20% more patients achieving a 50% reduction in seizure rate than placebo. The dose regression model shows increasing effect with increasing dose, though the increase is quite modest. For people taking 200 mg to 1000 mg per day, results indicate a response rate of between 38% (95% confidence interval (CI) 20.2 to 55.0) and 51% (95% CI 29.5 to 72.7), an improvement over placebo of 20% (CI −1.2 to 40.6) to 33% (CI 8.8 to 57.8).

We suspected evidence of publication bias on examination of a funnel plot for the outcome, 50% or greater reduction in seizure frequency, plus we detected statistical heterogeneity in the data set. The heterogeneity could be explained by both study quality (excluding studies associated with unclear risk of bias) and by topiramate dosage. Specifically, statistical heterogeneity was no longer detected when studies which only investigated the lowest dosage of topiramate (200 mg) were excluded from the analysis. This generates further support for the observed dose-response relationship as it suggests that lower dosage give a significantly different effect estimate compared to higher dosages, such that it generates methodological heterogeneity within the data set.

For seizure freedom, the results estimate that topiramate is over three times more likely to be effective in stopping seizures completely, than a placebo drug. Only half of the included studies reported data on this outcome, however, and, as a result, this finding must be interpreted with caution.

Results for the outcome, treatment withdrawal, showed that participants are significantly more likely to withdraw from treatment with add-on topiramate than add-on placebo. In trials of relatively short duration, such as those reviewed here, treatment withdrawal is likely to represent problems with tolerability rather than poor seizure control. With respect to adverse events, most of those investigated were significantly more likely to occur in the topiramate-treated group, except for headache and nausea and vomiting. The risk ratio (RR) for the significant adverse effects ranged from a low of 1.52 for dizziness to a high of 7.81 for impaired concentration. Although many of the adverse effects were significantly more likely with add-on topiramate, there was not sufficient information to determine whether this could be attributed to studies using higher doses.

Overall completeness and applicability of evidence

Primarily, this review aimed to determine the efficacy of topiramate as add-on treatment for people of

any age with drug-resistant focal epilepsy. Markedly, however, the majority of the data were obtained from adults aged 16 to 65 years old. Only one study specifically evaluated the use of add-on topiramate in children, aged 2 to 16 years (Elterman 1999), and, equally, only one study investigated its use in the elderly (over 65 years old; Zhang 2011). Consequently, the findings presented here cannot be easily generalised to all age groups and are, instead, largely representative of the effect of add-on topiramate in adults.

Similarly, although the results of this review indicate that topiramate is likely an effective add-on treatment with regard to seizure reduction, this review cannot tell us how topiramate compares with other antiepileptic drugs in this scenario. This is an extremely important issue for clinicians who are faced with an ever-increasing number of antiepileptic drugs to choose from. Head-to-head trials are needed to provide the evidence that is necessary to enable clinicians to make an evidence-based choice between antiepileptic drugs and their inclusion should be considered for future review updates.

Moreover, with the possibility of publication bias, we cannot be completely certain that we have identified all placebo-controlled trials evaluating add-on topiramate. The suspected publication bias suggests that there could be several small studies, possibly with negative results, which have remained unpublished and that may not have been highlighted by our searches. This generates uncertainty in our finding that add-on topiramate is more effective than placebo. The implications of this are addressed further in the subsequent subsections.

Additionally, this review focuses on the use of topiramate in drug-resistant focal epilepsy. The results cannot, therefore, be generalised to add-on treatment for generalised epilepsies. Likewise, no inference can be made about the effects of topiramate when used as monotherapy.

Certainty of the evidence

Out of the 12 included studies, we rated all but three of the studies as having unclear risk of bias. We rated the other three studies as having low risk of bias. Taking all the studies together, we rated the overall risk of bias as low and considered the evidence to be methodologically sound. The most common issue to generate risk of bias was the blinding of outcome assessors. Nine of the included studies did not provide explicit details on the blinding of outcome assessors, however, given the self-report aspect of the outcomes measured, i.e. seizure frequency and adverse effects experienced, the blinding of outcome assessors was deemed to have minimal impact on the effect size estimated, hence the overall assessment of low risk of bias.

We employed the GRADE approach to rate the level of certainty of evidence per outcome, the results of which are presented in Summary of findings table 1. We did not downgrade any of the outcomes for risk of bias, as reasoned above. For the main outcome of 50% or greater seizure reduction, we rated the certainty of evidence as high. We downgraded the evidence for 50% or greater seizure reduction once due to the influence that publication bias may have had on the overall effect estimate. Specifically, a lack of symmetry was noted in the funnel plot for the primary outcome during visual examination (Figure 4). This observation was then supported by the Egger test which detected significant publication bias within the meta-analysis (P = 0.001). We downgraded the evidence once more due to inconsistency resulting from significant statistical heterogeneity detected within the data set. We then upgraded the evidence once for a large effect size (RR > 2.00), and once again due to the dose-response relationship demonstrated for the outcome.

We judged the evidence for the alternative efficacy outcome, seizure freedom, to be of moderate certainty. We downgraded the evidence twice due to the very low number of events contributing to the meta-analysis, but then upgraded once because of the large effect size (RR > 2.00) observed. Similarly, we downgraded the certainty of evidence for the adverse effects: weight loss, paraesthesia, and difficulties with concentration, twice because these outcomes, likewise, featured an extremely low number of events (< 100 events). For the outcome, weight loss, we downgraded the evidence once again as a result of suspected publication bias (Egger test: P = 0.009). We then upgraded the evidence for weight loss once due to the large effect size observed, thus producing an overall judgement of low-certainty of evidence for this outcome. We downgraded the evidence for the outcome, concentration difficulties, once for suspected publication bias (Egger test: P = 0.019) but then upgraded this twice due to the very large effect size recognised (RR > 5.00). This led to an overall judgement of moderate-certainty of evidence for concentration difficulties. We also judged the evidence for paraesthesia as being of moderate certainty. We did not detect any publication bias in the data set (Egger test: P = 0.478), however, we could only upgrade the evidence once back to moderate certainty as the observed effect size was large, as opposed to very large.

In contrast, we only downgraded the evidence for the other two outcomes, treatment withdrawal and abnormal thinking, once for imprecision. Although the number of events was insufficient to satisfy the optimal information size, there were more events than were noted for the other outcomes (> 100 events). We then upgraded the evidence for both outcomes back to high certainty due to the large (treatment withdrawal) and very large (abnormal thinking) effect size revealed.

Potential biases in the review process

We strongly suspect that publication bias has impacted this review. We specifically suspect publication bias for three of the GRADE-assessed outcomes (50% or greater seizure reduction, concentration difficulties, and weight loss) after examining the resultant funnel plots and conducting the Egger test. Importantly, publication bias was also suspected for the outcome, seizure freedom, however, the low number of studies contributing data for this outcome prevented us from making a conclusive judgement regarding the funnel

plot (Figure 5), and this was reflected in the results of the Egger test (P = 0.09).

Studies showing positive results are more likely to be published than those expressing negative results and this consequently leads to an overestimation of the effect size (Murad 2018). It is thus possible that, in the instance of this particular review, we have overestimated the effectiveness of topiramate compared to placebo as an add-on therapy. Expanding the search terms in future updates could aid us in identifying any additional unpublished data sets to help resolve this issue. Additionally, we could contact more individuals that might have knowledge of any unpublished trials. We do, however, feel that, for the purposes of this current review update, we have exhausted all potential sources of data. This will, however, be reassessed and further pursued for the next review update.

Agreements and disagreements with other studies or reviews

The observations made in this review update are consistent with the previous versions of this review (Jette 2002; Jette 2008; Marson 1996; Marson 1997; Pulman 2014). Specifically, this review has indicated that topiramate is efficacious as an add-on treatment for drug-resistant focal epilepsy. This review has, however, also emphasised that treatment with topiramate remains significantly associated with certain adverse effects, including: concentration difficulties, paraesthesia, 'thinking abnormally', and weight loss. As with the earlier versions of this review, we are still unable to extrapolate the results to other types of epilepsy and cannot comment on the long-term effectiveness or tolerability of topiramate as an add-on treatment.

The results of this review are also consistent with other reviews (Perucca 1997; Privitera 1997), conducted independently of Cochrane, however, these reviews are now outdated. Notably, Perucca 1997 similarly reported that doses of topiramate between 200 mg/day to 1000 mg/day are effective at managing drug-resistant focal epilepsy, emphasising that even doses below 400 mg/day are likely to be beneficial. The other review identified (Privitera 1997), likewise noted a two- to three-fold difference in the number of people achieving 50% reduction in seizure frequency when allocated add-on topiramate compared to placebo. Both reviews also described ataxia, concentration difficulties, paraesthesias, fatigue, dizziness, somnolence and weight loss in their participant-reported adverse effects (Perucca 1997; Privitera 1997).

Of further significance, two of the trials included in this review explored dose-response relationships (Faught 1996; Privitera 1996). Faught 1996 considered responses at doses of 200 mg, 400 mg and 600 mg per day, whilst Privitera 1996 evaluated responses at 600 mg, 800 mg and 1000 mg per day. Results from Faught 1996 suggest that 400 mg/day topiramate increases the likelihood of a response compared to a 200 mg/day dose, but that no further increase is obtainable at doses of 600 mg/day. Results from Privitera 1996 also suggest little difference in response rates between doses of 600 mg/day to 1000 mg/day. Although neither study observed an increased response rate with doses in excess of 600 mg/day, this current review successfully demonstrated a significant dose-response relationship whilst including all doses from 200 mg/day to 1000 mg/day. Importantly, although the response rates were very similar for 600 mg/day and 800 mg/day, the response rate continued to increase again when participants were randomised to the highest dose, 1000 mg/day, contrary to the reports in these two studies.

Authors' conclusions

Implications for practice

Topiramate has efficacy as an add-on treatment for people with drug-resistant focal epilepsy. A daily dose of 200 mg is the lowest dose tested in the trials included in this review, and this would seem a reasonable starting dose. The dose regression model implied additional benefit with increased dosage, however, the increase was fairly modest. It is likely that higher doses will result in greater issues with adverse effects.

Implications for research

To evaluate further the place of topiramate in the armamentarium of available antiepileptic drugs, further studies are required addressing the following.

1. The long-term effects of add-on topiramate.
2. How topiramate compares with other add-on treatments in drug-resistant focal epilepsy.
3. The role of topiramate in childhood epilepsies.
4. How topiramate compares with standard antiepileptic drugs, such as monotherapy for focal or generalised epilepsies.
5. The dose-response relationship with adverse effects.

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Contributions of authors

Rebecca Bresnahan was responsible for the current update of this review and assessed studies for eligibility,

updated the methods and assessed risk of bias.

Juliet Hounsome extracted data and assessed risk of bias for the current update of this review.

Tony Marson acted as third review author and resolved any disagreements during the review process.

Jane L Hutton and Nathalie Jette contributed to the previous versions of this review and/or to the original protocol.

Declarations of interest

RB: none known
JH: none known
NJ: receives grant funding paid to her institution for grants unrelated to this work from NINDS (NIH U24NS107201, NIH IU54NS100064), PCORI and Alberta Health. She also receives an honorarium for her work as an Associate Editor of Epilepsia.
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Differences between protocol and review

In keeping with the previous review update, we used Mantel-Haenszel risk ratio (RR) as the preferred estimator of treatment effect. This is in contrast to the published protocol which stated that Peto's odds ratio (OR) would be the preferred estimator. Peto's OR is recommended for use when the event rate is very low and therefore it was not necessary to use this estimator in this review.

In accordance with the latest classification of epilepsies published by the International League Against Epilepsy (ILAE) (Scheffer 2017), the title of this review has been changed from 'Topiramate add-on for drug-resistant partial epilepsy' (registered for the original review and protocol) to 'Topiramate add-on therapy for drug-resistant focal epilepsy' (for the current update). Any reference to "partial epilepsy" or "refractory epilepsy" throughout this review has been changed to "focal epilepsy" and "drug-resistant epilepsy", respectively.

Published notes

Characteristics of studies

Characteristics of included studies

Ben-Menachem 1996

Methods	Double-blind, placebo-controlled, parallel-group study 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 8 weeks Treatment period: 13 weeks
Participants	A multicentre study (Sweden, Norway, Denmark, Germany) 56 people randomised (all with drug-resistant focal epilepsy): 28 to placebo and 28 to 800 mg topiramate Age range: 18 to 65 years Mean age: 37.2 years 84% males Other AEDs: 2 or fewer Median baseline monthly seizure frequency: 11.4 for placebo group, 14.2 for topiramate group
Interventions	800 mg topiramate per day or placebo
Outcomes	1. Percentage reduction in generalised seizure rate 2. Percentage responders (50% and 75%) 3. Adverse effects
Notes	Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization schedule" Comment: random permuted blocks
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Comment: identical tablets and packaging
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained due to the methods used
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: all participants were included in the analysis Quote: "intention-to-treat analysis"
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Chung 2014

Methods	Double-blind, placebo-controlled, parallel-group study 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 8 weeks Treatment period: 11 weeks
Participants	A multicentre study (Argentina, Australia, Belgium, Canada, Chile, Germany, Greece, Hungary, India, Israel, New Zealand, Poland, Russia, South Africa, Spain, and USA) 249 people randomised (all with drug-resistant focal epilepsy): 125 to placebo and 124 mg to 200 mg per day topiramate Age range: 18 to 75 years Mean age: 37.6 years 53% males Other AEDs: 1 or more Median baseline seizure frequency/week: 2.7 for placebo group, 2.3 for topiramate group
Interventions	200 mg topiramate per day or placebo
Outcomes	Primary outcome: median percentage reduction in weekly partial onset seizure frequency Secondary outcomes: 1. responder rate ($\geq$ 50% reduction in seizure frequency) 2. seizure freedom rate 3. clinician-reported Global Impression of Change (CGI-C) 4. patient-reported Quality of Life in Epilepsy-Problems (QOLIE-31-P) survey 5. adverse events 6. safety and tolerability outcomes including laboratory parameters, neurology and physical examination, vital signs, and electrocardiography
Notes	Trial sponsored by Upsher-Smith Laboratories, Inc

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization by an independent statistician was generated using permuted blocks with a block size of 4 without stratification"
Allocation concealment (selection bias)	Low risk	Quote: "The interactive voice response group programmed the randomization schedule for investigators to dispense study drug."
Blinding (performance bias and detection bias)	Low risk	Quote: "matching placebo"
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: no concerns about missing data Quote: "Efficacy analyses were performed using the intent-to-treat (ITT) population"
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Elterman 1999

Methods	Randomised, double-blind, placebo-controlled, parallel-group study 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 8 weeks Treatment period: 16 weeks
Participants	A multicentre study (USA, Costa Rica) 86 people were randomised (all with drug-resistant focal epilepsy): 45 to placebo and 41 to topiramate Age range: 2 to 16 years Mean age: 9.0 years for placebo group, 8.8 years for topiramate group 56% males Other AEDs: 2 or fewer, except for person who was on more than 2 AEDs Median baseline monthly seizure frequency: 19 for placebo group, 22 for topiramate group (focal-onset seizures)
Interventions	6 mg/kg/day topiramate or placebo
Outcomes	Primary outcome: median percentage reduction in average monthly focal-onset seizure rate Secondary outcomes: 1. median percentage reduction in average monthly seizure rate for secondarily generalised seizures 2. global evaluation of seizure severity 3. treatment responders 4. adverse events
Notes	Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random permuted blocks
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Quote: "tablets that were similar in shape, size and color"
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: all participants were included in the analysis Quote: "intention-to-treat basis"
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Faught 1996

Methods	Double-blind, placebo-controlled, parallel-group study 4 treatment arms: 1 placebo, 3 topiramate Pre-randomisation baseline period: 12 weeks Treatment period: 16 weeks
Participants	A multicentre study (USA) 181 people were randomised (all with drug-resistant focal epilepsy): 45 to placebo, 45 mg to 200 mg per day topiramate, 45 mg to 400 mg per day topiramate, 46 mg to 600 mg per day topiramate Age range: 19 to 68 years Mean age: 36.9 years Other AEDs: 2 or fewer 70% males Median baseline monthly seizure frequency: 10.8 (10.0 for placebo group, 11.5 for 200 mg/d topiramate group, 11.0 for 400 mg/d topiramate group, 11.2 for 600 mg/d topiramate group)
Interventions	200 mg topiramate per day or 400 mg topiramate per day or 600 mg topiramate per day or placebo
Outcomes	1. Percentage monthly seizure rate reduction 2. Percentage responders (50%) 3. Adverse effects
Notes	Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random permuted blocks
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Comment: identical tablets and packaging
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: no concerns about missing data Quote: "intention-to-treat efficacy analysis"
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Guberman 2002

Methods	Randomised, double-blind, placebo-controlled study
	3 treatment arms: 1 placebo, 2 topiramate Pre-randomisation baseline period: 4 weeks Treatment period: 12 weeks
Participants	A multicentre study (Hungary, Poland, Israel, Canada, Russia, Czech Republic) 263 people were randomised (all with drug-resistant focal epilepsy): 91 to placebo, 85 to topiramate escalated weekly by 25 mg/day to 200 mg/day, 83 to topiramate escalated weekly by 50 mg/day to 200 mg/day Age range: 18 to 67 years for placebo group, 18 to 64 years for topiramate groups Mean age: 36 years for placebo group, 37 years for topiramate groups 50% males for placebo group, 46% males for topiramate groups Other AEDs: 2 or fewer Median baseline monthly seizure frequency: 7 for placebo group, 7 for topiramate group
Interventions	200 mg topiramate per day escalated over 8 weeks by 25 mg/day increases weekly or 200 mg topiramate per day escalated over 4 weeks by 50 mg/day increases weekly or placebo
Outcomes	Primary outcome: medial % reduction from baseline in monthly focal-onset seizure frequency for the combined topiramate groups versus placebo group Secondary outcomes: 1. responder rate (50% reduction in seizure frequency) 2. adverse effects 3. other safety evaluation outcomes including clinical laboratory evaluations, neurology and physical examination, vital signs, and body weight measurements
Notes	Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized in equal proportions" Comment: insufficient information provided to determine judgement for sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: details regarding allocation concealment were not provided
Blinding (performance bias and detection bias)	Low risk	Comment: identical tablets and packaging
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: no concerns about missing data Quote: "intention-to-treat"
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Korean Topiramate Study Group 1999

Methods	Randomised, double –blind, placebo –controlled study 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 12 weeks Treatment period: 18 weeks
Participants	A multicentre study (Korea) 177 people were randomised (all with drug-resistant focal epilepsy): 86 to placebo, 91 to topiramate Age range: 16 to 65 years Mean age: 29.8 years for placebo group, 29.6 years for topiramate group 54% males Other AEDs: 2 or fewer Median baseline monthly seizure frequency: 5.6 for placebo group, 5.6 for topiramate group
Interventions	600 mg topiramate per day or placebo
Outcomes	1. Median seizure frequency reduction rate 2. Responder rate 3. Seizure-free rate 4. Global evaluation by participant and physician 5. Adverse effects
Notes	Trial sponsored by Janssen Korea Ltd

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random number tables with permuted blocks of 4
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Comment: identical tablets and packaging
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: 2 patients in the topiramate group and 1 in the placebo group were excluded from the analysis. It was determined that this did not represent a potentially clinically important impact Quote: "intention-to-treat analysis (ITTA) was performed for efficacy and safety measures"
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Privitera 1996

Methods	Double-blind, parallel-group study 4 treatment arms: 1 placebo, 3 topiramate Pre-randomisation baseline period: 12 weeks Treatment period: 18 weeks
Participants	A multicentre study (USA) 190 people were randomised (all with drug-resistant focal epilepsy): 47 to placebo, 48 to 600 mg topiramate, 48 to 800 mg topiramate, 47 to 1000 mg topiramate Age range: 18 to 68 years Mean age: 35.5 years 80% males Other AEDs: 2 or fewer Median baseline monthly seizure frequency: 11 (9.3 for placebo group, 10.0 for 600 mg/d topiramate group, 16.2 for 800 mg/d topiramate group, 11.7 for 1000 mg/d topiramate group)
Interventions	600 mg topiramate per day or 800 mg topiramate per day or 1000 mg topiramate per day or placebo
Outcomes	1. Percentage seizure rate reduction 2. Percentage responders ($\geq$ 50%) 3. Adverse effects
Notes	Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random permuted blocks
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Quote: "topiramate and placebo tablets were identical in appearance and packaging"
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Quote: "all 209 subjects who enrolled in the double-blind phase of the trial were included in the efficacy analysis"
Selective reporting (reporting bias)	Low risk	Comment: data published in full according to the protocol
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Rosenfeld 1996

Methods	Double-blind, placebo-controlled, parallel-group study 2 treatment arms: 1 placebo, 1 topiramate Prospective pre-randomisation baseline period: 8 weeks Treatment period: 19 weeks
Participants	A multicentre study (USA) 209 people were randomised (all with drug-resistant focal epilepsy): 42 to placebo, 167 to 1000 mg topiramate Age range 18 to 65 years Mean age: Unknown 49% male Other AEDs: 1 Baseline seizure frequency (unknown). Patients had to have a minimum of 6 focal seizures during the 8-week baseline phase
Interventions	1000 mg topiramate per day or placebo
Outcomes	Proportion with a 50% reduction in seizure frequency
Notes	Limited information regarding trial. All information was provided by a single poster abstract. Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random permuted blocks
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Quote: "tablets were identical in appearance and packaging"
Blinding of participants and personnel (performance bias)	Low risk	Comment: only states "double-blinded", and so blinding is likely though not confirmed
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: no concerns about missing data Quote: "intention-to-treat"
Selective reporting (reporting bias)	Low risk	Comment: appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Sharief 1996

Methods	Randomised, double-blind, placebo-controlled, parallel-group study 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 8 weeks Treatment period: 11 weeks
Participants	A multicentre study (Sweden, Spain, UK and France) 47 people were randomised (all with drug-resistant focal epilepsy): 24 to placebo, 23 to 400 mg topiramate Age range: 18 to 65 years Mean age: 34 years 85% males Other AEDs: 2 or fewer Median baseline monthly seizure frequency: 12.5 (10 for placebo group, 18 for topiramate group)
Interventions	400 mg topiramate per day or placebo
Outcomes	1. Percentage reduction in average seizure rate 2. Percentage responders (50%) 3. Adverse effects
Notes	Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random permuted blocks Quote: "computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Comment: identical tablets and packaging
Blinding of participants and personnel (performance bias)	Low risk	Comment: patients and clinical staff blinded
Blinding of outcome assessment (detection bias)	Low risk	Comment: investigators blinded
Incomplete outcome data (attrition bias)	Low risk	Comment: no participants were excluded from the analysis and intention-to-treat was followed
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Tassinari 1996

Methods	Double-blind, placebo-controlled, parallel-group study 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 8 weeks Treatment period: 12 weeks
Participants	A multicentre study (UK, Italy, France, Norway and Denmark) 60 people were randomised (all with drug-resistant focal epilepsy): 30 to placebo 30 to 600 mg topiramate Age range: 18 to 65 years Mean age: 32.9 years 68% males Other AEDs: 2 or fewer Median baseline monthly seizure frequency: 15.0 for placebo group, 16.8 for topiramate group
Interventions	600 mg topiramate per day or placebo
Outcomes	1. Percentage reduction in average seizure rate 2. Percentage responders (patients with 50% reduction in seizure rate) 3. Adverse effects
Notes	Trial sponsored by Johnson & Johnson

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random permuted blocks
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Quote: "topiramate and placebo tablets were identical"
Blinding of participants and personnel (performance bias)	Low risk	Comment: it is likely that blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: specific details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias)	Low risk	Comment: no concerns about missing data Quote: "intent-to-treat"
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Yen 2000

Methods	Double-blind, placebo-controlled, parallel-group 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 8 weeks Treatment period: 14 weeks
Participants	A single-centre study (China) 46 people were randomised (all with drug-resistant focal epilepsy): 23 to placebo, 23 to topiramate Age range: 18 to 54 years Mean age: 32.0 years for placebo group, 31.4 years for topiramate group 41% males Other AEDs: up to 4 or more Median baseline monthly seizure frequency: 5 to 10 for placebo group, < 5 for topiramate group
Interventions	300 mg topiramate per day or placebo
Outcomes	1. Percentage responders (or = 50%) 2. Investigator's global evaluation 3. Participant's overall assessment 4. Adverse effects
Notes	Trial sponsored in part by grants from Taipei Veterans General Hospital (88-V229) and the Yen Tjing Ling Medical Foundation

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: random permuted blocks Quote: "computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Comment: sealed, numbered packages allocated sequentially
Blinding (performance bias and detection bias)	Low risk	Quote: "matching placebo tablets"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "investigators, patients, study monitors and observers remained blinded to codes"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "investigators, patients, study monitors and observers remained blinded to codes"
Incomplete outcome data (attrition bias)	Low risk	Quote: "intention-to-treat efficacy analysis" Comment: no concerns about missing data
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appeared to be free of other sources of bias

Zhang 2011

Methods	Randomised, placebo-controlled trial 2 treatment arms: 1 placebo, 1 topiramate Pre-randomisation baseline period: 8 weeks Treatment period: 12 weeks
Participants	A single-centre study (Shanghai, China) 86 participants were randomised (documented drug-resistant focal epilepsy) Age range: > 65 years old eligible Mean age: 73.4 years 57% males 8 patients on 1 AED, 37 on 2 AEDs, 41 on 3 AEDs Median baseline monthly seizure frequency: 17.3 for placebo group, 16.9 for topiramate group
Interventions	200 mg per day topiramate or placebo
Outcomes	1. Percentage seizure reduction ($\geq$ 50% reduction (classified as responders); 25% to 50% reduction; change within 25% of baseline; $\geq$ 25% seizure increase) 2. Treatment withdrawal 3. Adverse effects
Notes	None No trial sponsorship information provided

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "were randomly assigned, according to a computer-generated randomization schedule"
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: no information provided
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias)	Low risk	Comment: no dropouts (data available for all patients)
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and prespecified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Footnotes

AED: antiepileptic drug

Characteristics of excluded studies

Christensen 2003

Reason for exclusion	Alternative dose-controlled study, no placebo control group

Chung 2009

Reason for exclusion	Active comparator-controlled study, no placebo control group

Coles 1999

Reason for exclusion	Study did not investigate outcomes of interest: 50% or greater reduction in seizure frequency, treatment withdrawal or adverse effects. Studied seizure severity as outcome using seizure severity scales

Novotny 2010

Reason for exclusion	Baseline period too short (48 hours)

Ramsay 2008

Reason for exclusion	Alternative dose-controlled study, no placebo control group

Footnotes

Characteristics of studies awaiting classification

Aranguiz 1991

Methods	A double-blind, parallel, placebo-controlled study
Participants	Patients with drug-resistant focal seizures
Interventions	Investigated oral doses of topiramate 100 mg, 200 mg and 300 mg twice daily
Outcomes	Not known
Notes	None

Kazibutowska 2000

Methods	RCT
Participants	45 patients aged 12 to 51 with simple focal seizures or complex focal seizures, with or without secondary generalisation receiving 1 to 4 AEDs
Interventions	Added tiagabine in 19 patients, gabapentin in 10 patients and topiramate in 16 patients to the previous treatment
Outcomes	Efficacy was evaluated as: seizure-free, improvement of at least 50%, no improvement, worsening. Results of treatment were as follows. 1. Seizure-free: tiagabine (3 cases, 15.9%), gabapentin (1 case, 10%), topiramate (2 cases, 12.5%) 2. Improvement of at least 50%: tiagabine (9 cases, 47.3%), gabapentin (2 cases, 20%), topiramate (8 cases, 50%) 3. No improvement: tiagabine (6 cases, 31.5%), gabapentin (7 cases, 70%), topiramate (5 cases, 31.25%) 4. Worsening: tiagabine (1 case, 5.3%), topiramate (1 case, 6.25%)
Notes	None

Footnotes

AED: antiepileptic drug
RCT: randomised controlled trial

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Topiramate compared to placebo for drug-resistant focal epilepsy

Add-on topiramate compared to placebo for drug-resistant focal epilepsy						
Patients or population: people with drug-resistant focal epilepsy **Setting:** outpatients **Intervention:** add-on topiramate **Comparison:** add-on placebo						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI; Adverse effects: 99% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with topiramate				

Outcome	Study population		Relative effect (95% CI)	№ of participants (studies)	Certainty	Comments
50% or greater reduction in seizure frequency (ITT analysis) Follow-up: range 11 to 19 weeks	Study population		RR 2.71 (2.05 to 3.59)	1650 (12 RCTs)	⊕⊕⊕⊕ High[a,b,c,f,h]	Topiramate increases the proportion of participants attaining a 50% or greater reduction in seizure frequency.
	163 per 1000	441 per 1000 (333 to 584)				
Seizure freedom Follow-up: range 11 to 19 weeks	Study population		RR 3.67 (1.79 to 7.54)	1177 (8 RCTs)	⊕⊕⊕⊖ Moderate[a,e,f]	Topiramate likely increases the proportion of participants achieving seizure freedom.
	17 per 1000	61 per 1000 (30 to 125)				
Treatment withdrawal Follow-up: range 11 to 19 weeks	Study population		RR 2.37 (1.66 to 3.37)	1650 (12 RCTs)	⊕⊕⊕⊕ High[a,d,f]	Topiramate increases the incidence of treatment withdrawal.
	61 per 1000	144 per 1000 (101 to 204)				
Adverse effects – weight loss/decrease Follow-up: range 11 to 18 weeks	Study population		RR 3.99 (1.82 to 8.72)	1070 (9 RCTs)	⊕⊕⊖⊖ Low[a,c,e,f]	Topiramate may produce a large increase in the proportion of participants experiencing weight loss.
	20 per 1000	81 per 1000 (37 to 177)				
Adverse effects – paraesthesia Follow-up: range 11 to 18 weeks	Study population		RR 3.65 (1.58 to 8.39)	1071 (7 RCTs)	⊕⊕⊕⊖ Moderate[a,e,f]	Topiramate likely increases the proportion of participants experiencing paraesthesia.
	25 per 1000	91 per 1000 (40 to 210)				
Adverse effects – 'thinking abnormally' Follow-up: range 12 to 19 weeks	Study population		RR 5.70 (2.26 to 14.38)	640 (4 RCTs)	⊕⊕⊕⊕ High[a,d,g]	Topiramate increases the proportion of participants reporting that they are 'thinking abnormally'.
	43 per 1000	243 per 1000 (96 to 614)				
Adverse effects – difficulty with concentration/concentration impaired/concentration–attention difficulties Follow-up: range 11 to 18 weeks	Study population		RR 7.81 (2.08 to 29.29)	702 (6 RCTs)	⊕⊕⊕⊖ Moderate[a,c,e,g]	Topiramate likely increases the number of participants who experience difficulty with concentration.
	11 per 1000	88 per 1000 (23 to 330)				

*The risk in the intervention group (and its 95% or 99% confidence interval, dependent on the outcome) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% or 99% CI, dependent on the outcome).

CI: confidence interval; **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.

Footnotes

[a]We did not downgrade evidence for risk of bias; we judged risk of bias across studies to be low. Ten studies did not describe the blinding of outcome assessors, one study failed to explain randomisation and allocation concealment and another did not describe any method of blinding. We, however, reasoned that the blinding of outcome assessors would minimally impact the estimated effect size due to the self-reported nature of the review outcomes.
[b]We downgraded the evidence once for inconsistency: we detected significant statistical heterogeneity.
[c]We downgraded the evidence once for publication bias: examination of funnel plot and Egger test indicates the

possibility of publication bias.

[d]We downgraded the evidence once for imprecision: the number of events (< 400) did not suffice optimal information size.

[e]We downgraded the evidence twice for imprecision: the number of events (< 100) did not suffice optimal information size.

[f]We upgraded the evidence once for large effect: RR > 2.00.

[g]We upgraded the evidence twice for large effect: RR > 5.00.

[h]We upgraded the evidence once for dose–response gradient: logistic regression demonstrated a significant dose–response relationship.

Additional tables

1 Study characteristics

Study name	Country	Participants	No. of previous AEDs	No. of participants	Baseline period	Treatment period
Ben–Menachem 1996	Sweden, Norway, Denmark, Germany	Adults	1 to 2	56	8 weeks	13 weeks
Chung 2014	Argentina, Australia, Belgium, Canada, Chile, Germany, Greece, Hungary, India, Israel, New Zealand, Poland, Russia, South Africa, Spain, USA	Adults	1 to ≥7	249	8 weeks	11 weeks
Elterman 1999	USA, Costa Rica	Children	1 to 2	86	8 weeks	16 weeks
Faught 1996	USA	Adults	1 to 2	181	12 weeks	16 weeks
Guberman 2002	Hungary, Poland, Israel, Canada, Russia, Czech Republic	Adults	1 to 2	263	4 weeks	12 weeks
Korean Topiramate Study Group 1999	Korea	Adults	1 to 2	177	12 weeks	18 weeks
Privitera 1996	USA	Adults	1 to 2	190	12 weeks	18 weeks
Rosenfeld 1996	USA	Adults	1	209	8 weeks	19 weeks
Sharief 1996	Sweden, Spain, UK, France	Adults	1 to 2	47	8 weeks	11 weeks
Tassinari 1996	UK, Italy, France, Norway, Denmark	Adults	1 to 2	60	8 weeks	12 weeks
Yen 2000	China	Adults	1 to 4	46	8 weeks	14 weeks
Zhang 2011	China	Elderly	1 to 3	86	8 weeks	12 weeks

Footnotes

AED: antiepileptic drug

2 Estimated response rates per dose and percentage difference in responders per dose compared to placebo

Dose (mg)	Fitted response rate (%)	95% CI		Dose (mg)	Difference in response rate from placebo (%)	95% CI	
		Lower	Upper			Lower	Upper
Placebo	17.8	6.3	29.4				
200	37.6	20.2	55.0	200	19.7	−1.2	40.6
300	38.1	−28.1	104.2	300	20.2	−46.9	87.3
400	37.5	7.8	67.3	400	19.7	−12.2	51.6
450	38.1	−16.1	92.4	450	20.3	−35.2	75.8
600	42.2	23.5	61.0	600	24.4	2.4	46.5
800	42.2	13.8	70.6	800	24.4	−6.3	55.1
1000	51.1	29.5	72.7	1000	33.3	8.8	57.8

Footnotes

CI: confidence intervals

References to studies

Included studies

Ben-Menachem 1996

[CRSSTD: 2903370]

Ben-Menachem E, Dam M, Henriksen O, Schmidt D. Double-blind, placebo-controlled trial of 800 mg/day topiramate as add-on therapy in patients with refractory partial epilepsy. Epilepsia 1995;36(Suppl 3):S150. [CRSREF: 2903371]

Ben-Menachem E, Dam M, Mikkelsen M, Engelskjon T, Henriksen O, Johannessen S, et al. Topiramate add-on treatment in patients with intractable partial epilepsy: a multicenter study. Epilepsia 1993;34(Suppl 2):109. [CRSREF: 2903372]

* Ben-Menachem E, Henriksen O, Dam M, Mikkelsen M, Schmidt D, Reid S, et al. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. Epilepsia 1996; 37(6):539-43. [CRSREF: 2903373; PubMed: 8641230]

Martinez-Lage J, Ben-Menachem E, Shorvon SD, Weber M. Double-blind, placebo-controlled trial of 400 mg/day topiramate as add-on therapy in patients with refractory partial epilepsy. Epilepsia 1995;36(Suppl 3):S149-50. [CRSREF: 2903374]

Ostergard L, Dam M, Mikkelsen M. Topiramate as add-on therapy in refractory partial epilepsy. Epilepsia 1992; 33(Suppl 3):105. [CRSREF: 2903375]

Chung 2014

[CRSSTD: 12150037]

Arnold S, Blatt I, Clark AM, Halvorsen MB, Nagaraddi VN. USL255, a once-daily, extended-release topiramate, has positive effects on clinical outcomes and quality of life: results from the phase 3 PREVAIL clinical trial. Epilepsy Currents 2014;14(Suppl 1):105, Abstract no: 1.223. [CRSREF: 12150038]

Blatt I, Chung SS, Hogan RE, Clark A, Anders B, Halvorsen M. Efficacy and safety of USL255, once-daily extended-release topiramate, in adults with partial onset seizures: the PREVAIL study. Epilepsia 2014;55(Suppl 2):42-43, Abstract no: p112. [CRSREF: 12150039]

Blatt I, Nagaraddi V, Hogan R, Arnold S, Lawson B, Anders B, et al. Efficacy of USL255 across partial-onset seizure types and refractory patient status: subgroup analyses from the PREVAIL study. Neurology 2014;82(10 Suppl):Abstract no: P3.263. [CRSREF: 12150040]

Blatt I, Nagaraddi VN, Anders B, Clark AM, Halvorsen MB, Hogan RE. USL255 is efficacious across all partial-onset seizure types and with a variety of concomitant antiepileptic drugs: Results from subgroup analyses of the phase 3 PREVAIL clinical trial. Epilepsy Currents 2014;14(Suppl 1):204, Abstract no: 2.116. [CRSREF: 12150041]

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* Chung SS, Fakhoury TA, Hogan RE, Nagaraddi VN, Blatt I, Lawson B, et al. Once-daily USL255 as adjunctive treatment of partial-onset seizures: randomized phase III study. Epilepsia 2014;55(7):1077-87. [CRSREF: 12150043; PubMed: 24902983]

Chung SS, Hogan R, Blatt I, Lawson PB, Nguyen H, Clark AM, et al. Long-term safety and sustained efficacy of USL255 (topiramate extended-release capsules) in patients with refractory partial-onset seizures. Epilepsy & Behavior 2016;59:13-20. [CRSREF: 12150044; PubMed: 27084978]

Chung SS. A review of the efficacy and safety of extended-release topiramate in the adjunctive treatment for refractory partial-onset seizures. Therapeutic Advances in Neurological Disorders 2015;8(3):131-6. [CRSREF: 12150045; PubMed: 25941540]

Clark AM, Chung SS, Blatt I, Anders B, Halvorsen MB, Hogan RE. Efficacy of USL255 (qudexyTM XR; Extended-release topiramate) in patients with refractory partial-onset seizures: PREVAIL and PREVAIL OLE. Epilepsy Currents 2015;15(Suppl 1):142-3, Abstract no: 1.307. [CRSREF: 12150046]

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Hogan RE, Blatt I, Lawson B, Nagaraddi V, Fakhoury TA, Anders B, et al. Efficacy of once-daily extended-release topiramate (USL255): a subgroup analysis based on the level of treatment resistance. Epilepsy & Behavior 2014; 41:136-9. [CRSREF: 12150049; PubMed: 25461205]

Lawson B, Chung SS, Clark AM, Halvorsen MB, Blatt I. Time to onset of efficacy and sustained treatment effects of USL255: results from the phase 3 PREVAIL clinical trial. Epilepsy Currents 2014;14(Suppl 1):104, Abstract no: 1.222. [CRSREF: 12150050]

Nagaraddi V, Chung S, Arnold S, Clark A, Anders B, Fakhoury T. Early onset of efficacy and safety outcomes with USL255 treatment: The PREVAIL study. Neurology 2014;82(10 Suppl):Abstract no: P3.264. [CRSREF: 12150051]

Elterman 1999

[CRSSTD: 2903376]

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Faught 1996

[CRSSTD: 2903378]

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Guberman 2002

[CRSSTD: 2903381]

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Privitera 1996

[CRSSTD: 2903389]

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Rosenfeld 1996

Unpublished data only [CRSSTD: 2903392]

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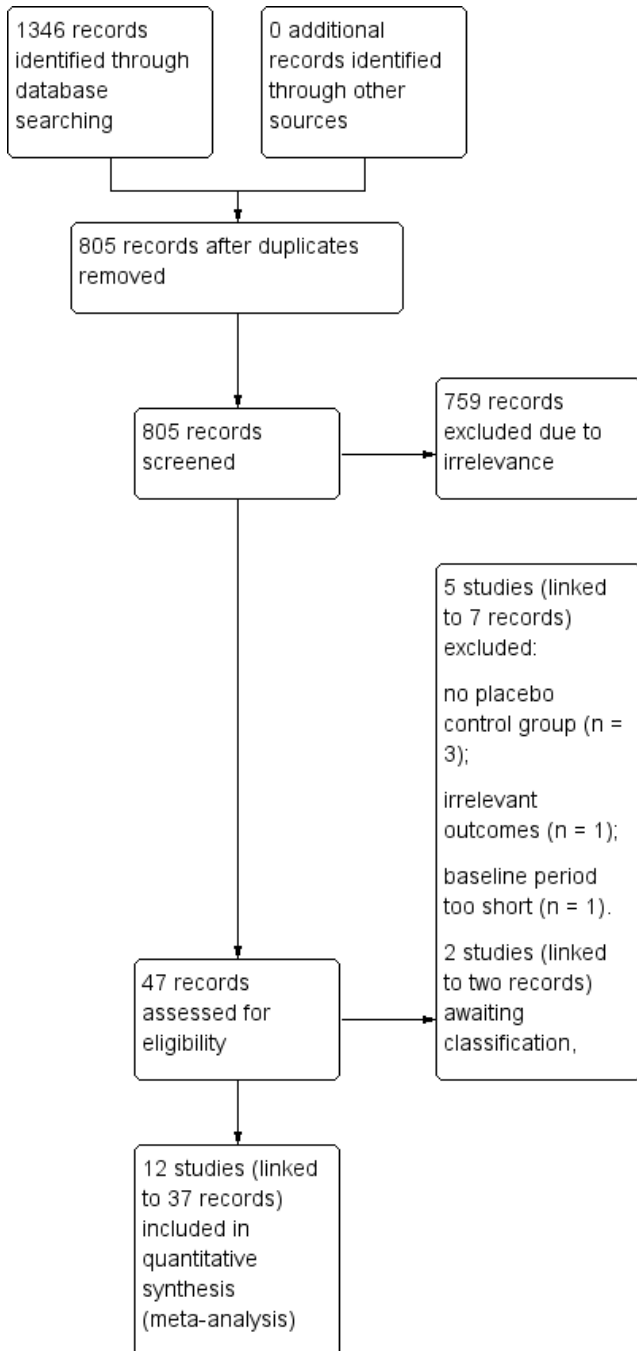
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Classification pending references

Data and analyses

1 Topiramate versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

1.1 50% reduction in seizure frequency – Sensitivity analysis by study quality	3	283	Risk Ratio(M–H, Fixed, 95% CI)	4.36 [2.24, 8.50]
1.2 50% reduction in seizure frequency – ITT analysis	12	1650	Risk Ratio(IV, Random, 95% CI)	2.71 [2.05, 3.59]
1.3 50% reduction in seizure frequency – Sensitivity analysis by patient characteristics (age)	11	1564	Risk Ratio(IV, Random, 95% CI)	2.85 [2.09, 3.88]
1.4 50% reduction in seizure frequency – Sensitivity analysis by intervention (dosage)	9	1052	Risk Ratio(M–H, Fixed, 95% CI)	3.32 [2.51, 4.38]
1.5 50% reduction in seizure frequency – Best–case analysis	12	1650	Risk Ratio(IV, Random, 95% CI)	3.54 [2.67, 4.69]
1.6 50% reduction in seizure frequency – Worst–case analysis	12	1650	Risk Ratio(IV, Random, 95% CI)	1.96 [1.54, 2.50]
1.7 Seizure freedom	8	1177	Risk Ratio(M–H, Fixed, 95% CI)	3.67 [1.79, 7.54]
1.8 Treatment withdrawal	12	1650	Risk Ratio(M–H, Fixed, 95% CI)	2.37 [1.66, 3.37]
1.9 Adverse effects	12		Risk Ratio(M–H, Fixed, 99% CI)	Subtotals only
1.9.1 Ataxia	4	757	Risk Ratio(M–H, Fixed, 99% CI)	2.29 [1.10, 4.77]
1.9.2 Difficulty with concentration/concentration impaired/concentration–attention difficulties	6	702	Risk Ratio(M–H, Fixed, 99% CI)	7.81 [2.08, 29.29]
1.9.3 Dizziness	8	1385	Risk Ratio(M–H, Fixed, 99% CI)	1.52 [1.07, 2.16]
1.9.4 Fatigue	10	1427	Risk Ratio(M–H, Fixed, 99% CI)	2.08 [1.37, 3.15]
1.9.5 Headache	9	1092	Risk Ratio(M–H, Fixed, 99% CI)	0.96 [0.67, 1.39]
1.9.6 Nausea/vomiting	4	492	Risk Ratio(M–H, Fixed, 99% CI)	1.50 [0.71, 3.15]
1.9.7 Paraesthesia	7	1071	Risk Ratio(M–H, Fixed, 99% CI)	3.65 [1.58, 8.39]
1.9.8 Somnolence	9	1462	Risk Ratio(M–H, Fixed, 99% CI)	2.44 [1.61, 3.68]
1.9.9 Speech difficulties/language problems	3	310	Risk Ratio(M–H, Fixed, 99% CI)	3.37 [0.80, 14.13]
1.9.10 Thinking abnormally	4	640	Risk Ratio(M–H, Fixed, 99% CI)	5.70 [2.26, 14.38]
1.9.11 Weight loss/decrease	9	1070	Risk Ratio(M–H, Fixed, 99% CI)	3.99 [1.82, 8.72]

Figures

Figure 1

```
┌─────────────────┐  ┌─────────────────┐
│ 1346 records    │  │ 0 additional    │
│ identified      │  │ records         │
│ through         │  │ identified      │
│ database        │  │ through other   │
│ searching       │  │ sources         │
└─────────────────┘  └─────────────────┘
```

805 records after duplicates removed

805 records screened

759 records excluded due to irrelevance

5 studies (linked to 7 records) excluded:

no placebo control group (n = 3);

irrelevant outcomes (n = 1);

baseline period too short (n = 1).

2 studies (linked to two records) awaiting classification,

47 records assessed for eligibility

12 studies (linked to 37 records) included in quantitative synthesis (meta-analysis)

Caption

Study flow diagram.

Figure 2

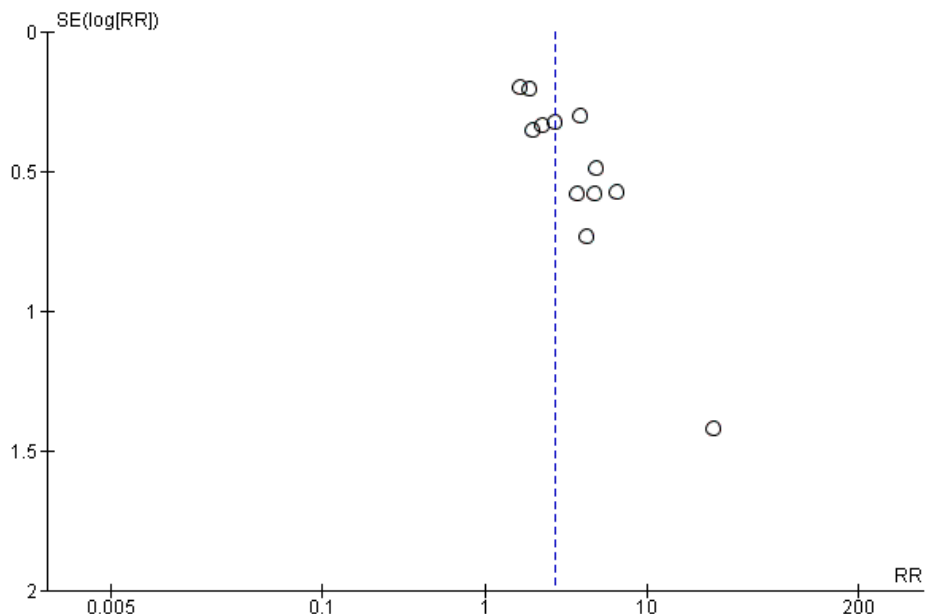'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Figure 3
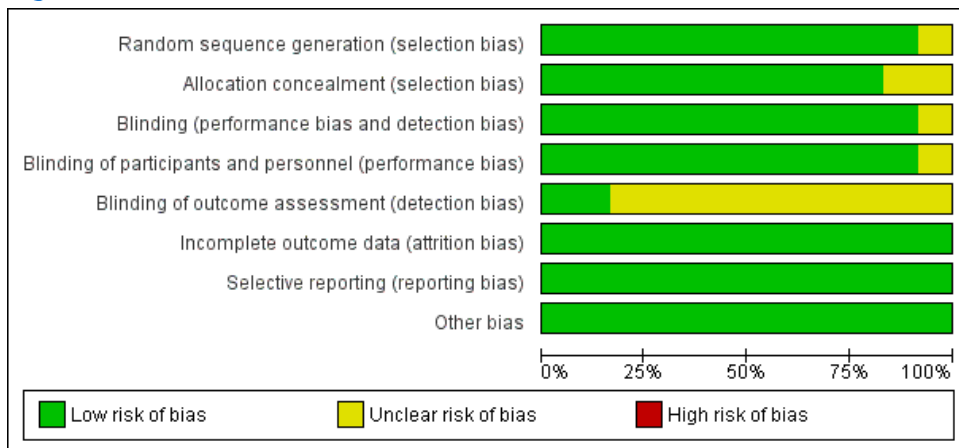
Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
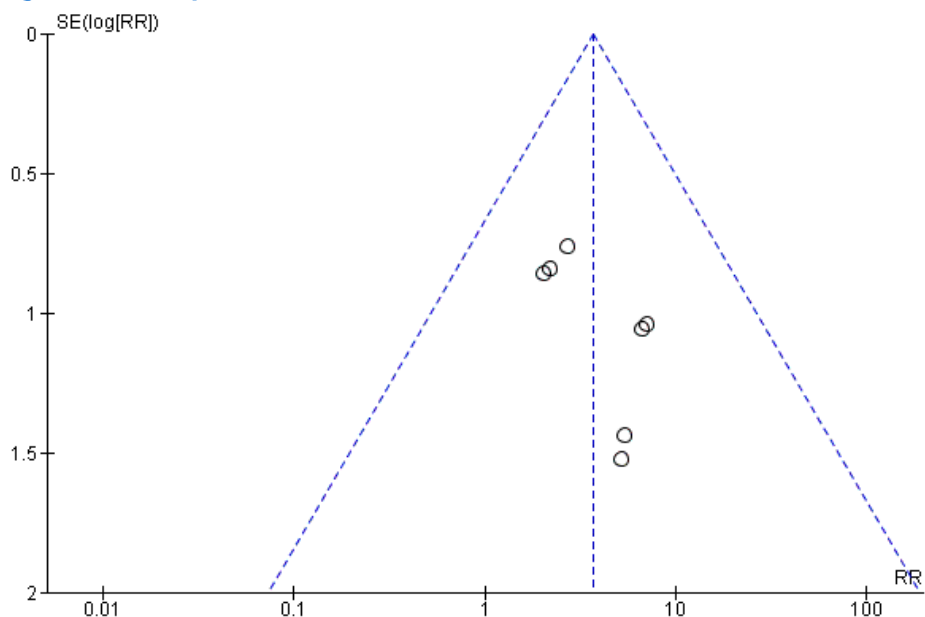
Figure 4 (Analysis 1.2)

Caption

Funnel plot of comparison: 1 Topiramate versus placebo, outcome: 1.2 50% reduction in seizure frequency – ITT analysis.

Figure 5 (Analysis 1.7)

Caption

Funnel plot of comparison: 1 Topiramate versus placebo, outcome: 1.7 Seizure freedom.

Sources of support

Internal sources

- No sources of support provided

External sources

Feedback

Appendices

1 CRS Web search strategy

1. Topiram* or Tipiram* or Topamax or TPM or Qudexy AND CENTRAL:TARGET

2. (monotherap* not (adjunct* or "add-on" or "add on" or adjuvant* or combination* or polytherap*)):TI AND CENTRAL:TARGET

3. #1 NOT #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. #7 AND #3

2 MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2011).

1. (Topiram$ or Tipiram$ or Topamax or TPM or Qudexy).tw.

2. exp Epilepsy/

3. exp Seizures/

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

5. 2 or 3 or 4

6. exp *Pre-Eclampsia/ or exp *Eclampsia/

7. 5 not 6

8. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

9. clinical trials as topic.sh.

10. trial.ti.

11. 8 or 9 or 10

12. exp animals/ not humans.sh.

13. 11 not 12

14. 1 and 7 and 13

15. (monotherap$ not (adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$)).ti.

16. 14 not 15

17. remove duplicates from 16

3 ClinicalTrials.gov search strategy

Interventional Studies | Epilepsies, Partial | Topiramate OR Topamax or TPM or Qudexy

4 WHO International Clinical Trials Registry Platform (ICTRP) search strategy

partial epilepsy OR focal epilepsy in the Condition AND

Topiramate OR Topamax OR TPM OR Qudexy in the Intervention

5 SCOPUS search strategy

((TITLE(Topiramate or Topamax) OR ABS(Topiramate or Topamax)) AND (TITLE((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study)) OR ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study))) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR seizure OR convuls* OR (syndrome W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) OR (TITLE-ABS-KEY(lafora* W/4 (disease OR epilep*)) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine))))) AND NOT (TITLE(monotherap* AND NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)))