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[Intervention Review]

Topiramate for juvenile myoclonic epilepsy

Jia Liu¹, Lu-Ning Wang², Yu-Ping Wang¹¹Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China. ²Department of Geriatric Neurology, Chinese PLA General Hospital, Beijing, China**Contact address:** Jia Liu, Department of Neurology, Xuanwu Hospital, Capital Medical University, Changchun Street 45, Beijing, 100053, China. Jason_liu1984@163.com.**Editorial group:** Cochrane Epilepsy Group.**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 1, 2019.**Citation:** Liu J, Wang LN, Wang YP. Topiramate for juvenile myoclonic epilepsy. *Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No.: CD010008. DOI: [10.1002/14651858.CD010008.pub4](https://doi.org/10.1002/14651858.CD010008.pub4).

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ABSTRACT

Background

Topiramate is a newer broad-spectrum antiepileptic drug (AED). Some studies have shown the benefits of topiramate in the treatment of juvenile myoclonic epilepsy (JME). However, there are no current systematic reviews to determine the efficacy and tolerability of topiramate in people with JME. This is an update of a Cochrane Review first published in 2015, and last updated in 2017.

Objectives

To evaluate the efficacy and tolerability of topiramate in the treatment of JME.

Search methods

For the latest update, on 10 July 2018 we searched the Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group's Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid 1946-), and [ClinicalTrials.gov](https://www.clinicaltrials.gov). We also searched ongoing trials registers, reference lists and relevant conference proceedings, and contacted study authors and pharmaceutical companies.

Selection criteria

We included randomized controlled trials (RCTs) investigating topiramate versus placebo or other AED treatment for people with JME, with the outcomes of proportion of responders and proportion of participants experiencing adverse events (AEs).

Data collection and analysis

Two review authors independently screened the titles and abstracts of identified records, selected studies for inclusion, extracted data, cross-checked the data for accuracy and assessed the methodological quality. We performed no meta-analyses due to the limited available data.

Main results

We included three studies with a total of 83 participants. For efficacy, a greater proportion of participants in the topiramate group had a 50% or more reduction in primarily generalized tonic-clonic seizures (PGTCS) compared with participants in the placebo group. There were no significant differences between topiramate and valproate in participants responding with a 50% or more reduction in myoclonic seizures or in PGTCS, or becoming seizure-free. Concerning tolerability, we ranked AEs associated with topiramate as moderate to severe, while we ranked 59% of AEs linked to valproate as severe complaints. Moreover, systemic toxicity scores were higher in the valproate group than the topiramate group.

Overall we judged all three studies to be at high risk of attrition bias and at unclear risk of reporting bias. We judged all three studies to be at low to unclear bias for the remaining risk of bias domains (random sequence, allocation, blinding). We judged the quality of the evidence from the studies to be very low.

Authors' conclusions

We have found no new studies since the last version of this review was published in 2017. This review does not provide sufficient evidence to support topiramate for the treatment of people with JME. Based on the current limited available data, topiramate seems to be better tolerated than valproate, but has no clear benefits over valproate in terms of efficacy. Well-designed, double-blind RCTs with large samples are required to test the efficacy and tolerability of topiramate in people with JME.

PLAIN LANGUAGE SUMMARY

Topiramate for juvenile myoclonic epilepsy

Background

Juvenile myoclonic epilepsy (JME) is characterized by involuntary (uncontrolled) twitching of muscles in the shoulders and arms after awakening, often starting in childhood.

Study characteristics

We searched scientific databases for clinical trials comparing the antiepileptic medication, topiramate, with placebo (a pretend treatment) or another antiepileptic drug in people with JME. We wanted to evaluate how well topiramate worked and if it had any side effects. The evidence is current to July 2018.

Key results

We included and analyzed three randomized controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) with 83 participants. Based on the information in these trials, it seems that topiramate is better tolerated than valproate, but is no more effective than valproate. Topiramate seemed to work better than placebo, but this result was based on a small number of included people.

Quality of the evidence

The quality of the evidence from the studies was very low and the results should be interpreted with caution. More randomized controlled trials with large numbers of participants are required to test how effective and well tolerated topiramate is in people with JME. Future trials should be well-designed and double-blinded (where neither the participant nor the researcher know which treatment has been given until after the results have been collected).

Conclusions

This review does not provide sufficient evidence to support topiramate for the treatment of people with JME.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Topiramate compared with placebo for juvenile myoclonic epilepsy

Topiramate compared with placebo for juvenile myoclonic epilepsy

Patient or population: people with juvenile myoclonic epilepsy

Settings: 18 centers in the USA; 10 centers in Europe; 1 center in Costa Rica

Intervention: topiramate

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Topiramate				
Proportion of responders (at least 50% seizure frequency reduction in PGTCs)	182 per 1000	727 per 1000 (197 to 1000)	RR 4.00 (1.08 to 14.75)	22 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	More participants taking topiramate responded with a 50% or more reduction in PGTCs compared with placebo (P = 0.04)
Proportion of participants who experienced at least one AE and individual AEs	See comment	See comment	NA	22 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	Number of participants experiencing at least one AE was not reported. Individual AEs: no significant differences were found in nausea, URTI, abnormal vision, or diarrhea between topiramate versus placebo
Number of participants who were seizure-free	Not reported	Not reported	NA			

*The basis for the **assumed risk** was the event rate in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: adverse event; **CI:** confidence interval; **PGTCs:** primarily generalized tonic-clonic seizures; **RR:** risk ratio; **URT:** upper respiratory tract infection

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

¹ The included trials were reported as randomized, double-blind trials, with insufficient methodological information.

² A relatively small number of participants were included in the analysis.

Summary of findings 2. Topiramate compared with valproate for juvenile myoclonic epilepsy

Topiramate compared with valproate for juvenile myoclonic epilepsy

Patient or population: people with juvenile myoclonic epilepsy

Settings: Cincinnati Children's Hospital Medical Center, Cincinnati, USA; Haeundae Paik Hospital, Busan, Republic of Korea

Intervention: topiramate

Comparison: valproate

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Valproate	Topiramate				
Proportion of responders (at least 50% seizure frequency reduction in myoclonic seizures)	1000 per 1000	857 per 1000 (670 to 1000)	RR 0.88 (0.67 to 1.15)	23 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	No significant difference was found.
Proportion of responders (at least 50% seizure frequency reduction in PGTCS)	750 per 1000	917 per 1000 (510 to 1000)	RR 1.22 (0.68 to 2.21)	16 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	No significant difference was found.
Proportion of participants who experienced at least one AE and individual AEs	See comment	See comment	NA	61 (2 studies)	⊕⊕⊕⊕ very low ^{1,2}	Number of participants experiencing at least one AE was not reported.

We found significant more events of paresthesia in topiramate, and more events of weight gain and tremor in valproate. There was no significant difference between groups for headache, concentration difficulty, fatigue, alopecia, dizziness, weight loss, psychomotor slowing, somnolence, nausea, appetite increase, insomnia, abnormal vision, rash, anorexia, hallucination or diarrhea.

Number of participants who were seizure-free	563 per 1000	636 per 1000 (343 to 1188)	RR 1.13 (0.61 to 2.11)	27 (1 study)	⊕⊕⊕⊕ very low ^{1,2}	No significant difference was found.

*The basis for the **assumed risk** was the event rate in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: Adverse event; **CI:** Confidence interval; PGTCs: primarily generalized tonic-clonic seizures; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

¹ The included trials were reported as randomized, double-blind trials, with insufficient methodological information.

² A relatively small number of participants were included in the analysis.

BACKGROUND

This review is an update of a previously published review in the *Cochrane Database of Systematic Reviews* (Liu 2017).

Description of the condition

Juvenile myoclonic epilepsy (JME) was first described by Janz in 1985. It is a primary generalized epilepsy which is characterized by irregular myoclonic jerks of shoulders and arms after awakening, and bilateral synchronous four-to-six per second spike-wave complexes (Janz 1985). JME accounts for 5% to 11% of all epilepsy cases and its prevalence varies between 10 and 20 per 100,000 population (Jallon 2005; Panayiotopoulos 1991). The age of onset ranges from six to 22 years old, but 50% of cases present between 13 and 16 years of age. Valproate is widely regarded as the first-line therapy in JME owing to its broad spectrum of activity. However, 20% of people with JME do not achieve satisfactory control with valproate (Calleja 2001). In addition, it is generally acknowledged that JME requires lifelong therapy and the adverse effects (AEs) in chronic valproate therapy are extensive (Sharpe 2008). Thus, alternative effective broad-spectrum agents are required.

Description of the intervention

Topiramate is a newer broad-spectrum agent that is effective in many seizure types, including focal onset and primarily generalized tonic-clonic seizures (PGTCS) and Lennox-Gastaut syndrome (Biton 1999; Guberman 2002; Sachdeo 1999). Topiramate during the first year after onset controls GTCS in 62.5% of people and myoclonic jerks in 68.8% of people, although 13.6% of people have an increase in frequency of absence seizures (Alfradique 2007). Moreover, topiramate has less risk of teratogenicity than valproate, and can be used as an alternative first-line agent in women of childbearing age (Montouris 2009).

How the intervention might work

As a sulphamate-substituted monosaccharide, the main mode of action of topiramate is through the inhibition of carbonic anhydrase. Meanwhile, it also has antiepileptic activity, which is probably attributed to other mechanisms, including modulation of voltage-dependent sodium channels, potentiation of GABAergic inhibition at a novel site on the gamma-aminobutyric acid-A (GABA-A) receptor and possible action at N-methyl-D-aspartate (NMDA) receptors (Hanaya 1998; White 2000; Zona 1997).

Why it is important to do this review

Some studies have found topiramate to be effective in people with JME. This review aims to evaluate the efficacy and tolerability of topiramate for people with JME.

OBJECTIVES

To evaluate the efficacy and tolerability of topiramate in the treatment of juvenile myoclonic epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) of topiramate versus placebo or other antiepileptic drug (AED) treatment for

people with juvenile myoclonic epilepsy (JME). We included randomized cross-over studies in meta-analyses using the results from paired analyses (Elbourne 2002).

Types of participants

Inclusion criteria

- People with a confirmed diagnosis of JME. Diagnostic criteria included myoclonic jerks and seizure onset in adolescence. We applied no limitation on age for enrolment.
- People with co-existent primarily generalized tonic-clonic seizures (PGTCS) with electroencephalogram (EEG)-confirmed JME were also eligible.

Exclusion criteria

- Previous discontinuation of topiramate owing to an adverse event (AE)
- Co-therapy with any other AED
- Use of an experimental medication or device within 30 days of study entry

Types of interventions

- Experimental intervention: topiramate
- Control intervention: placebo or other AED treatment
- Different control groups were separately analyzed

Types of outcome measures

We collected and analyzed the outcomes of all the participants initially randomized by intention-to-treat (ITT).

Primary outcomes

Efficacy

- Proportion of responders (defined as at least 50% reduction in seizure frequency from baseline to end of treatment)

Secondary outcomes

Efficacy

- Number of participants who were seizure-free

Tolerability

- Proportion of participants who experienced at least one AE
- Proportion of participants who experienced each individual AE, such as ataxia, dizziness, fatigue or nausea

Search methods for identification of studies

Electronic searches

Searches were run for the original review in July 2012 and subsequent searches were run on 2 November 2015, 21 February 2017, and 10 July 2018. For the latest update we searched the following databases:

- Cochrane Register of Studies (CRS Web, 10 July 2018), which includes the Cochrane Epilepsy Group's Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL), using the search strategy set out in [Appendix 1](#);
- MEDLINE (Ovid; 1946-), using the search strategy set out in [Appendix 2](#);

- [ClinicalTrials.gov](https://clinicaltrials.gov) (10 July 2018), using the search strategy set out in [Appendix 3](#).

Previously we also searched Embase (1 July 2015), using the search strategy set out in [Appendix 4](#). It is no longer necessary to search Embase, because randomized and quasi-randomized controlled trials from Embase are now included in CENTRAL.

Searching other resources

We also:

- searched reference lists of articles obtained from any source;
- searched conference proceedings likely to contain trials relevant to the review;
- contacted researchers, pharmaceutical companies and relevant trial authors to seek information about unpublished or incomplete trials.

We did not impose any language restrictions on our searches, and we attempted to obtain translations of articles where necessary.

Data collection and analysis

Selection of studies

Two review authors (LJ, WL) independently evaluated titles and abstracts of identified trials to determine if they fulfilled the inclusion criteria. We obtained all potentially relevant studies for further consideration. We listed the excluded studies and reported the reasons for exclusion. We resolved any disagreements by discussion or by involving an independent party if necessary.

Data extraction and management

Two review authors (LJ, WL) independently extracted eligible data from the published reports onto standardized forms, and cross-checked them for accuracy. We resolved disagreements regarding data extraction by discussion between the review authors.

We used checklists to record, independently, details of the following:

- study design;
- total study duration;
- methods of generating randomization schedule;
- method of concealment of allocation;
- blinding;
- use of an ITT analysis (all participants initially randomized were included in the analyses as allocated to groups);
- AEs and dropouts for all reasons;
- participants (country, number of participants, age, gender, inclusion and exclusion criteria);
- comparison (details of the intervention in treatment and control groups, details of co intervention(s) in both groups, duration of treatment);
- outcomes and time points of measures (number of participants in each group and outcome, regardless of compliance);
- factors for heterogeneity (sample size, missing participants, confidence interval (CI) and P value in measurement, subgroup analyses).

Assessment of risk of bias in included studies

Two review authors (LJ, WL) independently assessed 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 assessed six specific domains including: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias. We judged the result in each domain as low, high, or unclear risk of bias.

Measures of treatment effect

We tried to evaluate the data from all the participants initially randomized as far as practically possible. We expressed continuous outcomes as mean difference (MD) with 95% CI. For outcomes commonly reported dichotomously, such as the proportion of responders, we used risk ratio (RR) with 95% CI to express the effect size. If a trial (or group within a trial) reported no AEs or dropouts, we calculated the risk difference (RD) instead of RR, with 95% CI.

Unit of analysis issues

We dealt with any unit of analysis issues using the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2011](#)).

Dealing with missing data

We attempted to contact the principal investigator for further details if any data were missing. According to ITT analysis, all randomized participants were included. We planned to assign zero improvement of dichotomous outcomes for the withdrawals. We planned to consider different scenarios (best-case and worst-case) to account for missing data.

Assessment of heterogeneity

We planned to use the standard χ^2 statistic and I^2 statistic ([Higgins 2003](#)) to measure heterogeneity ([Deeks 2011](#)), and make a judgement, along with visual inspection of forest plots. For the χ^2 test, we would have rejected the hypothesis of tolerability if the P value was less than 0.10 and an I^2 greater than 50% would represent significant heterogeneity. In this case, we would have tried to explore factors for heterogeneity.

Assessment of reporting biases

We planned to assess the publication bias by funnel plot if we had found more than 10 studies. However, we only included three studies in our review.

Data synthesis

If we found neither clinical nor statistical heterogeneity, we planned to pool results using a fixed-effect model. We would have analyzed different controls separately. For statistical heterogeneity, we planned to incorporate the results into a random-effects model. For heterogeneity that could not be readily explained, we would not have pooled the data but only given a description of the results.

Summary of findings and quality of the evidence (GRADE)

We have presented two 'Summary of findings' tables; one for each comparison ([Summary of findings for the main comparison](#); [Summary of findings 2](#)). We reported all outcomes in the tables but made a general statement about the summary of findings

for individual adverse events and graded the evidence based on consideration of the evidence of all of the adverse events (Schünemann 2011).

We determined the quality of the evidence using the GRADE approach and downgraded evidence due to the presence of high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious and by two levels if very serious (GRADE 2013).

Subgroup analysis and investigation of heterogeneity

We planned to analyze subgroups of studies categorized according to different doses and durations of topiramate.

As a formal method of comparing subgroups, we used the Chi² test (to test for significant differences between subgroups of participants). For all statistical analyses, we used Review Manager 5 (RevMan 2014).

However, we did not perform subgroup analyses due to the limited available data.

Sensitivity analysis

We planned to use best-case and worst-case scenarios for taking into account missing data. We also planned to undertake

the following sensitivity analyses to investigate unexplained heterogeneity and to test the robustness of results:

- exclusion of cross-over trials from the analysis;
- exclusion studies at high risk of bias, with inadequate allocation concealment or lack of blinded outcome assessor;
- comparison of fixed-effect versus random-effects models.

However, we were unable to perform any of these analyses due to the limited available data.

RESULTS

Description of studies

Results of the search

The searches retrieved 119 references. We identified 59 papers after de duplicating the results (Figure 1). After screening the titles and abstracts, we obtained the full papers of four studies and assessed them for eligibility. We excluded one study, because it was non-randomized. There were no ongoing randomized controlled trials (RCTs).

Figure 1. Study flow diagram

Included studies

Three randomized studies with a total of 83 participants met the inclusion criteria.

One study enrolled 22 people with juvenile myoclonic epilepsy (JME) and evaluated the efficacy and tolerability of topiramate versus placebo (Biton 2005). The starting dose of topiramate 50 mg/day or equivalent placebo tablets was maintained for four weeks, then increased at two-week intervals to target dosages of 400 mg/day in adults or 6 mg/kg/day in children. Treatment was continued for an additional 12 weeks.

Two studies focused on the efficacy and tolerability of topiramate versus valproate in people with JME (Levisohn 2007; Park 2013).

In Levisohn 2007, 28 participants were assigned at a 2:1 ratio to topiramate (19 participants) or valproate (nine participants) for 26 weeks. The topiramate target dosage was 3 mg/kg/day to 4 mg/kg/day (maximum 9 mg/kg/day) for participants aged 12 to 16 years, and 200 mg/day (maximum 600 mg/day) for participants aged over 16 years. Valproate target dosages were 10 mg/kg/day in participants aged 12 to 16 years (overall maximum 60 mg/kg/day) and 750 mg/day in participants aged over 16 years. Medications were titrated at one- to two-week intervals according to clinical response, and were administered in divided doses.

In Park 2013, 33 participants were assigned at a 1:1 ratio to topiramate (16 participants) or valproate (17 participants) for 32 weeks. The assigned antiepileptic drug (AED) was titrated up to 1200 mg/day for valproate or 100 mg/day for topiramate. The dose of valproate was titrated up 300 mg/day for two weeks, whereas topiramate was increased 25 mg/day for two weeks. In participants with a poor response to medication during the 24-week maintenance phase, the dose of valproate was increased 300 mg/day for one month to a maximum dose of 2400 mg/day, and the dose of topiramate was increased 50 mg/day for one month to a maximum 300 mg/day. Further details of the included studies are provided in the Characteristics of included studies table.

Excluded studies

We excluded one study after full-text evaluation (Sousa Pda 2005). The reason for exclusion was due to the non-randomized design (see Characteristics of excluded studies table).

Risk of bias in included studies

All three included studies were subject to an assessment of bias on six domains. The information regarding risk of bias is provided in Figure 2 and Figure 3.

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Biton 2005	+	?	+	+	-	?	+
Levisohn 2007	+	+	+	+	-	?	+
Park 2013	+	?	?	?	-	?	+

Allocation

All three included studies reported the method of random sequence generation and we assessed them as being at low risk of bias. However, only one study described the details of allocation concealment (Levisohn 2007). For the studies without information of allocation concealment, we assessed them as being at unclear risk of bias.

Blinding

Two studies were double-blind RCTs with low risk of bias (Biton 2005; Levisohn 2007). One study was open-label, without information of blinding; we evaluated the study as being at high risk of bias for this domain (Park 2013).

Incomplete outcome data

All three studies had incomplete outcome data. The proportion of participants who discontinued was more than 10% in all the

studies. Therefore, we assessed all three studies as being at high risk of attrition bias.

Selective reporting

We intended to use the table of 'Outcome Reporting Bias In Trials (ORBIT)' to evaluate selective outcome reporting (Kirkham 2010). However, the reporting bias could not be assessed as none of pre-published protocols were available.

Other potential sources of bias

We found no other potential sources of bias. Insufficient numbers of trials were available for a funnel plot analysis.

Effects of interventions

See: [Summary of findings for the main comparison Topiramate compared with placebo for juvenile myoclonic epilepsy](#); [Summary of findings 2 Topiramate compared with valproate for juvenile myoclonic epilepsy](#)

Efficacy

Topiramate versus placebo

In [Biton 2005](#), significantly more participants taking topiramate responded with a 50% or more reduction in primarily generalized tonic-clonic seizures (PGTCS) compared with placebo (73% with topiramate versus 18% with placebo; risk ratio (RR) 4.00, 95% confidence interval (CI) 1.08 to 14.75, $P = 0.04$) ([Analysis 1.1](#)). The median PGTCS reduction after 20 weeks was 64% in the topiramate group and 38% in the placebo group, which was not significantly different.

Three participants taking topiramate had no PGTCS and one had no myoclonic seizures, and two participants taking placebo had no PGTCS. In five participants taking placebo, seizure frequency increased more than 50% from baseline (PGTCS, one participant; absence, three participants; myoclonic, one participant), while seizure frequency increased more than 50% in two participants taking topiramate (absence, one participant; myoclonic, one participant).

Topiramate versus valproate

In [Levisohn 2007](#), using intention-to-treat (ITT) analysis, fewer participants taking topiramate responded with a 50% or more reduction in myoclonic seizures compared with valproate, which was not significantly different (85% with topiramate versus 100% with valproate, RR 0.88, 95% CI 0.67 to 1.15) ([Analysis 2.1](#)). More participants taking topiramate responded with a 50% or more reduction in PGTCS compared with valproate, though this was still not significantly different (91% with topiramate versus 75% with valproate, RR 1.22, 95% CI 0.68 to 2.21) ([Analysis 2.2](#)).

For [Park 2013](#), 11/16 (68.9%) participants in the topiramate group completed 24-week maintenance therapy, in which 7/11 (64%) were seizure-free. Meanwhile 16/17 (94.1%) participants in the valproate group completed 24-week follow-up, in which 9/16 (56%) were seizure-free. This was not significantly different (RR 1.13, 95% CI 0.61 to 2.11) ([Analysis 2.3](#)).

In [Levisohn 2007](#), 8/12 (67%) participants in the topiramate group and 4/7 (57%) participants in the valproate group had no seizures during the 12-week maintenance period.

Tolerability

None of the studies reported the number of participants who experienced at least one adverse event (AE).

Topiramate versus placebo

In [Biton 2005](#), we found no significant difference between topiramate and placebo for the AEs of nausea ([Analysis 1.2](#)), upper respiratory tract infection ([Analysis 1.3](#)), abnormal vision ([Analysis 1.4](#)), or diarrhoea ([Analysis 1.5](#)).

Topiramate versus valproate

In [Levisohn 2007](#) and [Park 2013](#), We found significant more events of paresthesia in topiramate ([Analysis 2.4](#)), and more events of weight gain ([Analysis 2.5](#)) and tremor in valproate ([Analysis 2.6](#)). There was no significant difference between groups for the AEs of headache ([Analysis 2.7](#)), concentration difficulty ([Analysis 2.8](#)), fatigue ([Analysis 2.9](#)), alopecia ([Analysis 2.10](#)), dizziness ([Analysis 2.11](#)), weight loss ([Analysis 2.12](#)), psychomotor slowing ([Analysis](#)

[2.13](#)), somnolence ([Analysis 2.14](#)), nausea ([Analysis 2.15](#)), appetite increase ([Analysis 2.16](#)), insomnia ([Analysis 2.17](#)), abnormal vision ([Analysis 2.18](#)), rash ([Analysis 2.19](#)), anorexia ([Analysis 2.20](#)), hallucination ([Analysis 2.21](#)) or diarrhea ([Analysis 2.22](#)).

In [Levisohn 2007](#), systemic toxicity scores were higher in participants taking valproate at each evaluation (at four, eight, 14 and 26 weeks). Neurotoxicity scores did not substantially differ between treatment groups.

DISCUSSION

Summary of main results

For efficacy, there were significantly more participants in the topiramate group with a 50% or more reduction in primarily generalized tonic-clonic seizures (PGTCS) than in placebo group based on 22 randomized participants ([Biton 2005](#)). There were no significant differences between topiramate and valproate in participants who responded with a 50% or more reduction in myoclonic seizures or in PGTCS in 28 randomized participants ([Levisohn 2007](#)), or who were seizure-free in 33 randomized participants ([Park 2013](#)). Concerning tolerability, 23 adverse events (AEs) occurred in 11 participants taking topiramate, and seven AEs occurred in 11 participants taking placebo ([Biton 2005](#)). AEs associated with topiramate were ranked as moderate to severe, while 59% of AEs linked to valproate were ranked as severe complaints ([Park 2013](#)). Moreover, systemic toxicity scores were higher in valproate group than in the topiramate group ([Levisohn 2007](#)).

Overall completeness and applicability of evidence

The evidence for topiramate in the treatment of juvenile myoclonic epilepsy (JME) was insufficient. Because of the limited number of included studies and substantial heterogeneity in comparison (different controls) and outcomes design, meta-analysis was not applicable in the majority of cases. We found high risk of bias for incomplete outcome data in all the three randomized controlled trials (RCTs). Furthermore, the sample size of randomized participants was too small to reach a robust conclusion. For topiramate versus placebo, 22 participants were randomized, while there were 61 participants randomized in the comparison of topiramate versus valproate. Therefore, studies of high-quality and with large samples are required to strengthen the applicability of evidence.

Quality of the evidence

We found limitations in the methodology of all the included studies. Two RCTs did not provide any information on allocation concealment, therefore we assessed them as having unclear risk of bias ([Biton 2005](#); [Park 2013](#)). One RCT was not of double-blind design and so had high risk of bias in terms of blinding ([Park 2013](#)). All three RCTs had a high risk of attrition bias ([Biton 2005](#); [Levisohn 2007](#); [Park 2013](#)). We could not assess reporting bias as none of the pre-published protocols were available. We regard the quality of evidence to be very low and so the limited findings should be interpreted with caution.

Potential biases in the review process

The search for trials was rigorously performed based on the strategies in different electronic databases. To identify unpublished

or incomplete trials, we also searched for protocols, but found no eligible studies. In addition, due to the inclusion of only three RCTs, we could not assess publication bias using funnel plots. Therefore, we could not exclude the possibility that we did not identify unpublished trials.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review we have found no new studies. This review does not provide sufficient evidence to support the use of topiramate for the treatment of people with juvenile myoclonic epilepsy (JME). Based on the current limited data, topiramate seems to be better tolerated than valproate, but was no more efficacious than valproate. The evidence base for the choice of the most appropriate antiepileptic drug (AED) for JME is very weak.

Implications for research

Well-designed, double-blind, randomized controlled trials with large samples are required to test the efficacy and tolerability of topiramate in people with JME. Short-term studies on seizure outcomes when taking AEDs compared with not taking AEDs are helpful to provide a more complete view of the efficacy of current AEDs for JME.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Biton 2005

Methods	Randomized, double-blind, placebo-controlled study
Participants	22 participants with juvenile myoclonic epilepsy
Interventions	Starting dose of topiramate 50 mg/day or equivalent placebo tablets was maintained for 4 weeks, then increased at 2-week intervals to target dosages of 400 mg/day in adults or 6 mg/kg/day in children. Treatment was continued for an additional 12 weeks.
Outcomes	Reduction in PGTCs, myoclonic, absence and total generalized seizures, adverse events
Notes	The baseline period was 8 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomization schedule was prepared by the Robert Wood Johnson Pharmaceutical Research Institute before the beginning of the trial.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias)	Low risk	During the double-blind phase, investigators, participants, study monitors and observers remained masked to codes until after the clinical database was finalized.

Topiramate for juvenile myoclonic epilepsy (Review)

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Biton 2005 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	During the double-blind phase, investigators, participants, study monitors and observers remained masked to codes until after the clinical database was finalized.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants taking topiramate (18%) and 1 (9%) participant taking placebo discontinued treatment owing to adverse events.
Selective reporting (reporting bias)	Unclear risk	No pre published protocol
Other bias	Low risk	No other bias was found.

Levisohn 2007

Methods	Pilot, randomized controlled trial
Participants	28 participants with juvenile myoclonic epilepsy
Interventions	Participants were assigned as 2:1 ratio to topiramate (19 participants) or valproate (9 participants) for 26 weeks. The topiramate target dosage was 3 to 4 mg/kg/day (maximum 9 mg/kg/day) for participants aged 12 to 16 years and 200 mg/day (maximum 600 mg/day) for participants aged > 16 years. Valproate target dosages were 10 mg/kg/day in participants aged 12 to 16 years and 750 mg/day in participants aged > 16 years (overall maximum 60 mg/kg/day). Medications were titrated at 1- to 2-week intervals according to clinical response and were administered in divided doses
Outcomes	Seizure reduction, evaluation of improvement, systemic toxicity and neurotoxicity scores, adverse events
Notes	The baseline period was 3 months before study entry. A 14-week titration phase was followed by a 12-week maintenance phase.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blinded randomization was achieved by providing study sites with individual envelopes containing medication assignments generated by computer.
Allocation concealment (selection bias)	Low risk	Blinded randomization was achieved by providing study sites with individual envelopes containing medication assignments generated by computer.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participant, investigator and pharmacist remained blinded to medication assignment until screening was completed and the envelope was opened.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participant, investigator and pharmacist remained blinded to medication assignment until screening was completed and the envelope was opened.
Incomplete outcome data (attrition bias) All outcomes	High risk	7 (37%) participants treated with topiramate and 2 (22%) participants treated with valproate discontinued before the endpoint.

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Levisohn 2007 (Continued)

Selective reporting (reporting bias)	Unclear risk	No pre published protocol
Other bias	Low risk	No other bias was found.

Park 2013

Methods	Randomized open-label observational study
Participants	33 participants with juvenile myoclonic epilepsy
Interventions	Participants were assigned as 1:1 ratio to topiramate (16 participants) or valproate (17 participants) for 32 weeks. The assigned antiepileptic drug was titrated up to 1200 mg/day for valproate or 100 mg/day for topiramate. The dose of valproate was titrated up 300 mg/day for 2 weeks, whereas topiramate was increased 25 mg/day for 2 weeks. In participants with a poor response to medication during the 24-week maintenance phase, the dose of valproate was increased 300 mg/day for 1 month to a maximum dose of 2400 mg/day, and the dose of topiramate was increased 50 mg/day for 1 month to a maximum 300 mg/day.
Outcomes	Number of days without myoclonic seizures during the 24-week maintenance period, adverse events
Notes	Baseline period was not clear. An 8-week titration phase was followed by a 24-week maintenance phase.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants underwent computerized randomization in a 1:1 ratio to primary treatment with topiramate or valproate.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	1 (6%) participant who was randomized to topiramate was removed from the study due to severe anorexia. 4 (25%) participants from the topiramate group and 1 (6%) participant from the valproate group were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	No pre published protocol
Other bias	Low risk	No other bias was found.

PGTCS: primarily generalized tonic-clonic seizures.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Sousa Pda 2005	Not a randomized controlled trial

DATA AND ANALYSES

Comparison 1. Topiramate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of responders (at least 50% seizure frequency reduction in PGTCs)	1	22	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [1.08, 14.75]
2 Nausea	1	22	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.52, 5.33]
3 Upper respiratory tract infection	1	22	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.31, 7.30]
4 Abnormal vision	1	22	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.21, 18.98]
5 Diarrhea	1	22	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.21, 18.98]

Analysis 1.1. Comparison 1 Topiramate versus placebo, Outcome 1 Proportion of responders (at least 50% seizure frequency reduction in PGTCs).

Analysis 1.2. Comparison 1 Topiramate versus placebo, Outcome 2 Nausea.

Analysis 1.3. Comparison 1 Topiramate versus placebo, Outcome 3 Upper respiratory tract infection.

Analysis 1.4. Comparison 1 Topiramate versus placebo, Outcome 4 Abnormal vision.

Analysis 1.5. Comparison 1 Topiramate versus placebo, Outcome 5 Diarrhea.

Comparison 2. Topiramate versus valproate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of responders (at least 50% seizure frequency reduction in myoclonic seizures)	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.15]
2 Proportion of responders (at least 50% seizure frequency reduction in PGTCS)	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.68, 2.21]
3 Number of participants with seizure-free	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.61, 2.11]
4 Paresthesia	2	61	Risk Difference (M-H, Fixed, 95% CI)	0.19 [0.02, 0.35]
5 Weight gain	2	61	Risk Difference (M-H, Fixed, 95% CI)	-0.30 [-0.49, -0.10]
6 Tremor	1	33	Risk Difference (M-H, Fixed, 95% CI)	-0.24 [-0.45, -0.02]
7 Headache	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [0.32, 17.42]
8 Concentration difficulty	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.17, 11.83]
9 Fatigue	2	61	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.17, 2.21]
10 Alopecia	2	61	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 1.02]
11 Dizziness	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.10, 9.13]
12 Weight loss	1	28	Risk Difference (M-H, Fixed, 95% CI)	0.11 [-0.09, 0.30]
13 Psychomotor slowing	1	28	Risk Difference (M-H, Fixed, 95% CI)	0.11 [-0.09, 0.30]
14 Somnolence	2	61	Risk Difference (M-H, Fixed, 95% CI)	0.08 [-0.05, 0.21]
15 Nausea	2	61	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.04, 1.18]
16 Appetite increase	1	28	Risk Difference (M-H, Fixed, 95% CI)	-0.22 [-0.50, 0.05]
17 Insomnia	1	28	Risk Difference (M-H, Fixed, 95% CI)	-0.22 [-0.50, 0.05]
18 Abnormal vision	1	28	Risk Difference (M-H, Fixed, 95% CI)	-0.22 [-0.50, 0.05]
19 Rash	1	28	Risk Difference (M-H, Fixed, 95% CI)	-0.22 [-0.50, 0.05]
20 Anorexia	1	33	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [0.37, 27.58]
21 Hallucination	1	33	Risk Difference (M-H, Fixed, 95% CI)	0.06 [-0.09, 0.22]
22 Diarrhea	1	33	Risk Difference (M-H, Fixed, 95% CI)	-0.12 [-0.30, 0.06]

Analysis 2.1. Comparison 2 Topiramate versus valproate, Outcome 1 Proportion of responders (at least 50% seizure frequency reduction in myoclonic seizures).

Analysis 2.2. Comparison 2 Topiramate versus valproate, Outcome 2 Proportion of responders (at least 50% seizure frequency reduction in PGTCs).

Analysis 2.3. Comparison 2 Topiramate versus valproate, Outcome 3 Number of participants with seizure-free.

Analysis 2.4. Comparison 2 Topiramate versus valproate, Outcome 4 Paresthesia.

Analysis 2.5. Comparison 2 Topiramate versus valproate, Outcome 5 Weight gain.

Analysis 2.6. Comparison 2 Topiramate versus valproate, Outcome 6 Tremor.

Analysis 2.7. Comparison 2 Topiramate versus valproate, Outcome 7 Headache.

Analysis 2.8. Comparison 2 Topiramate versus valproate, Outcome 8 Concentration difficulty.

Analysis 2.9. Comparison 2 Topiramate versus valproate, Outcome 9 Fatigue.

Analysis 2.10. Comparison 2 Topiramate versus valproate, Outcome 10 Alopecia.

Analysis 2.11. Comparison 2 Topiramate versus valproate, Outcome 11 Dizziness.

Analysis 2.12. Comparison 2 Topiramate versus valproate, Outcome 12 Weight loss.

Analysis 2.13. Comparison 2 Topiramate versus valproate, Outcome 13 Psychomotor slowing.

Analysis 2.14. Comparison 2 Topiramate versus valproate, Outcome 14 Somnolence.

Analysis 2.15. Comparison 2 Topiramate versus valproate, Outcome 15 Nausea.

Analysis 2.16. Comparison 2 Topiramate versus valproate, Outcome 16 Appetite increase.

Analysis 2.17. Comparison 2 Topiramate versus valproate, Outcome 17 Insomnia.

Analysis 2.18. Comparison 2 Topiramate versus valproate, Outcome 18 Abnormal vision.

Analysis 2.19. Comparison 2 Topiramate versus valproate, Outcome 19 Rash.

Analysis 2.20. Comparison 2 Topiramate versus valproate, Outcome 20 Anorexia.

Analysis 2.21. Comparison 2 Topiramate versus valproate, Outcome 21 Hallucination.

Analysis 2.22. Comparison 2 Topiramate versus valproate, Outcome 22 Diarrhea.

APPENDICES

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

1. MeSH DESCRIPTOR Myoclonic Epilepsy, Juvenile Explode All AND CENTRAL:TARGET
2. "myoclonic epilepsy" OR "impulsive petit mal" OR "Janz syndrome" AND CENTRAL:TARGET
3. #1 OR #2 AND CENTRAL:TARGET
4. Topiram* or Tipiram* or Topamax or TPM or Qudexy OR epitomax AND CENTRAL:TARGET
5. #3 AND #4 AND CENTRAL:TARGET
6. >21/02/2017:CRSINCENTRAL AND CENTRAL:TARGET
7. #5 AND #6 AND CENTRAL:TARGET

Appendix 2. MEDLINE (Ovid) search strategy

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

1. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
2. clinical trials as topic.sh.
3. trial.ti.
4. 1 or 2 or 3
5. exp animals/ not humans.sh.
6. 4 not 5
7. exp Myoclonic Epilepsy, Juvenile/
8. (myoclonic epilepsy or impulsive petit mal or Janz syndrome).tw.
9. 7 or 8
10. (Topiram\$ or Tipiram\$ or Topamax or TPM or Qudexy or epitomax).tw.
11. 6 and 9 and 10
12. limit 11 to ed=20170221-20180710
13. 11 not (1\$ or 2\$).ed.
14. 13 and (2017\$ or 2018\$).dt.
15. 12 or 14
16. remove duplicates from 15

Appendix 3. ClinicalTrials.gov search strategy

Interventional Studies | Juvenile Myoclonic Epilepsy | Topiramate OR Topamax OR TPM OR Qudexy OR epitomax | First posted on or after 02/21/2017

Appendix 4. Embase search strategy

1. 'randomized controlled trial'/exp
2. 'controlled clinical trial'/exp
3. random*:ab.
4. placebo.ab.
5. 'clinical trial':ab.
6. 1 or 2 or 3 or 4 or 5
7. 'Myoclonic Epilepsy, Juvenile'/exp
8. myoclonic epilepsy:ab.
9. impulsive petit mal:ab.
10. Janz syndrome:ab.
11. 7 or 8 or 9 or 10
12. 'topiramate'/exp
13. topamax:ab.
14. epitomax:ab.
15. McN 4853:ab.
16. "2,3:4,5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate":ab.
17. 12 or 13 or 14 or 15 or 16
22. 6 and 11 and 17

WHAT'S NEW

Date	Event	Description
10 July 2018	New search has been performed	Updated searches. No new, relevant studies found.
10 July 2018	New citation required but conclusions have not changed	Conclusions not changed.

HISTORY

Protocol first published: Issue 8, 2012

Review first published: Issue 12, 2015

Date	Event	Description
21 February 2017	New search has been performed	Searches updated 21 February 2017; no new trials identified.
21 February 2017	New citation required but conclusions have not changed	Conclusions are unchanged.

CONTRIBUTIONS OF AUTHORS

Liu J and Wang LN formulated the idea and developed the basis for the review.

The manuscript was completed by Liu J and Wang LN, and revised by Wang YP.

Liu J was responsible for updating the review.

DECLARATIONS OF INTEREST

Jia Liu: none known

Lu-Ning Wang: none known

Yu-Ping Wang: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title as "Topiramate for juvenile myoclonic epilepsy", which meant both topiramate monotherapy and add-on studies would be included.

We added 'number of participants who were seizure-free' as the secondary outcome.

We added 'Summary of findings' tables for all outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [administration & dosage] [adverse effects] [*therapeutic use]; Myoclonic Epilepsy, Juvenile [*drug therapy]; Randomized Controlled Trials as Topic; Seizures [drug therapy]; Topiramate [adverse effects] [*therapeutic use]; Treatment Outcome; Valproic Acid [adverse effects] [therapeutic use]

MeSH check words

Adolescent; Child; Humans; Young Adult