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[Intervention Review]

Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in 2015, Issue 10.

Severe myoclonic epilepsy in infants (SMEI), also known as Dravet syndrome, is a rare, refractory form of epilepsy, for which stiripentol (STP) has been recently licensed as add-on therapy.

Objectives

To evaluate the efficacy and tolerability of STP and other antiepileptic drug treatments (including ketogenic diet) for patients with SMEI.

Search methods

For the latest update we searched the Cochrane Epilepsy Group Specialized Register (20 December 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO, 20 December 2016), MEDLINE (Ovid, 1946 to 20 December 2016) and ClinicalTrials.gov (20 December 2016). Previously we searched the World Health Organization (WHO) International Clinical Trials Registry Platform ICTRP, but this was not usable at the time of this update. We also searched the bibliographies of identified studies for additional references. We handsearched selected journals and conference proceedings and imposed no language restrictions.

Selection criteria

Randomised controlled trials (RCTs) or quasi-randomised controlled trials; double- or single-blinded or unblinded trials; and parallel-group studies. Administration of at least one antiepileptic drug therapy given singly (monotherapy) or in combination (add-on therapy) compared with add-on placebo or no add-on treatment.

Data collection and analysis

Review authors independently selected trials for inclusion according to predefined criteria, extracted relevant data and evaluated the methodological quality of trials. We assessed the following outcomes: 50% or greater seizure reduction, seizure freedom, adverse effects, proportion of dropouts and quality of life. We assessed outcomes by using a Mantel-Haenszel meta-analysis to calculate risk ratios (RRs) with 95% confidence intervals (95% CIs).

Main results

Since the last version of this review no new studies have been found. Specifically, we found no RCTs assessing drugs other than STP. The review includes two RCTs evaluating use of STP (total of 64 children). Both studies were generally at unclear risk of bias. A significantly higher proportion of participants had 50% or greater reduction in seizure frequency in the STP group compared with the placebo group

(22/33 versus 2/31; RR 10.40, 95% CI 2.64 to 40.87). A significantly higher proportion of participants achieved seizure freedom in the STP group compared with the placebo group (12/33 versus 1/31; RR 7.93, 95% CI 1.52 to 41.21). Investigators found no significant differences in proportions of dropouts from the STP group compared with the placebo group (2/33 versus 8/31; RR 0.24, 95% CI 0.06 to 1.03). Only one study explicitly reported the occurrence of side effects, noting that higher proportions of participants in the STP group experienced side effects than in the placebo group (100% versus 25%; RR 3.73, 95% CI 1.81 to 7.67). We rated the quality of the evidence as low to moderate according to GRADE criteria, as most information is from studies judged to be at an unclear risk of bias.

Authors' conclusions

Data derived from two small RCTs indicate that STP is significantly better than placebo with regards to 50% or greater reduction in seizure frequency and seizure freedom. Adverse effects occurred more frequently with STP. Additional adequately powered studies with long-term follow-up should be conducted to unequivocally establish the long-term efficacy and tolerability of STP in the treatment of patients with SMEI.

PLAIN LANGUAGE SUMMARY

Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy

Background

Severe myoclonic epilepsy in infants (SMEI), also known as Dravet syndrome, is a rare, drug-resistant form of epilepsy, for which stiripentol (STP) has been recently licensed for treatment when given in combination with other antiepileptic drugs. In this review, we evaluated the efficacy and tolerability of STP and other antiepileptic drugs for the treatment of SMEI.

Results

Upon systematically searching (20 December 2016) the medical literature, we found no randomised controlled trials (RCTs) assessing drugs other than STP. We found two RCTs evaluating the efficacy and tolerability of STP in 64 children with SMEI compared with placebo. Compared with patients given placebo, those receiving STP were more likely to be seizure-free or to have 50% or greater reduction in seizure frequency. Only one study explicitly reported the occurrence of side effects, which occurred more frequently in patients treated with STP. These data, derived from two small studies, indicate that STP is significantly better than placebo with regards to efficacy but is not as well-tolerated. Further studies should be conducted to unequivocally establish the long-term efficacy and tolerability of STP in the treatment of patients with SMEI.

The evidence is current to 20 December 2016.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

STP compared with placebo for SMEI

Patient or population: children with SMEI

Settings: community

Intervention: STP 50 mg/kg/day

Comparison: placebo

	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the Evidence (GRADE)
	Assumed risk	Corresponding risk			
Outcomes	Placebo	STP			
≥ 50% reduction in seizure frequency 2-month follow-up	6.5 per 100	67.6 per 100 (17.2 to 100)	RR 10.40 (2.64 to 40.87)	64 (2)	Moderate ^{1,2}
Seizure freedom 2-month follow-up	3.2 per 100	25.6 per 100 (4.9 to 100)	RR 7.93 (1.52 to 41.21)	64 (2)	Moderate ^{1,2}
Proportion of dropouts 2-month follow-up	25.8 per 100	6.2 per 100 (1.6 to 26.6)	RR 0.24 (0.06 to 1.03)	64 (2)	Moderate ¹
Adverse effects	25.0 per 100	93.3 per 100 (45.3 to 100)	RR 3.73 (1.81 to 7.67)	41 (1)	Low ³

*The assumed control risk (ACR) is calculated as the event rate in the placebo group. The corresponding intervention risk in the STP group (and its 95% CI) is based on the assumed risk in the comparison group (ACR) and the relative effect of the intervention (and its 95% CI) and is calculated according to following formula: corresponding intervention risk, per 100 = 100 * ACR * RR.

CI: confidence interval; RR risk ratio

GRADE Working Group grades of evidence

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

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

- ¹ Information is from two small studies at unclear and low risk of bias.
- ² Wide confidence intervals.
- ³ Only one small study at low and unclear risk of bias explicitly reported the occurrence of adverse effects

BACKGROUND

This review is an update of a review previously published in the Cochrane Database of Systematic Reviews (2015, Issue 10) and titled 'Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy' (Brigo 2015).

Description of the condition

Severe myoclonic epilepsy in infants (SMEI), also known as Dravet syndrome (Dravet 2005), is one of the most refractory forms of epilepsy, for which stiripentol (STP) has been recently licensed as add-on therapy. It is a rare disease, with an estimated incidence ranging from 1 per 20,000 (Yakoub 1992) to 1 per 40,000 children (Hurst 1990). De novo mutations in the sodium channel *SCN1A* are a major cause of this syndrome (Fujiwara 2003) and have been found in 40% to 70% of patients with typical SMEI (Nabbout 2003).

According to the International League Against Epilepsy (ILAE) classification (ILAE 1989), SMEI is defined as "febrile and afebrile generalized and unilateral, clonic or tonic-clonic, seizures, that occur in the first year of life in an otherwise normal infant and are later associated with myoclonus, atypical absences, and partial seizures. All seizure types are resistant to antiepileptic drugs (AEDs). Developmental delay becomes apparent within the second year of life and is followed by definite cognitive impairment and personality disorders."

In this nosologically and aetiologically homogeneous syndrome, seizures are refractory to conventional antiepileptic drugs (AEDs). Newer drugs, such as STP, have been proposed to achieve better seizure control in SMEI.

Description of the intervention

Stiripentol is a new AED developed in France and recently approved by the European Medicines Agency (EMA) for the treatment of individuals with Dravet syndrome, as adjunctive treatment with valproate (VPA) and clobazam (CLB), with promising effects (Chiron 2007).

Adverse events associated with STP have been determined to be related to a significant increase in plasma concentrations of VPA and CLB after the addition of STP (Perez 1999). They include drowsiness, ataxia, nausea, abdominal pain and loss of appetite with weight loss. Asymptomatic neutropenia is occasionally observed (Chiron 2007).

How the intervention might work

Stiripentol is structurally unrelated to any other marketed AED. A gamma-aminobutyric acid-ergic (GABAergic) effect of STP has been demonstrated in vitro (Quilichini 2006) and is probably due to an allosteric modulation of the GABA-A receptor (Fisher 2009). Therefore, the efficacy of STP could be related to potentiation of GABAergic inhibitory neurotransmission (Quilichini 2006) and enhancement of the action of benzodiazepines (Fisher 2009). In humans, STP also inhibits cytochrome P450 enzymes (CYP) in the liver, resulting in increased plasma concentrations of concomitant AEDs metabolised by CYP (Chiron 2005). In individuals with Dravet syndrome, such a pharmacokinetic interaction particularly applies to clobazam (Giraud 2006).

Why it is important to do this review

To date, studies evaluating STP in SMEI have been uncontrolled and have included few participants, leading to potentially biased estimates of treatment effect.

Recently, a systematic review with meta-analysis of individual participant data was conducted to evaluate the efficacy of available treatments for SMEI (Kassai 2008). Twenty-three uncontrolled studies and two randomised controlled trials (RCTs) comparing STP versus placebo were found. Overall, 64 children between three and 20 years of age were included in the two RCTs. The odds ratio of responding to STP relative to placebo was 32 (confidence interval (CI) 6.2 to 161), and STP reduced the seizure rate by 70% (93% to 47%). However, this review did not consider the tolerability of STP. Moreover to date, no study has systematically reviewed the literature on the role of other AEDs in the treatment of patients with SMEI.

In this systematic review, we aimed to assess and summarise existing evidence regarding efficacy and adverse effects of STP and other AEDs (including ketogenic diet, although this is a non-drug antiepileptic treatment) for people with SMEI.

OBJECTIVES

To evaluate the efficacy and tolerability of STP and other antiepileptic drug treatments (including ketogenic diet) for patients with SMEI.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies that met all of the following criteria.

- Randomised controlled trials (RCTs) or quasi-randomised controlled trials (e.g. sequence generated by date of birth or by clinical record number).
- Double-blinded, single-blinded or unblinded trials.
- Parallel-group studies.

We excluded all other study designs, including cohort studies, case-control studies, outcomes research, case studies, case series and expert opinions.

We imposed no language restrictions.

Types of participants

We considered people with a defined diagnosis of severe myoclonic epilepsy in infancy (SMEI)/Dravet syndrome based on ILAE criteria (ILAE 1989), regardless of age, sex, ethnicity and prior therapy, including children with disabilities.

Types of interventions

- Any trial that compared at least one antiepileptic drug therapy against placebo.
- Any trial that compared at least one antiepileptic drug therapy against no therapy.
- Any trial that compared at least one antiepileptic drug therapy against another therapy or a different dose of the same therapy.

We also included trials evaluating ketogenic diet.

Therapy may be given singly (monotherapy) or in combination (add-on therapy).

Types of outcome measures

Primary outcomes

- Fifty per cent or greater reduction in seizure frequency: proportion of participants with 50% or greater reduction in seizure frequency at the end of the study compared with the pre-randomisation baseline period.
- Seizure freedom: proportion of participants achieving total cessation of seizures by the end of the trial. We will use the most current ILAE proposed definition of seizure freedom: no seizures of any type for 12 months, or three times the longest (pre-intervention) seizure-free interval, whichever is longest (Kwan 2010).

For each outcome, we performed an intention-to-treat primary analysis to include all participants in the treatment group to which they were allocated, irrespective of treatment actually received. These analyses used intention-to-treat (ITT) data for all randomly assigned participants recorded during the entire treatment period, including both titration and evaluation phases.

Secondary outcomes

- Adverse effects.
 - Proportion of participants experiencing at least one adverse effect.
 - Proportion of participants experiencing each separate adverse effect.
- Proportion of dropouts/withdrawals due to side effects, lack of efficacy or other reasons. This is used as a measure of global effectiveness.
- Improvement in quality of life as assessed by validated and reliable rating scales.

Search methods for identification of studies

This search was run for the original review on 15 May 2013, and subsequent searches have been run on 27 April 2015 and 20 December 2016.

Electronic searches

For the latest update we searched the following databases on 20 December 2016.

- The Cochrane Epilepsy Group Specialised Register, using the search strategy set out in [Appendix 1](#).
- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO), using the search strategy set out in [Appendix 2](#).
- MEDLINE (Ovid, 1946-), using the search strategy set out in [Appendix 3](#).
- [ClinicalTrials.gov](#), using the search strategy set out in [Appendix 4](#).

As in previous versions, we intended to search the WHO International Clinical Trials Registry Platform (ICTRP) using the search strategy set out in [Appendix 5](#), but this was not usable at

the time of this update. In the first version of this review (Brigo 2013 B), we searched Scopus as a substitute for Embase using the search strategy set out in [Appendix 6](#), but this is no longer necessary because randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL.

We imposed no language restrictions.

Searching other resources

We contacted experts in the field for information about unpublished and ongoing studies. We reviewed the reference lists of articles retrieved by electronic searches to check for other relevant reports. To find other relevant trials, we reviewed conference proceedings not included in the Cochrane Epilepsy Group Specialised Register, after checking with the Information Specialist to avoid duplication of effort.

Data collection and analysis

Selection of studies

The review authors (FB,SCI and NLB) independently screened all titles and abstracts to assess the eligibility of publications identified by the searches. We excluded publications that did not meet the criteria at this stage. After screening, we assessed the full text of potentially eligible citations for inclusion. Review authors reached consensus on selection of trials and on the final list of studies.

Data extraction and management

Two review authors (FB and SCI) independently extracted the following characteristics of each included trial from published reports, when possible. We used data extraction forms and resolved disagreements by mutual agreement. We recorded data in the most raw form, when possible. In cases of missing or incomplete data, we contacted the principal investigators of included trials to request additional information.

Participant factors

- Age.
- Sex.
- Epileptic seizure types.
- Causes of epilepsy.
- Duration of epilepsy.
- Family history of epilepsy.
- Number of seizures or seizure frequency before randomisation.
- Presence of status epilepticus.
- Number and types of AEDs previously taken.
- Concomitant AEDs.
- Presence of neurological deficits/signs.
- Neuropsychological status.
- Electroencephalography (EEG) findings.
- Neuroradiological findings (computed tomography (CT)/magnetic resonance imaging (MRI)).

Trial design

- Criteria used to diagnose epilepsy.
- Inclusion and exclusion criteria.
- Method of randomisation.
- Method of allocation concealment.

- Method of blinding.
- Stratification factors.
- Number of participants allocated to each group.
- Length of baseline period, titration period, treatment period.

Intervention and control

- Intervention given to controls.
- Dosage of AEDs.

Follow-up data

- Duration of follow-up.
- Reasons for incomplete outcome data.
- Dropout or loss to follow-up rates.
- Methods of analysis (e.g. ITT, modified ITT, per protocol, worst-case or best-case scenario analysis).

Assessment of risk of bias in included studies

Two review authors (FB and SCI) assessed the risk of bias of each trial according to the approaches described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the risk of bias as low, high or unclear. We evaluated the following characteristics.

- 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 addressed.
- Selective reporting (reporting bias).
- Other bias, including outcome reporting bias (Kirkham 2010), assessed in accordance with recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We used statistical methods in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to measure treatment effect.

We analysed dichotomous data by calculating risk ratios (RRs) for each trial, with uncertainty in each trial expressed by the use of 95% confidence intervals (CIs). For dichotomous data, we calculated a weighted treatment effect across trials based on the meta-analysis.

Unit of analysis issues

Given the insufficient number of studies, we did not undertake a meta-regression to explore the effects of trial duration on treatment effects.

Dealing with missing data

For individual missing data, such as information on dropout or loss to follow-up, we performed an ITT analysis, using as the denominator the total number of people who underwent randomisation. We performed ITT analysis only for outcomes related to efficacy ($\geq 50\%$ reduction in seizure frequency and seizure freedom).

Assessment of heterogeneity

We performed visual inspection of forest plots to investigate the possibility of statistical heterogeneity. We evaluated homogeneity among trial results using a standard χ^2 test and rejected the hypothesis of homogeneity if the P value was less than 0.10.

We supplemented assessment of statistical heterogeneity by using the I^2 statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than to a sampling error (Higgins 2003).

We interpreted the I^2 for heterogeneity as follows.

- 0% to 40%: may not be important.
- 30% to 60%: represents moderate heterogeneity.
- 50% to 90%: represents substantial heterogeneity.
- 75% to 100%: represents considerable heterogeneity.

We combined trial outcomes to obtain a summary estimate of effect (and the corresponding CI) using a fixed-effect model, unless we noted significant heterogeneity (i.e. $I^2 > 75\%$).

We tested the robustness of our conclusions by performing a sensitivity analysis, as described later.

Assessment of reporting biases

The number of studies was insufficient to permit use of a funnel plot to assess reporting bias.

Data synthesis

We used statistical methods to measure treatment effect in accordance with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We synthesised trial results in a meta-analysis using the Mantel-Haenszel method for analysing dichotomous data.

We performed separate analyses on each intervention (AED or ketogenic diet) given singly (monotherapy) or in combination (add-on therapy). We analysed different control groups separately.

We synthesised data on all seizures. Lack of data precluded performance of an analysis according to seizure type. We used Review Manager to combine trial data.

We used GRADE (Guyatt 2008) quality assessment criteria in the 'Summary of findings' tables.

Sensitivity analysis

For participants with missing data (i.e. dropout participants), we used worst-case and best-case scenarios for efficacy outcomes ($\geq 50\%$ reduction in seizure frequency and seizure freedom).

Worst-case analysis

We assumed that participants randomly assigned but excluded from analysis (e.g. for not completing follow-up, with inadequate seizure data) were non-responders in the active treatment group and responders in the placebo/no treatment group.

Best-case analysis

We assumed that participants randomly assigned but excluded from analysis (e.g. for not completing follow-up, with inadequate seizure data) were responders in the active treatment group and non-responders in the placebo/no treatment group.

RESULTS**Description of studies****Results of the search**

The update of searches for this review yielded 18 results (Cochrane Epilepsy Group Specialised Register (0), CENTRAL (3), MEDLINE (5),

ClinicalTrials.gov (10)). After removing three duplicates and two obviously irrelevant items, we identified 13 articles for possible inclusion. On further evaluation of titles and abstracts, none of these articles met the inclusion criteria ([Figure 1](#)). Hence, review authors found no additional studies for inclusion in this updated version of this review. Two RCTs contributed to this review; the earliest was published in 2000 ([Chiron 2000](#)) and the most recent in 2002 ([Guerrini 2002](#)).

Figure 1. Study flow diagram. This diagram refers only to results of the updated searches for the present version of the review.

Included studies

Both included studies evaluated the use of stiripentol (STP) for the treatment of patients with SMEI.

Chiron 2000 was a randomised placebo-controlled add-on trial that was conducted at 15 French centres. This study included children ≥ 3 years of age with SMEI (defined as onset of epilepsy in the first year of life with clonic (or tonic-clonic) generalised seizures, but normal psychomotor development and normal electroencephalogram (EEG); appearance of myoclonia after one year of age; atypical absences; generalised spikes and waves on EEG; and mental delay) with at least four clonic (or tonic-clonic) generalised seizures per month, and with valproate (VPA) and clobazam (CLB) given as ongoing antiepileptic drugs (AEDs). Participants receiving other drugs (except progabide) and those whose parents were unable to comply regularly with drug delivery and completion of the daily seizure diary were excluded.

The trial included 42 participants with SMEI (one lost to follow-up). The STP group consisted of 21 participants (28.6% male, 71.4% female; mean age 9.4 years; range three to 16.7 years); the placebo group included 20 participants (55% male, 45% female; mean age 9.3 years, range 3.2 to 20.7 years). One participant allocated to STP could not be assessed (study authors provided no further information). Furthermore, five participants dropped out: one (5%) treated with STP and four (20%) given placebo. Reasons for dropping out were not explicitly reported. Study authors stated only that one dropout given placebo was withdrawn because of an adverse event (not further specified).

After a one-month baseline period, participants were randomly allocated to STP (50 mg/kg/day, twice or three times daily) or placebo as add-on therapy. This double-blind phase lasted two months and was followed by an open phase that lasted one month or longer. The maximum dose of co-medication was limited to 30 mg/kg/day for VPA and 0.5 mg/kg/day for CLB. Doses could be decreased by 10 mg/kg daily for VPA in cases of loss of appetite, and by 25% for CLB in cases of drowsiness or hyperexcitability. Participants were assessed every month during the double-blind

period of two months and in subsequent open treatment for one month or longer.

Guerrini 2002, an Italian study published as an abstract, was a randomised placebo-controlled double-blind add-on trial conducted in 22 refractory participants with SMEI (11 male, 11 female; 9.1 ± 4.0 years of age, range 3.5 to 18.9 years; sex and age for each study group not explicitly reported) under VPA + CLB therapy. Five participants dropped out: one (0.9%) given STP and four (36%) given placebo. Reasons for dropping out were not explicitly reported. During a one-month baseline period, VPA and CLB were administered at 20 mg/kg/24 hours and 0.5 mg/kg/24 hours, respectively. During the following two-month double-blind period, participants were randomly assigned to receive placebo ($n = 11$) or STP ($n = 11$) at 50 mg/kg/24 hours as add-on therapy. Responders were defined as having greater than 50% reduction in the rate of clonic seizures during the second month of the double-blind period compared with baseline.

A discrepancy is evident in the numbers of participants in this RCT reported in the abstract that provided study data and in the systematic review that included this study (**Kassai 2008**). Whereas the abstract specified that the study was conducted in 22 children (11 male, 11 female; age 9.1 ± 4.0 years, range 3.5 to 18.9 years), the systematic review provided different data (23 children, 56.1% male, 43.9% female, mean age 8.95 years, range 3.47 to 18.9 years). Such a discrepancy may be easily explained by the inclusion of an additional participant after publication of the abstract that reported preliminary study results. This additional participant could not be included in the sensitivity analysis, as whether the participant was male or female was not specified, nor did study authors indicate the group to which the participant was allocated.

Excluded studies

None of the 13 articles obtained by the updated search strategy (see **Results of the search**) appeared to meet the eligibility criteria and were therefore considered not relevant.

Risk of bias in included studies

See also **Figure 2**.

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

In the study of **Chiron 2000**, participants were randomly allocated with the use of a computer-generated list (low risk of selection bias). The trial was defined as "double-blind" with no further information (unclear risk of performance and detection bias). No outcome

data were missing (low risk of attrition bias), and, although the study protocol was not available, the published report included all expected outcomes, including those that were prespecified (low risk of reporting bias).

The study of [Guerrini 2002](#) was published as an abstract, hence very limited information was provided to permit judgement with regards to selection bias, performance and detection bias, attrition bias and reporting bias. It is worth reporting that this study was defined as "randomised" not in the abstract that provided data from this trial ([Guerrini 2002](#)), but in a subsequent systematic review ([Kassai 2008](#)) that included this study. Furthermore, in the abstract, the trial was simply defined as "double-blind" with no further information on blinding.

Effects of interventions

See: [Summary of findings 1 Summary of findings](#)

In the study of [Chiron 2000](#), the frequency of participants with 50% or greater reduction in seizure frequency was greater among those given STP (15 of 21 participants, 71%) than in those given placebo (one of 20 participants, 5%). One participant allocated to STP could not be assessed (no further information provided by study authors). Furthermore, five participants dropped out: one (5%) given STP and four (20%) given placebo. Reasons for dropping out were not explicitly reported. Study authors stated only that one dropout given placebo was withdrawn because of an adverse event (not further specified). Nine of 21 (43%) participants given STP but none given placebo became free of clonic (or tonic-clonic) seizures. In each group, one participant had status epilepticus. Absolute seizure frequency was significantly lower with STP than with placebo after a decrease of 69% with STP, but an increase of 7% with placebo. Drug-related adverse events were reported in 21 (100%) participants given STP versus five (25%) given placebo.

The RCT of [Guerrini 2002](#) chose as the main outcome 50% or greater reduction in seizure frequency. Five participants dropped out: one (0.9%) given STP and four (36%) given placebo. Reasons for dropping out were not explicitly reported. During the double-blind period, seven of 21 participants given STP (63.6%) reached 50% or greater reduction in seizure frequency, and three of 21 were seizure-free; one participant given placebo (9.1%) reached seizure freedom. At the end of the double-blind period, the percentage reduction in seizure rate from baseline was significantly higher with STP (72%) than with placebo (22%) (P value < 0.05). Study authors stated that the mean clonic seizure rate was lower with STP than with placebo, but this difference did not reach statistical significance because of the small number of participants and the large interindividual variability observed. However, study authors explicitly provided no statistical results. Five participants (one given STP and four given placebo) dropped out (reasons for dropping out were not explicitly reported).

Comparison STP versus placebo

Fifty per cent or greater reduction in seizure frequency

We identified two studies with 64 participants. We detected no significant statistical heterogeneity among trials. A statistically significantly higher proportion of participants had 50% or greater reduction in seizure frequency from the pre-randomisation baseline period in the STP group compared with the placebo group (22/33 versus 2/31 participants; risk ratio (RR) 10.40, 95% confidence interval (CI) 2.64 to 40.87).

Worst-case analysis

We identified two studies with 64 participants (hence including the two participants missing from the STP group and eight missing

from the placebo group). In this analysis, we assumed that the participants missing from the STP group did not experience 50% or greater reduction in seizure frequency and those missing from the placebo group did experience 50% or greater reduction in seizure frequency. We detected no significant statistical heterogeneity among trials. A statistically significantly higher proportion of participants had 50% or greater reduction in seizure frequency from the pre-randomisation baseline period in the STP group compared with the placebo group (22/33 versus 10/31 participants; RR 2.08, 95% CI 1.18 to 3.68).

Best-case analysis

We identified two studies with 64 participants (hence including two participants missing from the STP group and eight missing from the placebo group). In this analysis, we assumed that participants missing from the STP group experienced 50% or greater reduction in seizure frequency and those missing from the placebo group did not experience 50% or greater reduction in seizure frequency. We detected no significant statistical heterogeneity among trials. A statistically significantly higher proportion of participants with 50% or greater reduction in seizure frequency from the pre-randomisation baseline period was reported in the STP group compared with the placebo group (24/33 versus 2/31 participants; RR 11.35, 95% CI 2.91 to 44.31).

Seizure freedom

We identified two studies with 64 participants. We detected no significant statistical heterogeneity among trials. A statistically significantly higher proportion of participants with seizure freedom was reported in the STP group compared with the placebo group (12/33 versus 1/31 participants; RR 7.93, 95% CI 1.52 to 41.21).

Worst-case analysis

We identified two studies with 64 participants (hence including two participants missing from the STP group and eight missing from the placebo group). In this analysis, we assumed that participants missing from the STP group did not experience seizure freedom and those missing from the placebo group did experience seizure freedom. We detected no significant statistical heterogeneity among trials. No statistically significant difference in the proportion of participants with seizure freedom was reported in the STP group compared with the placebo group (12/33 versus 9/31 participants; RR 1.26, 95% CI 0.61 to 2.62).

Best-case analysis

We identified two studies with 64 participants (hence including two participants missing from the STP group and eight missing from the placebo group). In this analysis, we assumed that participants missing from the STP group did experience seizure freedom and those missing from the placebo group did not experience seizure freedom. We detected no significant statistical heterogeneity among trials. A statistically significant higher proportion of participants with seizure freedom was reported in the STP group compared with the placebo group (14/33 versus 1/31 participants; RR 9.21, 95% CI 1.80 to 47.01).

Adverse effects

Only one study ([Chiron 2000](#)) explicitly reported the occurrence of adverse effects, hence preventing pooling of results in a meta-analysis.

Chiron 2000 noted drug-related adverse events in 21 of 21 (100%) participants given STP versus five of 20 (25%) given placebo (RR 3.73, 95% CI 1.81 to 7.67). Adverse events most frequently observed with STP included drowsiness (19/21, 90% participants; RR 18.10, 95% CI 2.67 to 122.86) and loss of appetite (7/21, 33%; RR 14.32, 95% CI 0.87 to 235.36), which could result in loss of weight (6/21, 29%; RR 12.41, 95% CI 0.74 to 206.86), whereas weight gain was equally reported for STP (5/21; 24%) and placebo (4/20; 25%) (RR 1.19, 95% CI 0.37 to 3.81). Adverse events were regarded as severe in five of 21 (24%) participants given STP (drowsiness in three, loss of weight in two) and in one given placebo (drowsiness). Some events led to a decrease in the co-medication dose (in 17 participants), as planned by the protocol; these events then disappeared. Only one participant was withdrawn from the study because of an adverse event; he had been given placebo.

Guerrini 2002 did not explicitly report the occurrence of any adverse effects.

Proportion of dropouts

We identified two studies with 64 participants. We detected no significant statistical heterogeneity among trials and no statistically significant differences in the proportion of dropouts reported in the STP group compared with the placebo group (2/33 versus 8/31 participants; RR 0.24, 95% CI 0.06 to 1.03).

Improvement in quality of life

No study measured this outcome.

DISCUSSION

In this updated version of the systematic review, we identified no additional studies for inclusion. Therefore, the conclusions of the previous version (**Brigo 2015**) remain unchanged.

This systematic review of the literature with meta-analysis indicates that stiripentol (STP) is significantly better than placebo with regards to 50% or greater reduction in seizure frequency and seizure freedom in the treatment of patients with severe myoclonic epilepsy in infants (SMEI) (also called *Dravet syndrome*). Data on 50% or greater reduction in seizure frequency remained unchanged in the sensitivity analyses with worst- and best-case scenarios (performed as an intention-to-treat analysis using imputation for participants with missing data), hence supporting a good efficacy profile of STP compared with placebo. We noted no statistically significant differences in the proportions of dropouts reported in the STP group compared with the placebo group. Only one study explicitly reported the occurrence of adverse effects; a higher proportion of participants with side effects was reported in the STP group compared with the placebo group. No study measured quality of life. Another relevant limitation of included randomised controlled trials (RCTs) was the short-term follow-up duration (two months in each study). Results of this meta-analysis should be read with caution, mainly because of the limited number of included studies (each including a small number of participants). See [Summary of findings 1](#) for GRADE assessments of the quality of the evidence.

It is of paramount importance to identify epileptic syndromes that may be studied in RCTs assessing the efficacy of a new antiepileptic drug (AED). To identify these syndromes, the European Medicine Agency (EMA) recently recommended the following two-step

procedure: (1) an exploratory prospective-observational trial including a large variety of paediatric epilepsy syndromes, and (2) a subsequent RCT to be performed for each study that disclosed a signal for possible efficacy (**Chiron 2013**). A recent study aimed to determine a minimum threshold for this signal for efficacy, estimating the number of participants to be included in such exploratory prospective-observational trials. The threshold was defined as the lowest percentage of responders observed in a prospective-observational trial with a positive corresponding RCT. The minimum number of participants included for each syndrome in a prospective-observational trial with a new AED was estimated to reach at least this threshold of responders with a 95% confidence interval. The minimum responder threshold was found to be 25%. Among paediatric epileptic syndromes, SMEI was found to reach this threshold, with a minimal sample of 32 participants needed (**Chiron 2013**).

It is worth considering that only one of the included studies in the present meta-analysis had a sample size greater than 32 participants (**Chiron 2000**), whereas the meta-analysis assessed 64 participants, hence leading to increased statistical power. This highlights the importance of conducting systematic reviews with pooled analyses (meta-analyses) of data from the literature to achieve increased statistical power and improved precision.

Summary of main results

Data derived from two small RCTs indicate that STP is significantly better than placebo with regards to 50% or greater reduction in seizure frequency and seizure freedom. Adverse effects occurred more frequently with STP.

Quality of the evidence

Both included studies were conducted in small populations. Only one study explicitly reported the occurrence of adverse effects. No study measured quality of life. Both included studies had a short-term follow-up duration (two months). Although data derived from RCTs in small populations suggest that STP is significantly better than placebo in achieving seizure control, additional adequately powered studies with long-term follow-up duration should be conducted to unequivocally establish efficacy and tolerability of this drug among patients with SMEI.

Agreements and disagreements with other studies or reviews

Results of the present systematic review are consistent with those of a previous systematic review with meta-analysis of individual participant data (**Kassai 2008**), which included results of the two studies identified in the present review (**Chiron 2000**; **Guerrini 2002**). In this systematic review, the number of participants from the Italian study was different (23 children, 56.1% male, 43.9% female) from number given in the published abstract reporting study results (22 children, 11 male, 11 female; **Guerrini 2002**). Such a discrepancy may be easily explained by the inclusion of an additional participant after publication of the abstract reporting preliminary results of the study. However, it was impossible to include this additional participant in the sensitivity analysis, as it was not specified whether the participant was male or female, nor to which group the participant was allocated. Overall, 64 children between three and 20 years of age were included in the analysis of effects of treatment on seizure rate. STP resulted in an overall odds ratio (OR) of response of 32 (95% CI 6.2 to 161); 47 (5.1 to 438) in the

[Chiron 2000](#) and 20 (1.85 to 216) in the Italian study ([Guerrini 2002](#)). We detected no heterogeneity between these studies (P value = 0.63). The overall seizure rate was reduced by 70% (95% CI 47% to 93%); by 62% (P value < 0.05) in the French study, and by 74% in the Italian study (P value < 0.05). Review authors concluded that the two included RCTs were performed with the same objectives and design and showed that seizure frequency is greatly reduced by STP in children with SMEI after two months of treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review no new studies have been found. Data derived from two small RCTs indicate that STP is significantly better than placebo with regards to 50% or

greater reduction in seizure frequency and seizure freedom in the treatment of Dravet syndrome. Adverse effects occurred more frequently with STP.

Implications for research

Additional adequate RCTs with long-term follow-up duration (≥ 6 months) should be conducted to unequivocally establish the long-term efficacy and tolerability of STP in the treatment of patients with Dravet syndrome.

ACKNOWLEDGEMENTS

We wish to acknowledge the hard and valuable work of Monica Storti that went into the first version of this review ([Brigo 2013 B](#)).

REFERENCES

References to studies included in this review

Chiron 2000 {published data only}

Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO Study Group. *Lancet* 2000;**356**(9242):1638-42.

Guerrini 2002 {published data only}

Guerrini R, Tonnelier S, d'Athis P, Rey E, Vincent J, Pons G. Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial. *Epilepsia* 2002;**43**(Suppl 8):155.

Additional references

Chiron 2005

Chiron C. Stiripentol. *Expert Opinion on Investigational Drugs* 2005;**14**:905-11.

Chiron 2007

Chiron C. Stiripentol. *Neurotherapeutics* 2007;**4**:123.

Chiron 2013

Chiron C, Kassai B, Dulac O, Pons G, Nabbout R. A revisited strategy for antiepileptic drug development in children: designing an initial exploratory step. *CNS Drugs* 2013;**27**(3):185-95.

Dravet 2005

Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy: Dravet syndrome. *Advances in Neurology* 2005;**95**:71-102.

Fisher 2009

Fisher JL. The anti-convulsant stiripentol acts directly on the GABA(A) receptor as a positive allosteric modulator. *Neuropharmacology* 2009;**56**:190-7.

Fujiwara 2003

Fujiwara T, Sugawara T, Mazaki-Miyazaki E, Takahashi Y, Fukushima K, Watanabe M, et al. Mutations of sodium channel alpha subunit type 1 (SCN1A) in intractable childhood epilepsies with frequent generalized tonic-clonic seizures. *Brain* 2003;**126**:531-46.

Giraud 2006

Giraud C, Treluyer JM, Rey E, Chiron C, Vincent J, Pons G, et al. In vitro and in vivo inhibitory effect of stiripentol on clobazam metabolism. *Drug Metabolism and Disposition* 2006;**34**:608-11.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924-6.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Hurst 1990

Hurst DL. Epidemiology of severe myoclonic epilepsy in infancy. *Epilepsia* 1990;**31**:397-400.

ILAE 1989

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**:289-99.

Kassai 2008

Kassai B, Chiron C, Augier S, Cucherat M, Rey E, Gueyffier F, et al. Severe myoclonic epilepsy in infancy: a systematic review and a meta-analysis of individual patient data. *Epilepsia* 2008;**49**(2):343-8.

Kirkham 2010

Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, Williamson PR. impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c356.

Kwan 2010

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;**51**:1069-77.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from <http://handbook.cochrane.org/>.

Nabbout 2003

Nabbout R, Gennaro E, Dalla Bernardina B, Dulac O, Madia F, Bertini E, et al. Spectrum of SCN1A mutations in severe myoclonic epilepsy of infancy. *Neurology* 2003;**60**:1961-7.

Perez 1999

Perez J, Chiron C, Musial C, Rey E, Blehaut H, d'Athis P, et al. Stiripentol: efficacy and tolerability in children with epilepsy. *Epilepsia* 1999;**40**:1618-26.

Quilichini 2006

Quilichini PP, Chiron C, Ben-Ari Y, Gozlan H. Stiripentol, a putative antiepileptic drug, enhances the duration of opening of GABA-A receptor channels. *Epilepsia* 2006;**47**:704-16.

Yakoub 1992

Yakoub M, Dulac O, Jambaque I, Chiron C, Plouin P. Early diagnosis of severe myoclonic epilepsy in infancy. *Brain and Development* 1992;**14**:299-303.

References to other published versions of this review

Brigo 2013 A

Brigo F, Storti M, Del Felice A. Antiepileptic drugs for the treatment of severe myoclonic epilepsy in infancy. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: [10.1002/14651858.CD010483](https://doi.org/10.1002/14651858.CD010483)]

Brigo 2013 B

Brigo F, Storti M. Antiepileptic drugs for the treatment of severe myoclonic epilepsy in infancy. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: [10.1002/14651858.CD010483.pub2](https://doi.org/10.1002/14651858.CD010483.pub2)]

Brigo 2015

Brigo F, Igwe SC. Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy. *Cochrane Database of Systematic Reviews* 2015, Issue 10. [DOI: [10.1002/14651858.CD010483.pub3](https://doi.org/10.1002/14651858.CD010483.pub3)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chiron 2000

Study characteristics

Methods	Multi-centre randomised placebo-controlled double-blind add-on trial 1-month baseline period 2-month double-blind treatment period
Participants	42 participants with SMEI, 1 lost to follow-up STP group: 6 M, 15 F; age 9.4 years (mean) (range 3 to 16.7 years) Placebo group: 11 M, 9 F; age 9.3 years (mean) (range 3.2 to 20.7 years)
Interventions	STP 50 mg/kg/d vs placebo
Outcomes	<ul style="list-style-type: none"> 50% or greater reduction in clonic (or tonic-clonic) seizure frequency the second month of the double-blind period compared with baseline Count of clonic (or tonic-clonic) seizures during the second month of the double-blind period Percentage of change from baseline
Notes	Multi-centre study conducted in France Five patients dropped out during the double-blind period, one on stiripentol and four on placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly allocated with the use of a computer-generated list
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement. Trial defined as "double-blind" with no further information
Blinding of outcome assessment (detection bias)	Unclear risk	Information insufficient to permit judgement. Trial defined as "double-blind" with no further information

Chiron 2000 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available, but published report includes all expected outcomes, including those prespecified

Guerrini 2002

Study characteristics

Methods	Multi-centre randomised placebo-controlled double-blind add-on trial 1-month baseline period 2-month double-blind treatment period
Participants	22 refractory participants with SMEI: 11 M, 11 F; age 9.1 years (mean), range 3.5 to 18.9 years under valproate + clobazam therapy
Interventions	STP at 50 mg/kg/24 h vs placebo
Outcomes	50% or greater reduction in seizure frequency
Notes	Published as abstract. Further information provided in Kassai 2008 Multi-centre study conducted in Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process was insufficient to permit judgement. The study was defined as "randomised" not in the abstract reporting data of this trial, but in a systematic review (Kassai 2008)
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement. Trial defined as "double-blind" with no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement. Trial defined as "double-blind" with no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement

SMEI: severe myoclonic epilepsy in infants
STP: stiripentol

DATA AND ANALYSES

Comparison 1. STP versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 $\geq 50\%$ reduction in seizure frequency	2	64	Risk Ratio (M-H, Fixed, 95% CI)	10.40 [2.64, 40.87]
1.2 Seizure freedom	2	64	Risk Ratio (M-H, Fixed, 95% CI)	7.93 [1.52, 41.21]
1.3 Proportion of dropouts	2	64	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 1.03]
1.4 $\geq 50\%$ reduction in seizure frequency, worst-case analysis	2	64	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.18, 3.68]
1.5 $\geq 50\%$ reduction in seizure frequency, best-case analysis	2	64	Risk Ratio (M-H, Fixed, 95% CI)	11.35 [2.91, 44.31]
1.6 Seizure freedom, worst-case analysis	2	64	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.61, 2.62]
1.7 Seizure freedom, best-case analysis	2	64	Risk Ratio (M-H, Fixed, 95% CI)	9.21 [1.80, 47.01]
1.8 Participants with adverse effects (any type)	1	41	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [1.81, 7.67]
1.9 Drowsiness	1	41	Risk Ratio (M-H, Fixed, 95% CI)	18.10 [2.67, 122.86]
1.10 Loss of appetite	1	41	Risk Ratio (M-H, Fixed, 95% CI)	14.32 [0.87, 235.36]
1.11 Loss of weight	1	41	Risk Ratio (M-H, Fixed, 95% CI)	12.41 [0.74, 206.86]
1.12 Weight gain	1	41	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.37, 3.81]

Analysis 1.1. Comparison 1: STP versus placebo, Outcome 1: $\geq 50\%$ reduction in seizure frequency

Analysis 1.2. Comparison 1: STP versus placebo, Outcome 2: Seizure freedom

Analysis 1.3. Comparison 1: STP versus placebo, Outcome 3: Proportion of dropouts

Analysis 1.4. Comparison 1: STP versus placebo, Outcome 4: $\geq 50\%$ reduction in seizure frequency, worst-case analysis

Analysis 1.5. Comparison 1: STP versus placebo, Outcome 5: $\geq 50\%$ reduction in seizure frequency, best-case analysis

Analysis 1.6. Comparison 1: STP versus placebo, Outcome 6: Seizure freedom, worst-case analysis

Analysis 1.7. Comparison 1: STP versus placebo, Outcome 7: Seizure freedom, best-case analysis

Analysis 1.8. Comparison 1: STP versus placebo, Outcome 8: Participants with adverse effects (any type)

Analysis 1.9. Comparison 1: STP versus placebo, Outcome 9: Drowsiness

Analysis 1.10. Comparison 1: STP versus placebo, Outcome 10: Loss of appetite

Analysis 1.11. Comparison 1: STP versus placebo, Outcome 11: Loss of weight

Analysis 1.12. Comparison 1: STP versus placebo, Outcome 12: Weight gain

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 "severe myoclonic epilepsy" OR SMEI OR Dravet*

#2 #1 AND >27/04/2015:CRSCREATED

Appendix 2. CENTRAL via CRSO search strategy

#1 ("severe myoclonic epilepsy"):TI,AB,KY

#2 "SMEI":TI,AB,KY

#3 Dravet*:TI,AB,KY

#4 #1 OR #2 OR #3

#5 * NOT INMEDLINE AND 27/04/2015 TO 20/12/2016:CD

#6 #4 AND #5

Appendix 3. MEDLINE (Ovid) search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (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. severe myoclonic epilepsy.tw.
8. SMEI.tw.
9. Dravet\$ syndrome.tw.
10. 7 or 8 or 9
11. 6 and 10
12. remove duplicates from 11
13. limit 12 to ed=20150427-20161220

Appendix 4. ClinicalTrials.gov search strategy

"severe myoclonic epilepsy" OR SMEI OR Dravet* | received on or after 04/27/2015

Appendix 5. WHO International Clinical Trials Registry Platform ICTRP search strategy

severe myoclonic epilepsy OR SMEI OR Dravet* in the Condition

Date of registration 27/04/2015 onwards

Appendix 6. SCOPUS search strategy

(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("severe myoclonic epilepsy" OR SMEI OR Dravet*))

WHAT'S NEW

Date	Event	Description
22 June 2020	Amended	Clarification message from the Co-ordinating Editor added to the Declarations of interest statement about the review's compliance with the Cochrane conflict of interest policy , which includes the relevant parts of the Cochrane Commercial Sponsorship Policy .

HISTORY

Protocol first published: Issue 4, 2013

Review first published: Issue 11, 2013

Date	Event	Description
20 December 2016	New search has been performed	Searches updated 20 December 2016.
20 December 2016	New citation required but conclusions have not changed	No new studies; conclusions remain the same.
27 April 2015	New citation required but conclusions have not changed	No new studies; conclusions remain the same.
27 April 2015	New search has been performed	Searches updated 27 April 2015.

CONTRIBUTIONS OF AUTHORS

Francesco Brigo, Stanley C. Igwe and Nicola Luigi Bragazzi updated the previous version of this systematic review ([Brigo 2015](#)).

DECLARATIONS OF INTEREST

FB: Francesco Brigo has received speaker's honoraria and travel support from Eisai and UCB Pharma. He has also acted as a consultant for EISAI.

SI: none known.

NB: none known.

Clarification statement added from the Co-ordinating Editor on 22 June 2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the [Cochrane conflict of interest policy](#), which includes the relevant parts of the [Cochrane Commercial Sponsorship Policy](#). It will be updated within twelve 12 months. The update will have a majority of authors and lead author free of conflicts."

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the first version of this review ([Brigo 2013 B](#)), we searched Scopus as a substitute for Embase. In this present version and in the previous one ([Brigo 2015](#)), we searched only CENTRAL, as randomised and quasi-randomised controlled trials in Embase are now included in CENTRAL. In both previous versions ([Brigo 2013 B](#); [Brigo 2015](#)) we also searched the WHO International Clinical Trials Registry Platform (ICTRP), but this was currently unusable when running the searches for the present version.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Dioxolanes [adverse effects] [*therapeutic use]; Epilepsies, Myoclonic [*drug therapy]; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic; Seizures [drug therapy]

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Male