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Sulthiame monotherapy for epilepsy (Review)

Milburn-McNulty P, Powell G, Sills GJ, Marson AG

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[Intervention Review]

Sulthiame monotherapy for epilepsy

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ABSTRACT

Background

Epilepsy is a common neurological condition characterised by recurrent seizures. Sulthiame (STM) is widely used as an antiepileptic drug in Europe and Israel. In this review, we present a summary of evidence for the use of STM as monotherapy in epilepsy.

Objectives

To examine the efficacy and side effect profile of STM as monotherapy when compared with placebo or another antiepileptic drug.

Search methods

We searched the Cochrane Epilepsy Group Specialised Register (24 October 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 9), MEDLINE Ovid (1946 to 24 October 2013), SCOPUS (1823 to 24 October 2013), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (28 October 2013) and ClinicalTrials.gov (28 October 2013). We imposed no language restrictions. We contacted the manufacturers of STM and researchers in the field to ask about ongoing and unpublished studies.

Selection criteria

Randomised controlled monotherapy trials of STM in people of any age with epilepsy of any aetiology.

Data collection and analysis

Two review authors independently selected trials for inclusion and extracted the relevant data.

The following outcomes were assessed: (1) time to treatment failure; (2) time to 12-month remission; (3) proportion seizure free at 12 months; (4) adverse effects; and (5) quality of life scoring. Primary analyses were intention-to-treat when possible. A narrative analysis of the data was presented.

Main results

Two studies representing 100 participants with a diagnosis of benign epilepsy of childhood with centrotemporal spikes (BECTS) and one study representing 146 participants with a diagnosis of generalised tonic-clonic seizures (GTCS) were included. STM was given as monotherapy compared with placebo in the BECTS studies and compared with phenytoin in the GTCS study. An English translation of the full text of one of the BECTS studies could not be found, and analysis of this study was based solely on the English translation of the abstract. No data were reported for outcome (1), (2), (3) or (5). Reporting of adverse effects was incomplete. Participants receiving STM were significantly less likely to develop gingival hyperplasia than were participants receiving phenytoin in the GTCS study (risk ratio (RR) 0.03, 95% confidence interval (CI) 0.00 to 0.58). No further statistically significant adverse events were noted when STM was compared with phenytoin or placebo. Two ongoing studies comparing STM monotherapy versus placebo or levetiracetam in BECTS were identified.

Authors' conclusions

Small sample size, poor methodological quality and lack of data on important outcome measures prevent any meaningful conclusions regarding the efficacy and safety of sulthiame as monotherapy in epilepsy.

PLAIN LANGUAGE SUMMARY

Sulthiame monotherapy for epilepsy

Three randomised controlled trials with a total of 246 participants have been conducted to assess the efficacy and safety of sulthiame as monotherapy in epilepsy. Two studies have been conducted on benign epilepsy of childhood with centrotemporal spikes, and one study has been conducted on generalised tonic-clonic seizures. The quality of the evidence is limited by small sample sizes, significant risk of bias and the absence of data on important outcome measures and, in the case of one study, the lack of an English translation of the full-text manuscript. As a result, this review can draw no meaningful conclusions on the efficacy or safety of sulthiame as monotherapy in epilepsy. Our search (carried out in October 2013) revealed two ongoing studies on the use of sulthiame as monotherapy in benign epilepsy of childhood with centrotemporal spikes, the results of which may facilitate a more meaningful analysis in future updates of this review.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Sulthiame compared with placebo or phenytoin for epilepsy

Patient or population: participants with epilepsy

Settings: hospital

Intervention: sulthiame

Comparison: placebo or phenytoin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Sulthiame				
All adverse effects—sulthiame versus placebo **(benign epilepsy of childhood with centrotemporal spikes)** Six months	**943 per 1000**	**1935 per 1000**	Not estimable	One (66)	⊕⊕⊝⊝ **low**	Single, small study. Data for number of adverse events provided, however, no data on number of participants experiencing adverse events provided.
All adverse effects—sulthiame versus phenytoin **(generalised tonic-clonic seizures)** Six months	**250 per 1000**	**263 per 1000**	**RR 1.05** (0.54 to 2.07)	One (146)	⊕⊝⊝⊝ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.
Paraesthesia—sulthiame versus phenytoin **(generalised tonic-clonic seizures)** Six months	**Zero per 1000**	**123 per 1000**	**RR 8.32** (0.51 to 135.82)	One (146)	⊕⊝⊝⊝ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.

Dizziness—sulthiame versus phenytoin Six months	**Zero per 1000**	**44 per 1000**	**RR 3.16** (0.18 to 55.62)	One (146)	⊕⊖⊖⊖ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.
Headache—sulthiame versus phenytoin **(generalised tonic-clonic seizures)** Six months	**Zero per 1000**	**18 per 1000**	**RR 1.43** (0.07 to 2.41)	One (146)	⊕⊖⊖⊖ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.
Anorexia—sulthiame versus phenytoin **(generalised tonic-clonic seizures)** Six months	**63 per 1000**	**26 per 1000**	**RR 0.42** (0.07 to 2.41)	One (146)	⊕⊖⊖⊖ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.
Rash—sulthiame versus phenytoin **(generalised tonic-clonic seizures)** Six months	**31 per 1000**	**9 per 1000**	**RR 0.28** (0.02 to 4.36)	One (146)	⊕⊖⊖⊖ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.
Gingival hyperplasia—sulthiame versus phenytoin **(generalised tonic-clonic seizures)** Six months	**125 per 1000**	**Zero per 1000**	**RR 0.03** (0.00 to 0.58)	One (146)	⊕⊖⊖⊖ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.
Other—sulthiame versus phenytoin **(generalised tonic-clonic seizures)** Six months	**31 per 1000**	**44 per 1000**	**RR 1.4** (0.17 to 11.59)	One (146)	⊕⊖⊖⊖ **very low**	High risk of selection, performance, detection, attrition and reporting bias Inclusion of group with disproportionately large number of males. Unclear if data on adverse events reflects number of events or number of participants experiencing an event.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
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.

BACKGROUND

Description of the condition

Epilepsy is a common neurological condition that is characterised by recurrent seizures. It has an estimated worldwide prevalence of between eight and 10 per 1000 of the general population (World Health Organization 2001). Most patients will respond well to conventional antiepileptic drugs (AEDs) (Epilepsia 1997), although around 30% will not achieve remission (Sander 1993; Schmidt 1995; Brodie 1996) despite trying numerous AEDs, often in combination.

Description of the intervention

Sulthiame (STM) is a sulphonamide that is usually taken two to three times per day in tablet form. STM was initially investigated for use in epilepsy in clinical trials in the 1960s (Griffiths 1964) but was never licenced widely as a treatment for epilepsy. However, it is now widely used as an AED in some European countries and in Israel (Gross-Selbeck 2001; Koepp 2002; Engler 2003; Ben-Zeev 2004; Chahem 2007).

When used as monotherapy, STM has been reported to reduce the occurrence of seizures and electroencephalographic (EEG) discharges in study participants with benign epilepsy of childhood with centrotemporal spikes (BECTS) (Rating 2000; Bast 2003; Ben-Zeev 2004; Wirrell 2008), benign partial epilepsy of childhood (Engler 2003; Ben-Zeev 2004), symptomatic, localisation-related epilepsy and juvenile myoclonic epilepsy (Ben-Zeev 2004), as well as in adults with refractory epilepsy and learning disabilities (Koepp 2002). In addition, STM as an add-on therapy has been reported to reduce seizure activity in participants with refractory epilepsy (Livingston 1967; Chahem 2007; Miyajima 2009). Reported adverse effects of STM include deterioration of reading ability, memory, attention skills and mathematical ability (Wirrell 2008), mixed respiratory and metabolic acidosis (Weissbach 2010) and crystalluria (Go 2005).

How the intervention might work

At the time of this writing, no studies have systematically reviewed the literature on the mechanism of action of STM. Early studies suggested that the main antiepileptic properties of STM were indirect and were due to a pharmacokinetic interaction with phenytoin (PHT); by inhibiting the parahydroxylation of phenytoin by hepatic enzymes, STM increases the serum levels and half-life of PHT when taken in combination (Houghton 1974). More recent studies have identified that STM produces a modest intracellular acidosis in central neurons via its action as a carbonic anhydrase inhibitor, thereby reducing the frequency of action potentials and epileptiform bursts (Leniger 2002).

Why it is important to do this review

A summary of the best available evidence on the efficacy and tolerability of STM for patients with epilepsy is required to inform the use of this drug and decisions about further assessment of this drug.

OBJECTIVES

To examine the efficacy and side effect profile of STM as monotherapy when compared with placebo or another antiepileptic drug.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials.
- Double-blinded, single-blinded or unblinded trials.
- Placebo-controlled or actively controlled trials.
- Parallel-group or cross-over studies.

Types of participants

- Individuals with epilepsy of any aetiology.
- Persons of any age.

Types of interventions

- For the active intervention group, STM taken as monotherapy.
- For the control group, placebo or another AED taken as monotherapy.

Types of outcome measures

Primary outcomes

- Time to treatment failure (treatment withdrawal). This outcome reflects both efficacy and tolerability, as treatment may be withdrawn because of continued seizures, adverse effects or a combination of both. This outcome is recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy as the primary outcome measure in monotherapy trials (Commission 1998).

Secondary outcomes

- Time to 12-month remission.
- Proportion seizure free at 12 months.
- Any reported adverse effects such as, but not limited to, deterioration in cognitive ability, crystalluria or respiratory and metabolic acidosis. We will assess both the proportion of any adverse effect and the proportion of each individual adverse effect.
- Overall improvement or deterioration in quality of life as assessed by validated and reliable rating scales.

Search methods for identification of studies

Electronic searches

We searched the following databases.

- The Cochrane Epilepsy Group Specialised Register (24 October 2013), using the search term "sulthiame OR Ospolot".
- The Cochrane Central Register of Controlled Trials (CENTRAL, 2013, Issue 9, searched on 28 October 2013), using the search strategy outlined in Appendix 1.
- MEDLINE Ovid (1946 to 24 October 2013), using the search strategy outlined in Appendix 2.
- SCOPUS (1823 to 24 October 2013), using the search strategy outlined in Appendix 3.
- The World Health Organization (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/, 28 October 2013), using the search term "sulthiame OR Ospolot".

- ClinicalTrials.gov (http://clinicaltrials.gov/, 28 October 2013), using the search term "sulthiame OR Ospolot".

We imposed no language restrictions.

Searching other resources

We checked the reference lists of retrieved reports to check for additional reports of relevant studies, including conference proceedings. We contacted the manufacturers of STM and colleagues in the field to ask for information about ongoing or unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (PM-M and GP) independently assessed studies for inclusion. Disagreements were resolved by discussion. If any disagreements had not been resolved by discussion, a third review author (AGM) would have arbitrated.

Data extraction and management

We extracted data from the trials and assessed study design and demographic makeup of the participants, in addition to the outcomes listed in the Types of outcome measures section. All outcome measure data were separated into intervention group and control group data. Two review authors (PM-M and GP) assessed studies and extracted data independently, and disagreements were resolved by discussion. If any disagreements were not resolved by discussion, a third review author (AGM) arbitrated.

Outcome measures

- Time to treatment failure—number of events, time to treatment failure and reason for treatment failure.
- Time to 12-month remission—number of events and time to 12-month remission.
- Proportion seizure free at 12 months—number of events.
- Adverse effects—number of events and categorisation into specific adverse effects.
- Overall improvement or deterioration in quality of life—type of scale used, score before and after intervention and time postintervention quality of life scoring repeated.

Trial design

- Method of randomisation.
- Method of blinding.
- Method of allocation concealment.
- Cross-over or parallel trial.
- Duration of study.
- Duration of baseline period.
- Duration of treatment period.
- Duration of "washout" period for cross-over studies.
- Dose of STM.
- Description of how adverse effects were reported.
- Source of funding.

Demographic information

- Number of participants in intervention group.
- Number of participants in control group.
- Study setting.
- Country in which study was performed.
- Age.
- Sex.
- Ethnicity.
- Whether treatment naive (i.e. Has the participant taken any AEDs previously? If so, which?).
- Diagnostic criteria.
- Types of seizures and epilepsy.
- Number of seizures before the start of treatment.

Assessment of risk of bias in included studies

Two review authors (PM-M and GP) independently assessed the quality of the methodology of each study using the factors outlined in the Data extraction and management section. Disagreements were resolved by discussion. If any disagreements had not been resolved by discussion, a third review author (AGM) would have arbitrated. We assessed the risk of bias in the following areas and presented our findings for each included study in separate tables with the following sections.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Other bias.

We also presented our risk of bias findings for all studies in an ORBIT table (Kirkham 2010).

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs) and planned to express time-to-event outcomes by hazard ratios (HRs) with 95% CIs. If HRs had not been reported directly, we planned to use previously reported methods to approximate these values (Parmar 1998; Williamson 2002). For quality of life data, we planned to use mean differences (MDs) with 95% CIs.

Dealing with missing data

We planned to implement an intention-to-treat analysis for all primary and secondary outcomes. We planned to calculate any missing statistics from the raw data when possible.

Assessment of heterogeneity

We planned to assess methodological heterogeneity by comparing each trial for aspects outlined in the trial design section on Data extraction and management and to assess clinical heterogeneity by comparing each trial in terms of aspects outlined in the demographic information section of Data extraction and management. If a forest plot were appropriate, we would have performed a visual inspection to identify inconsistencies amongst studies and would have quantified this using the I^2 statistic with the following parameters acting as a guideline.

- 0% to 40%: might not be important.

- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity.

Assessment of reporting biases

We reported bias in accordance with Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2008). If sufficient randomised controlled trials had been identified, we would have prepared a funnel plot to help identify publication bias, and any visual asymmetry would have been further investigated by exploratory analysis. We attempted to obtain source data for all studies included in the analysis to assess any non-reported outcomes.

Data synthesis

We planned to analyse data in a meta-analysis using a fixed-effect model within Review Manager 5, provided this was clinically appropriate and if we found no evidence of substantial heterogeneity. If we had found evidence of substantial heterogeneity, we planned to explore the factors for heterogeneity. If substantial heterogeneity had not been readily explained, we planned to use a random-effects model to perform meta-analysis. Primary analysis was intention-to-treat, in which all participants were included in the intervention groups to which they were allocated, regardless of whether they received the treatment. We analysed data as set out in Measures of treatment effect. We analysed different control groups separately. A P value < 0.05 qualified statistical significance.

Subgroup analysis and investigation of heterogeneity

We planned to assess separately the effects of STM in participants with focal epilepsy and in participants with generalised epilepsy. We planned to assess separately the effects of different doses of STM.

Sensitivity analysis

To assess the influence on results of studies of poor methodological quality, we planned to undertake analyses with and without these studies.

RESULTS

Description of studies

Results of the search

Our search identified 72 papers and two ongoing studies. After the titles and abstracts were reviewed, 61 papers were rejected, as it was clear that they were not randomised controlled monotherapy studies comparing sulthiame (STM) versus placebo or active control in epilepsy. Three studies from four papers were included, six studies were rejected and two studies are ongoing studies for which we were unable to obtain data. One study (Borggraefe 2013) was identified as potentially eligible for inclusion. We were unable to evaluate its relevance and include it in this version of the review because of time constraints. We will address it in the next update of the review. Further evaluation of the remaining papers is presented below and in the tables Characteristics of included studies and Characteristics of excluded studies.

Included studies

Three studies (Basnec 2005; Li 2000; Rating 1999) met our inclusion criteria, comprising a total of 246 participants. One study (Rating 1999) accounted for two of the search results: Rating 1999 and Rating 2000. Each publication reported data for the same study.

Rating 1999 was a multi-centre randomised, double-blind, placebo-controlled, parallel-group study. Participants between the ages of three and 10 years, weighing between 10 and 50 kg and with a diagnosis of BECTS with at least two seizures in the past six months were recruited into the study. Participants with severe organic disease, acute porphyria, a history of mental illness, relevant hypersensitivity reactions, relevant renal, thyroid or hepatic dysfunction and somatic signs of puberty or AED treatment after the age of six months (unless treatment was provided for less than six months) were excluded. A total of 66 participants were randomly assigned. Partcipants in the intervention group had a median (range) age of 8.2 years (3.9 to 10.7 years), and participants in the placebo group had a median (range) age of 8.4 years (3.1 to 10.3 years). Interquartile age was not reported. A total of 31 participants received STM, and 35 received placebo. The intervention group consisted of 16 (52%) males and 15 (48%) females. The control group was made up of 24 (69%) males and 11 (31%) females. After a six-month historic baseline period, during which participants kept a seizure diary but received no intervention or placebo, participants were randomly assigned to receive STM (5 mg/kg/d) or placebo during a six-month treatment phase. No titration period was provided. Seizure activity was recorded by participants in a diary, and assessments occurred at screening, on day 14, on day 28, after three months and at the end of the six-month treatment phase. On day 14, assessment consisted of physical and neurological examinations, review of seizure diaries and evaluation of adverse effects, intercurrent illnesses and medications. During subsequent reviews, assessment included laboratory tests such as STM plasma levels and awake and asleep EEG changes.

Li 2000 was a multi-centre randomised, double-blind, active-controlled (PHT), parallel-group study in which an additional third group received STM openly. Participants with generalised tonic-clonic seizures (GTCS) who had experienced a seizure within three to six months of the study start date were recruited into the study. Participants in the intervention group had a mean (standard deviation (SD)) age of 29.53 (15.09) years, and participants in the placebo group had a mean (SD) age of 34.91 (15.12) years. Participants in the open group had a mean (SD) age of 27.69 (16.76) years. In all, 32 participants in the intervention group received STM, and 32 received PHT. A further 82 participants in the open group received STM. The intervention group consisted of 18 (56%) males and 14 (44%) females. The treatment phase lasted for six months; however, no information was provided on loading or titration periods or whether a historic baseline period was included. The control group was made up of 17 (53%) males and 15 (47%) females. The open group included 57 (70%) males and 25 (30%) females. At the start of the trial, participants were randomly assigned to receive STM (100 to 200 mg/d) or PHT (300 mg/d) as a double-blind treatment or STM (100 to 200 mg/d) as an open treatment. Treatment continued for six months, during which seizure frequency and adverse effects were measured on a monthly basis. Laboratory tests were carried out before treatment commenced and after the six-month treatment period had been

completed; they consisted of blood count, liver function, kidney function, electrocardiogram (ECG) and EEG.

Providing a robust analysis of Basnec 2005, which was published in Croatian, is difficult because of the lack of a reliable English translation of the full text. We will aim to obtain an English translation of the full text in future updates of this review and will discuss below information that can be obtained from the English translation of the abstract. Basnec 2005 was a multi-centre randomised, double-blind, placebo-controlled, parallel-group study. Details on dosing and study phases were not provided. Participants between the ages of three and 11 years who had experienced a single seizure only and had received no AED treatment were recruited into the study. Participants received STM or placebo, and data were collected on the proportion of participants who withdrew from treatment, the proportion of participants who experienced a second seizure within six months, the proportion of participants who experienced a second seizure after six months and the proportion of participants who experienced status epilepticus.

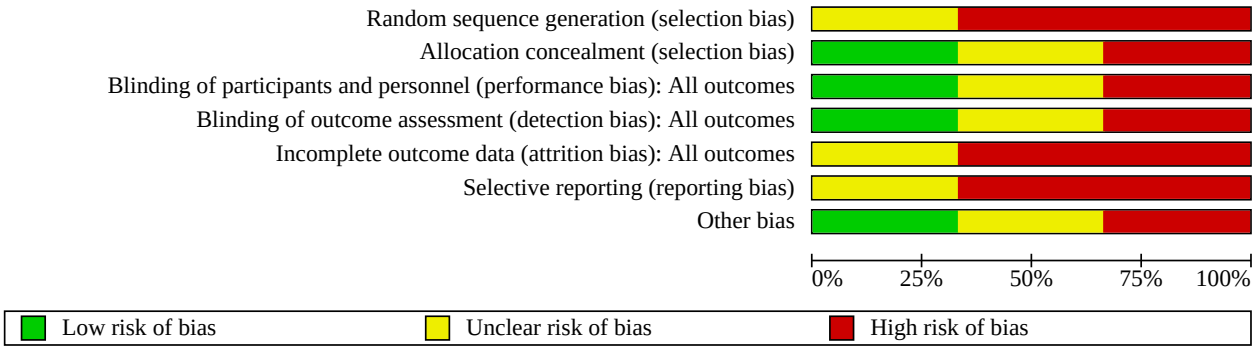
Excluded studies

Three studies (Ingram 1963; Griffiths 1964; Livingston 1967) administered STM to participants with epilepsy but did not include a placebo group. Amongst the excluded studies were two RCTs. One study (Debus 2004) compared STM versus placebo as an add-on therapy in epilepsy. Another study (Groppa 2006) compared STM versus placebo as monotherapy in healthy participants with no history of epilepsy, measuring axonal excitability of cortical neurons as a primary outcome. Two ongoing studies (ISRCTN66730162; ISRCTN97864911) compared STM versus placebo (ISRCTN66730162) or levetiracetam (ISRCTN97864911) as monotherapy in participants with BECTS. At the time of publication of this Cochrane review, data from either of these studies are not available. Future updates of this review will include data from ongoing studies once they become available.

Risk of bias in included studies

Figure 1 provides a summary of risk of bias in the included studies.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Rating 1999 states that participants were divided into blocks of four according to a preprepared list. The study authors do not explain how this list was formulated or how each block of four was assigned to treatment or placebo. A high proportion of males compared with females (69% vs 31%, respectively) was included in the control group. Li 2000 provides no information on how allocation was determined. A high proportion of males compared with females (70% vs 30%, respectively) was included in the open group. Basnec 2005 does not provide information on how allocation was determined.

Blinding

In Rating 1999, each participant had his or her designation held in a sealed coded envelope that was held by an investigator for emergency use only. Li 2000 provides no information on how blinding was performed. Basnec 2005 provides no information on how blinding was performed.

Incomplete outcome data

Rating 1999 was terminated early, after an interim analysis found superiority in the intervention group. Two participants from each group were removed from the study at this point. Six participants in the intervention group (four because of seizure and two because of early termination of the study) and 25 participants in the placebo group (21 because of seizure, two because of withdrawal of parental consent and two as the result of early termination of the study) withdrew from the study after randomisation. The paper defines the following events as treatment failure events: participants experiencing a first seizure after a seven-day run-in period, having intolerable adverse effects, developing another epileptic syndrome or being terminated from the trial by their parents or by themselves. The published paper does not make it clear whether intention-to-treat analysis was performed. Li 2000 provides no information on treatment withdrawal. All participants randomly assigned are included in the final analysis. It is plausible that this indicates that no participants withdrew from treatment, but this is not explicitly stated in the publication. Basnec 2005 states that four participants withdrew from treatment during the study but does not state from which group they withdrew. Analysis is performed without these participants rather than by using an intention-to-treat approach.

Selective reporting

Rating 1999 reports that a total of 31 participants withdrew from treatment but does not state whether intention-to-treat analysis

was performed. The total number of adverse effects experienced by each group was reported, but data on the individual frequency of each adverse effect were not reported. Data were not reported on time to treatment withdrawal, proportion of participants with a reduction in seizure frequency of 50% or greater, proportion of participants seizure free at 12 months or quality of life scale scores.

Li 2000 provided no data on time to treatment withdrawal or proportion of participants who withdrew from treatment. No data were reported on the proportion of participants with a reduction in seizure frequency of 50% or greater, the proportion of participants seizure free at 12 months or quality of life scale scores. Adverse effects, including individual frequencies of each adverse effect, were reported; however, data for the intervention group were combined with data from a much larger, unblinded open group that had an unusually large proportion of male participants compared with the other groups. It is unclear whether data provided on adverse effects is on number of events or number of participants experiencing an adverse effect.

It was not possible to assess Basnec 2005 in this domain because a reliable English language full-text version of the study was not available.

Other potential sources of bias

Rating 1999 utilised clearly stated inclusion and exclusion criteria, which are discussed in Included studies. Li 2000 provided clear inclusion criteria based on a recent history of GTCS; however, no information was provided on inclusion or exclusion criteria based on a participant's age, weight, comorbidities or previous AED use. The study authors combined treatment and open groups when performing an analysis of adverse effects and provided no separate data for the intervention group alone. Basnec 2005 provides in the abstract clear inclusion criteria based on age and a diagnosis of BECTS with a single seizure and no AED treatment. As the full-text has not yet been reviewed, it is impossible to fully appraise the inclusion and exclusion criteria for this study.

Effects of interventions

See: **Summary of findings 1** Summary of findings

Time to treatment withdrawal

No data were reported for this outcome.

Reduction in seizure frequency of 50% or greater

No data were reported for this outcome.

Proportion seizure free at 12 months

No data were reported for this outcome.

Adverse effects

Rating 1999 did not report the number of participants who experienced adverse effects. They did report a total of 60 events (1.9 events per participant) in the intervention group and 33 events (0.9 events per participant) in the placebo group. Adverse effects that occurred more than once included leukopenia, loss of strength and fatigue.

Li 2000 reported a total of 30 adverse effects (0.3 events per participant) in the combined intervention and open group and eight (0.3 events per participant) in the PHT group. Overall RR with 95% CIs for STM compared with PHT was 1.05 (95% CI 0.54 to 2.07). The individual adverse effects reported include the following.

- Paraesthesia—14 in STM group versus zero in PHT group (RR 8.32, 95% CI 0.51 to 135.82).
- Dizziness—five in STM groups versus zero in PHT group (RR 3.16, 95% CI 0.18 to 55.62).
- Headaches—two in STM groups versus zero in PHT group (RR 1.43, 95% CI 0.07 to 29.15).
- Anorexia—three in STM groups versus two in PHT group (RR 0.42, 95% CI 0.07 to 2.41).
- Rash—one in STM groups versus one in PHT group (RR 0.28, 95% CI 0.02 to 4.36).
- Gingival hyperplasia—zero in STM groups versus four in PHT group (RR 0.03, 95% CI 0.00 to 0.58).
- Other—five in STM groups versus one in PHT group (RR 1.40, 95% CI 0.17 to 11.59).

No significant difference in the total number of adverse effects was noted between the two groups (P value 0.88), and gingival hyperplasia was the only individual adverse effect that exhibited a significant difference between STM and PHT groups (P value 0.02).

Basnec 2005 provided no data on adverse effects in the abstract.

Quality of life

No data were reported for this outcome.

DISCUSSION

Three published studies were included in this review. Both Rating 1999 and Basnec 2005 compared STM as monotherapy versus placebo in the treatment of BECTS. Li 2000 compared STM versus PHT in the treatment of GTCS. Li 2000 was published in Chinese, and an English translation of the full manuscript was obtained for the purposes of this review. Basnec 2005 was published in Croatian. At the time of publication, the English translation of the abstract but not the full manuscript was available. Two ongoing studies (ISRCTN66730162; ISRCTN97864911) were also identified. ISRCTN97864911 compares STM monotherapy versus levetiracetam, and ISRCTN66730162 compares STM monotherapy versus placebo. Both studies are using STM as an intervention in BECTS. No data from the ongoing studies were available at the time of publication of this review.

Summary of main results

No data were reported by any of the studies on the proportion of participants with a reduction in seizure frequency of 50% or greater, the proportion of participants seizure free at 12 months or quality of life scale scores. Adverse effects of STM compared with placebo were reported incompletely by Rating 1999, and meaningful conclusions cannot be drawn here. Li 2000 reported data on adverse effects of STM compared with PHT, which combined the intervention group with a large group of participants who received STM openly and comprised a disproportionately large number of males. Li 2000 reported data suggesting that no significant difference was seen in the overall occurrence of adverse effects between STM and PHT groups (Analysis 1.1); however, the occurrence of gingival hyperplasia was significantly greater in the PHT group (Analysis 1.7). Li 2000 reported no significant difference

in the occurrence of paraesthesia (Analysis 1.2), dizziness (Analysis 1.3), headache (Analysis 1.4), anorexia (Analysis 1.5), rash (Analysis 1.6) or other adverse effects (Analysis 1.8) between STM and PHT groups. Basnec 2005 reported none of the outcomes specified in the protocol.

Overall completeness and applicability of evidence

Because data on important outcome measures were lacking, and because sample sizes were small and methodology was unclear in the included studies, little clinical relevance can be attributed to this review at this time.

Quality of the evidence

This review included two studies (Rating 1999; Basnec 2005), comprising a total of 100 participants, which compared STM as monotherapy versus placebo in participants with a diagnosis of BECTS, and one study (Li 2000) comprising a total of 146 participants, which compared STM as monotherapy versus PHT in participants with a history of GTCS. The methodological quality and the full range of data of Basnec 2005 cannot be adequately assessed at this time because a reliable English translation of the published paper could not be obtained. Rating 1999 states clearly inclusion and exclusion criteria for the study and gives a satisfactory explanation of a methodologically sound RCT. The quality of the evidence has been downgraded (to low) because of small sample size, lack of clarity on whether intention-to-treat analysis was performed and the absence of important outcome measures. The quality of evidence yielded by Li 2000 has been downgraded to very low because important outcome measures were omitted, and an explanation was not provided of how randomisation occurred, how allocation concealment was achieved and how treatment was blinded from participant and administrator. Concerns have been raised about the presence of a third group, populated mostly by males, which received STM openly and that group's subsequent inclusion in the analysis of adverse effects.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of available evidence, no meaningful conclusions can be drawn regarding the efficacy or safety of STM as monotherapy in epilepsy.

Implications for research

Currently two ongoing studies are comparing STM versus placebo or levetiracetam in BECTS. The results of these studies will be vital in informing clinical practice and will facilitate a more complete analysis of the intervention in future updates of this review. Studies should report data on time to treatment withdrawal, proportion of participants achieving a reduction in seizure frequency of 50% or greater, proportion of participants seizure free at 12 months and quality of life scale scores, in addition to adverse effects, to facilitate meaningful meta-analysis.

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CHARACTERISTICS OF STUDIES

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

Basnec 2005

Study characteristics	
Methods	Placebo-controlled, parallel-group, double-blind randomised controlled trial
Participants	Participants between three and 11 years of age with a diagnosis of BECTS who had experienced only one seizure and had received no AED 34 participants were randomly assigned. Unclear how many participants were allocated to each group Males versus females—not stated
Interventions	Sulthiame versus placebo
Outcomes	Proportion of participants withdrawing from treatment Proportion of participants experiencing a second seizure within six months Proportion of participants experiencing a second seizure after six months Proportion of participants experiencing status epilepticus
Notes	At the time of publication of this review, a full-text English translation is unavailable, and the above information is taken from the English translation of the abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unable to fully assess risk of bias because of lack of English language full-text manuscript
Allocation concealment (selection bias)	Unclear risk	Unable to fully assess risk of bias because of lack of English language full-text manuscript
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unable to fully assess risk of bias because of lack of English language full-text manuscript
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to fully assess risk of bias because of lack of English language full-text manuscript
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to fully assess risk of bias because of lack of English language full-text manuscript
Selective reporting (reporting bias)	Unclear risk	Unable to fully assess risk of bias because of lack of English language full-text manuscript
Other bias	Unclear risk	Unable to fully assess risk of bias because of lack of English language full-text manuscript

Li 2000

Study characteristics

Li 2000 *(Continued)*

Methods	Active-controlled, parallel-group, double-blind randomised controlled trial with a third group receiving sulthiame openly No historical baseline period, six-month treatment phase
Participants	Participants with generalised tonic-clonic seizures who had experienced a seizure within three to six months of the study start date Number of participants randomly assigned: 146 Number of participants in each group: intervention group: 32 (18 [56%] males and 14 [44%] females); control group: 32 (17 [53%] males and 15 [47%] females); open group: 82 (57 [70%] males and 25 [30%] females) Mean (SD) age, years: intervention group: 29.53 (15.09); control group: 34.91 (15.12): open group: 27.69 (16.76)
Interventions	Sulthiame (100 to 200 mg/d) versus phenytoin (100 mg TDS)
Outcomes	Adverse effects Treatment response defined as • Markedly improved: > 75% decrease in seizure frequency • Effective: 51% to 75% decrease in seizure frequency • Improved: 26% to 50% decrease in seizure frequency • Invalid or worsening: < 25% reduction in seizure frequency Laboratory tests prestudy and poststudy • Blood count • Liver function • Kidney function • ECG • EEG
Notes	This paper provides no information regarding participants withdrawing from the trial after randomisation. All participants were subsequently included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation not stated. High proportion of males versus females in open group
Allocation concealment (selection bias)	High risk	Method of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Method of blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	High risk	Method of blinding not stated

Li 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	No data provided on participants withdrawing from treatment
Selective reporting (reporting bias)	High risk	No data on proportion of participants with a reduction in seizure frequency of 50% or greater, proportion of participants seizure free at 12 months or quality of life scale scores. Data provided on adverse effects include blinded and unblinded participants. It is unclear whether data provided on adverse effects is on number of events or number of participants experiencing an adverse effect.
Other bias	High risk	Incomplete information on inclusion and exclusion criteria and on combination of treatment and open groups when analysis of adverse effects was performed; separate data for the intervention group alone not provided

Rating 1999

Study characteristics	
Methods	Placebo-controlled, parallel-group, double-blind randomised controlled trial Six-month historical baseline followed by six-month treatment phase
Participants	Participants between three and 10 years of age with a diagnosis of BECTS and at least two seizures in the past six months Number of participants randomly assigned: 66 Number of participants in each group: intervention group: 31 (16 [52%] males and 15 [48%] females); control group: 35 (24 [69%] males and 11 [31%] females) Median (range) age, years: intervention group: 8.2 (3.9 to 10.7); control group: 8.4 (3.1 to 10.3)
Interventions	Sulthiame (5 mg/kg/d) versus placebo
Outcomes	Adverse effects Proportion of participants in each group seizure free at six months Proportion of participants in each group experiencing a seizure during treatment period Proportion of participants withdrawing from treatment Proportion of participants withdrawing from treatment because of adverse effects Comparison of EEG prestudy and poststudy defined by the following groups • No normalisation • Transient normalisation • Constant normalisation
Notes	31 participants (six from the intervention group and 25 from the control group) withdrew from the study • Four participants from the intervention group withdrew because of seizure • Two participants from the intervention group withdrew because of early termination of the study • 21 participants from the control group withdrew because of seizure • Two participants from the control group withdrew because of withdrawal of parental consent

Rating 1999 *(Continued)*

- Two participants from the control group withdrew because of early termination of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Provides partial explanation of how participants were allocated to each group. High proportion of males versus females in open group
Allocation concealment (selection bias)	Low risk	Provides clear explanation of how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Provides clear explanation of blinding process
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Provides clear explanation of blinding process
Incomplete outcome data (attrition bias) All outcomes	High risk	Provides number of participants withdrawing from treatment but does not state whether intention-to-treat analysis was performed
Selective reporting (reporting bias)	High risk	No data on proportion of participants with a reduction in seizure frequency of 50% or greater, proportion of participants seizure free at 12 months or quality of life scale scores. Incomplete data on adverse effects
Other bias	Low risk	Inclusion and exclusion criteria clearly stated

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

Study	Reason for exclusion
Debus 2004	STM used as add-on therapy in the intervention group
Griffiths 1964	Not a randomised controlled trial
Groppa 2006	Study on the effect of STM as monotherapy on axonal excitability of cortical neurons in participants with no history of epilepsy
Ingram 1963	Not a randomised controlled trial
Livingston 1967	Not a randomised controlled trial
Moffat 1970	Study assessing the effects of STM on aggressive behaviour in both epileptic and non-epileptic participants

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

ISRCTN66730162

Study name	Investigating the relationship between sleep disturbance and learning in children with Benign Epilepsy of Childhood with Centrotemporal Spikes (BECCTS): a randomised double blind placebo controlled crossover trial
Methods	Randomised, double-blind, placebo-controlled, cross-over trial. Six-week treatment period (period A), followed by two-week washout period, followed by six weeks of alternate treatment (period B)

Participants	Inclusion criteria
	• Male and female children six to 16 years of age
	• Within six months of diagnosis with BECCTS and onset of symptoms
	• With clinical electroencephalographic (EEG) characteristics consistent with typical BECCTS
	• With no current or prior treatment for BECCTS
	• Signed informed (parental) consent
	Exclusion criteria
	• Inability to comply with assessments
	• Any serious intercurrent illness or uncontrolled disease that could compromise participation in the study
	• With contraindications for treatment with sulthiame
	  • History of hypersensitivity to sulphonamides
	  • History of acute porphyria
	  • History of hyperthyroidism
	  • History of arterial hypertension
	  • Impaired renal function
	  • Psychiatric disorder
	  • Hereditary galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption syndrome

Interventions	Sulthiame versus placebo
Outcomes	• Frequency of interictal epileptic discharges (IEDs) during slow wave sleep (SWS) on active treatment, relative to placebo, as measured by EEG at baseline, end of treatment period A and end of treatment period B • Sleep quality (efficiency, number of awakenings, density of sleep spindles and percentage rapid eye movement (REM) and percentage SWS on polysomnography) on active treatment relative to placebo, as measured at baseline, end of treatment period A and end of treatment period B • Performance on consolidation of learning (CoL) tasks on active treatment, relative to placebo, as measured (by validated CoL tools) at baseline, end of treatment period A and end of treatment period B • Performance on cognitive assessments including IQ and event-related potential (ERP) utilising the commonly employed auditory oddball paradigm as a measure of basic sensory processing and attention, as measured at baseline, end of treatment period A and end of treatment period B
Starting date	13 July 2011
Contact information	finbar.ocallaghan@bristol.ac.uk
Notes	

ISRCTN97864911

Study name	Head-to-head evaluation of the antiepileptic drugs, levetiracetam versus sulthiame, in a German multicentre, double-blind, controlled trial in children with benign epilepsy with centrotemporal spikes
Methods	Randomised, double-blind, active-controlled, parallel trial. Six-month treatment period
Participants	Inclusion criteria • Age between five and 14 years • Weight between 15 kg and 60 kg • At least two preceding seizures within the last six months before study start • Typical electroencephalogram (EEG) with Rolando focus (centrotemporal spike or sharp-wave focus) • Diagnosis of BECTS • Written informed consent from parents and child (if child is 8 years of age or older) Exclusion criteria • Other forms of epilepsy (e.g. continuous spikes and waves during slow sleep (CSWS), Landau-Kleffner syndrome) • Preceding treatment with antiepileptic drugs • Mental retardation (intelligence quotient (IQ) < 85) • Focal neurological deficit • Relevant major internistic disease (e.g. hepatopathy, nephropathy, endocrinopathy) • Participation in another clinical trial within the last 30 days
Interventions	Sulthiame versus levetiracetam
Outcomes	Primary outcome • "To evaluate the efficacy of levetiracetam in the treatment of children with BECTS compared to sulthiame". No further information on the primary outcome of this study is given Secondary outcomes • Safety and tolerability • Efficacy on EEG pattern • Cognitive effects
Starting date	1 June 2006
Contact information	florian.heinen@med.uni-muenchen.de
Notes	

DATA AND ANALYSES

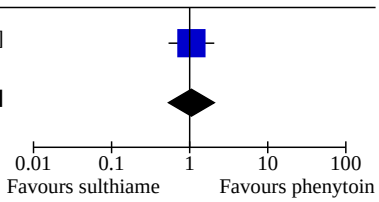
Comparison 1. Adverse effects (numbers of events)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All adverse effects—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.54, 2.07]
1.2 Paraesthesia—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	8.32 [0.51, 135.82]
1.3 Dizziness—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.18, 55.62]
1.4 Headache—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.07, 29.15]
1.5 Anorexia—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.07, 2.41]
1.6 Rash—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.02, 4.36]
1.7 Gingival hyperplasia—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.58]
1.8 Other—sulthiame versus phenytoin	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.17, 11.59]

Analysis 1.1. Comparison 1: Adverse effects (numbers of events), Outcome 1: All adverse effects—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	30	114	8	32	100.0%	1.05 [0.54 , 2.07]
Total (95% CI)		**114**		**32**	**100.0%**	**1.05 [0.54 , 2.07]**
Total events:	30		8			

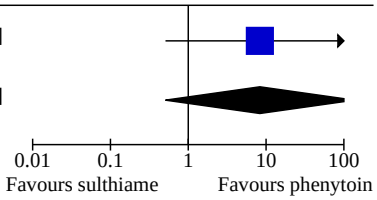
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Adverse effects (numbers of events), Outcome 2: Paraesthesia—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	14	114	0	32	100.0%	8.32 [0.51 , 135.82]
Total (95% CI)		**114**		**32**	**100.0%**	**8.32 [0.51 , 135.82]**
Total events:	14		0			

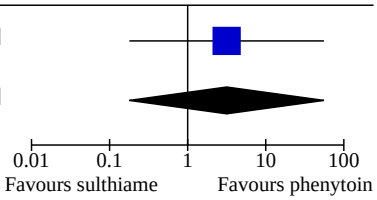
Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Adverse effects (numbers of events), Outcome 3: Dizziness—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	5	114	0	32	100.0%	3.16 [0.18 , 55.62]
Total (95% CI)		**114**		**32**	**100.0%**	**3.16 [0.18 , 55.62]**
Total events:	5		0			

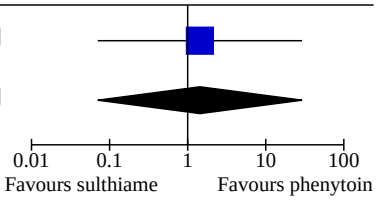
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Adverse effects (numbers of events), Outcome 4: Headache—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	2	114	0	32	100.0%	1.43 [0.07 , 29.15]
Total (95% CI)		**114**		**32**	**100.0%**	**1.43 [0.07 , 29.15]**
Total events:	2		0			

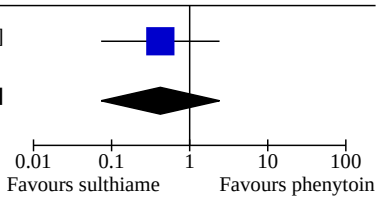
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Adverse effects (numbers of events), Outcome 5: Anorexia—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	3	114	2	32	100.0%	0.42 [0.07 , 2.41]
Total (95% CI)		**114**		**32**	**100.0%**	**0.42 [0.07 , 2.41]**
Total events:	3		2			

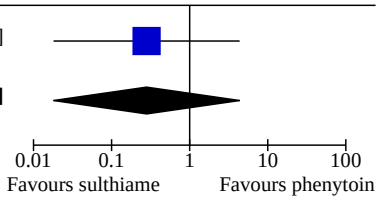
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Adverse effects (numbers of events), Outcome 6: Rash—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	1	114	1	32	100.0%	0.28 [0.02 , 4.36]
Total (95% CI)		**114**		**32**	**100.0%**	**0.28 [0.02 , 4.36]**
Total events:	1		1			

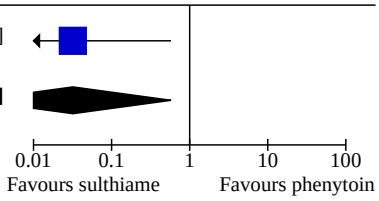
Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Adverse effects (numbers of events), Outcome 7: Gingival hyperplasia—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	0	114	4	32	100.0%	0.03 [0.00 , 0.58]
Total (95% CI)		**114**		**32**	**100.0%**	**0.03 [0.00 , 0.58]**
Total events:	0		4			

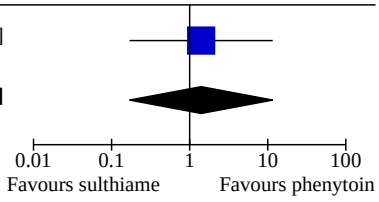
Heterogeneity: Not applicable
Test for overall effect: Z = 2.33 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Adverse effects (numbers of events), Outcome 8: Other—sulthiame versus phenytoin

Study or Subgroup	Sulthiame Events	Sulthiame Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2000	5	114	1	32	100.0%	1.40 [0.17 , 11.59]
Total (95% CI)		**114**		**32**	**100.0%**	**1.40 [0.17 , 11.59]**
Total events:	5		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.75)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL search strategy

#1 (epilep*) or (seizure*) or (convuls*)

#2 MeSH descriptor: [Epilepsy] explode all trees

#3 MeSH descriptor: [Seizures] explode all trees

#4 (#1 or #2 or #3)

#5 MeSH descriptor: [Eclampsia] explode all trees

#6 #4 not #5

#7 sulthiame or ospolot

#8 #6 and #7 in Trials

Appendix 2. MEDLINE Ovid search strategy

This strategy is based on the Cochrane highly sensitive search strategy for identifying randomised trials (Lefebvre 2011).

1. exp Epilepsy/

2. exp Seizures/

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

4. 1 or 2 or 3

5. exp Pre-Eclampsia/ or exp Eclampsia/

6. 4 not 5

7. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.

8. clinical trials as topic.sh.

9. trial.ti.

10. 7 or 8 or 9

11. exp animals/ not humans.sh.

12. 10 not 11

13. (sulthiame or Ospolot).tw.

14. 6 and 12 and 13

Appendix 3. SCOPUS search strategy

((TITLE-ABS-KEY(sulthiame OR sultiame OR Ospolot)) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR seizure OR convuls* OR (syndrome W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) OR (TITLE-ABS-KEY(lafora* W/4 (disease OR epilep*)) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) and (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 NOT (TITLE((adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*) AND NOT (monotherap* OR alone OR singl*)))

WHAT'S NEW

Date	Event	Description
26 May 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 9, 2012
Review first published: Issue 3, 2014

CONTRIBUTIONS OF AUTHORS

PM-M assessed studies for inclusion, assessed the methodological quality of studies, extracted data, performed analysis of the data and composed the final document.

GP assessed studies for inclusion, assessed the methodological quality of studies, extracted data and edited the final document.

GJS and AGM edited the final document.

DECLARATIONS OF INTEREST

Over the past 36 months, Dr Graeme J Sills has received financial support for consultancy, speaking engagements and conference attendance from a variety of pharmaceutical companies that market drugs for the treatment of epilepsy.

Anthony G Marson has received honoraria from GlaxoSmithKline for a lecture given. Also, a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool.

The other authors of this review have no known conflicts of interest.

Clarification statement added from the Co-ordinating Editor on 26 May 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 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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Addition of search strategy for SCOPUS database.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Early Termination of Clinical Trials; Epilepsy [*drug therapy]; Epilepsy, Tonic-Clonic [drug therapy]; Phenytoin [therapeutic use]; Randomized Controlled Trials as Topic; Thiazines [*therapeutic use]

MeSH check words

Adult; Child; Child, Preschool; Female; Humans; Male