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Prophylactic drug management for febrile seizures in children (Review)

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[Intervention Review]

Prophylactic drug management for febrile seizures in children

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ABSTRACT

Background

Febrile seizures occurring in a child older than one month during an episode of fever affect 2-4% of children in Great Britain and the United States and recur in 30%. Rapid-acting antiepileptics and antipyretics given during subsequent fever episodes have been used to avoid the adverse effects of continuous antiepileptic drugs.

This is an updated version of a Cochrane Review previously published in 2017.

Objectives

To evaluate primarily the effectiveness and safety of antiepileptic and antipyretic drugs used prophylactically to treat children with febrile seizures; and also to evaluate any other drug intervention where there is a sound biological rationale for its use.

Search methods

For the latest update we searched the following databases on 3 February 2020: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to 31 January 2020). CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane Review Groups including the Cochrane Epilepsy Group. We imposed no language restrictions and contacted researchers to identify continuing or unpublished studies.

Selection criteria

Trials using randomised or quasi-randomised participant allocation that compared the use of antiepileptics, antipyretics or recognised Central Nervous System active agents with each other, placebo, or no treatment.

Data collection and analysis

For the original review, two review authors independently applied predefined criteria to select trials for inclusion and extracted the predefined relevant data, recording methods for randomisation, blinding, and exclusions. For the 2016 update, a third review author checked all original inclusions, data analyses, and updated the search. For the 2020 update, one review author updated the search and performed the data analysis following a peer-review process with the original review authors. We assessed seizure recurrence at 6, 12, 18, 24, 36, 48 months, and where data were available at age 5 to 6 years along with recorded adverse effects. We evaluated the presence of publication bias using funnel plots.

Main results

We included 42 articles describing 32 randomised trials, with 4431 randomised participants used in the analysis of this review. We analysed 15 interventions of continuous or intermittent prophylaxis and their control treatments. Methodological quality was moderate to poor in most studies. We found no significant benefit for intermittent phenobarbital, phenytoin, valproate, pyridoxine, ibuprofen, or zinc sulfate versus placebo or no treatment; nor for diclofenac versus placebo followed by ibuprofen, paracetamol, or placebo; nor for continuous phenobarbital versus diazepam, intermittent rectal diazepam versus intermittent valproate, or oral diazepam versus clobazam.

There was a significant reduction of recurrent febrile seizures with intermittent diazepam versus placebo or no treatment at six months (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.48 to 0.85; 6 studies, 1151 participants; moderate-certainty evidence), 12 months (RR 0.69, 95% CI 0.56 to 0.84; 8 studies, 1416 participants; moderate-certainty evidence), 18 months (RR 0.37, 95% CI 0.23 to 0.60; 1 study, 289 participants; low-certainty evidence), 24 months (RR 0.73, 95% CI 0.56 to 0.95; 4 studies, 739 participants; high-certainty evidence), 36 months (RR 0.58, 95% CI 0.40 to 0.85; 1 study, 139 participants; low-certainty evidence), 48 months (RR 0.36, 95% CI 0.15 to 0.89; 1 study, 110 participants; moderate-certainty evidence), with no benefit at 60 to 72 months (RR 0.08, 95% CI 0.00 to 1.31; 1 study, 60 participants; very low-certainty evidence).

Phenobarbital versus placebo or no treatment reduced seizures at six months (RR 0.59, 95% CI 0.42 to 0.83; 6 studies, 833 participants; moderate-certainty evidence), 12 months (RR 0.54, 95% CI 0.42 to 0.70; 7 studies, 807 participants; low-certainty evidence), and 24 months (RR 0.69, 95% CI 0.53 to 0.89; 3 studies, 533 participants; moderate-certainty evidence), but not at 18 months (RR 0.77, 95% CI 0.56 to 1.05; 2 studies, 264 participants) or 60 to 72 months follow-up (RR 1.50, 95% CI 0.61 to 3.69; 1 study, 60 participants; very low-certainty evidence).

Intermittent clobazam compared to placebo at six months resulted in a RR of 0.36 (95% CI 0.20 to 0.64; 1 study, 60 participants; low-certainty evidence), an effect found against an extremely high (83.3%) recurrence rate in the controls, a result that needs replication.

When compared to intermittent diazepam, intermittent oral melatonin did not significantly reduce seizures at six months (RR 0.45, 95% CI 0.18 to 1.15; 1 study, 60 participants; very-low certainty evidence).

When compared to placebo, intermittent oral levetiracetam significantly reduced recurrent seizures at 12 months (RR 0.27, 95% CI 0.15 to 0.52; 1 study, 115 participants; very low-certainty evidence).

The recording of adverse effects was variable. Two studies reported lower comprehension scores in phenobarbital-treated children. Adverse effects were recorded in up to 30% of children in the phenobarbital-treated groups and 36% in benzodiazepine-treated groups. We found evidence of publication bias in the meta-analyses of comparisons for phenobarbital versus placebo (seven studies) at 12 months but not at six months (six studies); and valproate versus placebo (four studies) at 12 months. There were too few studies to identify publication bias for the other comparisons.

The methodological quality of most of the included studies was low or very low. Methods of randomisation and allocation concealment often did not meet current standards, and 'treatment versus no treatment' was more commonly seen than 'treatment versus placebo', leading to obvious risks of bias.

Authors' conclusions

We found reduced recurrence rates for intermittent diazepam and continuous phenobarbital, with adverse effects in up to 30% of children. The apparent benefit for clobazam treatment in one trial needs to be replicated. Levetiracetam also shows benefit with a good safety profile; however, further study is required. Given the benign nature of recurrent febrile seizures, and the high prevalence of adverse effects of these drugs, parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management, and, most importantly, the benign nature of the phenomenon.

PLAIN LANGUAGE SUMMARY

Prophylactic drug management for febrile seizures in children

Background

Seizures occurring with a fever (febrile seizures) in children are common and affect about one in 30 children under the age of six years. On average, one out of three children who have had a febrile seizure will have at least one more. We reviewed the evidence about the effect of drugs to prevent seizures (antiepileptics), drugs to lower temperature (antipyretics), and zinc in children with febrile seizures.

Objective

We wanted to know in how many children these drugs would prevent a recurrence of febrile seizures or cause unwanted effects.

Methods

We included 32 studies with a total of 4431 children in the review. Children who had had at least one febrile seizure were assigned to one of two or more treatment groups. The studies recorded any further seizures at various time intervals between six months and up to six years of age in each group. Unwanted medication effects were also noted.

Results

The study design and evidence quality in the studies of antiepileptic drugs was often low or very low. Poor methods known to lead to obvious risks of bias were used. One issue was with the methods used to assign children to study groups and how random this allocation was. Other issues included whether the parents or doctors, or both, knew which group each child was in or if a treatment was compared to no treatment with no placebo (dummy pill) used. The quality of the trials of antipyretics or zinc was better, with the evidence assessed as moderate to high.

Zinc therapy was found to provide no benefit. We also found no benefit in treating children just at the time of the fever with either antipyretic drugs or most antiepileptic drugs.

A significant result was noted in some instances. For example, at times between 6 and 48 months follow-up, intermittent diazepam (an antiepileptic drug) led to a reduction in the number of recurrent seizures by about a third. Continuous phenobarbital resulted in significantly fewer recurrences at 6, 12, and 24 months, but not at 18 and 60 to 72 months. One study showed that intermittent oral levetiracetam compared to placebo significantly reduced recurrent seizures at 12 months. When compared to intermittent diazepam, intermittent oral melatonin did not significantly reduce seizures at six months.

However, as recurrent seizures are only seen in about a third of children, this means that up to 16 children would have to be treated over a year or two to save just one child a further seizure. As febrile seizures are not harmful, we viewed these significant findings to be unimportant, in particular because adverse effects of the medications were common. Lower comprehension scores in phenobarbital-treated children were found in two studies. In general, adverse effects were recorded in up to about a third of children in both the phenobarbital- and benzodiazepine-treated groups. The benefit found for treatment with clobazam in one study published in 2011 needs to be repeated to test its reliability. Levetiracetam may be useful in treating children where family anxiety over possible seizure recurrence is high, but further study is required.

Authors' conclusions

There is currently insufficient evidence to support the use of continuous or intermittent treatment with zinc, antiepileptic or antipyretic drugs for children with febrile seizures. Febrile seizures can be frightening to witness. Parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management, and, most importantly, the benign nature of the phenomenon.

The evidence is current to February 2020.

Summary of findings 1. Intermittent oral or rectal diazepam compared to placebo or no treatment for febrile seizures in children

Intermittent oral or rectal diazepam compared to placebo or no treatment for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: intermittent oral or rectal diazepam
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or no treatment	Risk with intermittent oral or rectal diazepam			
Recurrent seizure at 6 months	179 per 1000	115 per 1000 (86 to 152)	RR 0.64 (0.48 to 0.85)	1151 (6 RCTs)	⊕⊕⊕⊖ **Moderate[1]**
Recurrent seizure at 12 months	254 per 1000	175 per 1000 (142 to 213)	RR 0.69 (0.56 to 0.84)	1416 (8 RCTs)	⊕⊕⊕⊖ **Moderate[1]**
Recurrent seizure at 18 months	336 per 1000	124 per 1000 (77 to 201)	RR 0.37 (0.23 to 0.60)	289 (1 RCT)	⊕⊕⊖⊖ **Low[2]**
Recurrent seizure at 24 months	273 per 1000	200 per 1000 (153 to 260)	RR 0.73 (0.56 to 0.95)	739 (4 RCTs)	⊕⊕⊕⊕ **High**
Recurrent seizure at 36 months	606 per 1000	351 per 1000 (242 to 515)	RR 0.58 (0.40 to 0.85)	139 (1 RCT)	⊕⊕⊖⊖ **Low[2]**
Recurrent seizure at 48 months	308 per 1000	111 per 1000 (46 to 274)	RR 0.36 (0.15 to 0.89)	110 (1 RCT)	⊕⊕⊕⊖ **Moderate[3]**
Recurrent seizure at 60 months or greater	200 per 1000	16 per 1000 (0 to 262)	RR 0.08 (0.00 to 1.31)	60 (1 RCT)	⊕⊖⊖⊖ **Very low[2,4]**

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to risk of bias: some of the RCTs contributing evidence had unsatisfactory allocation concealment and blinding.
[2]Downgraded twice due to serious risk of bias: the single RCT contributing evidence had unsatisfactory allocation concealment and no blinding.
[3]Downgraded once due to risk of bias: the single RCT contributing evidence had no blinding.
[4]Downgraded once due to imprecision: relative effect has very large confidence interval.

Summary of findings 2. Continuous phenobarbital compared to placebo or no treatment for febrile seizures in children

Continuous phenobarbital compared to placebo or no treatment for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: continuous phenobarbital
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or no treatment	Risk with continuous phenobarbital			
Recurrent seizure at 6 months	178 per 1000	105 per 1000 (75 to 148)	RR 0.59 (0.42 to 0.83)	833 (6 RCTs)	⊕⊕⊕⊖ **Moderate[1]**
Recurrent seizure at 12 months	308 per 1000	166 per 1000 (129 to 216)	RR 0.54 (0.42 to 0.70)	807 (7 RCTs)	⊕⊕⊖⊖ **Low[1,2]**
Recurrent seizure at 18 months	430 per 1000	331 per 1000 (241 to 451)	RR 0.77 (0.56 to 1.05)	264 (2 RCTs)	⊕⊕⊕⊖ **Moderate[1]**
Recurrent seizure at 24 months	345 per 1000	238 per 1000 (183 to 307)	RR 0.69 (0.53 to 0.89)	533 (3 RCTs)	⊕⊕⊕⊖ **Moderate[1]**
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	200 per 1000	300 per 1000 (122 to 738)	RR 1.50 (0.61 to 3.69)	60 (1 RCT)	⊕⊖⊖⊖ **Very low[3,4]**

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

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to risk of bias: some of the RCTs contributing evidence had unsatisfactory allocation concealment and blinding.
[2]Downgraded once due to potential reporting bias: funnel plot analysis detected risk of publication bias.
[3]Downgraded twice due to serious risk of bias: the single RCT contributing evidence had unsatisfactory allocation concealment and no blinding.
[4]Downgraded once due to imprecision: relative effect has very large confidence interval.

Summary of findings 3. Intermittent phenobarbital compared to placebo or no treatment for febrile seizures in children

Intermittent phenobarbital compared to placebo or no treatment for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: intermittent phenobarbital
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or no treatment	Risk with intermittent phenobarbital			
Recurrent seizure at 6 months	88 per 1000	121 per 1000 (59 to 247)	RR 1.37 (0.67 to 2.81)	281 (2 RCTs)	⊕⊖⊖⊖ **Very low[1,2,3]**
Recurrent seizure at 12 months	216 per 1000	218 per 1000 (140 to 343)	RR 1.01 (0.65 to 1.59)	281 (2 RCTs)	⊕⊕⊕⊖ **Moderate[1]**
Recurrent seizure at 18 months	Not reported				NA
Recurrent seizure at 24 months	294 per 1000	250 per 1000 (167 to 376)	RR 0.85 (0.57 to 1.28)	249 (1 RCT)	⊕⊕⊖⊖ **Low[4]**

Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	200 per 1000	166 per 1000 (56 to 488)	RR 0.83 (0.28 to 2.44)	60 (1 RCT)	⊕⊝⊝⊝ **Very low[3,4]**

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to risk of bias: some of the RCTs contributing evidence had unsatisfactory allocation concealment and blinding.
[2]Downgraded once due to inconsistency: trials had opposite effect sizes.
[3]Downgraded once due to imprecision: relative effect has very large confidence interval.
[4]Downgraded twice due to serious risk of bias: the single RCT contributing evidence had unsatisfactory allocation concealment and no blinding.

Summary of findings 4. Continuous oral phenytoin compared to placebo for febrile seizures in children

Continuous oral phenytoin compared to placebo for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: continuous oral phenytoin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with continuous oral phenytoin			
Recurrent seizure at 6 months	Not reported				NA
Recurrent seizure at 12 months	349 per 1000	342 per 1000 (192 to 603)	RR 0.98 (0.55 to 1.73)	90 (1 RCT)	⊕⊕⊝⊝ **Low[1]**

Recurrent seizure at 18 months	Not reported	NA
Recurrent seizure at 24 months	Not reported	NA
Recurrent seizure at 36 months	Not reported	NA
Recurrent seizure at 48 months	Not reported	NA
Recurrent seizure at 60 months or greater	Not reported	NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded twice due to serious risk of bias: the single RCT contributing evidence had unsatisfactory allocation concealment and no blinding.

Summary of findings 5. Continuous oral valproate compared to placebo or no treatment for febrile seizures in children

Continuous oral valproate compared to placebo or no treatment for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: continuous oral valproate
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or no treatment	Risk with continuous oral valproate			
Recurrent seizure at 6 months	118 per 1000	141 per 1000 (65 to 308)	RR 1.20 (0.55 to 2.62)	156 (2 RCTs)	⊕⊕⊖⊖ **Low[1]**
Recurrent seizure at 12 months	239 per 1000	196 per 1000 (124 to 308)	RR 0.82 (0.52 to 1.29)	255 (4 RCTs)	⊕⊕⊖⊖

					Low[1]
Recurrent seizure at 18 months	346 per 1000	45 per 1000 (7 to 332)	RR 0.13 (0.02 to 0.96)	48 (1 RCT)	⊕⊖⊖⊖ **Very low[1,2]**
Recurrent seizure at 24 months	212 per 1000	267 per 1000 (155 to 462)	RR 1.26 (0.73 to 2.18)	156 (2 RCTs)	⊕⊕⊖⊖ **Low[1]**
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded twice due to serious risk of bias: the single RCT contributing evidence had unsatisfactory allocation concealment and no blinding.
[2]Downgraded once due to imprecision: relative effect has very large confidence interval.

Summary of findings 6. Continuous oral pyridoxine compared to placebo for febrile seizures in children

Continuous oral pyridoxine compared to placebo for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: continuous oral pyridoxine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with continuous oral pyridoxine			

Recurrent seizure at 6 months	154 per 1000	72 per 1000 (23 to 228)	RR 0.47 (0.15 to 1.48)	107 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]
Recurrent seizure at 12 months	192 per 1000	127 per 1000 (52 to 310)	RR 0.66 (0.27 to 1.61)	107 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]
Recurrent seizure at 18 months	Not reported				NA
Recurrent seizure at 24 months	Not reported				NA
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to risk of bias: risk of attrition bias.
[2]Downgraded once due to imprecision: relative effect has very large confidence interval.

Summary of findings 7. Intermittent oral ibuprofen compared to placebo for febrile seizures in children

Intermittent oral ibuprofen compared to placebo for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: intermittent oral ibuprofen
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)

	Risk with placebo	Risk with intermittent oral ibuprofen			
Recurrent seizure at 6 months	210 per 1000	233 per 1000 (145 to 380)	RR 1.11 (0.69 to 1.81)	230 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 12 months	294 per 1000	279 per 1000 (185 to 421)	RR 0.95 (0.63 to 1.43)	230 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 18 months	Not reported				NA
Recurrent seizure at 24 months	387 per 1000	325 per 1000 (228 to 460)	RR 0.84 (0.59 to 1.19)	230 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 8. Intermittent oral clobazam compared to placebo for febrile seizures in children

Intermittent oral clobazam compared to placebo for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: intermittent oral clobazam
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with intermittent oral clobazam			
Recurrent seizure at 6 months	833 per 1000	300 per 1000 (167 to 533)	RR 0.36 (0.20 to 0.64)	60 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]
Recurrent seizure at 12 months	Not reported				NA
Recurrent seizure at 18 months	Not reported				NA
Recurrent seizure at 24 months	Not reported				NA
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to risk of bias: unclear details regarding allocation concealment, blinding, and attrition.
[2]Downgraded once due to applicability: very high recurrence rate in the placebo group (higher than expected).

Summary of findings 9. Continuous zinc sulfate for 6 months compared to placebo for febrile seizures in children

Continuous zinc sulfate for 6 months compared to placebo for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: continuous zinc sulfate for 6 months

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with continuous zinc sulfate for 6 months			
Recurrent seizure at 6 months	Not reported				NA
Recurrent seizure at 12 months	380 per 1000	220 per 1000 (118 to 414)	RR 0.58 (0.31 to 1.09)	100 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 18 months	Not reported				NA
Recurrent seizure at 24 months	Not reported				NA
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 10. Intermittent rectal diclofenac compared to placebo, followed by oral ibuprofen, paracetamol, or placebo after 8 hours, for febrile seizures in children

Intermittent rectal diclofenac compared to placebo, followed by oral ibuprofen, paracetamol, or placebo after 8 hours, for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: intermittent rectal diclofenac followed by oral ibuprofen, paracetamol, or placebo after 8 hours

Comparison: placebo followed by oral ibuprofen, paracetamol, or placebo after 8 hours

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo followed by oral ibuprofen, paracetamol, or placebo after 8 hours	Risk with intermittent rectal diclofenac followed by oral ibuprofen, paracetamol, or placebo after 8 hours			
Recurrent seizure at 6 months	149 per 1000	119 per 1000 (63 to 231)	RR 0.80 (0.42 to 1.55)	231 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 12 months	237 per 1000	163 per 1000 (95 to 275)	RR 0.69 (0.40 to 1.16)	231 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 18 months	272 per 1000	196 per 1000 (122 to 315)	RR 0.72 (0.45 to 1.16)	231 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 24 months	281 per 1000	222 per 1000 (143 to 348)	RR 0.79 (0.51 to 1.24)	231 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 11. Continuous phenobarbital compared to intermittent rectal or oral diazepam for febrile seizures in children

Continuous phenobarbital compared to intermittent rectal or oral diazepam for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: continuous phenobarbital
Comparison: intermittent rectal or oral diazepam

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with intermittent rectal or oral diazepam	Risk with continuous phenobarbital			
Recurrent seizure at 6 months	Not reported				NA
Recurrent seizure at 12 months	155 per 1000	229 per 1000 (116 to 455)	RR 1.48 (0.75 to 2.94)	145 (1 RCT)	⊕⊕⊖⊖ **Low[1]**
Recurrent seizure at 18 months	80 per 1000	100 per 1000 (29 to 350)	RR 1.25 (0.36 to 4.38)	100 (1 RCT)	⊕⊖⊖⊖ **Very low[1,2]**
Recurrent seizure at 24 months	Not reported				NA
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded twice due to serious risk of bias: the single RCT contributing evidence had unsatisfactory allocation concealment and no blinding.

[2]Downgraded once due to imprecision: relative effect has very large confidence interval.

Summary of findings 12. Intermittent rectal diazepam compared to intermittent rectal valproate for febrile seizures in children

Intermittent rectal diazepam compared to intermittent rectal valproate for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: intermittent rectal diazepam
Comparison: intermittent rectal valproate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with intermittent rectal valproate	Risk with intermittent rectal diazepam			
Recurrent seizure at 6 months	88 per 1000	123 per 1000 (51 to 304)	RR 1.41 (0.58 to 3.47)	169 (1 RCT)	⊕⊖⊖⊖ **Very low[1,2]**
Recurrent seizure at 12 months	175 per 1000	259 per 1000 (144 to 467)	RR 1.48 (0.82 to 2.67)	169 (1 RCT)	⊕⊕⊖⊖ **Low[1]**
Recurrent seizure at 18 months	Not reported				NA
Recurrent seizure at 24 months	Not reported				NA
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded twice due to serious risk of bias: the single RCT contributing evidence had unsatisfactory allocation concealment and no blinding.
[2]Downgraded once due to imprecision: relative effect has very large confidence interval.

Summary of findings 13. Intermittent oral diazepam compared to intermittent oral clobazam for febrile seizures in children

Intermittent oral diazepam compared to oral clobazam for febrile seizures in children

Patient or population: children with febrile seizures
Setting: outpatients
Intervention: intermittent oral diazepam
Comparison: oral clobazam

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with intermittent oral clobazam	Risk with intermittent oral diazepam			
Recurrent seizure at 6 months	Not reported				NA
Recurrent seizure at 12 months	42 per 1000	96 per 1000 (26 to 356)	RR 2.28 (0.62 to 8.42)	143 (2 RCTs)	⊕⊕⊖⊖ **Low[1,2]**
Recurrent seizure at 18 months	Not reported				NA
Recurrent seizure at 24 months	Not reported				NA
Recurrent seizure at 36 months	Not reported				NA
Recurrent seizure at 48 months	Not reported				NA
Recurrent seizure at 60 months or greater	Not reported				NA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk (the event rate in the control group) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded once due to risk of bias: unsatisfactory allocation concealment and blinding.
[2]Downgraded once due to imprecision: relative effect has very large confidence interval.

Summary of findings 14. Intermittent oral melatonin compared to intermittent oral diazepam for febrile seizures in children

Intermittent oral melatonin compared with intermittent oral diazepam for febrile seizures in children

Patient or population: children with febrile seizures

Settings: outpatients

Intervention: intermittent oral melatonin

Comparison: intermittent oral diazepam

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with oral diazepam	Risk with oral melatonin			
Recurrent seizures at 6 months	367 per 1000	167 per 1000 (66 to 422)	RR 0.45 (0.18 to 1.15)	60 (1 RCT)	⊕⊖⊖⊖ **Very low[1,2]**
Recurrent seizures at 12 months	Not reported				NA
Recurrent seizures at 18 months	Not reported				NA
Recurrent seizures at 24 months	Not reported				NA
Recurrent seizures at 36 months	Not reported				NA
Recurrent seizures at 48 months	Not reported				NA
Recurrent seizures at 60 months or greater	Not reported				NA

*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; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded twice due to risk of bias: single RCT and attrition bias.
[2]Downgraded once due to imprecision: large confidence interval that includes no effect.

Summary of findings 15. Intermittent oral levetiracetam compared to placebo (any antipyretics) for febrile seizures in children

Intermittent oral levetiracetam compared with placebo for febrile seizures in children

Patient or population: children with febrile seizures

Settings: outpatients

Intervention: intermittent oral levetiracetam

Comparison: placebo (any antipyretics)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with oral levetiracetam			
Recurrent seizures at 6 months	Not reported				NA
Recurrent seizures at 12 months	514 per 1000	141 per 1000 (77 to 267)	RR 0.27 (0.15 to 0.52)	115 (1 RCT)	⊕⊖⊖⊖ **Very low[1]**
Recurrent seizures at 18 months	Not reported				NA
Recurrent seizures at 24 months	Not reported				NA
Recurrent seizures at 36 months	Not reported				NA
Recurrent seizures at 48 months	Not reported				NA
Recurrent seizures at 60 months or greater	Not reported				NA

*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; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded three times due to risk of bias: single RCT and lack of allocation concealment and blinding of outcome assessors. Also, attrition bias due to increased follow-up losses.

BACKGROUND

This is an updated version of a Cochrane Review previously published in 2017 (Offringa 2017).

Description of the condition

The International League Against Epilepsy (ILAE) defines a febrile seizure as "a seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures" (ILEA 1993). The cumulative incidence of febrile seizures is estimated between 2% and 5% in the USA and Western Europe (Shinnar 2003; Verity 1991); between 6% to 9% in Japan; and 14% in India and Guam (ILEA 1993). Febrile seizures have a peak incidence at 18 months and are most common between the ages of six months and six years (Berg 1996; Hauser 1994; Offringa 1991).

In 2010, the ILAE proposed that febrile seizures could be organised by typical age at onset (i.e. infancy and childhood). Conventionally, febrile seizures have been classified as simple or complex based on duration, recurrence during the same illness episode, and the presence of focal features. Most febrile seizures are generalised tonic-clonic seizures, whilst about 30% to 35% of febrile seizures have one or more complex features (focal onset, duration > 10 minutes, or multiple seizures during the illness episode) (Berg 1996). Febrile status epilepticus, a subgroup of complex febrile seizures with seizures lasting more than 30 minutes, occur in about 5% of cases (Berg 1996).

Causation is thought to be multifactorial, with environmental factors and increasing evidence for genetic factors contributing to pathogenesis (Audenaert 2006; Offringa 1994). No single susceptibility gene for febrile seizures is known. In contrast, gene identification has been successful in families with genetic epilepsies with febrile seizures plus (GEFS+) where kindreds may well include children with Dravet syndrome (Berg 2010; Kasperaviciute 2013; Tang 2013). In these conditions, febrile seizures persist beyond the age of six years; mutations have been found in sodium voltage-gated channel alpha subunit 1 (SCN1A) and sodium voltage-gated channel beta subunit 1 (SCN1B) (both sodium channel genes important for neurotransmission) and gamma-aminobutyric acid type A receptor subunit gamma2 (GABRG2) (related to γ-aminobutyric acid, an important inhibitory neurotransmitter) (Audenaert 2006; Baulac 2004; Gérard 2002; Hirose 2003; Johnson 1998; Kananura 2002; Nabbout 2002; Nakayama 2006).

Description of the intervention

Despite the frequent nature of these seizures, debate regarding the optimal management arose at an early stage (Baumann 1999), and continues. After resolution of the acute episode, the possibility of recurrent seizures during subsequent febrile illnesses must be addressed. This risk of recurrent seizures in previously healthy, untreated children was estimated in a collaborative study that used the individual data from five follow-up studies with similar definitions of febrile seizures and risk factors (Offringa 1994). Of 2496 children with 1410 episodes of recurrent seizures in this study, 32% had at least one, 15% had at least two, and 7% had three or more recurrent seizures after a first febrile seizure. The hazard of recurrent seizures was highest between the ages of 12 and 24 months. A history of febrile or unprovoked seizures in a first-degree family member, a relatively low temperature at the first seizure, young age at onset (< 12 months), a family history of unprovoked seizures, and a partial initial febrile seizure were all associated with an increased risk of subsequent seizures.

If a child is considered to be at increased risk of frequent or complicated seizures (Berg 1990), prophylactic medication might be considered. However, such treatment may have adverse effects on the child's behaviour and cognitive development. The decision to treat thus requires assessment of the potential risks and benefits to the child. Since 1990, at least 300 articles have been published on the drug management of seizures associated with fever (Gram 1984). This has long been a controversial area, with a persistent variety of opinions on management. Part of this controversy reflects the fact that it is uncertain whether prophylactic medication with antiepileptics and antipyretics is effective and has no important adverse effects. Yet, phenobarbital has adverse effects such as irritability, hyperactivity, and somnolence, and may even lower the cognitive development of toddlers (Farwell 1990; Herranz 1988). To avoid the side effects of continuous antiepileptic drugs (AEDs), rapid-acting antiepileptics given only during fever periods have been used in an attempt to reduce the risk of recurrent febrile seizures. Phenobarbital at times of fever has been proven to be ineffective, probably because of the delay in achieving appropriate serum and tissue levels. Thus far, only prophylactic diazepam, given orally or rectally, has been studied in placebo-controlled trials. The efficacy of intermittent antipyretic treatment during febrile episodes in the prevention of seizure recurrence has recently been studied.

Newton 1988 assessed the efficacy of phenobarbital and valproate for the prophylactic treatment of febrile seizures by summarising the results of all eight British placebo-controlled clinical trials done before 1988. Data were pooled and analysed on an intention-to-treat basis. The overall odds ratio of recurrent febrile seizures was 0.8 for phenobarbital and 1.42 for valproate; neither result was statistically significant. The author therefore concluded that neither treatment should be recommended. A second meta-analysis summarised four published non-British randomised, placebo-controlled trials conducted up to 1996 using phenobarbital as a preventive treatment of febrile seizures (Rantala 1997). The risk of recurrences was lower in children receiving continuous phenobarbital therapy than in the placebo group (odds ratio 0.54, 95% confidence interval (CI) 0.33 to 0.90). On average, eight children would have to be treated with phenobarbital for two years continuously to prevent one febrile seizure (number needed to treat for an additional beneficial outcome (NNTB) 8, 95% CI 5 to 27) (Rantala 1997).

How the intervention might work

The rationale for using prophylactic antiepileptic drugs in children with febrile seizures is to raise seizure threshold in the face of a potentially triggering fever. Antipyretics are used to attenuate the effect of fever as a triggering factor. Previous studies have shown blood and cerebrospinal fluid zinc levels to be significantly lower in children with a febrile seizure tendency than in children with afebrile seizures. Zinc level is known to stimulate the excitatory neurotransmitter glutamate and to increase the inhibitory neurotransmitter gamma-amino-butyric acid.

Why it is important to do this review

We undertook this review to answer the question of whether prophylactic treatment with an antiepileptic or antipyretic drug can, when compared to no therapy, decrease the likelihood of future febrile seizures in children with febrile seizures.

OBJECTIVES

To evaluate primarily the effectiveness and safety of antiepileptic and antipyretic drugs used prophylactically to treat children with febrile seizures; and also to evaluate any other drug intervention where there is a sound biological rationale for its use.

METHODS

Criteria for considering studies for this review

Types of studies

We included all trials using randomised or quasi-randomised participant allocation that compared the use of antiepileptic, antipyretic agents or recognised Central Nervous System active agents with each other, or with placebo or no treatment.

Types of participants

Children aged between six months and seven years with a history of febrile seizures and who received treatment with an antiepileptic or antipyretic drug in an attempt to prevent recurrent seizures. We also planned subgroup analyses of neurologically healthy children, of children with previous recurrent seizures, and of studies limited to children at a perceived relatively high risk of recurrence.

Types of interventions

We included trials that compared one treatment with another or with placebo (or no treatment) in children with febrile seizures. Specific drugs included the benzodiazepines (diazepam, lorazepam, clobazam, and midazolam), phenytoin, phenobarbital, valproate, diclofenac, paracetamol, and ibuprofen. We planned a subgroup analysis of intermittent AED therapies versus continuous AED therapies, and of antipyretics during episodes of fever versus AED therapy during fever. A six-month course of zinc (shown previously to have been significantly lower in children with febrile seizures) was evaluated in one study.

Types of outcome measures

Primary outcomes

1. Efficacy: the proportion of children with recurrence of febrile or non-febrile seizures at certain time points after treatment onset (6 months, 12 months, 24 months, 36 months, and where data were available at age 5 to 6 years).

Secondary outcomes

1. Treatment adherence (as measured in the studies).
2. Safety: the incidence of specific adverse unwanted effects, including irritability, hyperactivity, somnolence, impaired cognitive development for phenobarbital and intermittent diazepam, gastro-enterologic unwanted effects for valproate and antipyretics, of any administered antiepileptic or antipyretic.
3. As it is of clinical interest, we analysed pooled data at the chosen study time points to estimate the recurrent febrile seizure risk in the placebo and no-treatment groups. This analysis could provide useful insight into the natural history of the disorder.

Search methods for identification of studies

Electronic searches

We ran searches for the original review in July 2008 and subsequent searches in November 2010, May 2011, November 2013, March 2015, July 2016, and October 2018. For the latest update, we searched the following databases on 3 February 2020. We imposed no language restrictions.

1. Cochrane Register of Studies (CRS Web), using the search strategy outlined in Appendix 1. CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane Review Groups including the Cochrane Epilepsy Group.
2. MEDLINE (Ovid) 1946 to 31 January 2020, using the search strategy outlined in Appendix 2.

For some previous updates, Embase, Scopus, and Database of Abstracts of Reviews of Effects (DARE) were searched; however, this was no longer necessary, because relevant studies in Embase and Scopus are included in CRS Web, and DARE is a closed archive.

Searching other resources

We checked the reference lists of articles identified by the electronic searches for additional studies. We also contacted researchers in the field to identify any ongoing or unpublished studies.

Data collection and analysis

Selection of studies

For this review update, three review authors (RN, KV, and MO) independently assessed trials for inclusion, resolving any disagreements by discussion.

Data extraction and management

For this review update, three review authors (RN, KV, and MO) extracted the outcome data specified above as well as the following data, resolving any disagreements by discussion. For the previous update of this review another review author (Martinus Cozijnsen) checked all the extracted data.

Methodological and trial design

1. Method of randomisation.
2. Method of double-blinding.
3. Whether any participants had been excluded from the reported analyses.

Where data were missing, we attempted to contact trial authors for this information.

Participant and demographic information

1. Total number of participants allocated to each treatment group or audited in any protocol.
2. The proportion of participants in each treatment group with a recurrence at certain time points (6, 12, 24, 36, 48, and 72 months, where these data were available).
3. Risk factors associated with recurrent seizures, i.e. age at first seizure below 18 months, positive family history of seizures, temperature at index seizure below 40.0 °C.

Assessment of risk of bias in included studies

One review author (KV) made an initial assessment of all included studies for risk of bias using the Cochrane 'Risk of bias' tool for randomised or quasi-randomised controlled trials (Higgins 2011). This was compared to an independent assessment by a second review author (RN or MO), with a third party resolving any disagreements by discussion.

Measures of treatment effect

We treated efficacy (recurrence of febrile or non-febrile seizures) as dichotomous outcomes expressed as risk ratios (RR) with 95% confidence intervals (CIs).

We summarised treatment adherence and incidence of adverse effects narratively according to the definitions reported in the study. We calculated NNTBs as the reciprocal of the absolute risk reduction (McQuay 1998).

Unit of analysis issues

There were no unit of analysis issues. Medication dosages were standard. Outcome measures were simply seizure recurrence. No studies were of a repeated-measure (longitudinal) nature or a cross-over design.

Dealing with missing data

At times, recurrence data had to be reconstructed from published survival curves. We were careful to cross-check these data with quoted cumulative incidence rates for in-study data. We cross-checked trial details against any additional published report of the trial and contacted the original trial authors in the case of missing data, errors, or inconsistencies (although the response was uniformly poor). No author provided individual-participant data when requested; however, the consistency checks we performed were satisfactory.

Assessment of heterogeneity

We assessed clinical heterogeneity by reviewing the differences across trials in the characteristics of recruited participants and treatment protocols. We assessed statistical heterogeneity using a Chi^2 test for heterogeneity. We assessed heterogeneity using the Q test ($P < 0.10$ for significance) and the I^2 statistic (where greater than 50% indicated considerable heterogeneity) (Higgins 2003), and visually by inspecting forest plots.

Assessment of reporting biases

We assessed the presence of publication bias using funnel plots for each meta-analysis that included results of five or more studies.

Data synthesis

We included studies comparing either different drugs or different treatment approaches, for example intermittent AED therapies versus continuous AED therapies, antipyretics during episodes of fever versus AED therapy during fever, or all versus placebo. The primary analysis was intention-to-treat and included all randomised participants analysed in the treatment groups to which they had been allocated, irrespective of which treatment they actually received.

We conducted meta-analysis if sufficient data were available, that is at least two trials looking at the same two treatments and the same outcomes. All meta-analyses were conducted using a fixed-effect model, regardless of the presence of heterogeneity. If we had concerns regarding variability of study design and whether pooling data was appropriate, we would not have performed meta-analysis.

We conducted meta-analysis only for the primary outcome of efficacy (recurrence of febrile or non-febrile seizures).

We summarised treatment adherence and incidence of adverse effects narratively according to the definitions reported in the study; we did not pool numerical data for these outcomes, due to variability in definitions and the level of detail reported in the studies.

Subgroup analysis and investigation of heterogeneity

We had no hypotheses needing subgroup analyses.

Sensitivity analysis

We considered there to be no need for any sensitivity analyses, as misdiagnosis of febrile seizures or their recurrence is unlikely within the reported study groups.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach as outlined in the GRADE Handbook to interpret findings (Schünemann 2013), and GRADEpro GDT software (which imports data from Review Manager 5 software) to create 15 'Summary of findings' tables for the primary outcome of efficacy (recurrence of febrile or non-febrile seizures) for each comparison for the following time points: 6 months, 12 months, 18 months, 24 months, 36 months, 48 months, and 60 or more months (GRADEpro GDT 2020; Review Manager 2020).

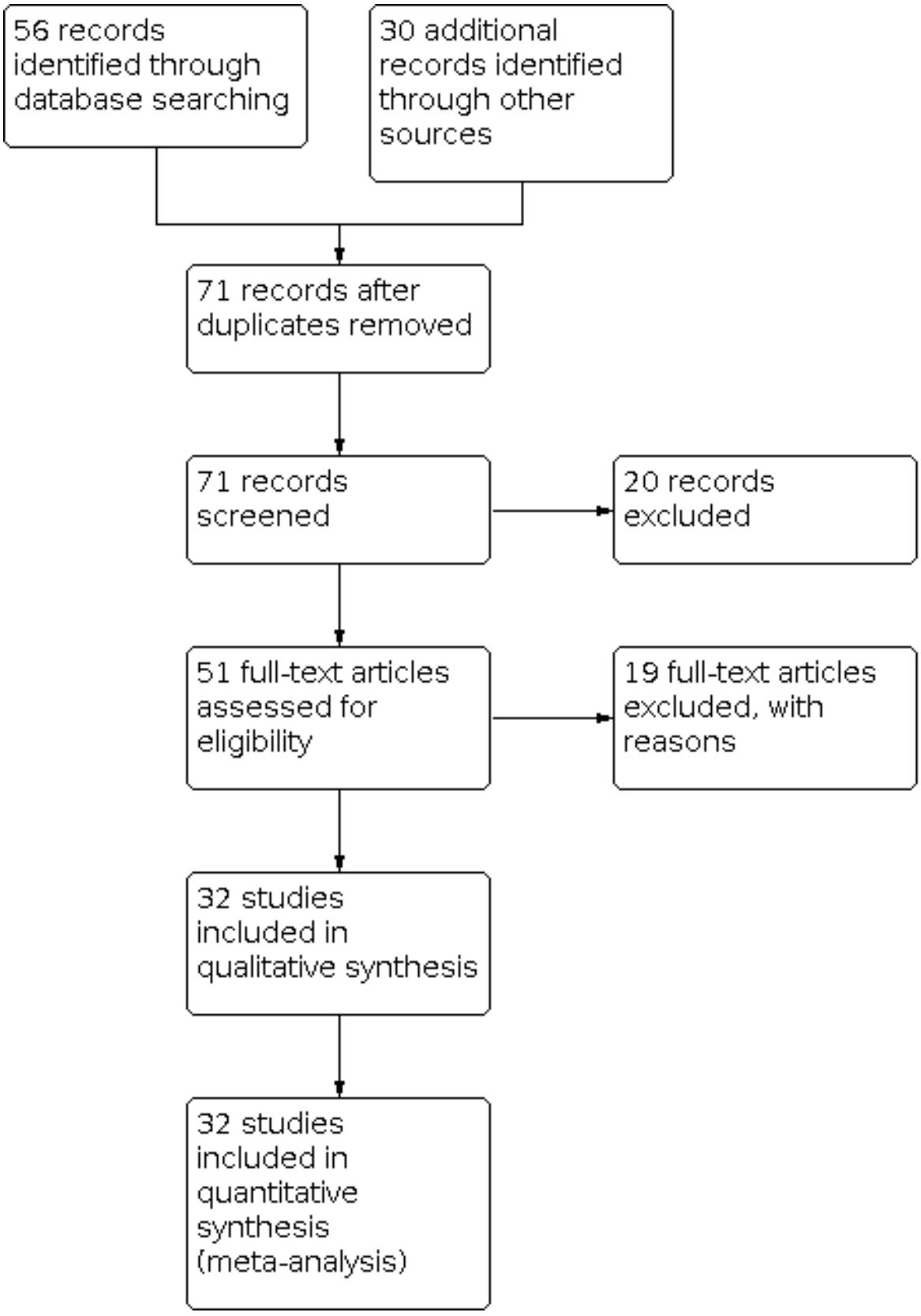
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Of 71 articles identified as potentially relevant, 32 articles met the inclusion criteria for the review (see Characteristics of included studies). Together, these 32 articles describe 32 randomised trials and their (long-term) follow-up. For the reasons for exclusion of the excluded studies, see Characteristics of excluded studies.

Included studies

The interventions compared against placebo or no treatment included intermittent oral diazepam in four studies (Autret 1990; Ramakrishnan 1986; Rosman 1993; Verrotti 2004) or rectal diazepam in five studies (Knudsen 1985; Mosquera 1987; Pavlidou 2006; Taghdiri 2011; Uhari 1995 (where a rectal dose was followed by oral doses for the time of the fever)), continuous phenobarbital in 10 studies (Bacon 1981; Camfield 1980; Farwell 1990; Heckmatt 1976; Mamelle 1984; McKinlay 1989; Ngwane 1980; Ramakrishnan 1986; Thilothammal 1993; Wolf 1977), intermittent phenobarbital in three studies (Mackintosh 1970; Ramakrishnan 1986; Wolf 1977), continuous oral phenytoin in one study (Bacon 1981), continuous oral valproate in five studies (Mamelle 1984; McKinlay 1989; Mosquera 1987; Ngwane 1980; Williams 1979), continuous oral pyridoxine in one study (McKiernan 1981), intermittent oral ibuprofen in one study (Van Stuijvenberg 1998), intermittent oral clobazam in one study (Bajaj 2005), continuous zinc sulfate for six months in one study (Fallah 2015), intermittent rectal diclofenac versus placebo followed by either ibuprofen or paracetamol or placebo after eight hours in one study (Strengell 2009), and intermittent oral levetiracetam versus any antipyretic given by way of a placebo (Hu 2014). Other studies compared interventions against each other: continuous phenobarbital versus intermittent diazepam in two studies (Garcia 1984; Salehiomran 2016); intermittent rectal diazepam versus intermittent rectal valproate in one study (Daugbjerg 1990); intermittent oral diazepam versus intermittent oral clobazam in two studies (Ghazavi 2016; Khosroshahi 2011); and intermittent oral melatonin versus intermittent oral diazepam in one study (Barghout 2019).

The included studies enrolled a total of 4542 participants with febrile seizures, of whom 4431 were used in the analysis of this review. The number of participants analysed for each intervention (number of participants included in placebo trials only) was as follows: diazepam 1476 (771); continuous phenobarbital 1075 (494); intermittent phenobarbital 341 (32); phenytoin 90 (90); valproate 303 (48); pyridoxine 107 (107); ibuprofen 230 (230); clobazam 60 (60); zinc sulfate 100 (100); diclofenac versus placebo followed by ibuprofen, paracetamol, or placebo after eight hours 231 (231); levetiracetam versus any unspecified antipyretic by way of a placebo 78 (37); continuous phenobarbital versus diazepam 245; diazepam versus valproate 169; diazepam versus clobazam 143; melatonin versus diazepam 60. It should be noted that a number of these papers included a comparison of outcomes in placebo versus one of two randomised seizure treatments (i.e. A versus C; B versus C). As no pooled analyses were done in which the effects of different antiepileptic or antipyretic drugs were summarised and compared with (placebo) controls, no unit of analysis errors were introduced. Families withdrew from these studies for various reasons, including change of residence, withdrawal of consent, and a variety of unacceptable adverse effects (detailed to the greatest degree possible in Table 1).

Study outcomes included a comparison of observed and expected seizure recurrence frequency at time points ranging between six and 48 months after randomisation, and in one case at 60 to 72 months (Ramakrishnan 1986).

A brief description of the 32 original studies reported in the articles included in this review

1. Autret 1990 was a study of 185 children, aged 8 to 36 months, after their first febrile seizure and with fewer than two risk factors for recurrence. Interventions were intermittent oral diazepam (0.5 mg load and 0.2 mg/kg maintenance) or placebo. Outcomes assessed were recurrent seizures at 12 months after randomisation and adverse medication effects during the 12 months of treatment.
2. Bacon 1981 reported a study involving 270 children following a first febrile seizure. This study had three arms: children were allocated either to treatment with continuous oral phenytoin 8 mg/kg/day, continuous phenobarbital 5 mg/kg/day, or placebo, and were followed for assessment of recurrent seizures at 12 months after randomisation and adverse medication effects during the 12 months of treatment.
3. Bajaj 2005 studied 60 children aged six months to five years presenting with one or more febrile seizures. Children were allocated to intermittent oral clobazam (0.75 mg/kg body weight twice daily) or placebo during the course of fever and followed for assessment of recurrent seizures at six months after randomisation and adverse medication effects during the six months of treatment.
4. Barghout 2019 studied 60 children aged six to 50 months with recurrent simple febrile seizures. Children were randomly allocated in two groups: one group (30 children) received oral melatonin 0.3 mg/kg/8 hours, and the other group (30 children) received oral diazepam 1 mg/kg/day divided into three doses. Both medications were given only during the febrile illness. The study groups were followed up for six months and were assessed for the recurrence of febrile seizures and the occurrence of adverse effects related to melatonin or diazepam.
5. Camfield 1980 was a study of 79 children aged 6 to 36 months following a first febrile seizure. Children were allocated either to treatment with continuous phenobarbital 4 to 5 mg/kg/day or to placebo (both groups treated with antipyretics) and followed for assessment of recurrent seizures at 12 months after randomisation. In their second paper, the authors assessed the adverse effects of phenobarbital in toddlers, including behavioural and cognitive aspects, during the 12 months of treatment using the same cohort.
6. Daugbjerg 1990 studied 169 children following a first febrile seizure. Children were allocated either to intermittent rectal diazepam (5 mg for those younger than three years or 7.5 mg for those three years or over) or intermittent valproate suppositories (150 mg for those weighing less than 10 kg or 300 mg for those weighing 10 kg or more). Children were followed for assessment of recurrent seizures at six and 12 months after randomisation and adverse medication effects during 12 months of treatment.
7. Fallah 2015 was a randomised, single-blind clinical study comparing zinc sulfate with placebo. One hundred children aged 1.5 to 5 years with a first simple febrile seizure, weight and height above the third percentile, and normal serum zinc levels were randomised to either daily zinc sulfate 2 mg/kg (maximum 50 mg) for six consecutive months or to placebo. The authors assessed seizure recurrence at 12 months and unwanted effects.

8. Farwell 1990 was a study of 217 children following a first febrile seizure who had at least one risk factor for recurrence. Children were allocated either to treatment with continuous phenobarbital 4 to 5 mg/kg/day or placebo and followed for assessment of recurrent seizures at 6, 12, 18, and 24 months after randomisation, and adverse medication effects after 24 months of treatment. Sleep disturbances were reported in a second paper, and late cognitive effects of phenobarbital for this study in a third publication.
9. Garcia 1984 studied 100 children aged six to 60 months following a first febrile seizure (simple or complex) with random allocation either to intermittent rectal diazepam (0.5 mg/kg/dose eight-hourly for the duration of the fever) or continuous phenobarbital (5 mg/kg/day) plus antipyretics for both group. Children were followed for assessment of recurrent seizures at 18 months after randomisation and adverse medication effects during the 18 months of treatment.
10. Ghazavi 2016 was an open-label trial that randomised children (six to 60 months of age) who presented with at least one simple febrile seizure. Children were treated with either oral diazepam 0.33 mg/kg every eight hours for two days or oral clobazam for two days dosed by child's weight (daily 5 mg when weight ≤ 5 kg, twice-daily 5 mg when weight 6 to 10 kg, twice-daily 7.5 mg when weight 11 to 15 kg, and twice-daily 10 mg when weight > 15 kg). The authors assessed seizure recurrence and adverse effects during a follow-up period of 12 months.
11. Heckmatt 1976 was a study of 165 children with a mean age of 20 months following a first febrile seizure. Children were allocated either to treatment with continuous phenobarbital 4 to 5 mg/kg/day or no treatment. The children were followed for assessment of recurrent seizures at six months after randomisation and adverse medication effects during the six months of treatment.
12. Hu 2014 studied a total of 115 children with seizure onset between 3 months and 5 years (but visiting age from 9 months to 8 years) with a history of 2 or more episodes of febrile seizures, with random assignment of 78 children to the levetiracetam group (receiving orally a dose of 15 to 30 mg/kg/day twice daily for 1 week starting at the fever onset (> 37.5 °C)) and 37 children to the control group (receiving any antipyretic for fever > 38.5 °C) (2:1 ratio). The study groups were followed up for 48 weeks and assessed for seizure frequency associated with febrile events, febrile seizure recurrence, and cost-effectiveness.
13. Khosroshahi 2011 studied 80 children aged six months to five years who had had one or more simple febrile seizures. Children were allocated either to intermittent oral diazepam (0.33 mg/kg dose every eight hours for two days) or intermittent oral clobazam for two days with the following dosages: 5 mg daily in children up to 5 kg; 5 mg twice daily in children 6 to 10 kg; 7.5 mg twice daily in children 11 to 15 kg; and 10 mg twice daily in children > 15 kg. Children were followed for assessment of recurrent seizures at 12 months after randomisation, and adverse medication effects during the 12 months of treatment.
14. Knudsen 1985 reported on a single study of 289 children following their first febrile seizure who were allocated either to intermittent rectal diazepam (5 mg for children less than three years, or 7.5 mg for those aged over three years) compared to no treatment. Children were followed for assessment of recurrent seizures at 6, 12, and 18 months after randomisation and adverse medication effects during the 18 months of treatment.
15. Mackintosh 1970 was a study of 32 children aged six to 16 months who had had a first febrile seizure. Children were allocated either to intermittent phenobarbital at 30 mg with acetyl acetic acid 150 mg or placebo, and followed for assessment of recurrent seizures at six and 12 months after randomisation; adverse medication effects were not addressed.
16. Mamelle 1984 reported on one study of 69 children aged six to 48 months following a first febrile seizure (excluding those with focal seizures or neuropsychiatric disorders). Children were allocated either to treatment with continuous phenobarbital 3 to 4 mg/kg/day, continuous oral valproate 30 to 40 mg/kg/day, or placebo, and followed for assessment of recurrent seizures at 18 months after randomisation; adverse medication effects were not addressed.
17. McKiernan 1981 studied 107 children aged six to 52 months who had had a first or second febrile seizure. Children in the active treatment arm received continuous oral pyridoxine (in two 20 mg doses) or placebo and were followed for assessment of recurrent seizures for 12 months after randomisation. We used estimates from the reported Kaplan-Meier curves to assess recurrent seizures at six and 12 months. Adverse medication effects were not addressed.
18. McKinlay 1989 was a study of 151 children aged six to 72 months who had had at least one previous febrile seizure or a complicated febrile seizure. This study had three arms: children were allocated either to treatment with continuous phenobarbital 5 mg/kg/day, continuous oral valproate 30 mg/kg/day, or no treatment and followed for assessment of recurrent seizures at 6, 12, and 24 months after randomisation, and adverse medication effects during the 24 months of treatment.
19. Mosquera 1987 studied 69 children following a first febrile seizure. This study had three arms: children were allocated to intermittent rectal diazepam 0.5 mg/kg every 8 hours, continuous oral valproate 30 mg/kg/day, or no treatment. Children were followed for assessment of recurrent seizures at 6, 12, and 24 months after randomisation; adverse medication effects were not addressed.
20. Ngwane 1980 was a study of 64 children aged six to 18 months following a first febrile seizure. This study had three arms. Children were allocated to either phenobarbital 3 to 6 mg/kg/day or valproate 30 to 60 mg/kg/day, whilst children who were eligible but not included were considered to be the control group receiving no treatment. Children were followed for a mean of 12 months after randomisation to assess recurrent seizures and adverse medication effects.
21. Pavlidou 2006 studied 139 children aged six to 36 months who were randomly assigned to receive either intermittent prophylaxis with rectal diazepam or no prophylaxis in a prospective controlled trial. Children were followed for assessment of recurrent seizures at 6, 12, and 36 months after randomisation and adverse medication effects during the 36 months of treatment.
22. Ramakrishnan 1986 studied 120 children aged two to 72 months following a first febrile seizure. Children were allocated to continuous phenobarbital 3 to 5 mg/kg/day, intermittent phenobarbital in the same dosage, intermittent oral diazepam 0.6 mg/kg/day, or no treatment, and were followed for assessment of recurrent seizures at 60 to 72 months after

randomisation and adverse medication effects during the period of treatment.

23. Rosman 1993 studied 406 children aged six to 60 months who had had at least one febrile seizure. The interventions were intermittent oral diazepam 1 mg/kg/day or placebo. Outcomes were recurrent seizures and adverse treatment effects during the 24 months of treatment. We used estimates from the reported Kaplan-Meier curves to assess recurrent seizures at 6, 12, and 24 months.
24. Salehiomran 2016 studied 145 children six to 60 months of age with ≥ 3 simple febrile seizures or with complex febrile seizure in a randomised controlled trial. Children were treated with either continuous phenobarbital 3 to 5 mg/kg/day in two doses for at least a year, or intermittent oral diazepam 0.33 mg/kg three times a day for two days at each febrile episode. Seizure recurrence and adverse effects were assessed at 12 months.
25. Strengell 2009 was a study of 231 children aged four months to four years who had had a first febrile seizure. All febrile episodes during follow-up were treated first with either intermittent rectal diclofenac or placebo. After eight hours, treatment was continued with oral ibuprofen 5 mg/kg up to four times a day, oral paracetamol 10 mg/kg up to four times a day, or placebo. Children were followed for assessment of recurrent seizures. We used estimates from the reported Kaplan-Meier curves to assess recurrent seizures at 6, 12, 18, and 24 months. Adverse medication effects were not addressed.
26. Taghdiri 2011 studied 80 children aged nine months to five years after their first febrile seizure. Children were treated with either rectal diazepam (0.5 mg/kg) combined with paracetamol or paracetamol only, and followed for 12 months for assessment of seizure recurrence.
27. Thilothammal 1993 studied 60 children aged six to 72 months following a first febrile seizure. Children were allocated to either treatment with continuous phenobarbital 5 mg/kg/day or placebo. An additional 30 children with an atypical seizure were not randomised but treated with phenobarbital (not included in our analyses). The children were then followed for assessment of recurrent seizures at six and 12 months and for adverse medication effects after six and 12 months of treatment.
28. Uhari 1995 studied 180 children following a first febrile seizure. Children were allocated to intermittent rectal followed by intermittent oral diazepam 0.6 mg/kg or placebo. Both groups were treated with antipyretics for the duration of the fever. Children were followed for assessment of recurrent seizures and adverse medication effects for 24 months. Kaplan-Meier curves were used to assess recurrence at six and 12 months.
29. Van Stuijvenberg 1998 studied 230 children aged 12 to 48 months who had had a febrile seizure and had at least one risk factor for recurrence. Children were allocated to either intermittent oral Ibuprofen 5 mg/kg/day or placebo and followed for assessment of recurrent seizures during the 24 months after randomisation. We used estimates from the reported Kaplan-Meier curves to assess recurrent seizures at 6, 12, and 24 months after randomisation; the study did not address adverse medication effects.
30. Verrotti 2004 studied 110 children aged six months to five years with one simple febrile seizure; 45 children were "randomly" allocated to treatment with intermittent oral diazepam (0.35 mg/kg every eight hours) during each episode of fever higher than 38.8 °C, continuing until the child had been afebrile for 24 hours; and 65 children were allocated to a group with no treatment. Children were followed for assessment of recurrent seizures at 48 months after randomisation and adverse medication effects during the 48 months of treatment. We used estimates from the reported Kaplan-Meier curves to assess recurrent seizures at 6, 12, and 24 months after randomisation.
31. Williams 1979 studied 58 children aged six to 72 months after two or more simple febrile seizures. Children were allocated to an active treatment group of continuous oral valproate 40 mg/kg/day or no treatment, and followed for assessment of recurrent seizures and adverse medication effects at 12 months after randomisation.
32. Wolf 1977 was a study of 355 children aged six to 48 months who had had a first febrile seizure. This study had three arms: children were allocated to continuous phenobarbital 3 to 4 mg/kg/day, intermittent phenobarbital 5 mg/kg/day, or no treatment, and were followed for assessment of recurrent seizures for a median of 28 months after randomisation and adverse medication effects during the 24 months of treatment. We used estimates from the reported Kaplan-Meier curves to assess recurrent seizures at 6, 12, and 24 months after randomisation. In a following paper, the authors reported behaviour disturbances and the long-term effect of phenobarbital on cognitive function.

Excluded studies

We excluded all studies which were not randomised controlled trials or if their experimental design was unclear (Minagawa 1981; Nemati 2019; Rosman 2001; Shimazaki 1997; Steardo 1980). We also excluded studies with a high rate of exclusion of participants (Antony 1983; Fayyazi 2018; Knudsen 1978), where no data were reported on prespecified outcomes of the review (Frelih 1997), or where we could not access a full-text article in English for the study (Addy 1977; Amouian 2013; Galli 1977; Kazemi 2013).

We also excluded one trial which assessed the acute treatment of convulsions (Lahat 2000), and one trial which assessed side effects of antiepileptic medications (Vining 1987), rather than recurrence of febrile convulsions. We excluded one trial of antipyretics that did not address the central issue of febrile seizure recurrence but rather researched the question of effect on temperature (Van Esch 1995). We excluded two trials that compared the effect of Traditional Chinese Medicine with regular antiepileptics, as safety of the former is not established against European Medicines Agency (EMA) or US Food and Drug Administration (FDA) standards. One trial did not present quantitative data in numbers, rendering it difficult to read, and had a high attrition rate without outcome data (lack of intention-to-treat data) (Rose 2005). We excluded two studies that assessed the impact of an antipyretic on reducing seizure recurrence during the same fever episode, that is to reduce complex febrile seizure occurrence (defined as more than one seizure during a febrile illness episode), which was outside the scope of this review (Murata 2018; Schnaiderman 1993).

Risk of bias in included studies

See Figure 2 for a summary of the risk of bias in each included study.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

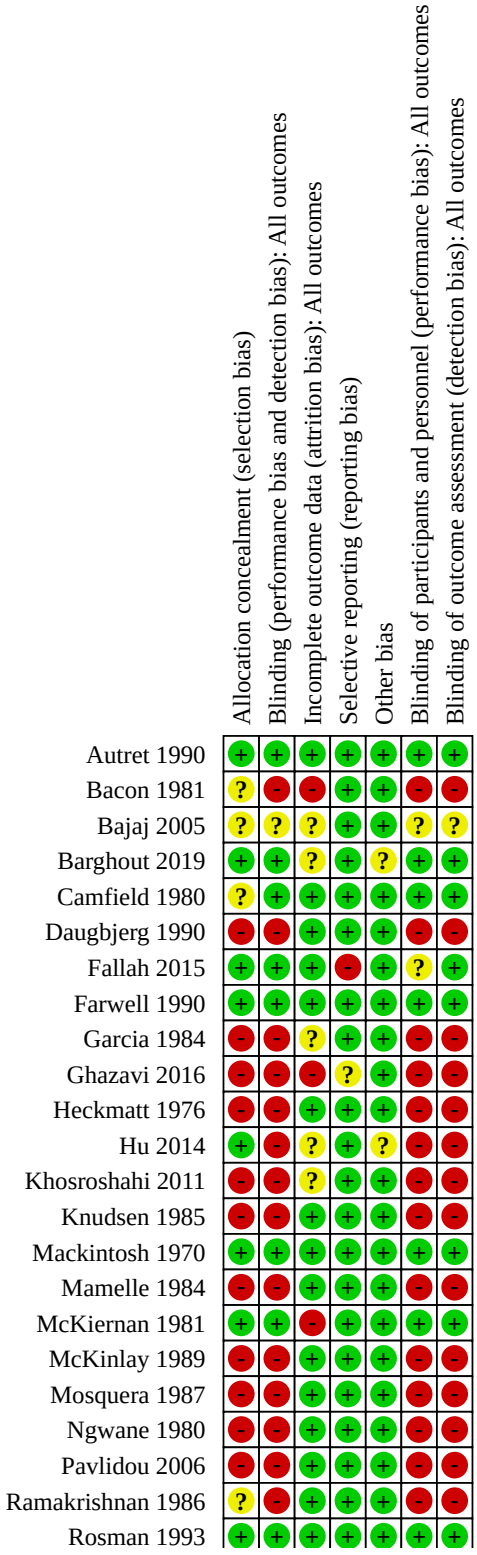
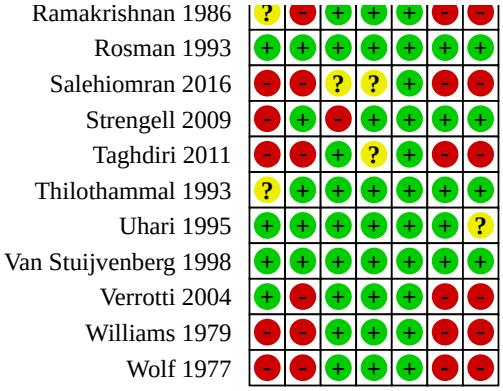


Figure 2. (Continued)



Allocation

Satisfactory allocation concealment was noted in 12 studies (Autret 1990; Barghout 2019; Fallah 2015; Farwell 1990; Hu 2014; Mackintosh 1970; McKiernan 1981; Rosman 1993; Strengell 2009; Uhari 1995; Van Stuijvenberg 1998; Verrotti 2004), and no concealment was attempted in 13 studies, which used a method of quasi-randomisation (Daugbjerg 1990; Garcia 1984; Heckmatt 1976; Khosroshahi 2011; Knudsen 1985; Mamelle 1984; McKinlay 1989; Mosquera 1987; Ngwane 1980; Pavlidou 2006; Taghdiri 2011; Williams 1979; Wolf 1977). The method of allocation concealment, if any, was unclear in the remaining studies.

Blinding

Twelve studies were double-blinded (Autret 1990; Bajaj 2005; Barghout 2019; Camfield 1980; Farwell 1990; Mackintosh 1970; McKiernan 1981; Rosman 1993; Strengell 2009; Thilothammal 1993; Uhari 1995; Van Stuijvenberg 1998); two studies were single-blinded (Fallah 2015; Mamelle 1984); and in 18 studies there was no blinding (Bacon 1981; Daugbjerg 1990; Garcia 1984; Ghazavi 2016; Heckmatt 1976; Hu 2014; Khosroshahi 2011; Knudsen 1985; McKinlay 1989; Mosquera 1987; Ngwane 1980; Pavlidou 2006; Ramakrishnan 1986; Salehiomran 2016; Taghdiri 2011; Verrotti 2004; Williams 1979; Wolf 1977).

Incomplete outcome data

In many of the included studies the data analysis did not involve all enrolled participants, as follows:

1. Autret 1990: nine of 185 included children were lost in the analyses - six on diazepam, three on placebo;
2. Bacon 1981: 69 of 270 enrolled participants were lost; the group allocation is uncertain, but the study groups were similar in size: 48 on phenobarbital, 47 on phenytoin, and 43 on placebo, with no recurrences in any group to the time of withdrawal;
3. Camfield 1980: two of 79 lost - one on phenobarbital, one on placebo;
4. Daugbjerg 1990: two withdrawn and four in each group lost to follow-up;
5. Farwell 1990: 26 of 217 lost - 10 on phenobarbital and 16 on placebo;
6. Heckmatt 1976: four of 165 lost - two on phenobarbital, two on no treatment;
7. Khosroshahi 2011: eight of 80 lost – five on clobazam and three on diazepam;
8. Knudsen 1985: 16 of 289 lost - five on diazepam and 11 on no treatment;
9. Mamelle 1984: four of 69 lost - one on valproate, two on phenobarbital, and one on placebo;
10. Mosquera 1987: four of 69 lost - all four on placebo;
11. Barghout 2019: of the 66 enrolled participants, six were not included in the analysis - three in the melatonin group due to recurrent seizures, and three in the diazepam group due to intolerable adverse effects and one for non-compliance.

It should be noted that most of the included studies were undertaken 20 to 30 years ago, since when the rigour of conducting and reporting randomised controlled trials has improved. We attempted to contact study authors to obtain individual-participant data, but without success.

Selective reporting

Protocols were not available for any of the included trials. We judged risk of bias based on the information included in the publications (see Characteristics of included studies for more information).

Other potential sources of bias

Study population sizes varied from 32 to 406. Numbers in treatment arm ranged from 16, Mackintosh 1970, to 204, Rosman 1993. The smaller studies were prone to distortion of treatment effect because of the small numbers of participants. Also, in a study assessing the effect of levetiracetam (Hu 2014), the unspecified use of "any antipyretic" in the control group was a pseudo placebo rather than a real placebo.

Publication bias

Four of the 38 analyses included results from more than five trials (Analysis 1.1, Analysis 1.2, Analysis 2.1, Analysis 2.2). We assessed publication bias with funnel plots for these analyses. We did not find evidence of publication bias for Analysis 1.1, Analysis 1.2, Analysis 2.1 (Figure 3, Figure 4, Figure 5). We did find evidence of publication bias for Analysis 2.2 (asymmetry indicated in Figure 6), in the meta-analyses of comparisons for phenobarbital versus placebo (seven studies) at 12 months but not at six months (six studies). We also found evidence of publication bias in the

meta-analyses of valproate versus placebo (four studies) at 12 months (Analysis 5.2). There were too few studies to permit an assessment of publication bias for the other comparisons.

Figure 3. Funnel plot of comparison: 1 Intermittent oral or rectal diazepam versus placebo or no treatment to recurrence at 6 months.

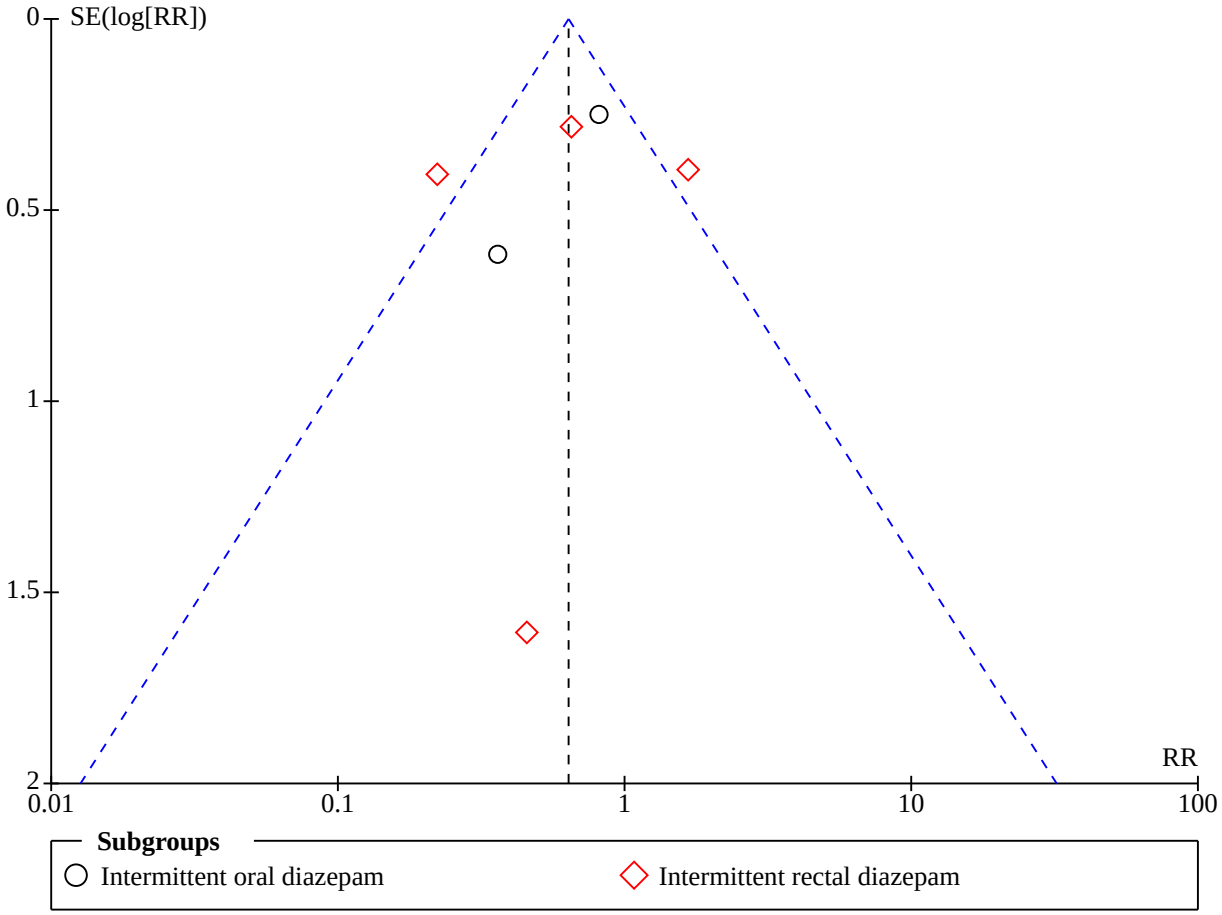


Figure 4. Funnel plot of comparison: 1 Intermittent oral or rectal diazepam versus placebo or no treatment to recurrence at 12 months.

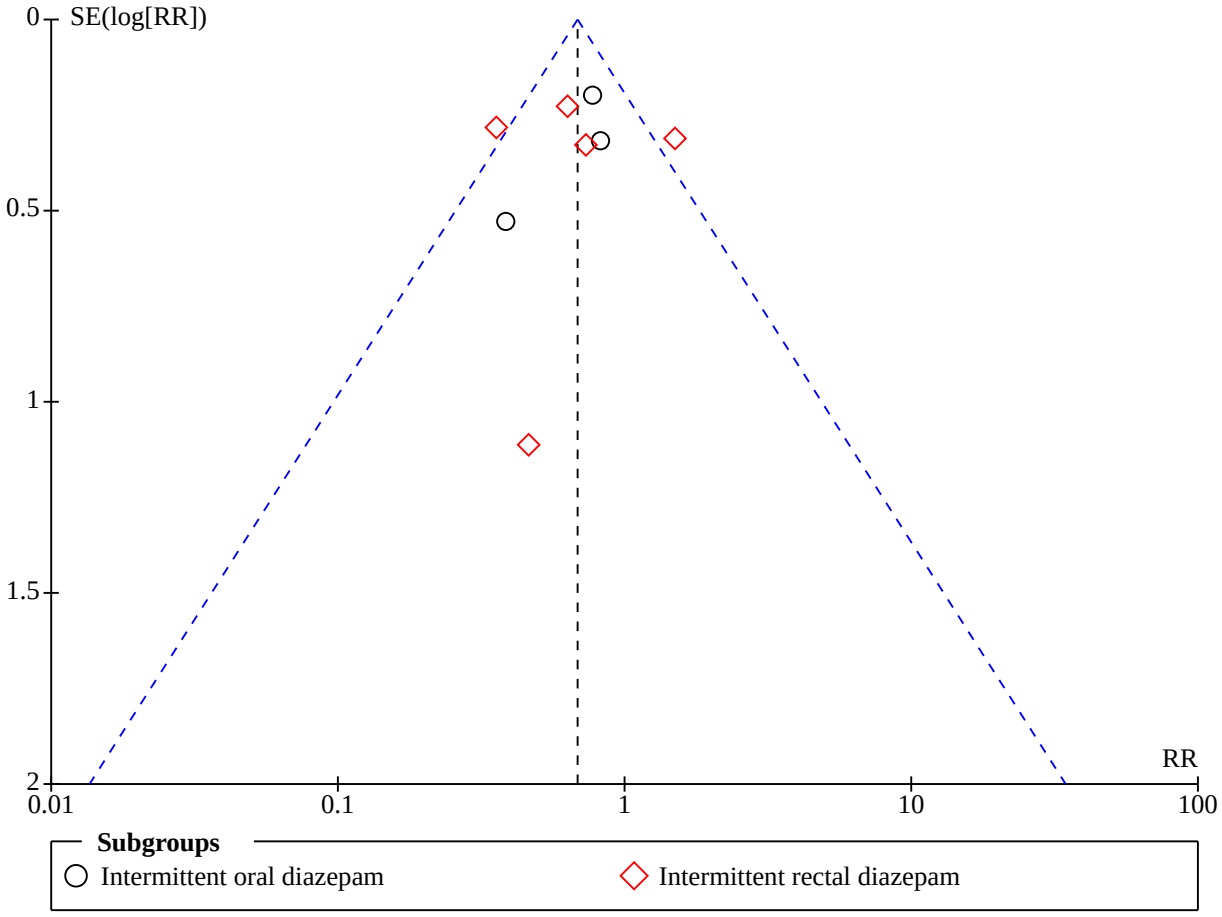


Figure 5. Funnel plot of comparison 2: Continuous phenobarbital versus placebo or no treatment to recurrence at 6 months: no evidence of publication bias.

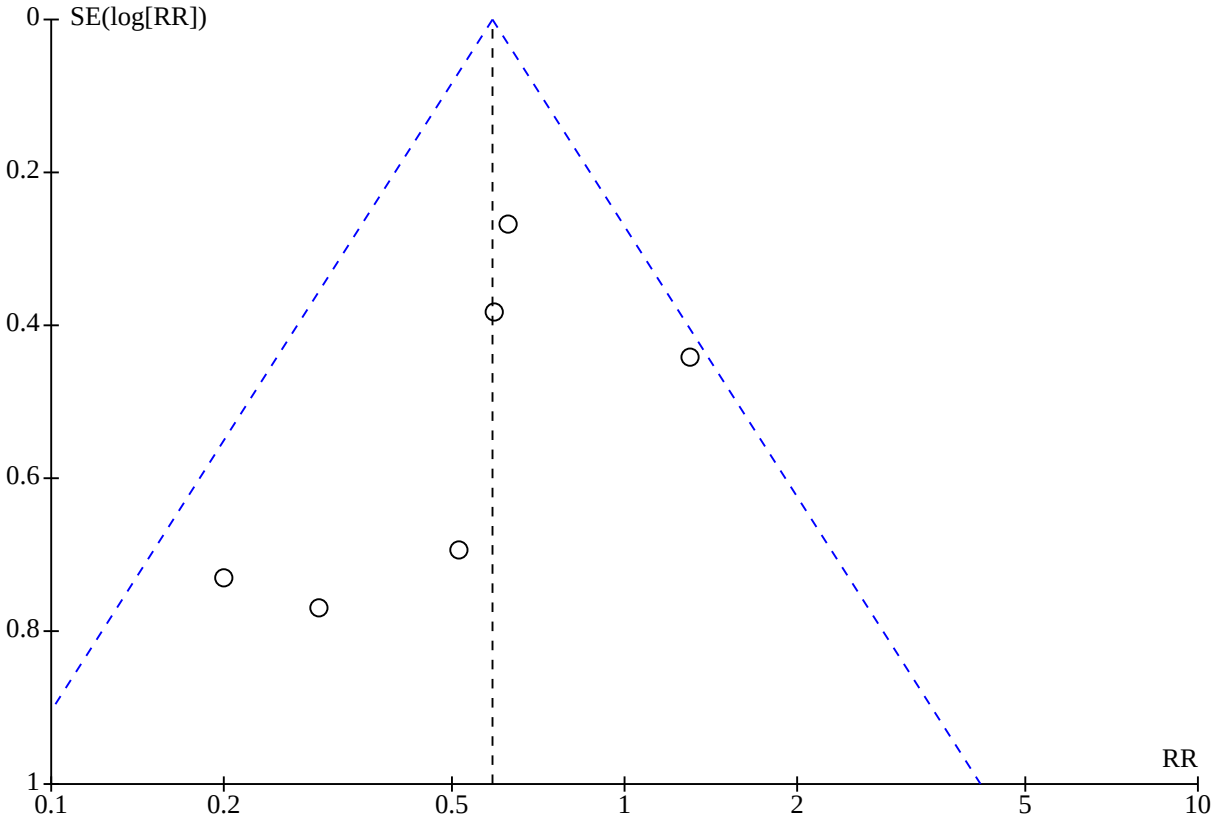
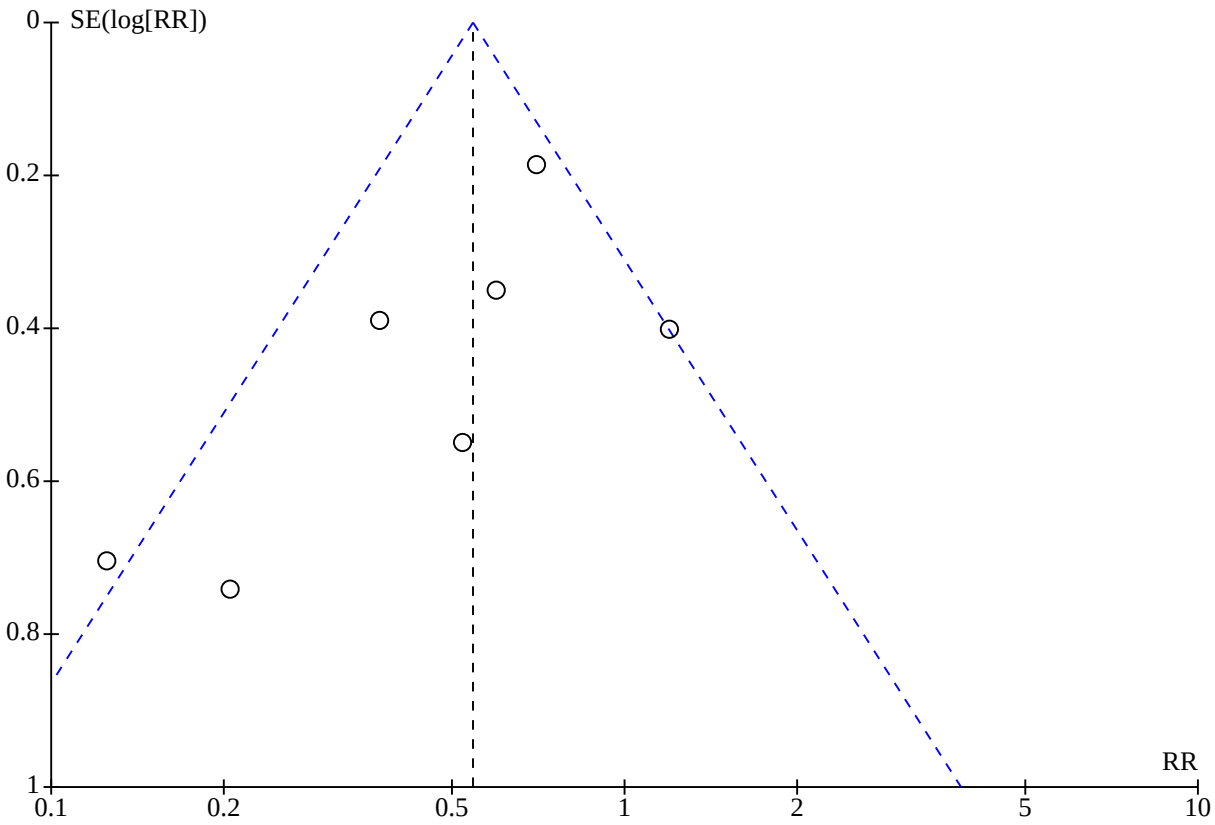


Figure 6. Funnel plot of comparison 2: Continuous phenobarbital versus placebo or no treatment to recurrence at 12 months: evidence of publication bias.



Effects of interventions

See: **Summary of findings 1** Intermittent oral or rectal diazepam compared to placebo or no treatment for febrile seizures in children; **Summary of findings 2** Continuous phenobarbital compared to placebo or no treatment for febrile seizures in children; **Summary of findings 3** Intermittent phenobarbital compared to placebo or no treatment for febrile seizures in children; **Summary of findings 4** Continuous oral phenytoin compared to placebo for febrile seizures in children; **Summary of findings 5** Continuous oral valproate compared to placebo or no treatment for febrile seizures in children; **Summary of findings 6** Continuous oral pyridoxine compared to placebo for febrile seizures in children; **Summary of findings 7** Intermittent oral ibuprofen compared to placebo for febrile seizures in children; **Summary of findings 8** Intermittent oral clobazam compared to placebo for febrile seizures in children; **Summary of findings 9** Continuous zinc sulfate for 6 months compared to placebo for febrile seizures in children; **Summary of findings 10** Intermittent rectal diclofenac compared to placebo, followed by oral ibuprofen, paracetamol, or placebo after 8 hours, for febrile seizures in children; **Summary of findings 11** Continuous phenobarbital compared to intermittent rectal or oral diazepam for febrile seizures in children; **Summary of findings 12** Intermittent rectal diazepam compared to intermittent rectal valproate for febrile seizures in children; **Summary of findings 13** Intermittent oral diazepam compared to intermittent oral clobazam for febrile seizures in children; **Summary of findings 14** Intermittent oral melatonin compared to intermittent oral diazepam for febrile seizures in children; **Summary of findings 15** Intermittent oral levetiracetam compared to placebo (any antipyretics) for febrile seizures in children

Below are the results of 15 comparisons, followed by a description of the recurrence risk of febrile seizures in the non-intervention groups and the occurrence of adverse medication effects.

1. Intermittent oral or rectal diazepam compared to placebo or no treatment

See Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Summary of findings 1.

Nine trials compared oral or rectal diazepam versus placebo or no treatment (Autret 1990; Knudsen 1985; Mosquera 1987; Pavlidou 2006; Ramakrishnan 1986; Rosman 1993; Taghdiri 2011; Uhari 1995; Verrotti 2004).

In three trials (Autret 1990; Rosman 1993; Uhari 1995), the control group received a placebo, and in the remaining six trials the controls received no treatment. Most trials assessed recurrence at 6 months (6 trials), 12 months (8 trials), and 24 months (4 trials); recurrence at 18, 36, 48, and 60 to 72 months was assessed by only one trial each.

All trials included participants with a first febrile seizure (FS), except Rosman 1993 (≥ 1 FS) and Taghdiri 2011 (all FSs), and some trials

included only participants with simple febrile seizures (Autret 1990; Verrotti 2004). This analysis contains two treatment subgroups (diazepam given orally or rectally), but within each subgroup some treatment differences existed.

Oral diazepam subgroup

In Autret 1990, diazepam was administered in a 0.5 mg/kg load with a maintenance dose during the febrile period of 0.2 mg/kg/day. Rosman 1993 used a slightly higher dose, of 1 mg/kg/day. Verrotti 2004 used 0.35 mg/kg every eight hours during each episode of fever higher than 38.8 °C, continuing until the child had been afebrile for 24 hours. Ramakrishnan 1986 used oral diazepam 0.2 mg/kg three times daily for the duration of the fever.

Rectal diazepam subgroup

Differences existed in the way the doses were calculated (either based on age or weight) and the interval and duration of the dosing. Knudsen 1985 was the only study to use an age-based dosing scheme (5 mg for age below 3 years and 7.5 mg for older children) with intervals of 12 hours during fever. Mosquera 1987 and Taghdiri 2011 used 0.5 mg/kg every eight hours during fever, whilst Pavlidou 2006 used 0.33 mg/kg every eight hours on the first day and every 12 hours on the following days. Uhari 1995 started with a first rectal dose (2.5 mg for < 7 kg, 5 mg for 7 to 15 kg, and 10 mg for > 15 kg) followed after six hours by oral diazepam 0.2 mg/kg every eight hours during fever for a maximum of two days.

There were significant overall findings at 6, 12, 18, 24, 36, and 48 months, but not at 60 to 72 months. At six months, 65 (11.4%) of 570 treated children had a recurrence compared with 104 (17.9%) of 581 children in the control group (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.48 to 0.85); number needed to treat for an additional beneficial outcome (NNT) 16, Analysis 1.1. At 12 months, 123 (17.5%) of 703 treated children had a recurrence compared with 181 (25.4%) of 713 children in the control group (RR 0.69, 95% CI 0.56 to 0.84); NNTB 13, Analysis 1.2. At 18 months, 19 (12.5%) of 152 treated children had a recurrence compared with 46 (33.6%) of 137 children in the control group (RR 0.37, 95% CI 0.23 to 0.60); NNTB 5, Analysis 1.3. At 24 months, 72 (20.3%) of 355 treated children had a recurrence compared with 105 (27.3%) of 384 in the control group (RR 0.73, 95% CI 0.56 to 0.95); NNTB 15, Analysis 1.4. At 36 months, 24 (54.5%) of 44 treated children had a recurrence compared with 43 (60.6%) of 71 children in the control group (RR 0.58, 95% CI 0.40 to 0.85); NNTB 4, Analysis 1.5. At 48 months, 5 (11.1%) of 45 treated children had a recurrence compared with 20 (30.8%) of 65 in the control group (RR 0.36, 95% CI 0.15 to 0.89); NNTB 6, Analysis 1.6. At 60 to 72 months, none (0%) of 30 treated children had a recurrence compared with 6 (20.0%) of 30 in the control group (RR 0.08, 95% CI 0.00 to 1.31); NNTB 5, Analysis 1.7.

Subgroup analyses did not always yield significant results when the overall analyses did. Oral diazepam did not reach significance at six months, and rectal diazepam was not significantly different at 24 months.

2. Continuous phenobarbital compared to placebo or no treatment

See Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6. Summary of findings 2.

Ten trials compared continuous phenobarbital versus placebo or no treatment (Bacon 1981; Camfield 1980; Farwell 1990; Garcia 1984; Heckmatt 1976; Mamelle 1984; McKinlay 1989; Ngwane 1980; Thilothammal 1993; Wolf 1977).

In five trials (Bacon 1981; Camfield 1980; Farwell 1990; Mamelle 1984; Thilothammal 1993), the control group received a placebo, and in the remaining five trials the controls received no treatment. Most trials assessed recurrence at 6 months (6 trials) and 12 months (7 trials), whilst recurrence at 18, 24, and 60 to 72 months was assessed in 2, 3, and 1 trials, respectively. Behavioural changes were assessed by Camfield 1980 at 12 months.

All trials included participants with a first seizure, except McKinlay 1989 (> 1 FS or complicated FS) and Thilothammal 1993 (≥ 2); three trials included only participants with simple febrile seizures (Camfield 1980; Ngwane 1980; Thilothammal 1993), and two trials included participants with complicated seizures (Farwell 1990: > 1 risk factor; McKinlay 1989: > 1 FS or complicated FS). Initial dosing varied between 3 to 6 mg/kg. Some trials adjusted dosing based on drug levels measured in saliva (Bacon 1981: 8 to 15 mg/L) or blood (Heckmatt 1976: 65 to 129 µmol/L; Mamelle 1984: > 60 µmol/L, Wolf 1977: 10 to 20 µg/mL). Dosing in the other trials was not adjusted during follow-up.

Continuous phenobarbital resulted in significantly fewer recurrences at 6, 12, and 24 months, but not at 18 and 60 to 72 months. At six months, 43 (10.4%) of 412 treated children had a recurrence compared with 75 (17.8%) of 421 children in the control group (RR 0.59, 95% CI 0.42 to 0.83); NNTB 14, Analysis 2.1. At 12 months, 67 (17.0%) of 395 treated children had a recurrence compared with 127 (30.8%) of 412 children in the control group (RR 0.54, 95% CI 0.42 to 0.70); NNTB 8, Analysis 2.2. At 18 months, 43 (33.3%) of 129 treated children had a recurrence compared with 58 (43.0%) of 135 children in the control group (RR 0.77, 95% CI 0.56 to 1.05); NNTB 10, Analysis 2.3. At 24 months, 61 (23.9%) of 255 treated children had a recurrence compared with 96 (34.5%) of 278 children in the control group (RR 0.69, 95% CI 0.53 to 0.89); NNTB 10, Analysis 2.4. At 60 to 72 months, 9 (30.0%) of 30 treated children had a recurrence compared with 6 (20.0%) of 30 children in the control group (RR 1.50, 95% CI 0.61 to 3.69); NNTB 10, Analysis 2.5.

3. Intermittent phenobarbital compared to placebo or no treatment

See Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Summary of findings 3.

Three trials compared intermittent phenobarbital versus placebo or no treatment (Mackintosh 1970; Ramakrishnan 1986; Wolf 1977).

In one trial (Mackintosh 1970), the control group received a placebo, and in the remaining two trials (Ramakrishnan 1986; Wolf 1977), the controls received no treatment. Recurrence was assessed at six and 12 months in two trials each, and at 24 and 60 to 72 months in one trial each.

All studies included children with a first febrile seizure; in addition, Mackintosh 1970 included only those with simple seizures. Dosing schemes differed between trials. In Mackintosh 1970, participants received an initial dose of 60 mg, followed by 30 mg every six hours for the duration of fever. In Ramakrishnan 1986, participants received 3 to 5 mg/kg/day divided into two doses, and in Wolf 1977,

participants received 5 mg/kg for the duration of fever, as well as an initial "load" of 30 mg/kg to a maximum of 120 mg.

Intermittent phenobarbital did not lead to fewer recurrences at 6, 12, 24, and 60 to 72 months. At six months, 18 (11.5%) of 156 treated children had a recurrence compared with 11 (8.8%) of 125 children in the control group (RR 1.37, 95% CI 0.67 to 2.81); NNTB 37, Analysis 3.1. At 12 months, 34 (21.8%) of 156 treated children had a recurrence compared with 27 (21.6%) of 125 children in the control group (RR 1.01, 95% CI 0.65 to 1.59); NNTB 500, Analysis 3.2. At 24 months, 35 (25.0%) of 140 treated children had a recurrence compared with 32 (29.4%) of 109 children in the control group (RR 0.85, 95% CI 0.57 to 1.28); NNTB 23, Analysis 3.3. At 60 to 72 months, 5 (16.7%) of 30 treated children had a recurrence compared with 6 (20.0%) of 30 children in the control group (RR 0.83, 95% CI 0.28 to 2.44); NNTB 31, Analysis 3.4.

4. Continuous oral phenytoin compared to placebo

See Analysis 4.1. Summary of findings 4.

One trial compared phenytoin to placebo (Bacon 1981).

Of the children allocated to phenytoin treatment, 16 (34.0%) of 47 had a recurrence at 12 months compared to 15 (34.9%) of 43 in the placebo group (RR 0.98, 95% CI 0.55 to 1.73); NNTB 112, Analysis 4.1.

5. Continuous oral valproate compared to placebo or no treatment

See Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4. Summary of findings 5.

Two trials compared valproate versus placebo or no treatment (McKinlay 1989; Mosquera 1987).

McKinlay 1989 included 151 children with more than one febrile seizure or with complicated febrile seizures, and compared valproate 30 mg/kg versus placebo, whilst Mosquera 1987 included 69 children with a first febrile seizure and compared valproate 30 mg/kg with no treatment.

Valproate reduced recurrence at 18 months, but not at 6, 12, and 24 months. At 18 months, 1 (4.5%) of 22 children in the active treatment group had a recurrence compared to 9 (34.6%) of 26 children in the control group (RR 0.13, 95% CI 0.02 to 0.96); NNTB 4, Analysis 5.3. At six months, 10 (14.1%) of 71 children in the active treatment group had a recurrence compared to 10 (11.8%) of 85 in the control group (RR 1.20, 95% CI 0.55 to 2.62); NNTB 44, Analysis 5.1. At 12 months, 24 (19.8%) of 121 treated children had a recurrence compared with 32 (23.9%) of 134 children in the control group (RR 0.82, 95% CI 0.52 to 1.29); NNTB 25, Analysis 5.2. At 24 months, 19 (26.8%) of 71 treated children had a recurrence compared with 18 (21.2%) of 85 children in the control group (RR 1.26, 95% CI 0.73 to 2.18); NNTB 18, Analysis 5.4.

6. Continuous oral pyridoxine compared to placebo

See Analysis 6.1; Analysis 6.2; Summary of findings 6.

Only one study compared pyridoxine with placebo (McKiernan 1981).

At six months, 4 (7.3%) of 55 children in the pyridoxine group had a recurrence compared to 8 (15.4%) of 52 children in the placebo group (RR 0.47, 95% CI 0.15 to 1.48); NNTB 13, Analysis 6.1. At 12 months, 7 (12.7%) of 55 children in the pyridoxine group had a recurrence compared to 10 (19.2%) of 52 children in the placebo group (RR 0.66, 95% CI 0.27 to 1.61); NNTB 16, Analysis 6.2.

7. Intermittent oral ibuprofen compared to placebo

See Analysis 7.1; Analysis 7.2; Analysis 7.3; Summary of findings 7.

Only one study compared intermittent ibuprofen with placebo (Van Stuijvenberg 1998).

At six months, 26 (23.4%) of 111 children in the active treatment group had a recurrence compared to 25 (21.0%) of 119 children in the placebo group (RR 1.11, 95% CI 0.69 to 1.81); NNTB 42, Analysis 7.1. At 12 months, 31 children (27.9%) of 111 in the active treatment group had a recurrent seizure compared to 35 (29.4%) of 119 children in the placebo group (RR 0.95, 95% CI 0.63 to 1.43); NNTB 67, Analysis 7.2. At 24 months, 36 (32.4%) of 111 children in the ibuprofen group had a recurrent seizure compared with 46 (38.7%) of 119 children in the placebo group (RR 0.84, 95% CI 0.59 to 1.19); NNTB 16, Analysis 7.3.

8. Intermittent oral clobazam compared to placebo

See Analysis 8.1; Summary of findings 8.

Only one study compared clobazam with placebo (Bajaj 2005).

At six months, 9 (30.0%) of 30 children in the clobazam group had a seizure recurrence compared to 25 (83.3%) of 30 children in the placebo group (RR 0.36, 95% CI 0.20 to 0.64); NNTB 2, Analysis 8.1.

9. Continuous zinc sulfate for six months compared to placebo

See Analysis 9.1.Summary of findings 9.

Only one study compared zinc sulfate to placebo (Fallah 2015).

At 12 months, 11 (22.0%) of 50 children allocated to six months daily zinc sulfate treatment had a seizure recurrence compared to 19 (38.0%) of 50 children allocated to placebo (RR 0.58, 95% CI 0.31 to 1.09), NNTB 7, Analysis 9.1.

10. Intermittent diclofenac compared to placebo, followed by ibuprofen, paracetamol, or placebo after eight hours

See Analysis 10.1; Analysis 10.2; Analysis 10.3; Analysis 10.4; Summary of findings 10.

Strengell 2009 randomised 231 children who had a first febrile seizure to receive either diclofenac (1.5 mg/kg) or placebo. After eight hours, treatment was randomly continued with either ibuprofen, paracetamol, or placebo. Since outcomes were unaffected by the second randomisation, we only considered the first in this meta-analysis. At six months, 14 (12.0%) of 117 children in the diclofenac group had a seizure recurrence compared to 17 (14.9%) of 114 children in the placebo group (RR 0.80, 95% CI 0.42 to 1.55), NNTB 25, Analysis 10.1. At 12 months, 19 (16.2%) of 117 children in the diclofenac group had a seizure recurrence compared to 27 (23.7%) of 114 children in the placebo group (RR 0.69, 95% CI 0.40 to 1.16); NNTB 14, Analysis 10.2. At 18 months, 23 (19.7%) of 117 children in the diclofenac group had a seizure recurrence compared to 31 (27.2%) of 114 children in the placebo group (RR 0.72, 95% CI 0.45 to 1.16); NNTB 14, Analysis 10.3. At 24 months, 26 (22.2%) of 117 children in the diclofenac group had a seizure recurrence compared

to 32 (28.1%) of 114 children in the placebo group (RR 0.79, 95% CI 0.51 to 1.24); NNTB 17, Analysis 10.4.

11. Continuous phenobarbital compared to intermittent rectal or oral diazepam

See Analysis 11.1; Analysis 11.2; Summary of findings 11.

Two studies compared phenobarbital with intermittent diazepam (Garcia 1984; Salehiomran 2016).

At 12 months, 17 (23.0%) of 74 children treated with continuous phenobarbital had a recurrence versus 11 (15.5%) of 71 children treated with intermittent oral diazepam (RR 1.48, 95% CI 0.75 to 2.94); NNTB 14, Analysis 11.1. At 18 months, 5 (10.0%) of 50 children in the phenobarbital group had a seizure recurrence compared to 4 (8.0%) of 50 children in the intermittent rectal diazepam group (RR 1.25, 95% CI 0.36 to 4.38); NNTB 50, Analysis 11.2.

12. Intermittent rectal diazepam compared to intermittent rectal valproate

See Analysis 12.1; Analysis 12.2; Summary of findings 12.

Only one study compared intermittent rectal diazepam with intermittent valproate (Daugbjerg 1990).

At six months, 11 (12.4%) of 89 children allocated to intermittent rectal diazepam had a recurrent seizure compared to 7 (8.8%) of 80 children allocated to intermittent valproate (RR 1.41, 95% CI 0.58 to 3.47); NNTB 28, Analysis 12.1. At 12 months, 23 (25.8%) of 89 children allocated to intermittent rectal diazepam had a seizure recurrence compared to 14 (17.5%) of 80 children allocated to intermittent valproate (RR 1.48, 95% CI 0.82 to 2.67); NNTB 12, Analysis 12.2.

13. Intermittent oral diazepam compared to intermittent oral clobazam

See Analysis 13.1; Summary of findings 13.

Two studies compared intermittent diazepam with intermittent clobazam (Ghazavi 2016; Khosroshahi 2011). At 12 months, 3 (4.2%) of 71 children in the clobazam group had a seizure recurrence compared to 7 (9.7%) of 72 in the diazepam group (RR 2.28, 95% CI 0.62 to 8.42); NNTB 19, Analysis 13.1.

14. Intermittent oral melatonin versus intermittent oral diazepam

See Analysis 14.1; Summary of findings 14.

One study compared intermittent oral melatonin with intermittent oral diazepam (Barghout 2019). One group received intermittent oral melatonin 1 mg/kg/day divided every eight hours. The other group received oral diazepam 0.3 mg/kg every eight hours. Both drugs were given only during the febrile illness, started at the beginning of fever and discontinued within 48 to 72 hours.

At six months, 5 (17%) of 30 children in the melatonin group had seizure recurrence compared to 11 (37%) of 30 children in the diazepam group (RR 0.45, 95% CI 0.18 to 1.15); NNTB 5, Analysis 14.1. Comparing the treatment efficacy in seizure reduction, there was no statistically significant difference between the two treatment groups. There was no control group in this study.

15. Intermittent oral levetiracetam compared to placebo (any antipyretics)

See Analysis 15.1; Summary of findings 15.

One study compared intermittent oral levetiracetam with a control group receiving any antipyretics as a placebo (Hu 2014). Children in the levetiracetam group received a dose of 15 to 30 mg/kg per day twice daily at the onset of fever (temperature > 37.5 °C) for one week, followed by dose tapering of 50% every two days until complete withdrawal at the second week. At 12 months, 11 (14%) of 78 children in the levetiracetam group had experienced seizure recurrence compared to 19 (51%) of 37 children in the antipyretics control group (RR 0.27, 95% CI 0.15 to 0.52); NNTB 3, Analysis 15.1. Levetiracetam significantly reduced the recurrence rate of febrile seizures in comparison to the control group (P < 0.001).

Treatment adherence

Seventeen of the 32 included trials assessed treatment adherence using various approaches. Their results are summarised in Table 1. Some measures were relatively crude, for example Camfield 1980 reported the presence or absence of the drug in serum samples. Others, such as Heckmatt 1976 and McKinlay 1989, measured drug levels on a random, ad hoc basis. There was no reported consistency between the relationship of drug levels ascertained in this way and seizure control. This is in accordance with current clinical practice, which recommends drug level measurement only when non-adherence is suspected; in such a situation only the presence or absence of the drug is helpful. Our observations serve to emphasise the importance of intention-to-treat analysis.

Adverse events and medication effects

Antiepileptic drugs are known for frequent and sometimes severe side effects in children. A variety of adverse effects were reported in some studies. Some of these adverse effects were described as “unacceptable” or as reasons for the child to stop medication and, in some instances, to leave the trial. A descriptive summary, detailed to the greatest degree possible from the information provided in the articles, is shown in Table 2. We consider the fact that adverse effects were not addressed at all in eight of the included studies and only in one arm of the study in a further two studies as a measure of the generally poor quality of these studies.

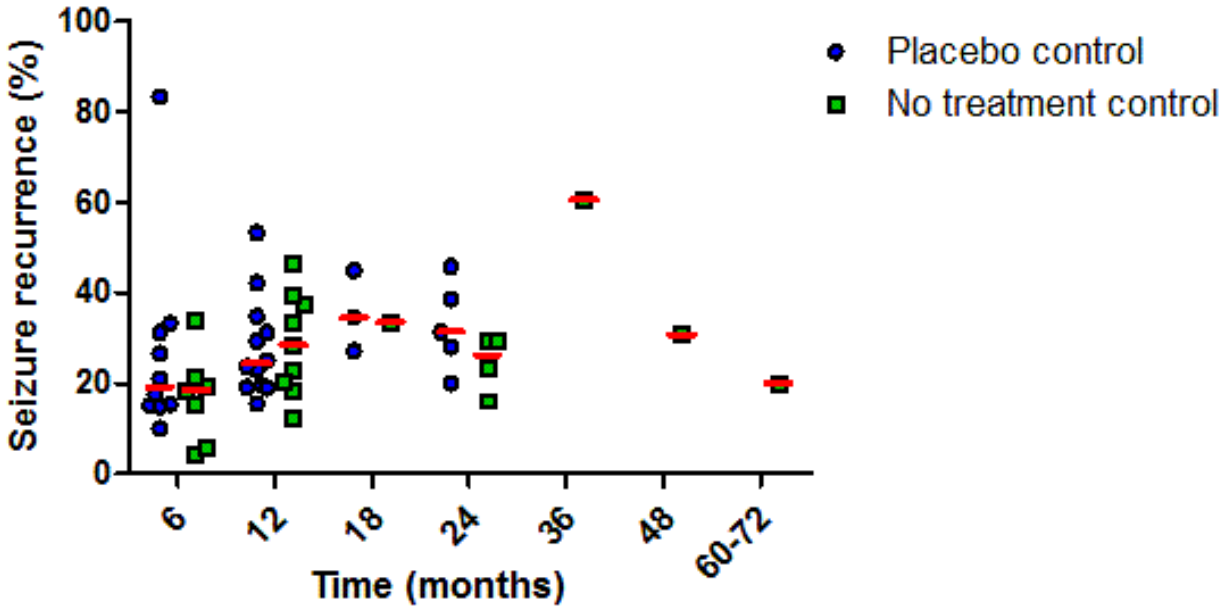
Camfield 1980 was the only study to address behavioural change in a focused way. The authors recorded the incidence of behavioural changes in those children allocated to the active phenobarbital treatment group in comparison to the placebo group at 12-month follow-up. Fifteen of 35 (42.8%) children allocated to phenobarbital reported behavioural change or sleep disturbance, compared to eight of 30 (26.3%) allocated to the placebo group (RR 1.61, 95% CI 0.79 to 3.26; Analysis 2.6). More detail on the adverse effects in this study is provided in Table 2.

Farwell 1990 compared intelligence quotients (IQs) between phenobarbital and control groups, finding significantly lower Wide Range Achievement (WRAT-R) reading achievement standard scores in the phenobarbital group (87.6 versus 95.6; P = 0.007), and a non-significant mean difference of 3.71 IQ points on the Stanford-Binet (102.2 versus 105.7; P = 0.09). There was insufficient evidence to attribute these lower scores to phenobarbital, but have recorded the information here as a topic for further study.

Recurrence risk of febrile seizures in the non-intervention groups

As a number of studies included children with risk factors known to be associated with a higher recurrence risk, the data on this issue were skewed towards higher recurrence risk in the placebo or control groups. Nonetheless, viewing pooled data on this issue allowed us to weigh the clinical importance of any significant results in the intervention arms of the studies. The data are summarised below and in Figure 7.

Figure 7. Seizure recurrence in the control groups of the included trials; red lines indicate median recurrence rates at each time point, by control group type.



Recurrence risk in control groups at six months: data were pooled from the studies of Bajaj 2005; Camfield 1980; Farwell 1990; Heckmatt 1976; Hu 2014; Knudsen 1985; Mackintosh 1970; McKiernan 1981; McKinlay 1989; Mosquera 1987; Pavlidou 2006; Rosman 1993; Strengell 2009; Thilothammal 1993; Uhari 1995; Van Stuijvenberg 1998; Verrotti 2004; Wolf 1977. A total of 278 (20.2%) of 1370 children had a recurrent febrile seizure within six months of study entry (placebo-controlled trials: 185/841 (21.9%); no-treatment controlled trials: 93/529 (17.6%)).

Recurrence risk at 12 months: data were pooled from the studies of Autret 1990; Bacon 1981; Camfield 1980; Fallah 2015; Farwell 1990; Knudsen 1985; Mackintosh 1970; McKiernan 1981; McKinlay 1989; Mosquera 1987; Ngwane 1980; Pavlidou 2006; Rosman 1993; Strengell 2009; Taghdiri 2011; Thilothammal 1993; Uhari 1995; Van Stuijvenberg 1998; Verrotti 2004; Williams 1979; Wolf 1977. A total of 415 (26.7%) of 1554 children had a recurrent seizure at 12 months (placebo-controlled trials: 262/1009 (26.0%); no-treatment controlled trials: 153/545 (28.1%)).

Recurrent risk at 18 months: data were pooled from the studies of Farwell 1990; Knudsen 1985; Mamelle 1984; Strengell 2009. A total of 135 (35.0%) of 386 children had a recurrent seizure within 18 months (placebo-controlled trials: 89/249 (35.7%); no-treatment controlled trials: 46/137 (33.6%)).

Risk of recurrence at 24 months: data were pooled from the studies of Farwell 1990; McKinlay 1989; Mosquera 1987; Rosman 1993; Strengell 2009; Uhari 1995; Van Stuijvenberg 1998; Verrotti 2004; Wolf 1977. A total of 279 (31.2%) of 895 children had a documented recurrent febrile seizure at 24 months (placebo-controlled trials: 210/636 (33.0%); no-treatment controlled trials: 69/259 (26.6%)).

Risk of recurrence at 36 months: data were only included from Pavlidou 2006: 43 (60.5%) recurrences amongst 71 children receiving no treatment.

Risk of recurrence at 48 months: only data from Verrotti 2004 were available: 20 (30.8%) of 65 children receiving no treatment had a documented recurrent febrile seizure at 48 months.

Recurrent risk at 60 to 72 months: data were only included from Ramakrishnan 1986: 6 (20.0%) of 30 children receiving no treatment had a recurrent seizure at 60 to 72 months.

DISCUSSION

Summary of main results

We have noted no significant benefit for intermittent phenobarbital, phenytoin, valproate, pyridoxine, ibuprofen, or zinc sulfate versus placebo or no treatment; nor for diclofenac versus placebo followed by ibuprofen, paracetamol, or placebo; nor for continuous phenobarbital versus diazepam, intermittent rectal diazepam versus intermittent valproate, or oral diazepam versus clobazam. In a comparison of oral melatonin with oral diazepam, no significant difference in seizure recurrence rate was noted. There was a significant reduction of recurrent febrile seizure risk with

intermittent diazepam versus placebo or no treatment at all time points, except for 60 to 72 months, with an RR ranging from 0.37 to 0.73 and an NNTB from 5 to 14 patients (rounded to integer). A significant reduction in febrile seizure recurrence risk was also seen for continuous phenobarbital compared with placebo or no treatment in each meta-analysis that included three or more trials (at 6, 12, and 24 months, but not at 18 and 60 to 72 months). Risk ratios ranged from 0.54 at 12 months to 0.69 at 24 months, with an NNTB of 8 to 10.

Another significant reduction in febrile seizure recurrence was seen for intermittent clobazam compared to placebo at six months follow-up: the RR was 0.36, with an NNTB of 2. However, with an extraordinarily high number of recurrences in 25 out of 30 (83.3%) children in the control group, we feel the play of chance has most likely led to an unrepeatable apparent beneficial effect for the treatment group. The median recurrence rate in the control groups of all of the included trials was approximately 20% at six months (Figure 7), indicating how potentially misleading this study's findings are likely to be.

In our 2020 review update we included Hu 2014, which is the first study to compare the effect of levetiracetam with a placebo for the prophylactic drug management for febrile seizures in children. Levetiracetam significantly reduced the recurrence rate of febrile seizures in comparison to the control group (RR 0.27, 95% CI 0.15 to 0.52), with an NNTB of 3. This means that 3 patients need to be treated with levetiracetam in order to reduce seizure recurrence in comparison to the control group. The limitation of this study was that the control drug was not a real placebo but rather any antipyretic given above a defined body temperature.

As has been indicated, the recording of adverse effects in these studies was highly variable and often nonexistent. Camfield 1980 documented lower comprehension scores in phenobarbital-treated children (yet with small numbers), which correlated with length of phenobarbital treatment. The findings were supported by the data of Farwell 1990. In general, adverse effects were recorded in up to 30% of children in the phenobarbital-treated group, although notably the studies by Bacon 1981 and Camfield 1980 (the latter for behavioural change or sleep disturbance) observed no difference in the control groups. Knudsen 1985 noted mild transient adverse effects in up to 36% of children in the diazepam-treated groups. Hu 2014 reported a lack of unwanted adverse effects in the levetiracetam-treated group, with only 1 of the 78 children (1.2%) having developed somnolence. Barghout 2019 noted that melatonin was overall well-tolerated, with 4 of the 30 studied children showing mild side effects, accounting for 13.3% of the studied group.

Fallah 2015 offered a novel approach by evaluating the effect of zinc supplementation on febrile seizure recurrence risk. Previous studies demonstrated blood and cerebrospinal fluid zinc levels to be significantly lower in children with febrile seizures than in children with afebrile seizures. Zinc level is known to stimulate pyridoxal kinase enzyme activity and the decarboxylation of glutamic acid, as well as increase brain gamma-amino-butyric acid (GABA) levels. Although it was hypothesised that decreased zinc levels might play a role in the pathogenesis of febrile seizures supplementation in this study, zinc supplementation conferred no significant benefit over placebo (RR 0.58, 95% CI 0.31 to 1.09).

Figure 7 offers useful data when counselling parents on the natural history of the condition. As might be predicted, there was no significant difference in recurrence rate between children treated with placebo and those given no treatment. For each follow-up period, recurrence rates stayed remarkably similar at between 20% and 35%, except for the remarkable 36-month follow-up rate in Pavlidou 2006 of 60.5%, an outlier that is unlikely to be repeated. This continuing risk serves to emphasise the importance of conveying appropriate supportive advice to parents (see next paragraph).

In summary, we found reduced recurrence rates in children treated with intermittent diazepam or continuous phenobarbital. Both drugs led to the advent of mild to moderate adverse effects in up to 30% of recipients. However, given that the long-term outcome of children with febrile seizures is good, irrespective of whether their febrile seizures are successfully prevented or not, only short-term benefits may be expected from treatment, and they should be weighed against possible drug-related adverse events. To emphasise the point, it should be considered that 100 children would need to be treated with either intermittent diazepam or phenobarbital to save up to 10 children from a recurrence, whilst causing 33 children unwanted effects. The current review has identified the efficacy of levetiracetam with a very low incidence of adverse effects. If this effect is repeated in other studies, levetiracetam may be considered as a prophylactic treatment option in selected families where anxiety over potential febrile seizure recurrence is high. Melatonin treatment had a similarly low incidence of adverse events; we believe further studies are needed to demonstrate its effectiveness versus placebo. The mainstay of intervention should be the provision of information to the families involved on recurrence risk, first aid management, and the benign nature of the phenomenon. Parents should be provided with contact details for medical services so that they will feel supported in the event of a recurrence, which inevitably leads to anxiety and fright for the vast majority of those involved.

Overall completeness and applicability of evidence

Completeness

The two interventions found to be effective in reducing future seizure recurrence were supported by 9 (intermittent diazepam) and 10 (continuous phenobarbital) unique trials of predominantly low quality. The results of the related meta-analyses were fairly consistently in favour of the intervention, more so for diazepam (for which there was only one trial with results favouring control) than for phenobarbital (which had two trials favouring control). The majority of these trials included children after their first simple febrile seizure. Consequently, there is reasonable evidence to conclude their effectiveness to prevent a recurrent seizure in this population, with an NNTB ranging from 5 to 14.

Applicability

All studies concern the population at risk of recurrent febrile seizures, and evaluate commonly used medical interventions. Knudsen 1991 has indicated that the long-term outcome of children with febrile seizures is good, irrespective of whether their febrile seizures are successfully prevented or not. His early observations on the benign nature of the phenomenon for most children is in keeping with common experience in clinical practice and the opinion cited in standard texts. No additional long-term benefit can therefore be expected in addition to the reduced risk of recurrence

for both intermittent diazepam and continuous phenobarbital. This benefit should be weighed against the clear risk of adverse events. Hence the decision to treat must rest on whether quality of life and shorter-term morbidity may be altered by the use of drugs.

Quality of the evidence

Most of the reviewed trials date from 20 or more years ago, and their methodological quality would today be recognised as needing improvement. Methods of randomisation and allocation concealment often do not meet current standards, and 'treatment versus no treatment' is more commonly seen than 'treatment versus placebo', leading to obvious sources of bias. Nonetheless, the size of the data pool did permit us to draw some conclusions about the value of intervention with medication for this common childhood phenomenon.

Potential biases in the review process

The review authors worked closely together at each step of the review, double-checking each other's assessments. We found that the methodological quality of most of the antiepileptic drug studies was very low, low, or moderate. The 'Risk of bias' tables identify examples of selection, performance and detection, attrition, and reporting bias. Publication bias is also likely, as shown in the present analysis. We contacted all UK neurologists and select North American colleagues before the original review to assess this risk. They were asked to declare if they knew of any studies unpublished for showing a lack of treatment effect. None of them came forward with an example.

Agreements and disagreements with other studies or reviews

We are not aware of any other current review, or that our review findings and conclusion contradict those of any other review published more than 20 years ago.

AUTHORS' CONCLUSIONS

Implications for practice

There were some significant results, although no clinically important benefits, for the management of children with febrile seizures with intermittent diazepam and continuous phenobarbital. No benefit was demonstrated for phenytoin, valproate, pyridoxine, intermittent phenobarbital, or antipyretics in the form of intermittent ibuprofen, paracetamol, or diclofenac in the management of febrile seizures. Intermittent clobazam conferred some benefit at six months follow-up, but the result may be difficult to replicate. Levetiracetam requires further assessment. Zinc supplementation offered no benefit. Parents should be supported with adequate contact details of medical services and information on recurrence, first aid management and, most importantly, the benign nature of the phenomenon.

Implications for research

If future studies are to be considered, then due attention should be given to the quality of randomisation allocation and concealment with placebo as a control. Adverse effects should be recorded systematically for both intervention and control groups. However, given the long-term benign nature of the phenomenon of febrile seizures and the relatively higher rate of reporting of adverse effects to date, unless a significant case can be made, it seems difficult to justify further research in this area.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Autret 1990

Study characteristics	
Methods	Double-blind RCT
Participants	185, age 8 to 36 months, first FS, < 2 RF
Interventions	Intermittent oral diazepam, 0.5 mg load, 0.2 mg maintenance per kilo, or placebo
Outcomes	RS at 12 months, adverse effects at 12 months
Notes	Attrition: 6 diazepam, 3 placebo; results presented as participant days; significant hyperactivity in diazepam group; 1 SUDEP in placebo group

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Centralised allocation
Blinding (performance bias and detection bias)	Low risk	Double-blind

Autret 1990 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 (6 diazepam, 3 placebo) of 185 withdrawn
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Bacon 1981

Study characteristics		
Methods	RCT	
Participants	207, after first FS	
Interventions	Phenytoin, 8 mg per kilo, or phenobarbital 5 mg per kilo, or placebo	
Outcomes	RS at 12 months, adverse effects	
Notes	Attrition: 69	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Allocation methodology and concealment not discussed in publication.
Blinding (performance bias and detection bias) All outcomes	High risk	Outcome rater blinded, doctor not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	45 lost; 12 moved; 5 behaviour; 5 epilepsy; 2 rash = 69 of 207
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.

Bacon 1981 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome rater blinded, doctor not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome rater blinded, doctor not blinded.

Bajaj 2005

Study characteristics	
Methods	Double-blind RCT
Participants	60 children aged 6 months to 5 years
Interventions	Clobazam (0.75 mg/kg body weight twice daily) or placebo, during the course of fever
Outcomes	Seizure recurrence at 6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Double-blind design, not stated how this was done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Sixty patients who completed the study duration of six months were only considered”; unclear out of how many participants originally
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Barghout 2019

Study characteristics	
Methods	Double-blind RCT
Participants	60 children aged 6 months to 5 years
Interventions	Oral melatonin 0.3 mg/kg every 8 h or oral diazepam 0.3 mg/kg every 8 h during febrile illness
Outcomes	Primary outcome: recurrence of febrile seizures at 6 months Secondary outcome: occurrence of adverse effects related to melatonin or diazepam
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	• Computer-generated random sequence – block • Concealment of random allocation by sequentially numbered, sealed, opaque envelopes • Treating physicians, outcome assessors, statisticians not aware of the allocation sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	• Only the pharmacist was aware of the treatment. • Neither the physician nor the parents were aware of the treatment child received. • The outcome assessors were not aware of the prophylactic treatment used during febrile illness.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	• 66 were randomised; 6 losses in follow-up (3 in melatonin group, 3 in diazepam group) (9% loss of primary sample) • Equal number of losses in each group. Finally 60 analysed, 30 in each group. No significant difference between 2 groups post exclusion of the 6 participants • The 6 losses (3 in the melatonin group due to recurrent seizures, 3 in the diazepam group (2 due to adverse effects and 1 for non-compliance to treatment)) might have slightly changed their analysis as compared to a genuine ITT analysis.
Selective reporting (reporting bias)	Low risk	Prespecified (primary and secondary) outcomes have been reported.
Other bias	Unclear risk	• Lack of placebo control group • Relied on compliance of parents in giving medications
Blinding of participants and personnel (performance bias) All outcomes	Low risk	• Only the pharmacist was aware of the treatment. • Neither the physician nor parents were aware of the treatment child received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors were not aware of the prophylactic treatment used during the febrile illness.

Camfield 1980

Study characteristics	
Methods	Double-blind RCT
Participants	79, 6 to 36 months, first simple FS
Interventions	Phenobarbital 4 to 5 mg per kilo or placebo, both with antipyretics
Outcomes	RS at 6 months, RS at 12 months, behavioural changes at 12 months
Notes	Attrition: 2, 1 from each group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not stated how this was done
Blinding (performance bias and detection bias) All outcomes	Low risk	Special placebo manufactured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 of 79 lost; 4 with side effects, but data collected on 10 of these
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded

Daugbjerg 1990

Study characteristics	
Methods	RCT, open-label
Participants	169, first FS
Interventions	Rectal diazepam 5 mg for < 3 years; 7.5 mg for 3 years or over; or valproate suppository 150 mg for < 10 kg; 300 mg for 10 kg or more
Outcomes	RS at 6 months, 12 months, adverse effects
Notes	2 withdrawn, 4 lost during follow-up

Daugbjerg 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Odd/even dates - no concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding (selection bias)
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 of 169 withdrawn; 4 lost to follow-up in each group
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Fallah 2015

Study characteristics	
Methods	Single-centre, randomised, single-blind clinical study
Participants	Children aged 1.5 to 5 years with first simple FS, weight and height above the third percentile, and normal serum zinc level
Interventions	Group 1: Daily zinc sulfate 2 mg/kg (maximum 50 mg) for 6 consecutive months Group 2: Placebo
Outcomes	Seizure recurrence at 12 months, side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Computer-generated equal simple randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blind design

Fallah 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up, no exclusions
Selective reporting (reporting bias)	High risk	Recurrence data at 3, 6, and 9 months not given. Kaplan-Meier method used to report results, no absolute numbers.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Randomisation and blinding were done by an investigator with no clinical involvement in the trial. Data collectors, outcome assessors, and data analysts were all kept blinded to the allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation and blinding were done by an investigator with no clinical involvement in the trial. Data collectors, outcome assessors, and data analysts were all kept blinded to the allocation.

Farwell 1990

Study characteristics	
Methods	Double-blind RCT
Participants	217, first FS, > 1 RF
Interventions	Phenobarbital 4 to 5 mg per kilo or placebo
Outcomes	RS at 6 months, RS at 12 months, RS at 18 months, RS at 24 months. IQ after 2 and 3 to 5 years, sleep disturbances
Notes	Attrition: 26 (10 phenobarbital, 16 placebo)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate concealment using minimisation methodology as described by Pocok and Simon
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo control, blinding maintained with fake phenobarbital levels
Incomplete outcome data (attrition bias) All outcomes	Low risk	86% placebo, 77% phenobarbital completed.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.

Farwell 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding maintained with fake phenobarbital levels.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding maintained with fake phenobarbital levels.

Garcia 1984

Study characteristics		
Methods	RCT	
Participants	100, 6 to 60 months, first FS	
Interventions	During fever: either rectal diazepam 0.5 mg/kg/dose x 8-hourly or phenobarbital 5 mg/kg/day, plus antipyretics for both groups	
Outcomes	RS at 18 months; adverse effects	
Notes	No attrition	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	None
Blinding (performance bias and detection bias) All outcomes	High risk	None
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Ghazavi 2016

Study characteristics	
Methods	Single-centre, randomised, open-label trial
Participants	Children 6 to 60 months of age with at least 1 simple FS
Interventions	Oral diazepam 0.33 mg/kg every 8 hours for 2 days or oral clobazam for 2 days dosed by child's weight (daily 5 mg when weight ≤ 5 kg, twice-daily 5 mg when 6 to 10 kg, twice-daily 7.5 mg when 11 to 15 kg, twice-daily 10 mg when > 15 kg)
Outcomes	RS at 12 months and adverse effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Randomisation methodology not mentioned.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Not discussed
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Heckmatt 1976

Study characteristics	
Methods	Quasi-RCT
Participants	165, first FS, mean age 20 months
Interventions	Phenobarbital 4 to 5 mg per kilo or no treatment
Outcomes	RS at 6 months

Heckmatt 1976 *(Continued)*

Notes	Attrition: 4 (2 per arm), unblinded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Alternate-day allocation
Blinding (performance bias and detection bias) All outcomes	High risk	None
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of 165 lost, but 39 of 88 stopped treatment
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Hu 2014

Study characteristics

Methods	Unblinded RCT, block randomisation
Participants	115 children, with onset age between 3 months and 5 years, with a history of 2 or more episodes of FS within the last 6 months
Interventions	Treatment group: oral levetiracetam first week 15 to 30 mg/kg/d in 2 divided doses; second week: dose tapering 50% every 2 days Control group: antipyretic when temperature > 38.5 °C with or without antibiotics
Outcomes	Primary outcome: seizure frequency associated with febrile events and FS recurrence rate during the 48-week follow-up Second outcome: cost-effectiveness of the 2 groups
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Hu 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	• Computer-generated block randomisation • Managed by centralised control who managed the randomisation code • Sequentially numbered envelope corresponding to the individual
Blinding (performance bias and detection bias) All outcomes	High risk	• Unblinded (both physicians and parents) • Unblinded outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	115 randomised (2:1) and 22 excluded (19.1% loss); increased losses • 18 in the levetiracetam group • 4 in the control group No significant differences between 2 groups in the constituent ratio
Selective reporting (reporting bias)	Low risk	Clearly defined primary outcome with clear reporting
Other bias	Unclear risk	• Did not divide levetiracetam group into high and low dose but used a range of doses • Suggested to use any antipyretic (not active control - pseudo placebo)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both were unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded outcome assessors

Khosroshahi 2011

Study characteristics	
Methods	RCT
Participants	80 children, 1 or more simple febrile seizures
Interventions	Oral diazepam 0.33 mg/kg/dose every 8 hours for 2 days or oral clobazam for 2 days with the following dosage: 5 mg daily in children ≤ 5 kg; 5 mg twice daily in children 6 to 10 kg; 7.5 mg twice daily in children 11 to 15 kg; 10 mg twice daily in children > 15 kg
Outcomes	Recurrent seizures at 12 months
Notes	Attrition: 5 in clobazam group and 3 in diazepam group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Method of allocation not stated.

Khosroshahi 2011 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8 (10%) attrition. Clobazam: lost to follow-up (n = 5); poor compliance (n = 2); change drug by other physician (n = 2); repeated seizure without fever (n = 1). Diazepam: lost to follow-up (n = 3); poor compliance (n = 1); prolonged use of drug (n = 1); inaccessible (n = 1)
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Knudsen 1985

Study characteristics		
Methods	Quasi-RCT	
Participants	289, first FS	
Interventions	Intermittent rectal diazepam 5 mg for children < 3 years, 7.5 for > 3 years or no treatment	
Outcomes	RS at 6 months, RS at 12 months, RS at 18 months	
Notes	Attrition: 16 (5 diazepam and 11 no treatment)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Odd/even date allocation
Blinding (performance bias and detection bias) All outcomes	High risk	None
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 of 289 excluded (parents demanded treatment change).
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.

Knudsen 1985 *(Continued)*

Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Mackintosh 1970

Study characteristics		
Methods	Double-blind RCT	
Participants	32, 6 to 60 months, first simple FS	
Interventions	Phenobarbital 30 mg with acetylsalicylic acid 150 mg, or placebo	
Outcomes	RS at 6 months, RS at 12 months	
Notes	Histogram used in estimations of recurrence risks.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate. "The child was allocated randomly to either treatment or control group and neither the physician nor the mother knew to which group the child had been allocated"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Length of follow-up differed.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Mamelle 1984

Study characteristics		
Methods	Single-blind RCT	
Participants	69, 6 to 48 months, first FS, excluded focal and neuropsychiatric disorders	
Interventions	Phenobarbital 3 to 4 mg per kilo, or valproate 30 to 40 mg per kilo, or placebo	
Outcomes	RS at 18 months, length of follow-up differed (mean > 20 months)	
Notes	Attrition: 4	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of 69 dropped out.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded

McKiernan 1981

Study characteristics	
Methods	Double-blind RCT
Participants	107, 6 to 52 months, first or second FS
Interventions	Pyridoxine 20 mg 2 times or placebo
Outcomes	RS at 6 months, RS at 12 months

McKiernan 1981 *(Continued)*

Notes	Kaplan-Meier used in estimations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. "Neither the investigators nor the parents were aware of which vitamin the children were receiving."
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigator blinded, pharmacist unblinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	80 of 107 completed at 6 months.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigator blinded, pharmacist unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and investigator blinded, pharmacist unblinded.

McKinlay 1989

Study characteristics

Methods	Quasi-RCT
Participants	151, 6 to 72 months, > 1 previous FS, or complicated FS
Interventions	Phenobarbital 5 mg per kilo, or valproate 30 mg per kilo, or no treatment
Outcomes	RS at 6 months, RS at 12 months, RS at 24 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Alternate participants allocated.
Blinding (performance bias and detection bias) All outcomes	High risk	None

McKinlay 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	24 (13%) lost to follow-up
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Mosquera 1987

Study characteristics		
Methods	RCT	
Participants	69, first FS	
Interventions	Intermittent rectal diazepam 0.5 mg/kg every 8 hours during fever, valproate 30 mg per kilo, or no treatment	
Outcomes	RS at 6 months, RS at 12 months, RS at 24 months	
Notes	Attrition: 4 from the control group unaccounted for	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Allocation concealment not discussed in the publication.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label, no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seemingly no attrition
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.

Mosquera 1987 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label, no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label, no blinding

Ngwane 1980

Study characteristics		
Methods	Quasi-RCT, included participants were randomised to the 2 treatment arms; the participants that refused or were otherwise not included but eligible were considered the "nothing arm"	
Participants	64, 6 to 18 months, first simple FS	
Interventions	Phenobarbital 3 to 6 mg per kilo, or valproate 30 to 60 mg per kilo, or no treatment	
Outcomes	RS at 12 months, adverse effects	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Although the physicians were blinded to the 2 interventions, no randomisation or blinding was used for the no-treatment control group.
Blinding (performance bias and detection bias) All outcomes	High risk	Although the physicians were blinded to the 2 interventions, no randomisation or blinding was used for the no-treatment control group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of 43 in trial withdrew due to side effects.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although the physicians were blinded to the 2 interventions, no randomisation or blinding was used for the no-treatment control group.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Although the physicians were blinded to the 2 interventions, no randomisation or blinding was used for the no-treatment control group.

Pavlidou 2006

Study characteristics	
Methods	RCT
Participants	139 children aged 6 to 36 months; first febrile seizure
Interventions	Rectal diazepam 0.33 mg/kg 8-hourly first day and then 12-hourly second day versus no prophylaxis
Outcomes	Recurrent seizures 6 months, 12 months, and 3 years
Notes	6 children lost to follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Quasi-random, alternate-day allocation to intervention groups
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition 6 of 145
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Ramakrishnan 1986

Study characteristics	
Methods	RCT
Participants	120, 2 to 72 months, first FS
Interventions	Phenobarbital 3 to 5 mg per kilo, or intermittent phenobarbital same dose, or intermittent diazepam 0.6 mg per kilo, or no treatment
Outcomes	RS at 60 to 72 months
Notes	No attrition reported, unblinded study.

Ramakrishnan 1986 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not used; “Randomly divided in 4 groups of 30 each”
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Apparently no withdrawal
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Rosman 1993

Study characteristics	
Methods	Double-blind RCT
Participants	406, 6 to 60 months, at least 1 FS
Interventions	Intermittent oral diazepam 1 mg per kilo per day or placebo
Outcomes	RS at 6 months, RS at 12 months, RS at 24 months
Notes	Kaplan-Meier used in estimations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. "Only the pharmacist and the biostatisticians knew the details of the randomisation schedule."
Blinding (performance bias and detection bias) All outcomes	Low risk	Manufactured placebo

Rosman 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	29 (12 diazepam, 17 placebo) of 406 withdrew due to side effects or frequent recurrence.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate. "Only the pharmacist and the biostatisticians knew the details of the randomisation schedule."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate. "Only the pharmacist and the biostatisticians knew the details of the randomisation schedule."

Salehiomran 2016

Study characteristics	
Methods	Single-centre RCT
Participants	Children 6 to 60 months of age with ≥ 3 simple FS or with complex FS
Interventions	Continuous phenobarbital 3 to 5 mg/kg/day in 2 doses for at least a year, or intermittent oral diazepam 0.33 mg/kg 3 times a day for 2 days
Outcomes	RS at 12 months, adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Randomisation methodology not mentioned.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 participants excluded based on exclusion criteria. Loss to follow-up not discussed.
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	No bias identified.

Salehiomran 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Strengell 2009

Study characteristics	
Methods	Randomised, placebo-controlled, double-blind trial
Participants	231, 4 to 48 months, first febrile seizure; 63 of 231 children had had a complicated first seizure
Interventions	Random allocation first into 2 groups (rectal diclofenac (1.5 mg/kg suppository) versus placebo) and then to 3 groups (oral placebo versus paracetamol (15 mg/kg) versus ibuprofen (10 mg/kg)) - each up to 4 times per day as long as temperature > 38 °C
Outcomes	Actuarial analysis of seizure recurrence up to 24 months
Notes	Participants included in analyses for as long as they had participated in study because Kaplan-Meier used with no imputations for the dropouts.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Open random allocation schedule. "The allocation sequence for rectal medications was generated by two of the authors (M.U. and H.R.) by the use of random-number tables. The allocation was performed as a block randomization with permuted blocks with a block size of 4."
Blinding (performance bias and detection bias) All outcomes	Low risk	Special preparations made for drugs/placebos by pharmaceutical companies.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition: 50 of 231 randomised: 34 did not want to continue; 9 lost; 7 others dropped out for a variety of reasons
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Special preparations made for drugs/placebos by pharmaceutical companies.
Blinding of outcome assessment (detection bias)	Low risk	Special preparations made for drugs/placebos by pharmaceutical companies.

Strengell 2009 *(Continued)*
All outcomes

Taghdiri 2011

Study characteristics		
Methods	Quasi-RCT	
Participants	80 children aged 9 months to 5 years, simple seizure	
Interventions	Rectal diazepam (0.5 mg/kg) and paracetamol versus paracetamol only	
Outcomes	RS at 12 months	
Notes	Letter to the editor, brief study description	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

Thilothammal 1993

Study characteristics	
Methods	Double-blind RCT
Participants	90, but only 60 used in randomisation; aged 6 to 72 months; 2 or more simple seizures, 60 simple FS (30 placebo, 30 phenobarbital), 30 atypical (phenobarbital)

Thilothammal 1993 *(Continued)*

Interventions	Phenobarbital 5 mg per kilo or placebo
Outcomes	RS at 6 months, RS at 12 months
Notes	No attrition

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 4 dropouts
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate placebo. "The assessment of recurrence, side-effects and compliance were done by one investigator who was blind to the type of treatment throughout the study period.

Uhari 1995

Study characteristics

Methods	Double-blind RCT
Participants	180, first FS
Interventions	Intermittent rectal followed by oral diazepam 0.6 mg per kilo or placebo, both with antipyretics
Outcomes	RS at 6 months, RS at 12 months, RS at 24 months
Notes	Kaplan-Meier used in estimations at 6 and 12 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. "Only the statistician knew the details of the randomization schedule."

Uhari 1995 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Not clearly stated, but claiming to be "double blind" and using a placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 of 180 withdrew from study.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not clearly stated, but claiming to be "double blind" and using a placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly stated. Unknown if person assessing outcomes was blinded

Van Stuijvenberg 1998

Study characteristics		
Methods	Double-blind RCT	
Participants	230, 12 to 48 months, FS at least 1 risk factor	
Interventions	Intermittent oral ibuprofen 5 mg per kilo per day or placebo	
Outcomes	RS at 6 months, RS at 12 months, RS at 24 months	
Notes	Kaplan-Meier used in estimations.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation schedule, stratified by centre. "Only the biostatistician and the hospital pharmacists knew the actual treatment allocation."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	23 of 230 without outcome data
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.

Van Stuijvenberg 1998 *(Continued)*

Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded

Verrotti 2004

Study characteristics	
Methods	RCT
Participants	110, 6 to 60 months, 1 simple febrile seizure, no risk factors
Interventions	Oral diazepam 0.35 mg/kg every 8 hours, during each episode of fever higher than 38 °C, continuing until child afebrile for 24 hours versus no treatment
Outcomes	RS at 6 months, RS at 12 months, RS at 24 months, RS at 48 months
Notes	Kaplan-Meier used in estimations at months 6, 12, and 24.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A statistician randomly assigned each child to Group A or B; the doctors who followed these children did not know the randomisation.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding, open-label treatment vs no treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data available on 110 of 113 children, yet 45 intervention children are compared to 65 controls.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None, open-label treatment vs no treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	None, open-label treatment vs no treatment

Williams 1979

Study characteristics	
Methods	RCT
Participants	58, 6 to 72 months, 2 or more simple FS
Interventions	Valproate 40 mg per kilo or no treatment
Outcomes	RS at 12 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	High risk	None
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Wolf 1977

Study characteristics	
Methods	Quasi-RCT
Participants	355, 6 to 48 months, first FS
Interventions	Phenobarbital 3 to 4 mg per kilo, or intermittent phenobarbital 5 mg per kilo, or no treatment
Outcomes	RS at 6 months, RS at 12 months, RS at 24 months, late cognition and behaviour, and adverse effects

Wolf 1977 *(Continued)*

Notes	Kaplan-Meier used in estimations. Duration of follow-up differed: 28 (6 to 70) months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Not used. Children were randomly assigned according to the last digit of the chart number.
Blinding (performance bias and detection bias) All outcomes	High risk	None
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study design with actuarial analysis gave little attrition.
Selective reporting (reporting bias)	Low risk	Stated outcome objective met.
Other bias	Low risk	No bias identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	None
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

FS: febrile seizure
ITT: intention-to-treat
RCT: randomised controlled trial
RF: risk factor
RS: recurrent seizure
SUDEP: sudden unexpected death in epilepsy

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

Study	Reason for exclusion
Addy 1977	Abstract only
Amouian 2013	Abstract in English, but main text in Farsi
Antony 1983	72 children randomised, 36 to phenobarbital and 36 to carbamazepine, but 32 not included in the final analysis. In 15 there was no follow-up, 5 were excluded because of low or no antiepileptic drug level, 9 were excluded because of unacceptable adverse effects, 2 had afebrile seizures, and 1 child was incorrectly entered. Unfortunately no follow-up detail is given for any of these 32 children (44%!).
Fayyazi 2018	High rate of exclusion to start with unusual selection criteria The attrition rate is high with no attendant information on the lost children. We cannot analyse data on intention-to-treat basis.

Study	Reason for exclusion
	The quantitative data are not presented numerically, making them difficult to read.
Frelih 1997	No data reported to estimate the occurrence of any of the prespecified outcomes.
Galli 1977	Unable to obtain copy of paper
Kazemi 2013	Published in Farsi
Knudsen 1978	Further exclusions from analysis of 16 children in phenobarbital group due to adverse effects or parents' "dislike to it". No follow-up data given for these 16 children (+ 24 lost to follow-up).
Lahat 2000	Not a recurrence study - acute treatment only
Minagawa 1981	Not randomised, unclear allocation, with different numbers of participants per group; the only randomisation was in 15 children to measure drug levels. Outside scope of this review
Murata 2018	This study evaluated the ability of paracetamol to reduce febrile seizure recurrences during the same fever episode, which is out of the scope of our review. Furthermore, the rates of recurrence in the first 24 hours seem very high in this study's control group.
Nemati 2019	We have concerns that this study had no experimental design and was not a randomised controlled trial. The authors mention that they had a problem obtaining parental consent to receive topiramate. The issue was investigated, and to paraphrase participants left the study not due to medication events, but because from their point of view topiramate was not commonly used to treat febrile seizures and was therefore undesirable.
Rose 2005	Randomised controlled trial, but with inadequate follow-up (range of 0 to 14 months); data interpretation at 6 months impossible
Rosman 2001	Research question asking about parental experiences
Schnaiderman 1993	This study evaluated if seizure recurrence can be reduced during the first 24 hours of an admission due to an episode of a simple febrile convulsion (not stated whether it is the child's first febrile seizure), i.e. to reduce complex seizure (defined as more than 1 seizure during a febrile illness episode). This is not within the scope of our review, where we are looking at recurrences during *subsequent* febrile illnesses.
Shimazaki 1997	Not randomised; unclear allocation; different numbers of participants per group
Steardo 1980	Not randomised; unclear allocation; different numbers of participants per group
Van Esch 1995	Research question of effect on temperature, not on seizure recurrence
Vining 1987	Side effects study not on children with febrile convulsions

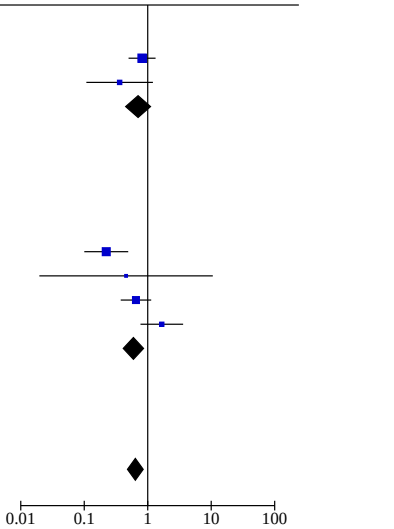
DATA AND ANALYSES

Comparison 1. Intermittent oral or rectal diazepam compared to placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Recurrent seizure @ 6 months	6	1151	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.85]
1.1.1 Intermittent oral diazepam	2	516	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.45, 1.11]
1.1.2 Intermittent rectal diazepam	4	635	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.41, 0.86]
1.2 Recurrent seizure @ 12 months	8	1416	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.56, 0.84]
1.2.1 Intermittent oral diazepam	3	701	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.53, 0.99]
1.2.2 Intermittent rectal diazepam	5	715	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.50, 0.86]
1.3 Recurrent seizure @ 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3.1 Intermittent rectal diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Recurrent seizure @ 24 months	4	739	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.95]
1.4.1 Intermittent oral diazepam	2	516	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.45, 0.85]
1.4.2 Intermittent rectal diazepam	2	223	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.67, 1.90]
1.5 Recurrent seizure @ 36 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5.1 Intermittent rectal diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 Recurrent seizure @ 48 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6.1 Intermittent oral diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7 Recurrent seizure @ 60 to 72 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7.1 Intermittent oral diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

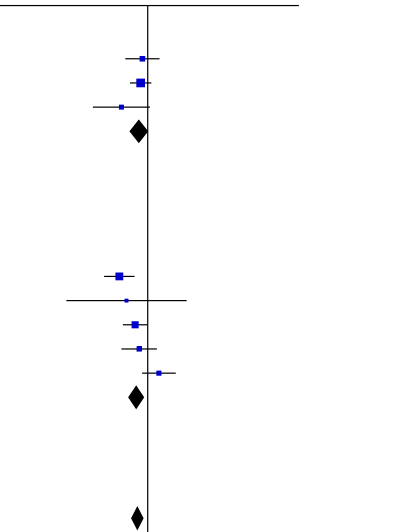
Analysis 1.1. Comparison 1: Intermittent oral or rectal diazepam compared to placebo or no treatment, Outcome 1: Recurrent seizure @ 6 months

Study or Subgroup	Intermittent diazepam Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Intermittent oral diazepam						
Rosman 1993	25	202	31	204	29.8%	0.81 [0.50 , 1.33]
Verrotti 2004	3	45	12	65	9.5%	0.36 [0.11 , 1.21]
Subtotal (95% CI)		**247**		**269**	**39.3%**	**0.70 [0.45 , 1.11]**
Total events:	28		43			
Heterogeneity: Chi² = 1.51, df = 1 (P = 0.22); I² = 34%						
Test for overall effect: Z = 1.52 (P = 0.13)						
1.1.2 Intermittent rectal diazepam						
Knudsen 1985	7	147	27	126	28.1%	0.22 [0.10 , 0.49]
Mosquera 1987	0	18	1	25	1.2%	0.46 [0.02 , 10.60]
Pavlidou 2006	15	68	24	71	22.7%	0.65 [0.38 , 1.13]
Uhari 1995	15	90	9	90	8.7%	1.67 [0.77 , 3.61]
Subtotal (95% CI)		**323**		**312**	**60.7%**	**0.59 [0.41 , 0.86]**
Total events:	37		61			
Heterogeneity: Chi² = 12.83, df = 3 (P = 0.005); I² = 77%						
Test for overall effect: Z = 2.77 (P = 0.006)						
Total (95% CI)		**570**		**581**	**100.0%**	**0.64 [0.48 , 0.85]**
Total events:	65		104			
Heterogeneity: Chi² = 14.52, df = 5 (P = 0.01); I² = 66%						
Test for overall effect: Z = 3.09 (P = 0.002)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%						



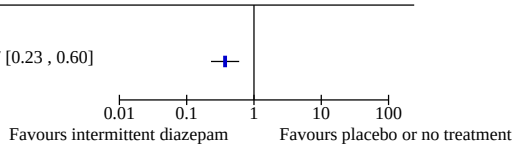
Analysis 1.2. Comparison 1: Intermittent oral or rectal diazepam compared to placebo or no treatment, Outcome 2: Recurrent seizure @ 12 months

Study or Subgroup	Intermittent diazepam Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Intermittent oral diazepam						
Autret 1990	15	93	18	92	10.1%	0.82 [0.44 , 1.53]
Rosman 1993	36	202	47	204	26.0%	0.77 [0.52 , 1.14]
Verrotti 2004	4	45	15	65	6.8%	0.39 [0.14 , 1.08]
Subtotal (95% CI)		**340**		**361**	**42.9%**	**0.72 [0.53 , 0.99]**
Total events:	55		80			
Heterogeneity: Chi² = 1.71, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 2.03 (P = 0.04)						
1.2.2 Intermittent rectal diazepam						
Knudsen 1985	15	147	36	126	21.6%	0.36 [0.21 , 0.62]
Mosquera 1987	1	18	3	25	1.4%	0.46 [0.05 , 4.10]
Pavlidou 2006	20	68	33	71	18.0%	0.63 [0.41 , 0.99]
Taghdiri 2011	11	40	15	40	8.3%	0.73 [0.39 , 1.39]
Uhari 1995	21	90	14	90	7.8%	1.50 [0.82 , 2.76]
Subtotal (95% CI)		**363**		**352**	**57.1%**	**0.66 [0.50 , 0.86]**
Total events:	68		101			
Heterogeneity: Chi² = 11.94, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**703**		**713**	**100.0%**	**0.69 [0.56 , 0.84]**
Total events:	123		181			
Heterogeneity: Chi² = 13.86, df = 7 (P = 0.05); I² = 49%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						



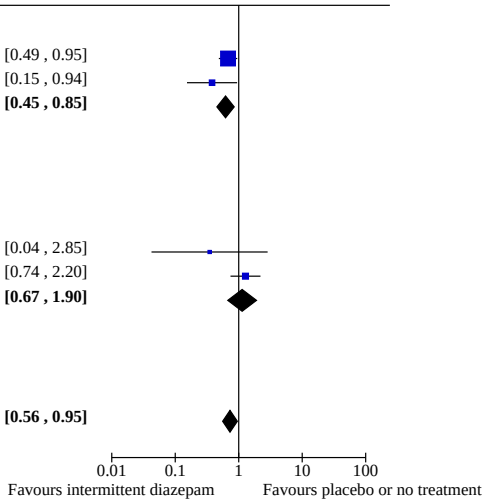
Analysis 1.3. Comparison 1: Intermittent oral or rectal diazepam compared to placebo or no treatment, Outcome 3: Recurrent seizure @ 18 months

Study or Subgroup	Intermittent diazepam Events	Total	Placebo or no treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Intermittent rectal diazepam					
Knudsen 1985	19	152	46	137	0.37 [0.23 , 0.60]



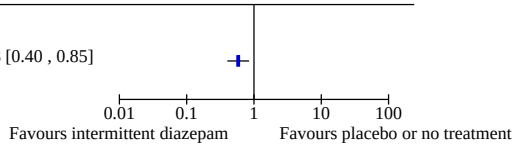
Analysis 1.4. Comparison 1: Intermittent oral or rectal diazepam compared to placebo or no treatment, Outcome 4: Recurrent seizure @ 24 months

Study or Subgroup	Intermittent diazepam Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Intermittent oral diazepam						
Rosman 1993	43	202	64	204	63.3%	0.68 [0.49 , 0.95]
Verrotti 2004	5	45	19	65	15.5%	0.38 [0.15 , 0.94]
Subtotal (95% CI)		**247**		**269**	**78.8%**	**0.62 [0.45 , 0.85]**
Total events:	48		83			
Heterogeneity: Chi² = 1.39, df = 1 (P = 0.24); I² = 28%						
Test for overall effect: Z = 2.99 (P = 0.003)						
1.4.2 Intermittent rectal diazepam						
Mosquera 1987	1	18	4	25	3.3%	0.35 [0.04 , 2.85]
Uhari 1995	23	90	18	90	17.9%	1.28 [0.74 , 2.20]
Subtotal (95% CI)		**108**		**115**	**21.2%**	**1.13 [0.67 , 1.90]**
Total events:	24		22			
Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 29%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**355**		**384**	**100.0%**	**0.73 [0.56 , 0.95]**
Total events:	72		105			
Heterogeneity: Chi² = 6.73, df = 3 (P = 0.08); I² = 55%						
Test for overall effect: Z = 2.33 (P = 0.02)						
Test for subgroup differences: Chi² = 3.78, df = 1 (P = 0.05), I² = 73.5%						



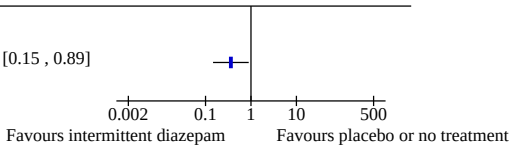
Analysis 1.5. Comparison 1: Intermittent oral or rectal diazepam compared to placebo or no treatment, Outcome 5: Recurrent seizure @ 36 months

Study or Subgroup	Intermittent diazepam Events	Total	Placebo or no treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Intermittent rectal diazepam					
Pavlidou 2006	24	68	43	71	0.58 [0.40 , 0.85]



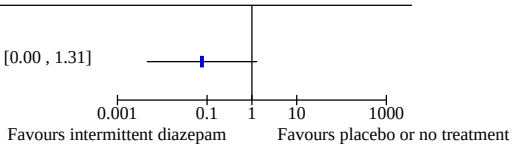
Analysis 1.6. Comparison 1: Intermittent oral or rectal diazepam compared to placebo or no treatment, Outcome 6: Recurrent seizure @ 48 months

Study or Subgroup	Intermittent diazepam Events	Total	Placebo or no treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Intermittent oral diazepam					
Verrotti 2004	5	45	20	65	0.36 [0.15 , 0.89]



Analysis 1.7. Comparison 1: Intermittent oral or rectal diazepam compared to placebo or no treatment, Outcome 7: Recurrent seizure @ 60 to 72 months

Study or Subgroup	Intermittent diazepam Events	Total	Placebo or no treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Intermittent oral diazepam					
Ramakrishnan 1986	0	30	6	30	0.08 [0.00 , 1.31]



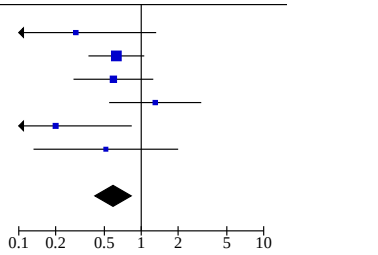
Comparison 2. Continuous phenobarbital compared to placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Recurrent seizure @ 6 months	6	833	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.83]
2.2 Recurrent seizure @ 12 months	7	807	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.42, 0.70]
2.3 Recurrent seizure @ 18 months	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.05]
2.4 Recurrent seizure @ 24 months	3	533	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.89]
2.5 Recurrent seizure @ 60 to 72 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.6 Behavioural changes	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.79, 3.26]

Analysis 2.1. Comparison 2: Continuous phenobarbital compared to placebo or no treatment, Outcome 1: Recurrent seizure @ 6 months

Study or Subgroup	Continuous phenobarbitone Events	Total	placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Camfield 1980	2	39	7	40	9.3%	0.29 [0.06 , 1.32]
Farwell 1990	18	108	29	109	38.8%	0.63 [0.37 , 1.06]
Heckmatt 1976	10	88	14	73	20.6%	0.59 [0.28 , 1.25]
McKinlay 1989	8	41	9	60	9.8%	1.30 [0.55 , 3.09]
Thilothammal 1993	2	30	10	30	13.5%	0.20 [0.05 , 0.84]
Wolf 1977	3	106	6	109	8.0%	0.51 [0.13 , 2.00]
Total (95% CI)		**412**		**421**	**100.0%**	**0.59 [0.42 , 0.83]**
Total events:	43		75			

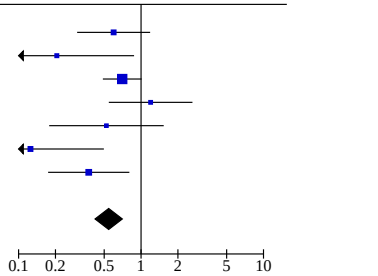
Heterogeneity: Chi² = 6.32, df = 5 (P = 0.28); I² = 21%
Test for overall effect: Z = 3.04 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Continuous phenobarbital compared to placebo or no treatment, Outcome 2: Recurrent seizure @ 12 months

Study or Subgroup	Continuous phenobarbitone Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bacon 1981	10	48	15	43	12.6%	0.60 [0.30 , 1.19]
Camfield 1980	2	39	10	40	7.9%	0.21 [0.05 , 0.88]
Farwell 1990	32	108	46	109	36.5%	0.70 [0.49 , 1.01]
McKinlay 1989	9	41	11	60	7.1%	1.20 [0.55 , 2.63]
Ngwane 1980	4	23	7	21	5.8%	0.52 [0.18 , 1.53]
Thilothammal 1993	2	30	16	30	12.8%	0.13 [0.03 , 0.50]
Wolf 1977	8	106	22	109	17.3%	0.37 [0.17 , 0.80]
Total (95% CI)		**395**		**412**	**100.0%**	**0.54 [0.42 , 0.70]**
Total events:	67		127			

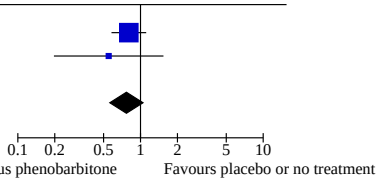
Heterogeneity: Chi² = 12.84, df = 6 (P = 0.05); I² = 53%
Test for overall effect: Z = 4.65 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Continuous phenobarbital compared to placebo or no treatment, Outcome 3: Recurrent seizure @ 18 months

Study or Subgroup	continuous phenobarbitone Events	Total	placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Farwell 1990	39	108	49	109	85.8%	0.80 [0.58 , 1.11]
Mamelle 1984	4	21	9	26	14.2%	0.55 [0.20 , 1.54]
Total (95% CI)		**129**		**135**	**100.0%**	**0.77 [0.56 , 1.05]**
Total events:	43		58			

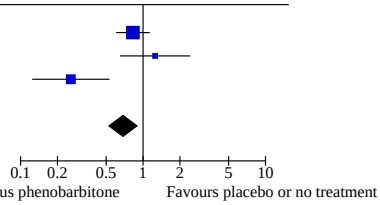
Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Continuous phenobarbital compared to placebo or no treatment, Outcome 4: Recurrent seizure @ 24 months

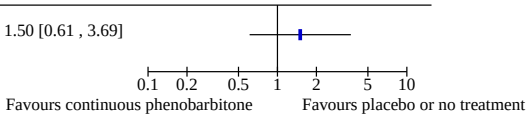
Study or Subgroup	Continuous phenobarbitone Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Farwell 1990	41	108	50	109	53.7%	0.83 [0.60 , 1.13]
McKinlay 1989	12	41	14	60	12.3%	1.25 [0.65 , 2.43]
Wolf 1977	8	106	32	109	34.0%	0.26 [0.12 , 0.53]
Total (95% CI)		**255**		**278**	**100.0%**	**0.69 [0.53 , 0.89]**
Total events:	61		96			

Heterogeneity: Chi² = 11.56, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 2.80 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Continuous phenobarbital compared to placebo or no treatment, Outcome 5: Recurrent seizure @ 60 to 72 months

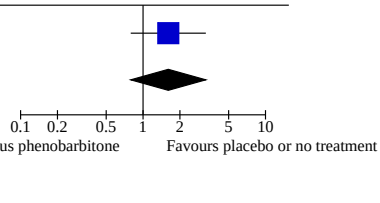
Study or Subgroup	Continuous phenobarbitone Events	Total	Placebo or no treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ramakrishnan 1986	9	30	6	30	1.50 [0.61 , 3.69]



Analysis 2.6. Comparison 2: Continuous phenobarbital compared to placebo or no treatment, Outcome 6: Behavioural changes

Study or Subgroup	Continuous phenobarbitone Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Camfield 1980	15	35	8	30	100.0%	1.61 [0.79 , 3.26]
Total (95% CI)		**35**		**30**	**100.0%**	**1.61 [0.79 , 3.26]**
Total events:	15		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



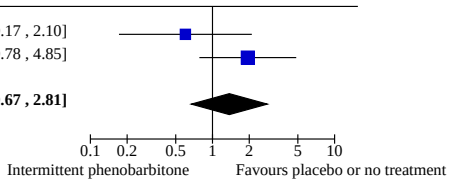
Comparison 3. Intermittent phenobarbital compared to placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Recurrent seizure @ 6 months	2	281	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.67, 2.81]
3.2 Recurrent seizure @ 12 months	2	281	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.65, 1.59]
3.3 Recurrent seizure @ 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.4 Recurrent seizure @ 60 to 72 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Intermittent phenobarbital compared to placebo or no treatment, Outcome 1: Recurrent seizure @ 6 months

Study or Subgroup	Intermittent phenobarbitone Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mackintosh 1970	3	16	5	16	42.6%	0.60 [0.17 , 2.10]
Wolf 1977	15	140	6	109	57.4%	1.95 [0.78 , 4.85]
Total (95% CI)		**156**		**125**	**100.0%**	**1.37 [0.67 , 2.81]**
Total events:	18		11			

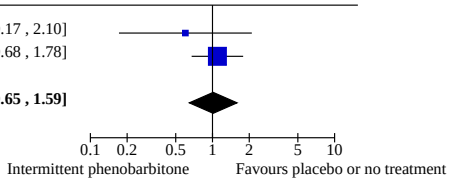
Heterogeneity: Chi² = 2.24, df = 1 (P = 0.13); I² = 55%
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Intermittent phenobarbital compared to placebo or no treatment, Outcome 2: Recurrent seizure @ 12 months

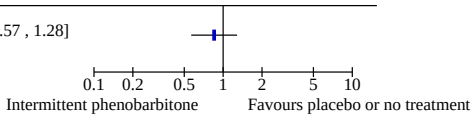
Study or Subgroup	Intermittent phenobarbitone Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mackintosh 1970	3	16	5	16	16.8%	0.60 [0.17 , 2.10]
Wolf 1977	31	140	22	109	83.2%	1.10 [0.68 , 1.78]
Total (95% CI)		**156**		**125**	**100.0%**	**1.01 [0.65 , 1.59]**
Total events:	34		27			

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



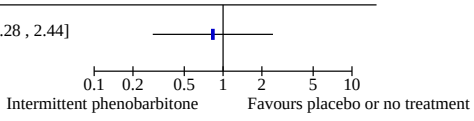
Analysis 3.3. Comparison 3: Intermittent phenobarbital compared to placebo or no treatment, Outcome 3: Recurrent seizure @ 24 months

Study or Subgroup	Intermittent phenobarbitone Events	Total	Placebo or no treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
Wolf 1977	35	140	32	109	0.85 [0.57 , 1.28]



Analysis 3.4. Comparison 3: Intermittent phenobarbital compared to placebo or no treatment, Outcome 4: Recurrent seizure @ 60 to 72 months

Study or Subgroup	Intermittent phenobarbitone Events	Total	Placebo or no treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ramakrishnan 1986	5	30	6	30	0.83 [0.28 , 2.44]

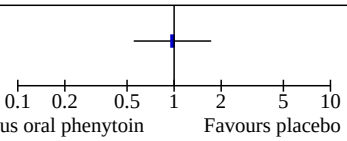


Comparison 4. Continuous oral phenytoin compared to placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Continuous oral phenytoin compared to placebo, Outcome 1: Recurrent seizure @ 12 months

Study or Subgroup	Continuous oral phenytoin Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bacon 1981	16	47	15	43	0.98 [0.55 , 1.73]



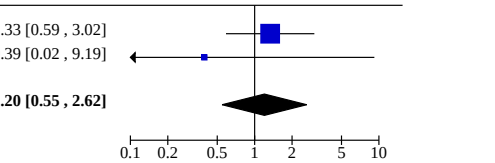
Comparison 5. Continuous oral valproate compared to placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Recurrent seizure @ 6 months	2	156	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.55, 2.62]
5.2 Recurrent seizure @ 12 months	4	255	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.29]
5.3 Recurrent seizure @ 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.4 Recurrent seizure @ 24 months	2	156	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.73, 2.18]

Analysis 5.1. Comparison 5: Continuous oral valproate compared to placebo or no treatment, Outcome 1: Recurrent seizure @ 6 months

Study or Subgroup	Continuous oral valproate Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McKinlay 1989	10	50	9	60	85.6%	1.33 [0.59 , 3.02]
Mosquera 1987	0	21	1	25	14.4%	0.39 [0.02 , 9.19]
Total (95% CI)		**71**		**85**	**100.0%**	**1.20 [0.55 , 2.62]**
Total events:	10		10			

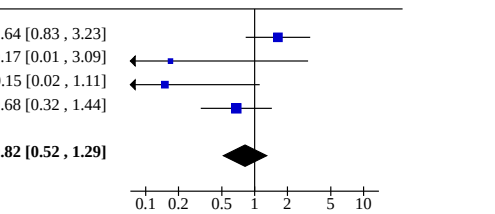
Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



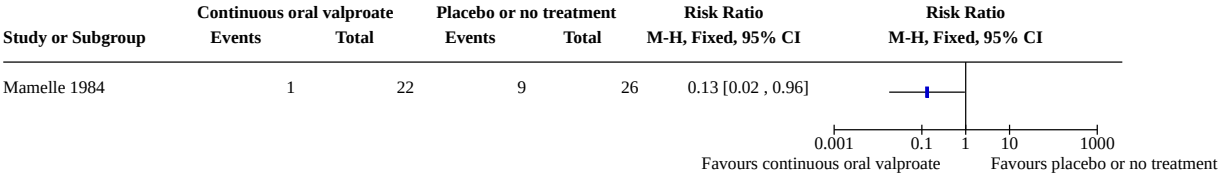
Analysis 5.2. Comparison 5: Continuous oral valproate compared to placebo or no treatment, Outcome 2: Recurrent seizure @ 12 months

Study or Subgroup	Continuous oral valproate Events	Total	Placebo or no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McKinlay 1989	15	50	11	60	31.8%	1.64 [0.83 , 3.23]
Mosquera 1987	0	21	3	25	10.2%	0.17 [0.01 , 3.09]
Ngwane 1980	1	20	7	21	21.7%	0.15 [0.02 , 1.11]
Williams 1979	8	30	11	28	36.2%	0.68 [0.32 , 1.44]
Total (95% CI)		**121**		**134**	**100.0%**	**0.82 [0.52 , 1.29]**
Total events:	24		32			

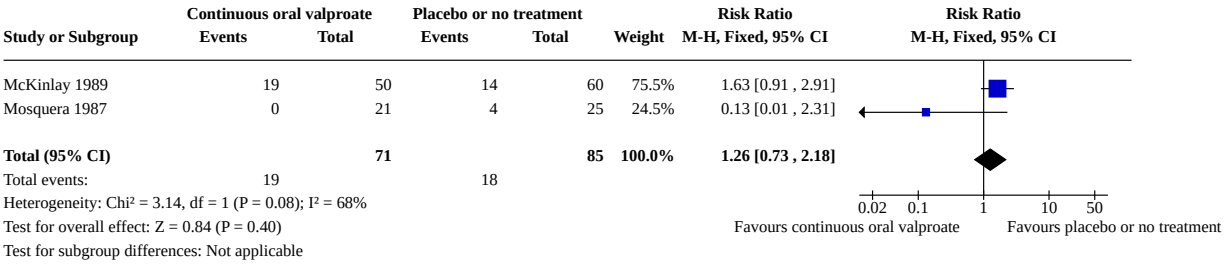
Heterogeneity: Chi² = 8.10, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Continuous oral valproate compared to placebo or no treatment, Outcome 3: Recurrent seizure @ 18 months



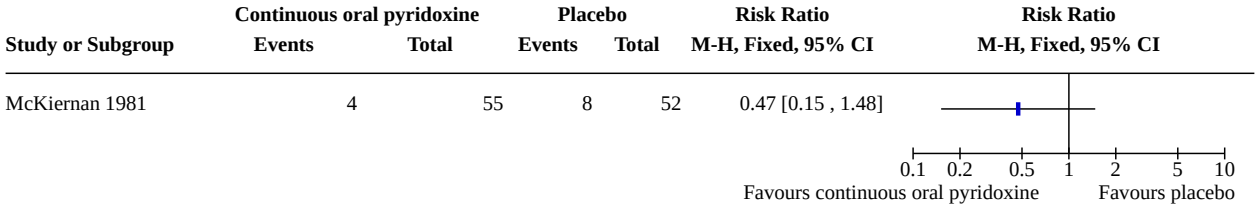
Analysis 5.4. Comparison 5: Continuous oral valproate compared to placebo or no treatment, Outcome 4: Recurrent seizure @ 24 months



Comparison 6. Continuous oral pyridoxine compared to placebo

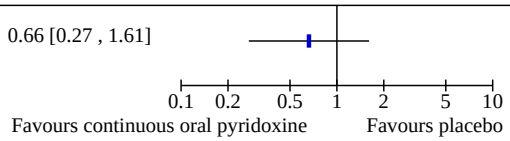
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Recurrent seizure @ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Continuous oral pyridoxine compared to placebo, Outcome 1: Recurrent seizure @ 6 months



Analysis 6.2. Comparison 6: Continuous oral pyridoxine compared to placebo, Outcome 2: Recurrent seizure @ 12 months

Study or Subgroup	Continuous oral pyridoxine Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
McKiernan 1981	7	55	10	52	0.66 [0.27 , 1.61]	

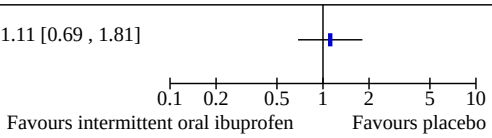


Comparison 7. Intermittent oral ibuprofen compared to placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Recurrent seizure @ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.2 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.3 Recurrent seizure @ 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

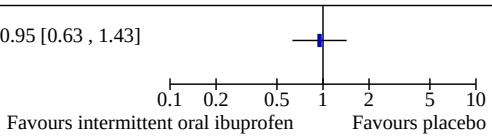
Analysis 7.1. Comparison 7: Intermittent oral ibuprofen compared to placebo, Outcome 1: Recurrent seizure @ 6 months

Study or Subgroup	Intermittent oral ibuprofen Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Van Stuijvenberg 1998	26	111	25	119	1.11 [0.69 , 1.81]	



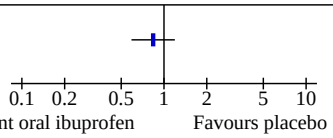
Analysis 7.2. Comparison 7: Intermittent oral ibuprofen compared to placebo, Outcome 2: Recurrent seizure @ 12 months

Study or Subgroup	Intermittent oral ibuprofen Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Van Stuijvenberg 1998	31	111	35	119	0.95 [0.63 , 1.43]	



Analysis 7.3. Comparison 7: Intermittent oral ibuprofen compared to placebo, Outcome 3: Recurrent seizure @ 24 months

Study or Subgroup	Intermittent oral ibuprofen Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Van Stuijvenberg 1998	36	111	46	119	0.84 [0.59 , 1.19]

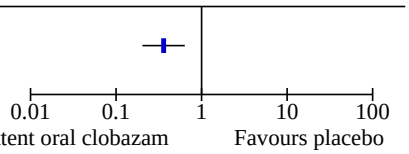


Comparison 8. Intermittent oral clobazam compared to placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Recurrent seizure @ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Intermittent oral clobazam compared to placebo, Outcome 1: Recurrent seizure @ 6 months

Study or Subgroup	Clobazam Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bajaj 2005	9	30	25	30	0.36 [0.20 , 0.64]

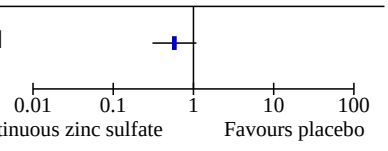


Comparison 9. Continuous zinc sulfate for 6 months compared to placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Continuous zinc sulfate for 6 months compared to placebo, Outcome 1: Recurrent seizure @ 12 months

Study or Subgroup	Continuous zinc sulfate Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Fallah 2015	11	50	19	50	0.58 [0.31 , 1.09]

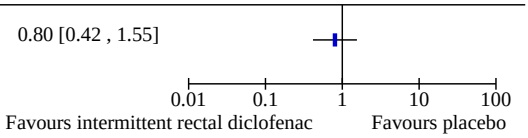


Comparison 10. Intermittent rectal diclofenac compared to placebo followed by oral ibuprofen, paracetamol, or placebo after 8 hours

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Recurrent seizure @ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.3 Recurrent seizure @ 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.4 Recurrent seizure @ 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

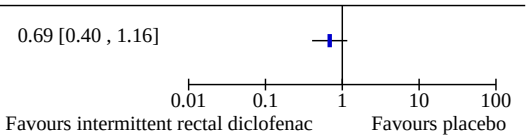
Analysis 10.1. Comparison 10: Intermittent rectal diclofenac compared to placebo followed by oral ibuprofen, paracetamol, or placebo after 8 hours, Outcome 1: Recurrent seizure @ 6 months

	Intermittent rectal diclofenac		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Strengell 2009	14	117	17	114	0.80 [0.42 , 1.55]	



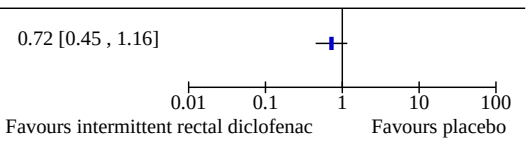
Analysis 10.2. Comparison 10: Intermittent rectal diclofenac compared to placebo followed by oral ibuprofen, paracetamol, or placebo after 8 hours, Outcome 2: Recurrent seizure @ 12 months

	Intermittent rectal diclofenac		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Strengell 2009	19	117	27	114	0.69 [0.40 , 1.16]	

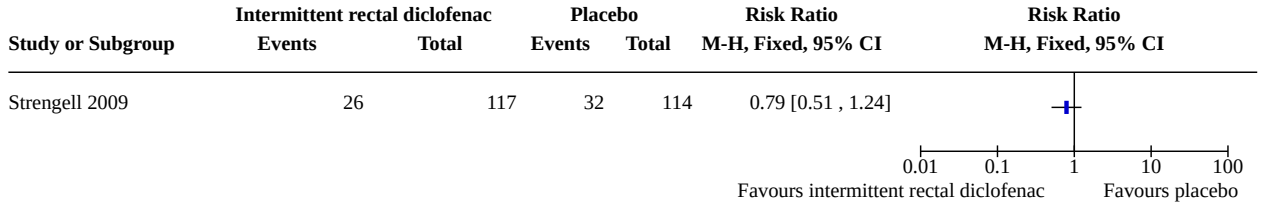


Analysis 10.3. Comparison 10: Intermittent rectal diclofenac compared to placebo followed by oral ibuprofen, paracetamol, or placebo after 8 hours, Outcome 3: Recurrent seizure @ 18 months

	Intermittent rectal diclofenac		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Strengell 2009	23	117	31	114	0.72 [0.45 , 1.16]	



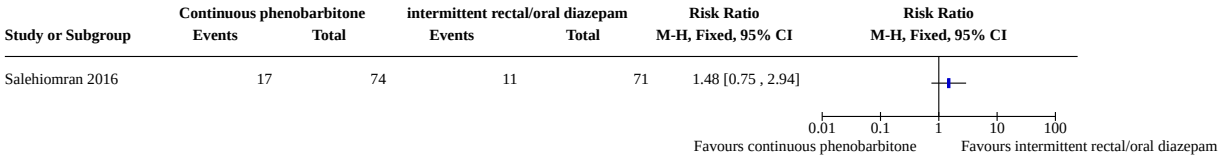
Analysis 10.4. Comparison 10: Intermittent rectal diclofenac compared to placebo followed by oral ibuprofen, paracetamol, or placebo after 8 hours, Outcome 4: Recurrent seizure @ 24 months



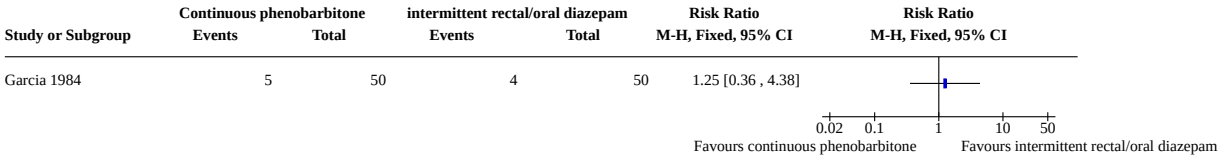
Comparison 11. Continuous phenobarbital compared to intermittent rectal or oral diazepam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.2 Recurrent seizure @ 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 11.1. Comparison 11: Continuous phenobarbital compared to intermittent rectal or oral diazepam, Outcome 1: Recurrent seizure @ 12 months



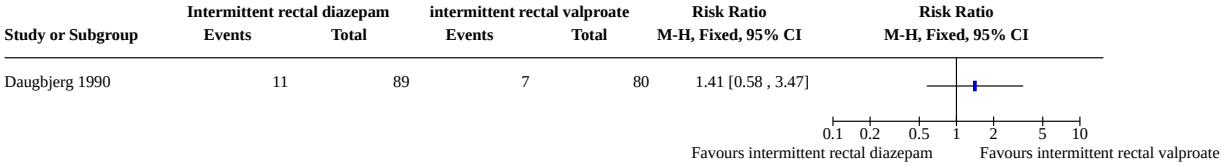
Analysis 11.2. Comparison 11: Continuous phenobarbital compared to intermittent rectal or oral diazepam, Outcome 2: Recurrent seizure @ 18 months



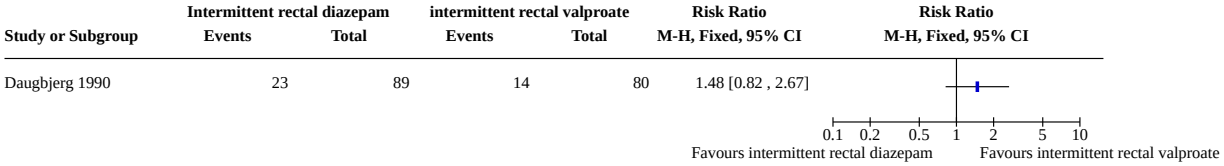
Comparison 12. Intermittent rectal diazepam compared to intermittent rectal valproate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Recurrent seizure @ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.2 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 12.1. Comparison 12: Intermittent rectal diazepam compared to intermittent rectal valproate, Outcome 1: Recurrent seizure @ 6 months



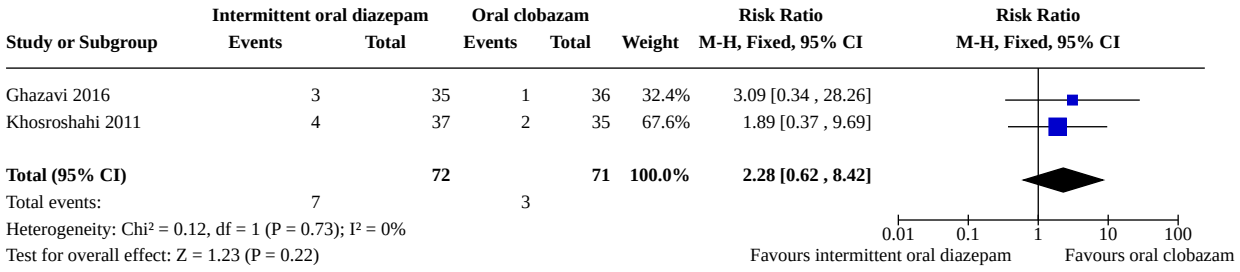
Analysis 12.2. Comparison 12: Intermittent rectal diazepam compared to intermittent rectal valproate, Outcome 2: Recurrent seizure @ 12 months



Comparison 13. Intermittent oral diazepam compared to oral clobazam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Recurrent seizure @ 12 months	2	143	Risk Ratio (M-H, Fixed, 95% CI)	2.28 [0.62, 8.42]

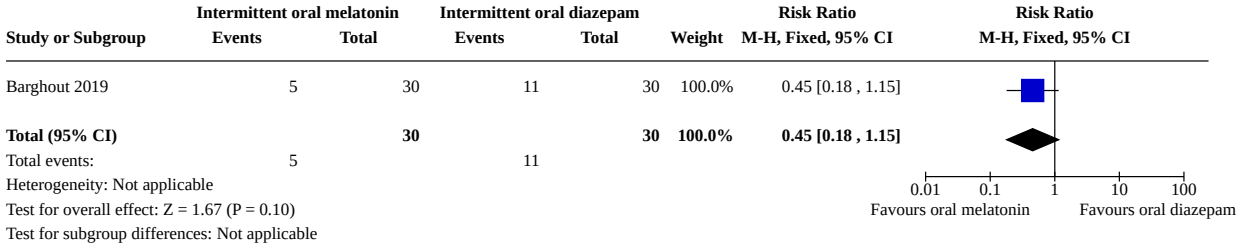
Analysis 13.1. Comparison 13: Intermittent oral diazepam compared to oral clobazam, Outcome 1: Recurrent seizure @ 12 months



Comparison 14. Intermittent oral melatonin compared to intermittent oral diazepam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Recurrent seizure @ 6 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.18, 1.15]

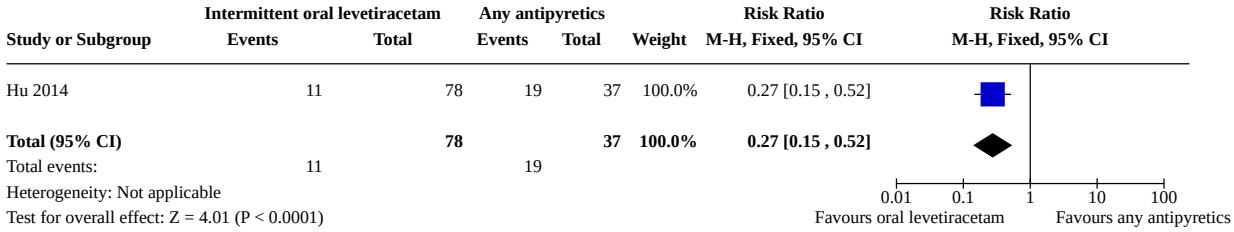
Analysis 14.1. Comparison 14: Intermittent oral melatonin compared to intermittent oral diazepam, Outcome 1: Recurrent seizure @ 6 months



Comparison 15. Intermittent oral levetiracetam compared to placebo (any antipyretics)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Recurrent seizure @ 12 months	1	115	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.15, 0.52]

Analysis 15.1. Comparison 15: Intermittent oral levetiracetam compared to placebo (any antipyretics), Outcome 1: Recurrent seizure @ 12 months



ADDITIONAL TABLES

Table 1. Treatment adherence

Study	Treatment groups	Assessed	Method	Outcome	Treatment adjusted based on adherence assessment?
Autret 1990	-DZP (oral) -PCB	Yes	Treatment diary	7% (1/15) of participants with relapses in DZP group were adherent versus 39% (7/18) in PCB group.	No
Bacon 1981	-PT -PB (cont.) -PCB	Yes	Saliva and plasma	Recurrence was positively related to median drug levels for PB, but not related for PT. PB: 0/4 (0%) at < 5 mg/L; 5/19 (26%) at 5 to 8 mg/L; 5/25 (20%) at > 8 mg/L	Yes

Table 1. Treatment adherence *(Continued)*

				PT: 3/9 (33%) at < 0.5 mg/L, 9/19 (47%) at 0.5 to 1.0 mg/L, 4/19 (21%) at > 1.0 mg/L	
Bajaj 2005	-CBZ -PCB	No	-	-	-
Barghout 2019	-MEL -DZP (oral)	Yes	Return of used package of drugs during the follow-up visits by parents	Not reported. There was 1 participant with non-compliance in the primary sample (1/66), but this participant was not included in data analysis of the 60 participants.	No
Camfield 1980	-PB (cont.) -PCB	Yes	Riboflavin urine check, and serum PB	Urine samples available in 65% (PB) and 56% (PCB); more than 90% of all samples tested positive. PB levels: mean 1.3 to 1.5 mg/dL, 70% to 81% within therapeutic range (≥ 1.0 mg/dL)	Yes
Daugbjerg 1990	-DZP (rectal) -VP	No	-	-	-
Fallah 2015	-ZNC -PCB	No	-	-	-
Farwell 1990	-PB (cont.) -PCB	Yes	Riboflavin urine check, PB blood levels	Riboflavin results not reported. 2/3 (66%) of PB blood levels tested were above 645.9 µmol/L or 15 µg/mL.	Yes
Ghazavi 2016	-CBZ -DZP (oral)	No	-	-	-
Garcia 1984	-DZP (rectal) -PB (cont.)	No	-	-	-
Heckmatt 1976	-PB (cont.) -NT	Yes	PB plasma levels	82% (40/49) had a mean PB plasma level above 65 µmol/L. All 4 recurrences in the PB group occurred in children with levels above 65 µmol/L.	Yes
Hu 2014	-LEV (int.) -PCB	Yes	Parents/caregivers were contacted every 12 weeks.	Poor compliance in 4/78 (5.1%) LEV children and 1/37 (2.7%) PCB children	No
Khosroshahi 2011	-DZP (oral) -CBZ	No	-	-	-
Knudsen 1985	-DZP (rectal) -NT	Yes	Historically in case of recurrence	Unclear report: "Parents treated the seizure as prescribed in 56/77 (72%) of the cases".	No

Table 1. Treatment adherence *(Continued)*

				Origin of the denominator is unclear, as 21 recurrences occurred in DZP and 77 in NT.	
Mackintosh 1970	-PB (int.) -PCB	No	-	-	-
Mamelle 1984	-PB (cont.) -VP -PCB	Yes	Blood levels	Unclear report	Yes
McKiernan 1981	-PDX -PCB	Yes	Historically and counting of tablets used	Not reported	Yes
McKinlay 1989	-PB (cont.) -VP -NT	Yes	PB and VP serum levels	PB: level checked 25/41 (61%) of children. Therapeutic level at time of recurrence: 5/12 (42%); level in those with non-recurrence: 9/29 therapeutic, 11/29 subtherapeutic, 9/29 not done VP: level checked 36/50 (72%) of children. Therapeutic level at time of recurrence: 12/20 (60%); level in children with non-recurrence: 13/30 therapeutic, 6/30 subtherapeutic, 11/30 not done	No
Mosquera 1987	-DZP (rectal) -VP -NT	No	-	-	
Ngwane 1980	-PB (cont.) -VP	Yes	Blood levels (random moments)	35 measures in 28 of 39 included children (72%): 16 in PB, of which 4 (25%) below therapeutic range, and 19 in VP, of which 1 (5%) below therapeutic range	No
Pavlidou 2006	-DZP (rectal) -NT	No	-	-	-
Ramakrishnan 1986	-PB (cont.) -PB (int.) -DZP (oral) -NT	No	-	-	-
Rosman 1993	-DZP (oral) -PCB	Yes	Riboflavin urine check	1257 DZP samples, 66% of all reported fever days, 96% of samples tested positive 982 PCB samples, 95% of all reported fever days, 95% of samples tested positive	No
Salehiomran 2016	-DZP (oral) -PB (cont.)	No	-	-	-

Table 1. Treatment adherence *(Continued)*

Strengell 2009	-DCF -PCB	No	-	-	-
Taghdiri 2011	-DZP (rectal) -NT	No	-	-	-
Thilothammal 1993	-PB (cont.) -PCB	Yes	Counting sachets	"Poor compliance" in 2/30 (7%) PB children and in 1/30 (3%) PCB children. All children with "poor compliance" also had a recurrence.	No
Uhari 1995	-DZP -PCB	No	-	-	-
Van Stuijvenberg 1998	-IBU -PCB	No	-	-	-
Verrotti 2004	-DZP (oral) -NT	Yes	Unclear, asked at recurrence	All 5 recurrences in DZP group were non-compliant.	No
Williams 1979	-VP -NT	Yes	Random VP plasma samples	Checked in 21/30 (70%) VP children: all showed measurable levels, but 2 below target concentration	No
Wolf 1977	-PB (cont.) -PB (int.) -NT	Yes	4-monthly blood check in the continuous PB group	78 of 106 cont. PB children (74%) had PB concentrations above target in at least 50% of their samples. These include 5 of the 7 children (71%) who had a recurrence in this group.	Yes

CBZ = clobazam; DCF = diclofenac; DZP = diazepam; IBU = ibuprofen; LEV = levetiracetam; MEL = melatonin; NT = no treatment; PB = phenobarbital; PCB = placebo; PDX = pyridoxine; PT = phenytoin; VP = valproate; ZNC = zinc sulfate; cont. = continuous; int. = intermittent

Table 2. Unwanted medication effects

First author	Number of children	Adverse medication effects, as reported in article
Autret 1990	177	Hyperactivity (defined as agitation and inability to remain still), significantly (P < 0.003) more frequent in diazepam group (138 vs 34 days). No significant differences noted for normal vigilance or drowsiness; normal staggering or impossible "walking". 1 sudden unexpected death in placebo group
Bacon 1981	138, 43 control, 48 phenobarbital, 47 phenytoin	Rash in 1 child on phenobarbital, ataxia in 5 children on phenytoin. Behavioural items: whinginess; crying a lot, bad temper, tantrums, dislike of being left, unsteadiness, desire for cuddling, difficulty feeding, noisiness, thumb sucking. No significant difference for any of these items between phenobarbital/phenytoin or placebo group. Any behavioural change attributed to hospitalisation.
Bajaj 2005	60	Drug reactions Group A (clobazam) Group B (placebo); n (%) n (%): weakness 1 (3.3) 11 (33.3); irritability 4 (13.3) 1 (3.3); sedation 5 (16.7) 5 (16.7); anorexia 2 (6.6) 5 (16.7); nausea and vomiting 0, 2 (6.6); abdominal pain 0, 1 (3.3); diarrhoea 1 (3.3) 3 (10); headache 1 (3.3) 5 (16.7)

Table 2. Unwanted medication effects *(Continued)*

Barghout 2019	60	Oral diazepam 7/30 (23.3%): somnolence 3 (10%); ataxia/dizziness 2 (6.7%); vomiting 1 (3.3%); irritability 1 (3.3%) Oral melatonin 4/30 (13.3%): vomiting 3 (10%); diarrhoea 1 (3.3%)
Camfield 1980	79	At 12 months there was no difference between phenobarbital and placebo groups for behavioural change or sleep disturbance. Placebo group: transient adverse effects in 8 of 30; phenobarbital group: transient adverse effects 15 of 35. Significant negative correlation between phenobarbital serum level and memory concentration subscores on Binet scores. Lower comprehension scores showed significant correlation with length of phenobarbital treatment (but n = 7 at 8 months and n = 9 at 12 months, therefore small numbers).
Daugbjerg 1990	169	Diazepam seen in 42 (47%), as follows: sedation 33 (37%), ataxia 42 (47%), hyperkinesia 21 (24%), diarrhoea, urge to defecate 1 (1%), depression 1 (1%). Valproic acid: sedation 9 (11%), ataxia 3 (4%), hyperkinesia 6 (7%), diarrhoea, urge to defecate 14 (18%). Vomiting 1 (1%), bleeding per rectum 1 (1%), abdominal pain 3 (4%), aggressiveness 3 (4%)
Fallah 2015	100	No serious side effects were witnessed in the 2 groups. Gastrointestinal side effects including vomiting in 5 (10%) children, heartburn in 2 (4%), and abdominal pain in 1 (2%) child were seen in 16% of the zinc sulfate group. All of the side effects were well tolerated and disappeared in 2 to 3 weeks, and supplementation continued. Vomiting occurred in 2 children (4%) in the control group.
Farwell 1990	217	Investigators compared intelligence quotients (IQs) of a group randomly assigned to phenobarbital to a group randomly assigned to placebo. After 2 years, mean IQ 8.4 points lower in phenobarbital group (95% CI -13.3 to −3.5, P = 0.006). 6 months later after discontinuing medication, IQ 5.2 points lower in phenobarbital group (95% CI −10.5 to 0.04, P = 0.052). Proportion remaining seizure-free did not differ significantly between treatment groups. 14 total sleep time, night awakenings, and lengthy awakenings compared between phenobarbital and placebo groups; no difference noted between groups, except subset of predisposed children did experience an increase in night awakenings (i.e. those already recorded to have frequent sleep disturbances at study entry). 35: retesting of group after school entry. Phenobarbital-treated group had Wide Range Achievement Test (WRAT-R) reading achievement score significantly lower than placebo group: 87.6 vs 95.6; P = 0.007. No significant difference for IQ on Stamford Binet
Garcia 1984	100	Adverse effects: diazepam 5 (10%), phenobarbital 3 (6%). Nature of adverse effects not stated.
Ghazavi 2016	71	Ataxia: diazepam 4/35 (11%), clobazam 1/36 (3%)
Heckmatt 1976	161	Overall, 39 of 88 stopped taking phenobarbital: 16 behaviour (overactivity, unpleasant behaviour, temper, not sleeping) (12 improved); 23 for a variety of reasons, e.g. drowsy/unsteady. 3 in control group reported behaviour problems.
Hu 2014	115	Levetiracetam group: 1/78 (1.2%) somnolence; control group: no adverse effects
Knudsen 1985	152	No severe adverse effects. Mild transient: 36% sedation, 15% euphoria, 8% ataxia, 2% aggression. Adverse effects not addressed in report on follow-up.

Table 2. Unwanted medication effects *(Continued)*

Khosroshahi 2011	72	Adverse effects of clobazam were noted to be lower than with diazepam. Sedation was noted more often with diazepam compared to clobazam (P < 0.001). No further details given.
Mamelle 1984		Adverse effects not addressed.
Mackintosh 1970	32	Adverse effects not addressed.
McKiernan 1981	107	Adverse effects not addressed.
McKinlay 1989	151	13 of 41 on phenobarbital had disturbed behaviour or drowsiness, or both; 1 vomiting; 2 rash; 1 unacceptable taste. 8 stopped treatment, 3 within 3 months. 5 of 50 on valproate drowsy initially; 2 behavioural problems; 1 vomited; 1 diarrhoea. 2 stopped taking drug. 16 control group adverse effects not addressed.
Mosquera 1987	69	Adverse effects not addressed.
Ngwane 1980	43	5 of 23 on phenobarbital had adverse effects within 72 hours; drug was withdrawn in 2 of these (details not given). 4 of 20 on valproate had adverse effects, most commonly diarrhoea.
Pavlidou 2006	139	Adverse effects were only reported in the diazepam group. These were described as mild and transient and included somnolence and irritability.
Ramakrishnan 1986	120	Adverse effects not addressed.
Rosman 1993	288	Of 135 children on placebo, 1 "moderate" maculopapular rash. Of 153 on diazepam, 59 (39%) at least moderate adverse effects: ataxia 30%, lethargy 29%, irritability 24%; moderate adverse effects: unclear speech 6%, hyperactivity 6%, insomnia 5%, hallucinations 0.7% (percentages of those 59 (39%) overall who had adverse effects). Mild adverse effects paralleled moderate numbers.
Salehiomran 2016	145	Side effects of phenobarbital like hyperkinesia, irritability, and restlessness were observed in some children, but diazepam-related side effects, except for sedation, were not seen.
Strengell 2009	231	Adverse effects not addressed.
Van Stuijvenberg 1998	230	Adverse effects not addressed.
Thilothammal 1993	90	"Intolerable" side effects presented in 2 of 30 children with simple febrile seizures on phenobarbital and 1 of 30 children with atypical febrile seizures. Recorded adverse effects were "mainly hyperkinetic behaviour, extreme irritability, fussiness and aggressiveness". Details of percentages are not given.
Uhari 1995	180	Adverse effects not addressed.
Verrotti 2004	110	Adverse effects were only reported in the treatment group, and included ataxia, lethargy, and irritability: 14 children (31.1%) had ataxia, 13 (28.8%) presented lethargy, and 11 children (24.4%) had irritability. These adverse effects lasted no more than 36 hours.
Williams 1979	58	7 of 30 children taking valproate (23%) had adverse effects: 4 diarrhoea or vomiting; 1 increased appetite; 1 increased daytime activity, night terrors, and confusion; 1 anorexia, withdrawn and crying. Adverse effects in control group not detailed.

Table 2. Unwanted medication effects *(Continued)*

Wolf 1977	355	Phenobarbital 34 of 109 (32%) discontinued continuous phenobarbital, reasons as follows: 16% hyperactivity; 1% irritability; 3% rash; 2% lethargy; 10% parental non-compliance. Long-term effect of phenobarbital on cognitive function: group of 50 matched for age, sex, rash, and socio-economic status for difference in cognitive function to median age of 57.5 months (phenobarbital-treated children) and 59.6 months (children not receiving phenobarbital).

APPENDICES

Appendix 1. CRS Web search strategy

1. MESH DESCRIPTOR Seizures, Febrile EXPLODE ALL WITH QUALIFIER DT PC AND CENTRAL:TARGET

2. (febrile and (seizure* or convulsion*)):AB,KW,MC,MH,TI AND CENTRAL:TARGET

3. MeSH DESCRIPTOR Epilepsy Explode All WITH QUALIFIER DT AND CENTRAL:TARGET

4. MESH DESCRIPTOR Seizures EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET

5. MeSH DESCRIPTOR Anticonvulsants Explode All AND CENTRAL:TARGET

6. (antiepilep* or anti-epilep* or anticonvulsant* or anti-convulsant* or AED or AEDs):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

7. #3 OR #4 OR #5 OR #6 AND CENTRAL:TARGET

8. MeSH DESCRIPTOR Midazolam Explode All AND CENTRAL:TARGET

9. (Dalam OR Dormicum OR Dormire OR Epistatus OR Fulsed OR Garen OR Hypnovel OR Ipnovel OR Midazolam* OR Nocturna OR Setam OR Terap OR Versed):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

10. #8 OR #9 AND CENTRAL:TARGET

11. MeSH DESCRIPTOR Methazolamide Explode All AND CENTRAL:TARGET

12. (Methazolamid* OR Methylacetazolamide OR Neptazane):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

13. #11 OR #12 AND CENTRAL:TARGET

14. MeSH DESCRIPTOR Propofol Explode All AND CENTRAL:TARGET

15. (Anepol OR Diprivan OR Disoprivan OR Disoprofol OR Fresofol OR Hypro OR Lipuro OR Plofed OR Profol OR Propofil OR Propofol* OR Propolipid OR Propovan OR Propoven OR Provive OR Recofol):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

16. #14 OR #15 AND CENTRAL:TARGET

17. MeSH DESCRIPTOR Temazepam Explode All AND CENTRAL:TARGET

18. (Dasuen OR Euhypnos OR Hydroxydiazepam OR Levanxol OR Methyloxazepam OR Nocturne OR Norkotral OR Normison OR Normitab OR Nortem OR Oxydiazepam OR Planum OR Pronervon OR Remestan OR Restoril OR Signopam OR Temaze OR Temazep* OR Temtabs OR Tenox):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

19. #17 OR #18 AND CENTRAL:TARGET

20. MeSH DESCRIPTOR Thiopental Explode All AND CENTRAL:TARGET

21. (Bomathal OR Farmotal OR Nesdonal OR Penthiobarbit* OR Pentothal OR Sodipental OR Thiomebumal OR Thionembutal OR Thiopent* OR Tiobarbital OR Tiopental* OR Trapanal):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

22. #20 OR #21 AND CENTRAL:TARGET

23. #7 OR #10 OR #13 OR #16 OR #19 OR #22 AND CENTRAL:TARGET

24. (Acemit OR Acetamide OR Acetazolamid* OR Avva OR Azm OR Azol OR Diacarb OR Diamox OR Diazomid OR Diluran OR Edemox OR Glaupax):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

25. (Barbexaclon*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

26. (Beclamid* OR Chloracon OR Hibicon OR Posedrine OR Nydrane OR Seclar):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

27. (Brivaracetam*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

28. (Bromide*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

29. (Carbamazepin* OR Carbamazepen* OR Carbamezepin* OR CBZ OR SPD417 OR "Apo-Carbamazepine" OR Atretol OR Biston OR Calepsin OR Carbagen OR Carbatrol OR Carbazepin* OR Carbelan OR Epitol OR Equetro OR Finlepsin OR Karbamazepin OR Lexin OR Neurotop OR "Novo-Carbamaz" OR "Nu-Carbamazepine" OR Sirtal OR Stazepin* OR "Taro-Carbamazepine" OR Tegretal OR Tegretol OR Telesmin OR Teril OR Timonil):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

30. (Carisbamat* OR Comfyde OR "RWJ-333369" OR "YKP 509"):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

31. (Chlormethiazol* OR Distraneurin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

32. (Aedon OR Anxirloc OR Castilium OR Chlorepin OR Clarmyl OR Clobam OR Clobamax OR Clobator OR Clobazam* OR Clofritis OR Clopax OR Clorepin OR Frisium OR Grifoclobam OR Karidium OR Lucium OR Mystan OR Noiafren OR Onfi OR Sederlona OR Sentil OR Urbadan OR Urbanil OR Urbanol OR Urbanyl):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

33. (Antelepsin OR Antilepsin OR Chlonazepam OR Cloazepam OR Clonazepam* OR Clonex OR Clonopin OR Iktorivil OR Klonopin OR Kriadex OR Landsen OR Paxam OR Petril OR Ravotril OR Rivatril OR Rivotril OR “ro 5-4023” OR “ro 54023”):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

34. (Calner OR Clorazepat* OR Justum OR Mendon OR "Novo-Clopate" OR Tranxene OR Tranxilium):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

35. (Diapam OR Diastat OR Diazemuls OR Diazepam* OR Nervium OR Relanium OR Valium):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

36. (Dimethadion* OR Dimethyloxazolidinedione):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

37. (Divalproex* OR Divalprax OR Ergenyl OR Valance OR Valcote OR Zalkote):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

38. (Eslicarbazepin* OR Exalief OR Stedesa OR Zebinix):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

39. (Esilgan OR Estazolam* OR Eurodin OR Nuctalon OR Prosom OR Tasedan):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

40. (Ethadion*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

41. (Aethosuximid* OR Emeside OR Ethosucci* OR Ethosuxide OR Ethosuximid* OR Etosuximid* OR Zarontin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

42. (Ethotoin* OR Peganone):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

43. (Felbamat* OR Felbatol OR Felbamyl OR Taloxa):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

44. (Flunarizin* OR Sibelium):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

45. (Cerebyx OR Fosphenytoin* OR Prodilantin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

46. (Gabapentin* OR Aclonium OR Fanatrex OR Gabapetin OR Gabarone OR GBP OR Gralise OR Neogab OR Neurontin OR "Novo-Gabapentin" OR Nupentin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

47. ("CCD-1042" OR Ganaxolon*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

48. (Erlosamide OR Harkoseride OR Lacosamid* OR Vimpat):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

49. (Lamotrigin* OR Elmendos OR Epilepax OR "GW 273293" OR Lamictal OR Lamictin OR Lamitor OR Lamitrin OR Lamogine OR Lamotrine OR LTG):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

50. (Levetiracetam* OR Keppra OR LEV OR Levitiracetam):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

51. (Ativan OR Intensl OR Loraz OR Lorazepam* OR Lormetazepam* OR Temesta):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

52. (Losigamon*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

53. ("Magnesium sulfat*" OR "Magnesium sulphat*"):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

54. (Medazepam* OR Nobrium OR Rudotel OR Rusedal):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

55. (Mephenytoin* OR Mesantoin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

56. (Dapaz OR Equanil OR Meprobamat* OR Meprospan OR Miltown OR Tranmep OR Visano):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

57. (Celontin OR Mesuximid* OR Methsuximide OR Petinutin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

58. (Mephobarbit* OR Mebaral OR Mephyltaletten OR Methylphenobarbit* OR Metilfenobarbital OR Phemiton OR Prominal):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

59. (Erimin OR Nimetazepam*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

60. (Alodorm OR Arem OR Insoma OR Mogadon OR Nitrados OR Nitrazadon OR Nitrazepam* OR Ormodon OR Paxadorm OR Remnos OR Somnite OR Pacisyn):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

61. (Oxcarbazepin* OR Actinium OR Barzepin OR Carbox OR Deprectal OR "GP 47680" OR Lonazet OR OCBZ OR Oxalepsy OR OXC OR Oxcarbamazepine OR Oxetol OR Oxpin OR Oxrate OR Oxtellar OR Oxypine OR Pharozepine OR Prolepsi OR Timox OR Trexapin OR Trileptal OR Trileptin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

62. (Paraldehyd*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

63. (Paramethadion*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

64. (E2007 OR Fycompa OR Perampanel*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

65. (Phenacemid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

66. (Ethylphenacemid* OR Pheneturid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

67. (Adonal OR Aephenal OR Agrypnal OR Amylofene OR Aphenylbarbit OR Aphenyletten OR Barbenyl OR Barbinal OR Barbiphen* OR Barbipil OR Barbita OR Barbivis OR Barbonal OR Barbophen OR Bardorm OR Bartol OR Bialminal OR "Blu-Phen" OR Cabronal OR Calmetten OR Calminal OR Cardenal OR Chinoin OR Codibarbita OR Coronaletta OR Cratecil OR Damoral OR Dezibarbitur OR Dormina OR Dormiral OR Dormital OR Doscalun OR Duneryl OR Ensobarb OR Ensodorm OR Epanal OR Epidorm OR Epilol OR Episedal OR Epsylone OR Eskabarb OR Etilfen OR Euneryl OR Fenbital OR Fenemal OR Fenobarbital OR Fenosed OR Fenylettae OR Gardenal OR Gardepanyl OR Glysoletten OR Haplopan OR Haplos OR Helional OR Hennoletten OR Henotal OR Hypnaletten OR Hypnette OR "Hypno-Tablinetten" OR Hypnogen OR Hypnolone OR Hypnoltol OR Hysteps OR Lefebar OR Leonal OR Lephebar OR Lepinal OR Lepinaletten OR Linasen OR Liquital OR Lixophen OR Lubergal OR Lubrokal OR Lumen OR Lumesettes OR Lumesyn OR Luminal OR Lumofridetten OR Luphenil OR Luramin OR Molinal OR Neurobarb OR Nirvonal OR Noptil OR "Nova-Pheno" OR Nunol OR Parkotal OR PB OR Pharmetten OR "Phen-Bar" OR Phenaemal OR Phenemal* OR Phenobal OR Phenobarbit* OR Phenobarbyl OR Phenoluric OR Phenolurio OR Phenomet OR Phenonyl OR Phenoturic OR Phenylethylbarbit* OR Phenylethylmalonylurea OR Phenyletten OR Phenyral OR Phob OR Polcominal OR Prominal OR Promptonal OR "Seda-Tablinen" OR Sedabar OR Sedicat OR Sedizorin OR Sedlyn OR Sedofen OR Sedonal OR Sedonettes OR Sevenal OR Sinoratox OR Solfoton OR "Solu-Barb" OR Sombutol OR Somnolens OR Somnoletten OR Somnosan OR Somonal OR Spasepilin OR Starifen OR Starilettae OR Stental OR Talpheno OR Teolaxin OR Teoloxin OR Thenobarbital OR Theoloxin OR Triabarb OR Tridezibarbitur OR Triphenatol OR Versomnal OR Zadoletten OR Zadonal):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

68. (Phensuximid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

69. (Aleviatin OR Antisacer OR Auranile OR Causoin OR Citrullamon OR Citrulliamon OR Comital OR Comitoina OR Convul OR Danten OR Dantinal OR Dantoin* OR Denyl OR "Di-Hydan" OR "Di-Lan" OR "Di-Phetine" OR Didan OR Difenilhidantoin* OR Difenin OR Difetoin OR Difhydan OR Dihycon OR Dihydantoin OR Dilabid OR Dilantin* OR Dillantin OR Dintoin* OR Diphantoin OR Diphedal OR Diphedan OR Diphenat OR Diphenin* OR Diphentoin OR Diphentyn OR Diphenylan OR Diphenylhydantoin* OR Diphenylhydatanoin OR Ditoinate OR Ekko OR Elepsindon OR Enkelfel OR Epamin OR Epanutin OR Epasmir OR Epdantoin* OR Epelin OR Epifenyl OR Epihydan OR Epilan OR Epilantin OR Epinat OR Epised OR Eptal OR Eptoin OR Fenantoin OR Fenidantoin OR Fenitoin* OR Fentoin OR Fenylepsin OR Fenytoin* OR "Gerot-epilan-D" OR Hidan OR Hidant* OR Hindatal OR Hydant* OR Ictalis OR Idantoi* OR Iphenylhydantoin OR Kessodanten OR Labopal OR Lehydan OR Lepitoin OR Lepsin OR Mesantoin OR Minetoin OR "Neos-Hidantoina" OR Neosidantoina OR Novantoina OR Novophenytoin OR "Om-hidantoina" OR "Om-Hydantoine" OR Oxylan OR Phanantin* OR Phenatine OR Phenatoine OR Phenhydan* OR Phenitoin OR Phentoin OR Phentytoin OR Phenytek OR Phenytex OR Phenytoin* OR PHT OR Ritmenal OR Saceril OR Sanepil OR Silantin OR Sinergina OR Sodanthon OR Sodanto* OR Solantin OR Solantoin OR Solantyl OR Sylantoic OR Tacosal OR Thilophenyl OR TOIN OR Zentronal OR Zentropil):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

70. (Lyrica OR Pregabalin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

71. (Mysoline OR Primidon* OR Sertan):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

72. (Gabrene OR Garene OR Halogabide OR Halogenide OR Progabid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

73. (Ecovia OR Remacemid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

74. ("D-23129" OR "D23129" OR EZG OR Ezogabin* OR Retigabin* OR RTG OR Trobalt OR Potiga):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

75. (Rilutek OR Riluzol* OR Trifluoromethoxybenzothiazol*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

76. (Inovelon OR Rufinamid* OR Xilep):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

77. (Seletracetam*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

78. (Diacomit OR Stiripentol*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

79. (Sulthiam* OR Sultiam* OR Ospolot):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

80. (Talampanel*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

81. (Tiagabin* OR Gabitril):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

82. (Tiletamin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

83. (Topiramat* OR Qudexy OR Tipiramate OR Topamax OR "Topiramic acid" OR TPM):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

84. (Tridione OR Trimethadion*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

85. (Valnoctamid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

86. (Avugane OR Baceca OR Convulex OR Delepsine OR Depacon OR Depakene OR Depakine OR Depakote OR Deproic OR DPA OR Encorate OR Epiject OR Epilex OR Epilim OR Episenta OR Epival OR Ergenyl OR Mylproin OR Orfiril OR Orlept OR Selenica OR Stavzor OR Valcote OR Valparin OR Valpro* OR VPA):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

87. (Depamide OR Valpromid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

88. (GVG OR Sabril OR Vigabatrin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

89. (Zonisamid* OR Exceglan OR Excegram OR Excegran OR ZNS OR Zonegran):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

90. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 AND CENTRAL:TARGET

91. MESH DESCRIPTOR Antipyretics EXPLODE ALL AND CENTRAL:TARGET

92. antipyretic* or antifebril* AND CENTRAL:TARGET

93. (acetaminophen or paracetamol):AB,KW,MC,MH,TI AND CENTRAL:TARGET

94. MESH DESCRIPTOR Ibuprofen EXPLODE ALL AND CENTRAL:TARGET

95. (ibuprofen OR aspirin OR dipyron*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

96. #91 OR #92 OR #93 OR #94 OR #95 AND CENTRAL:TARGET

97. #90 OR #96 AND CENTRAL:TARGET

98. #2 AND #97 AND CENTRAL:TARGET

99. #1 OR #98 AND CENTRAL:TARGET

100. #99 AND >03/10/2018:CRSCREATED AND CENTRAL:TARGET

Appendix 2. MEDLINE search strategy

This strategy includes the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2020).

1. exp Seizures, Febrile/dt, pc [Drug Therapy, Prevention & Control]

2. (febrile and (seizure$ or convulsion$)).tw.

3. exp *Epilepsy/dt [Drug Therapy]

4. exp Seizures/dt [Drug Therapy]

5. exp Anticonvulsants/

6. (antiepilep$ or anti-epilep$ or anticonvulsant$ or anti-convulsant$ or AED or AEDs).tw.

7. exp Midazolam/

8. (Dalam or Dormicum or Dormire or Epistatus or Fulsed or Garen or Hypnovel or Ipnovel or Midazolam* or Nocturna or Setam or Terap or Versed).tw.

9. exp Methazolamide/

10. (Methazolamid* or Methylacetazolamide or Neptazane).tw.

11. exp Propofol/

12. (Anepol or Diprivan or Disoprivan or Disoprofol or Fresofol or Hypro or Lipuro or Plofed or Profol or Propofil or Propofol* or Propolipid or Propovan or Propoven or Provive or Recofol).tw.

13. exp Temazepam/

14. (Dasuen or Euhypnos or Hydroxydiazepam or Levanxol or Methyloxazepam or Nocturne or Norkotral or Normison or Normitab or Nortem or Oxydiazepam or Planum or Pronervon or Remestan or Restoril or Signopam or Temaze or Temazep* or Temtabs or Tenox).tw.

15. exp Thiopental/

16. (Bomathal or Farmotal or Nesdonal or Penthiobarbit* or Pentothal or Sodipental or Thiomebumal or Thionembutal or Thiopent* or Tiobarbital or Tiopental* or Trapanal).tw.

17. (Acemit or Acetamide or Acetazolamid* or Avva or Azm or Azol or Diacarb or Diamox or Diazomid or Diluran or Edemox or Glaupax).tw.

18. Barbexaclon*.tw.

19. (Beclamid* or Chloracon or Hibicon or Posedrine or Nydrane or Seclar).tw.

20. Brivaracetam*.tw.

21. Bromide*.tw.

22. (Carbamazepin* or Carbamazepen* or Carbamezepin* or CBZ or SPD417 or "Apo-Carbamazepine" or Atretol or Biston or Calepsin or Carbagen or Carbatrol or Carbazepin* or Carbelan or Epitol or Equetro or Finlepsin or Karbamazepin or Lexin or Neurotop or "Novo-Carbamaz" or "Nu-Carbamazepine" or Sirtal or Stazepin* or "Taro-Carbamazepine" or Tegretal or Tegretol or Telesmin or Teril or Timonil).tw.

23. (Carisbamat* or Comfyde or "RWJ-333369" or "YKP 509").tw.

24. (Chlormethiazol* or Distraneurin).tw.

25. (Aedon or Anxirloc or Castilium or Chlorepin or Clarmyl or Clobam or Clobamax or Clobator or Clobazam* or Clofritis or Clopax or Clorepin or Frisium or Grifoclobam or Karidium or Lucium or Mystan or Noiafren or Onfi or Sederlona or Sentil or Urbadan or Urbanil or Urbanol or Urbanyl).tw.

26. (Antelepsin or Antilepsin or Chlonazepam or Cloazepam or Clonazepam* or Clonex or Clonopin or Iktorivil or Klonopin or Kriadex or Landsen or Paxam or Petril or Ravotril or Rivatril or Rivotril or "ro 5-4023" or "ro 54023").tw.

27. (Calner or Clorazepat* or Justum or Mendon or "Novo-Clopate" or Tranxene or Tranxilium).tw.

28. (Diapam or Diastat or Diazemuls or Diazepam* or Nervium or Relanium or Valium).tw.

29. (Dimethadion* or Dimethyloxazolidinedione).tw.

30. (Divalproex* or Divalprax or Ergenyl or Valance or Valcote or Zalkote).tw.

31. (Eslicarbazepin* or Exalief or Stedesa or Zebinix).tw.

32. (Esilgan or Estazolam* or Eurodin or Nuctalon or Prosom or Tasedan).tw.

33. Ethadion*.tw.

34. (Aethosuximid* or Emeside or Ethosucci* or Ethosuxide or Ethosuximid* or Etosuximid* or Zarontin).tw.

35. (Ethotoin* or Peganone).tw.

36. (Felbamat* or Felbatol or Felbamyl or Taloxa).tw.

37. (Flunarizin* or Sibelium).tw.

38. (Cerebyx or Fosphenytoin* or Prodilantin).tw.

39. (Gabapentin* or Aclonium or Fanatrex or Gabapetin or Gabarone or GBP or Gralise or Neogab or Neurontin or "Novo-Gabapentin" or Nupentin).tw.

40. ("CCD-1042" or Ganaxolon*).tw.

41. (Erlosamide or Harkoseride or Lacosamid* or Vimpat).tw.

42. (Lamotrigin* or Elmendos or Epilepax or "GW 273293" or Lamictal or Lamictin or Lamitor or Lamitrin or Lamogine or Lamotrine or LTG).tw.

43. (Levetiracetam* or Keppra or LEV or Levitiracetam).tw.

44. (Ativan or Intensl or Loraz or Lorazepam* or Lormetazepam* or Temesta).tw.

45. Losigamon*.tw.

46. ("Magnesium sulfat*" or "Magnesium sulphat*").tw.

47. (Medazepam* or Nobrium or Rudotel or Rusedal).tw.

48. (Mephenytoin* or Mesantoin).tw.

49. (Dapaz or Equanil or Meprobamat* or Meprospan or Miltown or Tranmep or Visano).tw.

50. (Celontin or Mesuximid* or Methsuximide or Petinutin).tw.

51. (Mephobarbit* or Mebaral or Mephyltaletten or Methylphenobarbit* or Metilfenobarbital or Phemiton or Prominal).tw.

52. (Erimin or Nimetazepam*).tw.

53. (Alodorm or Arem or Insoma or Mogadon or Nitrados or Nitrazadon or Nitrazepam* or Ormodon or Paxadorm or Remnos or Somnite or Pacisyn).tw.

54. (Oxcarbazepin* or Actinium or Barzepin or Carbox or Deprectal or "GP 47680" or Lonazet or OCBZ or Oxalepsy or OXC or Oxcarbamazepine or Oxetol or Oxpin or Oxrate or Oxtellar or Oxypine or Pharozepine or Prolepsi or Timox or Trexapin or Trileptal or Trileptin).tw.

55. Paraldehyd*.tw.

56. Paramethadion*.tw.

57. (E2007 or Fycompa or Perampanel*).tw.

58. Phenacemid*.tw.

59. (Ethylphenacemid* or Pheneturid*).tw.

60. (Adonal or Aephenal or Agrypnal or Amylofene or Aphenylbarbit or Aphenyletten or Barbenyl or Barbinal or Barbiphen* or Barbipil or Barbita or Barbivis or Barbonal or Barbophen or Bardorm or Bartol or Bialminal or "Blu-Phen" or Cabronal or Calmetten or Calminal or Cardenal or Chinoin or Codibarbita or Coronaletta or Cratecil or Damoral or Dezibarbitur or Dormina or Dormiral or Dormital or Doscalun or Duneryl or Ensobarb or Ensodorm or Epanal or Epidorm or Epilol or Episedal or Epsylone or Eskabarb or Etilfen or Euneryl or Fenbital or Fenemal or Fenobarbital or Fenosed or Fenylettae or Gardenal or Gardepanyl or Glysoletten or Haplopan or Haplos or Helional or

Hennoletten or Henotal or Hypnaletten or Hypnette or "Hypno-Tablinetten" or Hypnogen or Hypnolone or Hypnoltol or Hysteps or Lefebar or Leonal or Lephebar or Lepinal or Lepinaletten or Linasen or Liquital or Lixophen or Lubergal or Lubrokal or Lumen or Lumesettes or Lumesyn or Luminal or Lumofridetten or Luphenil or Luramin or Molinal or Neurobarb or Nirvonal or Noptil or "Nova-Pheno" or Nunol or Parkotal or PB or Pharmetten or "Phen-Bar" or Phenaemal or Phenemal* or Phenobal or Phenobarbit* or Phenobarbyl or Phenoluric or Phenolurio or Phenomet or Phenonyl or Phenoturic or Phenylethylbarbit* or Phenylethylmalonylurea or Phenyletten or Phenyral or Phob or Polcominal or Prominal or Promptonal or "Seda-Tablinen" or Sedabar or Sedicat or Sedizorin or Sedlyn or Sedofen or Sedonal or Sedonettes or Sevenal or Sinoratox or Solfoton or "Solu-Barb" or Sombutol or Somnolens or Somnoletten or Somnosan or Somonal or Spasepilin or Starifen or Starilettae or Stental or Talpheno or Teolaxin or Teoloxin or Thenobarbital or Theoloxin or Triabarb or Tridezibarbitur or Triphenatol or Versomnal or Zadoletten or Zadonal).tw.

61. Phensuximid*.tw.

62. (Aleviatin or Antisacer or Auranile or Causoin or Citrullamon or Citrulliamon or Comital or Comitoina or Convul or Danten or Dantinal or Dantoin* or Denyl or "Di-Hydan" or "Di-Lan" or "Di-Phetine" or Didan or Difenilhidantoin* or Difenin or Difetoin or Difhydan or Dihycon or Dihydantoin or Dilabid or Dilantin* or Dillantin or Dintoin* or Diphantoin or Diphedal or Diphedan or Diphenat or Diphenin* or Diphentoin or Diphentyn or Diphenylan or Diphenylhydantoin* or Diphenylhydatanoin or Ditoinate or Ekko or Elepsindon or Enkelfel or Epamin or Epanutin or Epasmir or Epdantoin* or Epelin or Epifenyl or Epihydan or Epilan or Epilantin or Epinat or Epised or Eptal or Eptoin or Fenantoin or Fenidantoin or Fenitoin* or Fentoin or Fenylepsin or Fenytoin* or "Gerot-epilan-D" or Hidan or Hidant* or Hindatal or Hydant* or Ictalis or Idantoi* or Iphenylhydantoin or Kessodanten or Labopal or Lehydan or Lepitoin or Lepsin or Mesantoin or Minetoin or "Neos-Hidantoina" or Neosidantoina or Novantoina or Novophenytoin or "Om-hidantoina" or "Om-Hydantoine" or Oxylan or Phanantin* or Phenatine or Phenatoine or Phenhydan* or Phenitoin or Phentoin or Phentytoin or Phenytek or Phenytex or Phenytoin* or PHT or Ritmenal or Saceril or Sanepil or Silantin or Sinergina or Sodanthon or Sodanto* or Solantin or Solantoin or Solantyl or Sylantoic or Tacosal or Thilophenyl or TOIN or Zentronal or Zentropil).tw.

63. (Lyrica or Pregabalin*).tw.

64. (Mysoline or Primidon* or Sertan).tw.

65. (Gabrene or Garene or Halogabide or Halogenide or Progabid*).tw.

66. (Ecovia or Remacemid*).tw.

67. ("D-23129" or "D23129" or EZG or Ezogabin* or Retigabin* or RTG or Trobalt or Potiga).tw.

68. (Rilutek or Riluzol* or Trifluoromethoxybenzothiazol*).tw.

69. (Inovelon or Rufinamid* or Xilep).tw.

70. Seletracetam*.tw.

71. (Diacomit or Stiripentol*).tw.

72. (Sulthiam* or Sultiam* or Ospolot).tw.

73. Talampanel*.tw.

74. (Tiagabin* or Gabitril).tw.

75. Tiletamin*.tw.

76. (Topiramat* or Qudexy or Tipiramate or Topamax or "Topiramic acid" or TPM).tw.

77. (Tridione or Trimethadion*).tw.

78. Valnoctamid*.tw.

79. (Avugane or Baceca or Convulex or Delepsine or Depacon or Depakene or Depakine or Depakote or Deproic or DPA or Encorate or Epiject or Epilex or Epilim or Episenta or Epival or Ergenyl or Mylproin or Orfiril or Orlept or Selenica or Stavzor or Valcote or Valparin or Valpro* or VPA).tw.

80. (Depamide or Valpromid*).tw.

81. (GVG or Sabril or Vigabatrin*).tw.

82. (Zonisamid* or Exceglan or Excegram or Excegran or ZNS or Zonegran).tw.

83. or/3-82

84. exp Antipyretics/

85. (antipyretic$ or antifebril$).tw.

86. (acetaminophen or paracetamol).tw.

87. exp Ibuprofen/ or ibuprofen.tw.

88. (aspirin or dipyron$).tw.

89. 84 or 85 or 86 or 87 or 88

90. 83 or 89

91. 2 and 90

92. 1 or 91

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

94. clinical trials as topic.sh.

95. trial.ti.

96. 93 or 94 or 95

97. exp animals/ not humans.sh.

98. 96 not 97

99. 92 and 98

100. limit 99 to ed=20181002-20200203

101. 99 not (1$ or 2$).ed.

102. 101 and (2018$ or 2019$ or 2020$).dt.

103. 100 or 102

104. remove duplicates from 103

WHAT'S NEW

Date	Event	Description
3 February 2020	New citation required but conclusions have not changed	Conclusions are unchanged.
3 February 2020	New search has been performed	Searches updated 3 February 2020; two new studies identified and included.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 4, 2012

Date	Event	Description
21 July 2016	New citation required but conclusions have not changed	Conclusions are unchanged.
21 July 2016	New search has been performed	Searches updated 21 July 2016; four new studies were identified and added as included studies in the review.

CONTRIBUTIONS OF AUTHORS

Martin Offringa is the guarantor for this review. Martin Offringa and Richard Newton were involved at all stages of the review, from conception to completion. Martinus Cozijnsen had joined for the 2016 update and asked to be removed for the 2020 update, as he has left academia. For the current update, Katerina Vraka joined the review author team and completed the search update. All review authors independently assessed trials for inclusion, appraised papers, and extracted data. In the case where a review author was an investigator on an identified study, that review author did not take part in the study selection, data extraction, risk of bias assessment stages for that study. All review authors jointly prepared the review. Sarah Nevitt provided support with the creation of the 'Summary of findings' tables.

DECLARATIONS OF INTEREST

Martin Offringa: none known.

Richard Newton was one of the investigators of the included study (McKinlay 1989). He did not take part in the study selection, data extraction and risk of bias assessment stages for that study.

Sarah Nevitt: none known.

Katerina Vraka: none known.

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Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (NIHR), UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In a post hoc change from the protocol, in line with current Cochrane recommendations we have reported 15 'Summary of findings' tables, one for each comparison in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Antipyretics [adverse effects] [*therapeutic use]; Confidence Intervals; Placebos [therapeutic use]; Publication Bias; Randomized Controlled Trials as Topic; Recurrence; Seizures, Febrile [*prevention & control]

MeSH check words

Child; Child, Preschool; Humans; Infant