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Prophylactic drug management for febrile seizures in children (Review)

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TABLE OF CONTENTS

[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% to 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.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2016, Issue 7); MEDLINE (1966 to July 2016); Embase (1966 to July 2016); Database of Abstracts of Reviews of Effectiveness (DARE) (July 2016). We imposed no language restrictions. We also contacted researchers in the field to identify continuing or unpublished studies.

Selection criteria

Trials using randomised or quasi-randomised participant allocation that compared the use of antiepileptic, antipyretic or other plausible agents with each other, placebo or no treatment.

Data collection and analysis

Two review authors (RN and MO) 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 author (MC) checked all original inclusions, data analyses, and updated the search. Outcomes assessed were seizure recurrence at 6, 12, 18, 24, 36, and 48 months and at age 5 to 6 years in the intervention and non-intervention groups, and adverse medication effects. We assessed the presence of publication bias using funnel plots.

Main results

We included 40 articles describing 30 randomised trials with 4256 randomised participants. We analysed 13 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 phenobarbitone, phenytoin, valproate, pyridoxine, ibuprofen or zinc sulfate versus placebo or no treatment; nor for diclofenac versus placebo followed by ibuprofen, acetaminophen or placebo; nor for continuous phenobarbitone 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, with a risk ratio (RR) of 0.64 (95% confidence interval (CI) 0.48 to 0.85 at six months), RR of 0.69 (95% CI 0.56 to 0.84) at 12 months, RR 0.37 (95% CI 0.23 to 0.60) at 18 months, RR 0.73 (95% CI 0.56 to 0.95) at 24 months, RR 0.58 (95% CI 0.40 to 0.85) at 36 months, RR 0.36 (95% CI 0.15 to 0.89) at 48 months, with no benefit at 60 to 72 months. Phenobarbitone versus placebo or no treatment reduced seizures at 6, 12 and 24 months but not at 18 or 72 month follow-up (RR 0.59 (95% CI 0.42 to 0.83) at 6 months; RR 0.54 (95% CI 0.42 to 0.70) at 12 months; and RR 0.69 (95% CI 0.53 to 0.89) at 24 months). Intermittent clobazam compared to placebo at six months resulted in a RR of 0.36 (95% CI 0.20 to 0.64), an effect found against an extremely high (83.3%) recurrence rate in the controls, which is a result that needs replication.

The recording of adverse effects was variable. Lower comprehension scores in phenobarbitone-treated children were found in two studies. In general, adverse effects were recorded in up to 30% of children in the phenobarbitone-treated group and in up to 36% in benzodiazepine-treated groups. We found evidence of publication bias in the meta-analyses of comparisons for phenobarbitone versus placebo (eight studies) at 12 months but not at six months (six studies); and valproate versus placebo (four studies) at 12 months, with too few studies to identify publication bias for the other comparisons.

Most of the reviewed antiepileptic drug trials are of a methodological quality graded as low or very low. 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 risks of bias. Trials of antipyretics and zinc were of higher quality.

Authors' conclusions

We found reduced recurrence rates for children with febrile seizures for intermittent diazepam and continuous phenobarbitone, with adverse effects in up to 30%. Apparent benefit for clobazam treatment in one trial needs to be replicated to be judged reliable. 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 in children are common and affect about one in thirty 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 on children with febrile seizures.

Objective

We wanted to know in how many children these drugs would prevent a recurrence or bring unwanted effects.

Methods

We included 30 studies with a total of 4256 children in the review. Children who had had at least one febrile seizure were put into groups who either had the study treatment or not. The studies recorded any further seizures at various time intervals between 6 months and up to 6 years of age in each group. Unwanted medication effects were also noted.

Results

The quality of study design and evidence provided by these studies was often low or very low for the antiepileptic drugs. Poor methods known to lead to obvious risks of bias were used. This was to do with the way children were put in each group and how random this allocation was. Other issues included whether the parents and/or doctors knew which group each child was in or perhaps if the study was of treatment compared to no treatment. The quality of trials of antipyretics or zinc was better, with the evidence graded moderate to high.

Zinc therapy gave no benefit. Nor was there benefit in treating children just at the time of the fever with either antipyretic drugs or most antiepileptic drugs.

At times a significant result was noted. In statistics this means there was a less than 1 in 20 chance of this happening by chance. 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 phenobarbitone resulted in significantly fewer recurrences at 6, 12 and 24 months, but not at 18 and 60 to 72 months

However, as recurrent seizures are only seen in about a third of children anyway 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 (in the statistical sense) to be unimportant. This is particularly so as adverse effects of the medications were common. Lower comprehension scores in phenobarbitone-treated children were found in two studies. In general, adverse effects were recorded in up to about a third of

children in both the phenobarbitone and benzodiazepine-treated groups. The benefit found for treatment with clobazam in one study published in 2011 needs to be repeated to show that this finding is reliable.

Author's conclusions

Neither continuous nor intermittent treatment with zinc, antiepileptic or antipyretic drugs can be recommended 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 21 July 2016.

Summary of findings for the main comparison. 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)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with Intermittent oral or rectal diazepam				
Recurrent seizure at 6 months	179 per 1,000	115 per 1,000 (86 to 152)	RR 0.64 (0.48 to 0.85)	1151 (6 RCTs)	⊕⊕⊕⊖ **Moderate[1]**	
Recurrent seizure at 12 months	254 per 1,000	175 per 1,000 (142 to 213)	RR 0.69 (0.56 to 0.84)	1416 (8 RCTs)	⊕⊕⊕⊖ **Moderate[1]**	
Recurrent seizure at 18 months	336 per 1,000	124 per 1,000 (77 to 201)	RR 0.37 (0.23 to 0.60)	289 (1 RCT)	⊕⊕⊖⊖ **Low[2]**	
Recurrent seizure at 24 months	273 per 1,000	200 per 1,000 (153 to 260)	RR 0.73 (0.56 to 0.95)	739 (4 RCTs)	⊕⊕⊕⊕ **High**	
Recurrent seizure at 36 months	606 per 1,000	351 per 1,000 (242 to 515)	RR 0.58 (0.40 to 0.85)	139 (1 RCT)	⊕⊕⊖⊖ **Low[2]**	
Recurrent seizure at 48 months	308 per 1,000	111 per 1,000 (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 1,000	16 per 1,000 (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; **RR:** Risk ratio;

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

[1]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 conf idence interval.

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

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

Patient or population: Children with febrile seizures
Setting: Outpatients
Intervention: Continuous phenobarbitone
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with Continuous phenobarbitone				
Recurrent seizure at 6 months	178 per 1,000	105 per 1,000 (75 to 148)	RR 0.59 (0.42 to 0.83)	833 (6 RCTs)	⊕⊕⊕⊖ **Moderate[1]**	
Recurrent seizure at 12 months	308 per 1,000	166 per 1,000 (129 to 216)	RR 0.54 (0.42 to 0.70)	807 (7 RCTs)	⊕⊕⊖⊖ **Low[1,2]**	
Recurrent seizure at 18 months	430 per 1,000	331 per 1,000 (241 to 451)	RR 0.77 (0.56 to 1.05)	264 (2 RCTs)	⊕⊕⊕⊖ **Moderate[1]**	
Recurrent seizure at 24 months	345 per 1,000	238 per 1,000 (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 1,000	300 per 1,000 (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; **RR:** Risk ratio;

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

[1]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 conf idence interval.

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

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

Patient or population: Children with febrile seizures
Setting: Outpatients
Intervention: Intermittent phenobarbitone
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with Intermittent phenobarbitone				
Recurrent seizure at 6 months	88 per 1,000	121 per 1,000 (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 1,000	218 per 1,000 (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 1,000	250 per 1,000 (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 1,000	166 per 1,000 (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; **RR:** Risk ratio;

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

[1]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 conf idence 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)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Continuous oral phenytoin				
Recurrent seizure at 6 months	Not reported				NA	
Recurrent seizure at 12 months	349 per 1,000	342 per 1,000 (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; **RR:** Risk ratio;

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

[1]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)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with Continuous oral valproate				
Recurrent seizure at 6 months	118 per 1,000	141 per 1,000 (65 to 308)	RR 1.20 (0.55 to 2.62)	156 (2 RCTs)	⊕⊕⊝⊝ **Low[1]**	
Recurrent seizure at 12 months	239 per 1,000	196 per 1,000 (124 to 308)	RR 0.82 (0.52 to 1.29)	255 (4 RCTs)	⊕⊕⊝⊝ **Low[1]**	
Recurrent seizure at 18 months	346 per 1,000	45 per 1,000 (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 1,000	267 per 1,000 (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; **RR:** Risk ratio;

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

[1]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 conf idence 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)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Continuous oral pyridoxine				
Recurrent seizure at 6 months	154 per 1,000	72 per 1,000 (23 to 228)	RR 0.47 (0.15 to 1.48)	107 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]	
Recurrent seizure at 12 months	192 per 1,000	127 per 1,000 (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; **RR:** Risk ratio;

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

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

[1]Downgraded once due to risk of bias: risk of attrition bias.
[2]Downgraded once due to imprecision: relative effect has very large conf idence 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)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Intermittent oral ibuprofen				
Recurrent seizure at 6 months	210 per 1,000	233 per 1,000 (145 to 380)	RR 1.11 (0.69 to 1.81)	230 (1 RCT)	⊕⊕⊕⊕ **High**	
Recurrent seizure at 12 months	294 per 1,000	279 per 1,000 (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 1,000	325 per 1,000 (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; **RR:** Risk ratio;

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

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)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Intermittent oral clobazam				
Recurrent seizure at 6 months	833 per 1,000	300 per 1,000 (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; **RR:** Risk ratio;

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

[1]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)	Quality of the evidence (GRADE)	Comments
	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 1,000	220 per 1,000 (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; **RR:** Risk ratio;

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

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

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

Patient or population: Children with febrile seizures
Setting: Outpatients
Intervention: Intermittent rectal diclofenac
Comparison: placebo followed after 8 hours by oral ibuprofen, acetaminophen or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo followed after 8 hours by oral ibuprofen, acetaminophen or placebo	Risk with Intermittent rectal diclofenac				

Recurrent seizure at 6 months	149 per 1,000	119 per 1,000 (63 to 231)	RR 0.80 (0.42 to 1.55)	231 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 12 months	237 per 1,000	163 per 1,000 (95 to 275)	RR 0.69 (0.40 to 1.16)	231 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 18 months	272 per 1,000	196 per 1,000 (122 to 315)	RR 0.72 (0.45 to 1.16)	231 (1 RCT)	⊕⊕⊕⊕ **High**
Recurrent seizure at 24 months	281 per 1,000	222 per 1,000 (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; **RR:** Risk ratio;

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

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

Continuous phenobarbitone compared to intermittent rectal/oral diazepam for febrile seizures in children

Patient or population: Children with febrile seizures
Setting: Outpatients
Intervention: Continuous phenobarbitone
Comparison: intermittent rectal/oral diazepam

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with intermittent rectal/oral diazepam	Risk with Continuous phenobarbitone				
Recurrent seizure at 6 months	Not reported				NA	
Recurrent seizure at 12 months	155 per 1,000	229 per 1,000 (116 to 455)	RR 1.48 (0.75 to 2.94)	145 (1 RCT)	⊕⊕⊖⊖ **Low[1]**	
Recurrent seizure at 18 months	80 per 1,000	100 per 1,000 (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; **RR:** Risk ratio;

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

[1]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 conf idence 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)	Quality of the evidence (GRADE)	Comments
	Risk with intermittent rectal valproate	Risk with Intermittent rectal diazepam				
Recurrent seizure at 6 months	88 per 1,000	123 per 1,000 (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 1,000	259 per 1,000 (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; **RR:** Risk ratio;

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

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

[1]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 conf idence interval.

Summary of findings 13. Intermittent oral diazepam compared to 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)	Quality of the evidence (GRADE)	Comments
	Risk with oral clobazam	Risk with Intermittent oral diazepam				
Recurrent seizure at 6 months	Not reported				NA	
Recurrent seizure at 12 months	42 per 1,000	96 per 1,000 (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; **RR:** Risk ratio;

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

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

BACKGROUND

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 US 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 (that is, 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, and about 30% - 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 *SCN1A* and *SCN1B* (both sodium channel genes important for neurotransmission) and *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 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. Thus, the decision to treat 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 the 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 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 phenobarbitone and valproate for the prophylactic treatment of febrile seizures by summarising the results from all eight British placebo-controlled clinical trials that were done before 1988. Data were pooled and analysed on an intention-to-treat basis. The overall odds ratio of recurrent febrile seizures for phenobarbitone was 0.8 and for valproate 1.42; neither result was statistically significant. The author therefore concluded that neither treatment is to be recommended. A second meta-analysis summarised four published non-British randomised, placebo-controlled trials that had been done 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 (NNT) 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 demonstrated 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 whether prophylactic treatment with an antiepileptic drug or an antipyretic can, as 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 was 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 or antipyretic agents with each other or with placebo or with 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 drug or an 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 if they 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, phenobarbitone, valproate, diclofenac, acetaminophen 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

Efficacy - 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 at age five 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 a useful insight into the natural history of the disorder.

Search methods for identification of studies

Electronic searches

We searched the following databases. We imposed no language restrictions.

a) Cochrane Epilepsy Group Specialised Register (21 July 2016).

b) Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 21 July 2016).

c) MEDLINE (Ovid) (1950 to 21 July 2016).

d) Embase (1966 to 21 July 2016).

Details of the search strategies used are outlined in Appendix 1.

Searching other resources

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

Data collection and analysis

Selection of studies

Two review authors (RN and MO) independently assessed trials for inclusion, resolving any disagreements by discussion. For the 2016 update, a third review author (MC) checked all original inclusions.

Data extraction and management

Two review authors (RN and MO) extracted the outcome data specified above as well as the following data, resolving any disagreements by discussion. For the 2016 update a third review author (MC) checked all data extracted.

Methodological and trial design:
a. method of randomisation;
b. method of double blinding;
c. whether any participants had been excluded from the reported analyses.
Where data were missing, we tried to contact original authors for this information.

Participant and demographic information:
a. total number of participants allocated to each treatment group or audited in any protocol;
b. the proportion of participants in each treatment group with a recurrence at certain time points (6 months, 12 months, 24 months, 36 months, 48 months and 72 months, where these data were available);
c. 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

Review author MC made an initial assessment of all included studies for risk of bias using the Cochrane 'Risk of bias' tool for RCTs (Higgins 2011). This was compared to an independent assessment by either 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 and expressed them 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 numbers needed to treat (NNTs) as the reciprocal of the absolute risk reduction (McQuay 1998).

Unit of analysis issues

We did not have any unit of analysis issues. Medication dosages were standard. Outcome measures were simply seizure recurrence. No studies were of a repeated measure (longitudinal) nature or of 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 this with quoted cumulative incidence rates for in-study data. We cross-checked trial details against any additional published report of the trial and contacted original trial authors if we found missing data, errors or inconsistencies (although the response was uniformly poor). No author provided individual patient data (IPD) when requested but we are satisfied with the consistency checks we performed.

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 (greater than 50% indicating 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 group to which they were 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-effects model, regardless of the presence of heterogeneity. If we had concerns regarding variability of study design and whether pooling data was appropriate, meta-analysis would not have been conducted.

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 felt 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 Quality of the Evidence (GRADE)

In a post hoc change from protocol, we present 13 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8; Summary of findings 9; Summary of findings 10; Summary of findings 11; Summary of findings 12; Summary of findings 13); one for each comparison of the review.

The primary outcome of efficacy (recurrence of febrile or non-febrile seizures) was reported in all tables at the following time points: 6 months, 12 months, 18 months, 24 months, 36 months, 48 months, 60 or more months.

We determined the quality of the evidence by using the GRADE approach, where evidence was downgraded in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. Evidence is downgraded once if the limitation is considered to be serious and twice if very serious.

RESULTS

Description of studies

Results of the search

Among 86 articles identified as potentially relevant, 40 articles met the criteria for this review (*see* Characteristics of included studies). Together, these 40 articles describe 30 randomised trials and their (long-term) follow-up. The details of the other 46 studies are given in 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 phenobarbitone in 10 studies (Bacon 1981; Camfield 1980; Farwell 1990; Heckmatt 1976; Mamelle 1984; McKinlay 1989; Ngwane 1980; Ramakrishnan 1986; Thilothammal 1993; Wolf 1977), intermittent phenobarbitone in three studies (Mackintosh 1970; Ramakrishnan 1986; Wolf 1977), continuous oral phenytoin in one study (Bacon 1981), continuous oral valproate in five studies (McKinlay 1989; Mamelle 1984; 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); and intermittent rectal diclofenac ver-

sus placebo followed after eight hours by either ibuprofen or acetaminophen or placebo in one study (Strengell 2009). Other studies compared interventions against each other: continuous phenobarbitone and intermittent diazepam in two studies (Garcia 1984; Salehiomran 2016); intermittent rectal diazepam and intermittent rectal valproate in one study (Daugbjerg 1990); and a comparison between intermittent oral diazepam and intermittent oral clobazam in two studies (Ghazavi 2016; Khosroshahi 2011).

These studies enrolled 4361 participants with febrile seizures among whom 4256 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 phenobarbitone 1075 (494); intermittent phenobarbitone 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 after eight hours by ibuprofen, acetaminophen or placebo 231 (231); continuous phenobarbitone versus diazepam 245; diazepam versus valproate 169; diazepam versus clobazam 143. It should be noted that a number of these papers included a comparison of outcomes in placebo versus one of two randomised seizure treatments (that is 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, we did not introduce unit-of-analysis errors. Families withdrew from these studies for various reasons, including change of residence, withdrawal of consent, and a variety of unacceptable adverse effects detailed in so far as was possible in the additional table 'Unwanted medication effects' (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 (Ramakrishnan 1986) at 60 to 72 months.

A brief description of the 30 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. There were three arms to this study. Children were allocated either to treatment with continuous oral phenytoin 8 mg/kg/day, continuous phenobarbitone 5 mg/kg/day, or placebo and 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. 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 phenobarbitone 4 to 5 mg/kg/day or 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 phenobarbitone in toddlers, including behavioural and cognitive aspects, during the 12 months of treatment using the same cohort.
5. 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 of more). They were followed for assessment of recurrent seizures at six and 12 months after randomisation and adverse medication effects during 12 months of treatment.
6. Fallah 2015 was a randomised single-blind clinical study comparing zinc sulfate with placebo. One hundred children, aged 1½ to 5 years, with a first simple febrile seizure, with weight and height above the third percentile and with normal serum zinc levels, were randomised to either daily zinc sulfate 2 mg/kg (maximum 50 mg) for six consecutive months or to placebo. Authors assessed seizure recurrence at 12 months and unwanted effects.
7. Farwell 1990 was a study of 217 children following a first febrile seizure and who had at least one risk factor for recurrence. They were allocated either to treatment with continuous phenobarbitone 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.
8. 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 phenobarbitone (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 these 18 months of treatment.
9. 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. They were treated with either oral diazepam 0.33 mg/kg every eight hours for two days or oral clobazam for two days dosed by participant'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, and twice daily 10 mg when > 15 kg). In a follow-up period of 12 months, authors assessed seizure recurrence and adverse effects.
10. Heckmatt 1976 was a study of 165 children with a mean age of 20 months following a first febrile seizure. They were allocated either to treatment with continuous phenobarbitone 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.
11. Khosroshahi 2011 studied 80 children aged six months to five years who had had one or more simple febrile seizures. They 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 six 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 these 12 months of treatment.

12. Knudsen 1985 reported on a single study of 289 children following their first febrile seizure, 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. They were followed for assessment of recurrent seizures at 6, 12, and 18 months after randomisation and adverse medication effects during 18 months of treatment.
13. Mackintosh 1970 was a study of 32 children aged six to 16 months who had had a first febrile seizure. They were allocated either to intermittent phenobarbitone 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.
14. 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). These were allocated either to treatment with continuous phenobarbitone 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.
15. 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 doses of 20 mg) or placebo. They 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.
16. 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. There were three arms to this study. Children were allocated either to treatment with continuous phenobarbitone 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.
17. Mosquera 1987 studied 69 children following a first febrile seizure and allocated to intermittent rectal diazepam 0.5 mg/kg/dose, 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.
18. Ngwane 1980 was a study of 64 children aged six to 18 months following a first febrile seizure. There were three arms to this study with allocation either to phenobarbitone 3 to 6 mg/kg/day or valproate 30 to 60 mg/kg/day. Patients that were eligible but not included were consider 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.
19. Pavlidou 2006 studied 139 children aged six to 36 months that were randomly assigned in a prospective controlled trial to receive either intermittent prophylaxis with rectal diazepam or no prophylaxis. The children were followed for assessment of recurrent seizures at 6, 12, and 36 months after randomisation and adverse medication effects during 36 months of treatment.
20. Ramakrishnan 1986 studied 120 children aged two to 72 months following a first febrile seizure. These children were allocated to continuous phenobarbitone 3 to 5 mg/kg/day, intermittent phenobarbitone in the same dosage, intermittent oral diazepam 0.6 mg/kg/day or no treatment. They were followed for assessment of recurrent seizures at 60 to 72 months after randomisation and adverse medication effects during the period of treatment.
21. 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 24 months of treatment. We used estimates from the reported Kaplan Meier curves to assess recurrent seizures at 6, 12, and 24 months.
22. 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. Included participants were either treated with continuous phenobarbitone 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 was assessed at 12 months, as were adverse effects.
23. 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 acetaminophen 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.
24. Taghdiri 2011 studied 80 children, aged nine months to five years after their first febrile seizure, and treated them with either rectal diazepam (0.5 mg/kg) combined with acetaminophen or acetaminophen only. Children were followed for 12 months for assessment of recurrence.
25. Thilothammal 1993 studied 60 children aged six to 72 months following a first febrile seizure and allocated either to treatment with continuous phenobarbitone 5 mg/kg/day or placebo. An additional 30 children with an atypical seizure were not randomised but treated with phenobarbitone (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.
26. Uhari 1995 studied 180 children following a first febrile seizure and 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. They 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.
27. Van Stuijvenberg 1998 studied 230 children aged 12 to 48 months who had a febrile seizure and at least one risk factor for recurrence. Children were allocated either to intermittent oral Ibuprofen 5 mg/kg/day or placebo and followed for assessment

of recurrent seizures during 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; adverse medication effects were not addressed.

28. 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. They 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.
29. Williams 1979 studied 58 children aged six to 72 months after two or more simple febrile seizures. Children in the active treatment group were allocated to continuous oral valproate 40 mg/kg/day and were compared with children on no treatment. They were followed for assessment of recurrent seizures and adverse medication effects at 12 months after randomisation.
30. Wolf 1977 was a study of 355 children aged six to 48 months who had had a first febrile seizure. There were three arms to this study. Children were allocated either to continuous phenobarbitone 3 to 4 mg/kg/day, intermittent phenobarbitone 5 mg/kg/day or no treatment. They were followed for assessment of recurrent seizures for a median of 28 months after randomisation and adverse medication effects during 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 RCTs. Some trials confined the analysis to participants completing the trial period free of unwanted effects, in which case we had no access to the outcome of those who stopped treatment early when they could not tolerate it. As we felt that the lack of intention-to-treat data introduced an important potential for bias, we excluded these trials. One trial of antipyretics did not address the central issue of febrile seizure recurrence but researched the question of effect on temperature, and was also excluded.

Risk of bias in included studies

Allocation

Satisfactory allocation concealment was noted in 10 of the 30 included studies (Autret 1990; Fallah 2015; Farwell 1990; Mackintosh 1970; McKiernan 1981; Rosman 1993; Strengell 2009; Uhari 1995; Van Stuijvenberg 1998; Verrotti 2004); no concealment was attempted in 13 of the 30 included studies (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), which used a method of quasi-randomisation. In the remainder of the studies the method of allocation concealment, if any, was unclear.

Blinding

Eleven studies were double-blinded (Autret 1990; Bajaj 2005; 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 there was no blinding in 17 studies (Bacon 1981; Daugbjerg 1990; Garcia 1984; Ghazavi 2016; Heckmatt 1976; 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 studies the data analysis did not include all enrolled participants as follows: Autret 1990: nine of 185 included children were lost in the analyses - six on diazepam, three on placebo; Bacon 1981: 69 of 270 enrolled participants lost - unsure of group allocation but study groups similar in size - i.e. 48 on phenobarbitone, 47 on phenytoin and 43 on placebo with no recurrences in any to the time of withdrawal; Camfield 1980: two of 79 lost - one on phenobarbitone, one on placebo; Daugbjerg 1990: two withdrawn and four in each group lost to follow-up; Farwell 1990: 26 of 217 lost - 10 on phenobarbitone and 16 on placebo; Heckmatt 1976: four of 165 lost - two on phenobarbitone, two on no treatment; Khosroshahi 2011: eight of 80 lost – five on clobazam and three on diazepam; Knudsen 1985: 16 of 289 lost - five on diazepam and 11 on no treatment; Mamelle 1984: four of 69 lost - one on valproate, two on phenobarbitone and one on placebo; Mosquera 1987: four of 69 lost - all four on placebo. It must be noted that most of the included studies were undertaken 20 to 30 years ago, since when the rigour of conducting and reporting RCTs has improved. We attempted to contact study authors to obtain IPD, but without success.

Selective reporting

Protocols were not available for any of the included trials. We made a judgement of the risk of bias based on the information included in the publications (see Characteristics of included studies and 'Summary of findings' tables for more information).

Other potential sources of bias

Study population sizes varied from 32 to 406. These were associated with numbers in one treatment arm ranging from 16 (Mackintosh 1970) up to 204 (Rosman 1993). The smaller studies were prone to distortion of treatment effect because of the small numbers of participants.

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). For these analyses, we assessed publication bias with funnel plots. We did not find evidence of publication bias for Analysis 1.1, Analysis 1.2 and Analysis 2.1 (Figure 1, Figure 2 and Figure 3), but we did find evidence of publication bias for Analysis 2.2 (asymmetry indicated in Figure 4). There were too few studies to comment on whether there was publication bias for the other comparisons.

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

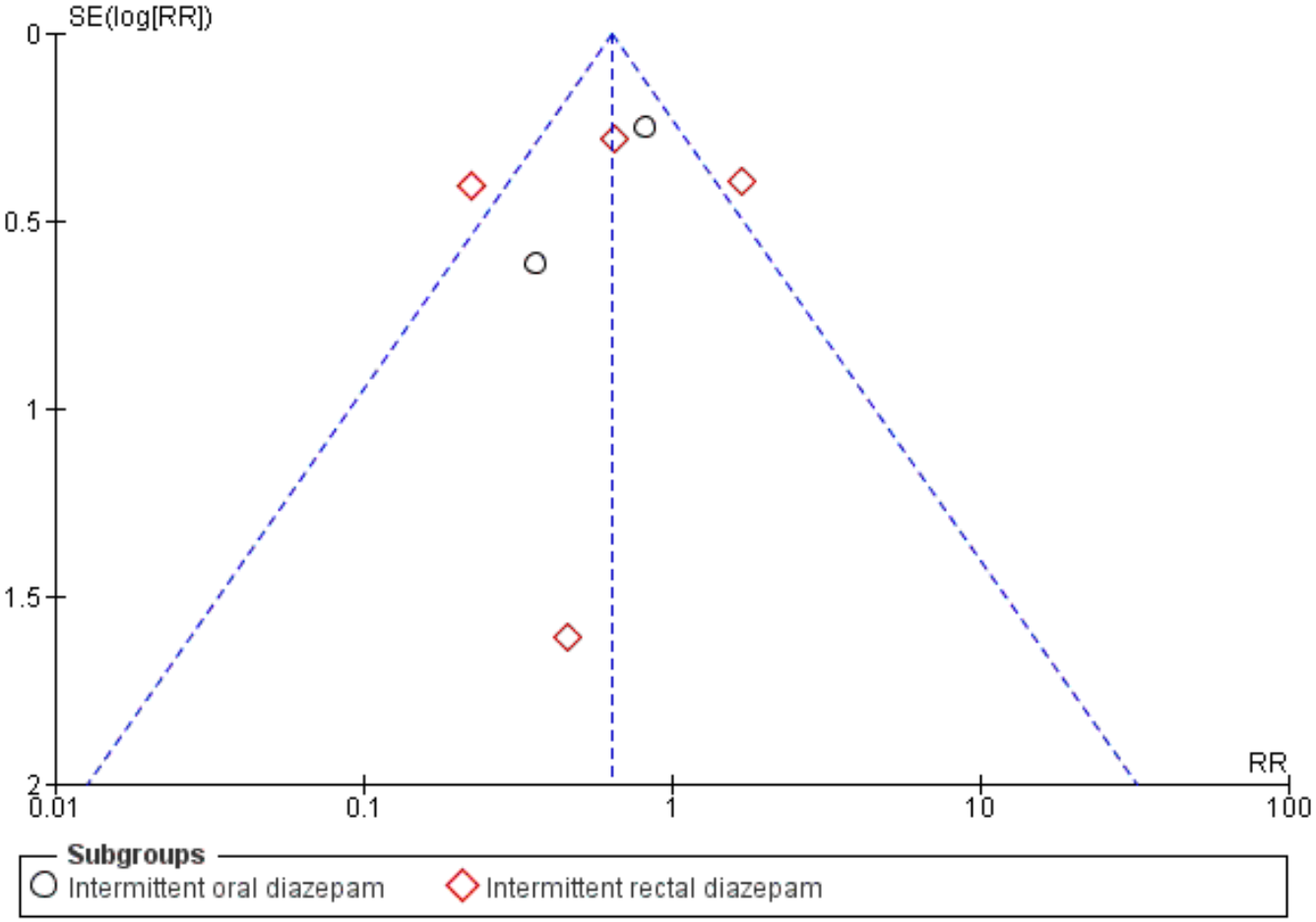


Figure 2. Funnel plot of comparison: 1 Intermittent oral or rectal diazepam versus placebo or no treatment at recurrence at 12 months.

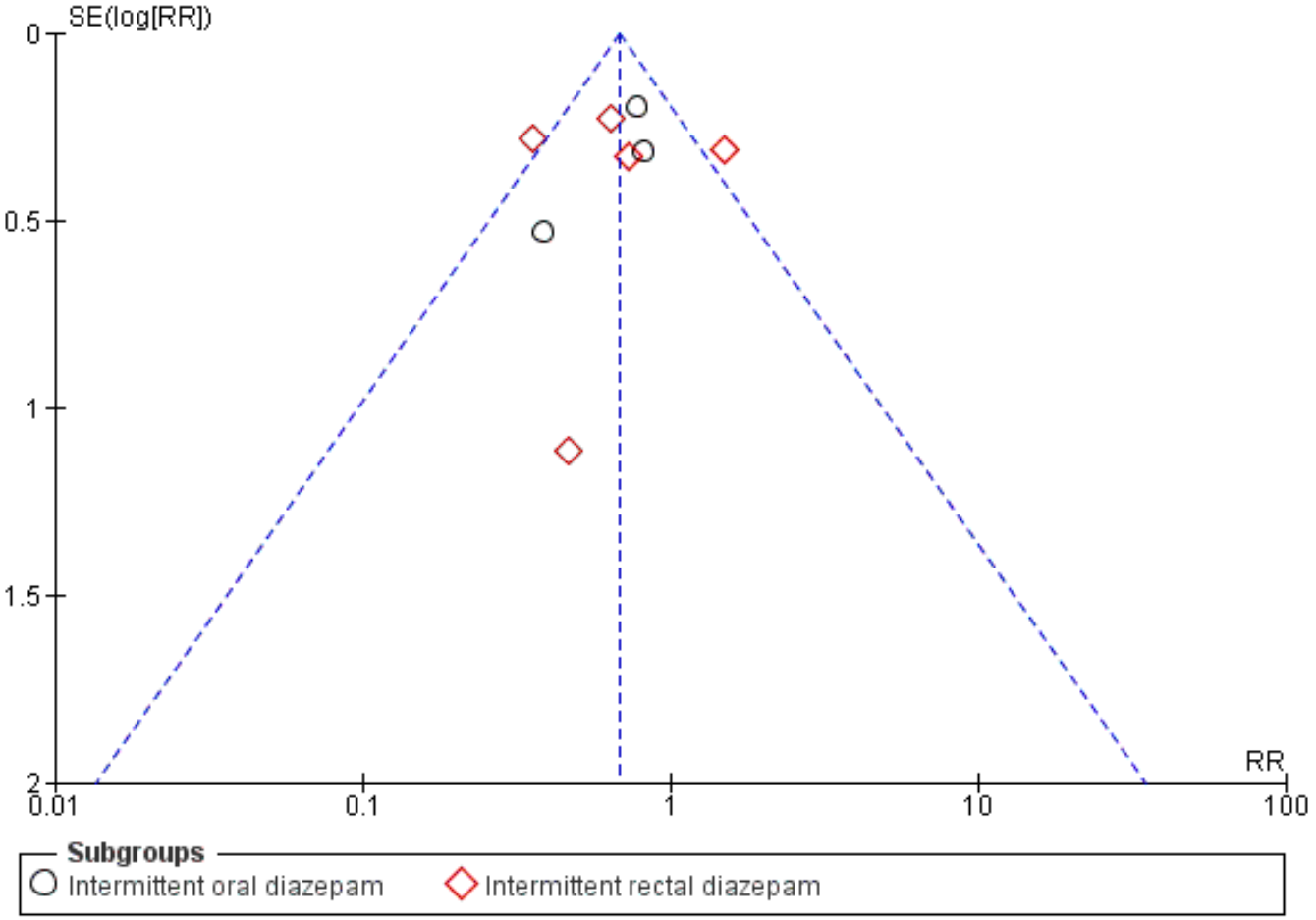


Figure 3. Funnel plot of comparison 2: continuous phenobarbitone versus placebo or no treatment to recurrence at 6 months: no evidence of publication bias.

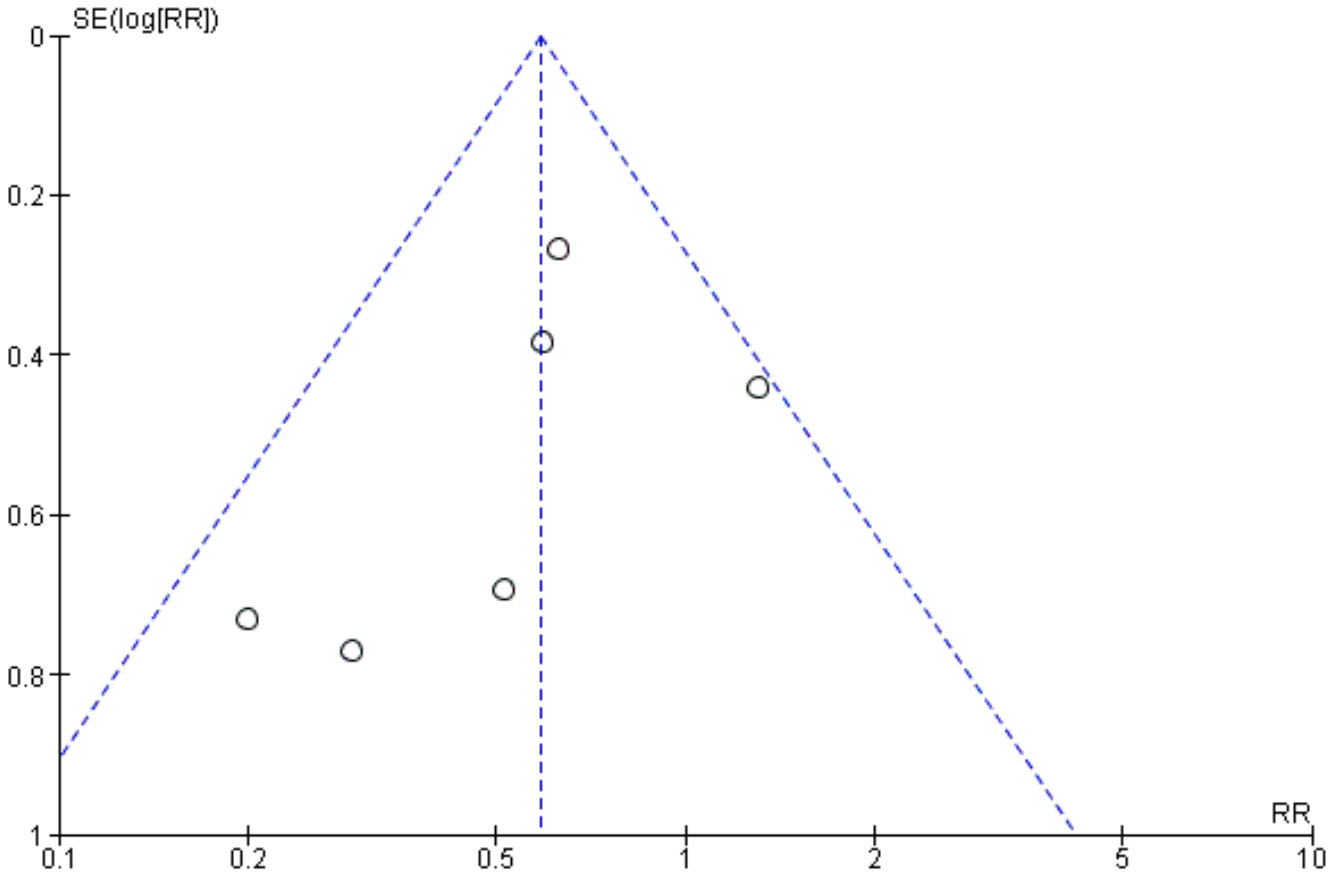
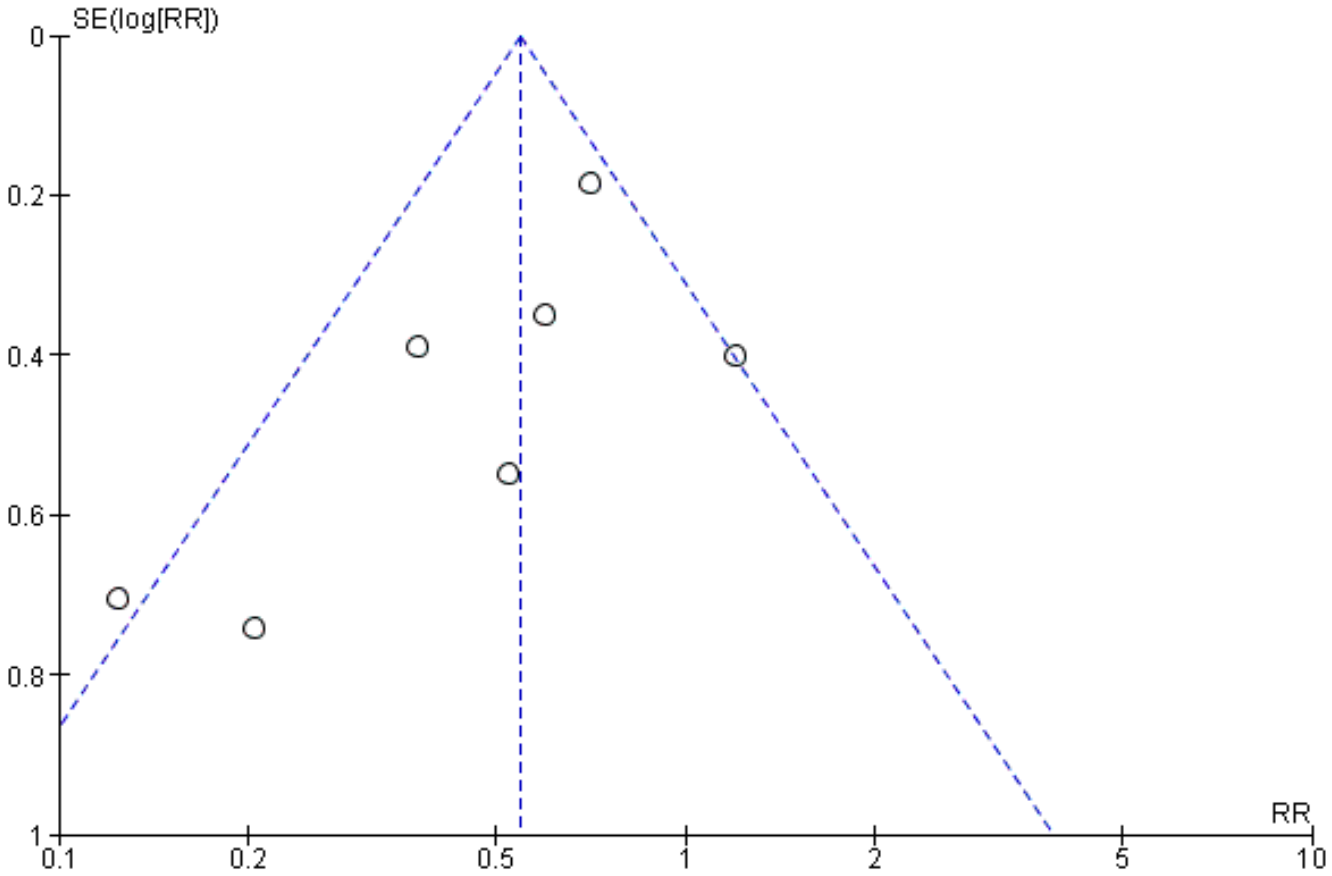


Figure 4. Funnel plot of comparison 2: continuous phenobarbitone versus placebo or no treatment to recurrence at 12 months: evidence of publication bias.



Effects of interventions

See: **Summary of findings for the main comparison** Intermittent oral or rectal diazepam compared to placebo or no treatment for febrile seizures in children; **Summary of findings 2** Continuous phenobarbitone compared to placebo or no treatment for febrile seizures in children; **Summary of findings 3** Intermittent phenobarbitone 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 after 8 hours by oral ibuprofen, acetaminophen or placebo for febrile seizures in children; **Summary of findings 11** Continuous phenobarbitone 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 oral clobazam for febrile seizures in children

We describe the results of 13 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 versus 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)

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 placebos and in the remaining six the controls received no treatment. Most trials assessed recurrence at 6 (6 trials), 12 (8 trials) and 24 months (4 trials), recurrence at 18, 36, 48 and 60 to 72 was only assessed by 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 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. First, the 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. Second, the 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 using an age-based dosing scheme (5 mg for age above 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, while Pavlidou 2006 used 0.33 mg/kg every eight hours on 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 7 to 15 kg and 10 mg > 15 kg) followed after six hours by oral diazepam 0.2 mg/kg every eight hours during fever with a maximum of two days.

There were significant overall findings at 6, 12, 18, 24, 36 and 48 months, 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% CI 0.48 to 0.85); 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); NNT 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); NNT 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); NNT 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); NNT 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); NNT 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); NNT 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 phenobarbitone versus placebo or no treatment (see Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6).

Ten trials compared continuous phenobarbitone 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 placebos and in the remaining five the controls received no treatment. Most trials assessed recurrence at 6 months (6 trials) and 12 months (7 trials), while recurrence at 18, 24 and 60 to 72 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 included only participants with simple febrile seizures (Camfield 1980; Ngwane 1980; Thilothammal 1993), and two 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 - 15 mg/L) or blood (Heckmatt 1976: 65 - 129 µmol/l; Mamelle 1984: > 60 µmol/l, Wolf 1977: 10 - 20 µg/ml). In the other trials dosing was not adjusted during follow-up.

Continuous phenobarbitone 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); NNT 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 0.55, 95% CI 0.42 to 0.70); NNT 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); NNT 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); NNT 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); NNT 10, Analysis 2.5

3. Intermittent phenobarbitone versus placebo or no treatment (see Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4).

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

In one trial (Mackintosh 1970) the control group received placebos and in the remaining two (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, and 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. Participants included in Ramakrishnan 1986 received 3 - 5 mg/kg/day divided into two doses, and participants included in Wolf 1977 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 phenobarbitone 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); NNT 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); NNT 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); NNT 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); NNT 31, Analysis 3.4.

4. Phenytoin versus placebo (see Analysis 4.1)

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 the 43 in the placebo group (RR 0.98, 95% CI 0.55 to 1.73); NNT 112, Analysis 4.1.

5. Valproate versus placebo or no treatment (see Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4).

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, while Mosquera 1987 included 69 children with a first febrile seizure and treated with valproate 30 mg/kg or no treatment.

Valproate only 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); NNT 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); NNT 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); NNT 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); NNT 18, Analysis 5.4.

6. Pyridoxine versus placebo (see Analysis 6.1; Analysis 6.2).

McKiernan 1981 was the only study comparing pyridoxine with placebo.

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

7. Intermittent ibuprofen versus placebo (see Analysis 7.1; Analysis 7.2; Analysis 7.3).

Van Stuijvenberg 1998 was the only study comparing intermittent ibuprofen with placebo.

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

8. Intermittent clobazam versus placebo (see Analysis 8.1).

Bajaj 2005 was the only study comparing clobazam with placebo.

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

9. Zinc sulfate versus placebo (see Analysis 9.1).

Fallah 2015 was the only study comparing zinc sulfate to placebo.

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), NNT 7, Analysis 9.1.

10. Diclofenac versus placebo followed, after eight hours, by ibuprofen, acetaminophen or placebo (see Analysis 10.1; Analysis 10.2; Analysis 10.3; Analysis 10.4).

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, acetaminophen or placebo. Since outcomes were unaffected by the second randomisation, we only consider the first in this meta-analysis. At six months, 14 (12.0%) of 117 children allocated to the diclofenac group had a seizure recurrence compared to 17 (14.9%) of 114 children allocated to the placebo group (RR 0.80, 95% CI 0.42 to 1.55), NNT 25, Analysis 10.1. At 12 months, 19 (16.2%) of 117 children allocated to the diclofenac group had a seizure recurrence compared to 27 (23.7%) of 114 children allocated to the placebo group (RR 0.69, 95% CI 0.40 to 1.16); NNT 14, Analysis 10.2. At 18 months, 23 (19.7%) of 117 children allocated to the diclofenac group had a seizure recurrence compared to 31 (27.2%) of 114 children allocated to the placebo group (RR 0.72, 95% CI 0.45 to 1.16); NNT 14, Analysis 10.3. At 24 months, 26 (22.2%) of 117 children allocated to the diclofenac group had a seizure recurrence compared to 32 (28.1%) of 114 children allocated to the placebo group (RR 0.79, 95% CI 0.51 to 1.24); NNT 17, Analysis 10.4.

11. Phenobarbitone versus intermittent diazepam (see Analysis 11.1; Analysis 11.2).

Two studies compared phenobarbitone with intermittent diazepam (Garcia 1984, Salehiomran 2016).

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

12. Intermittent rectal diazepam versus intermittent valproate (see Analysis 12.1; Analysis 12.2).

This comparison was examined in one study, 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 the valproate treatment group (RR 1.41, 95% CI 0.58 to 3.47); NNT 28, Analysis 12.1. At 12 months, 23 (25.8%) of 89 children allocated to the intermittent rectal diazepam group had a seizure recurrence compared to 14 (17.5%) of 80 children allocated to the valproate group (RR 1.48, 95% CI 0.82 to 2.67); NNT 12, Analysis 12.2.

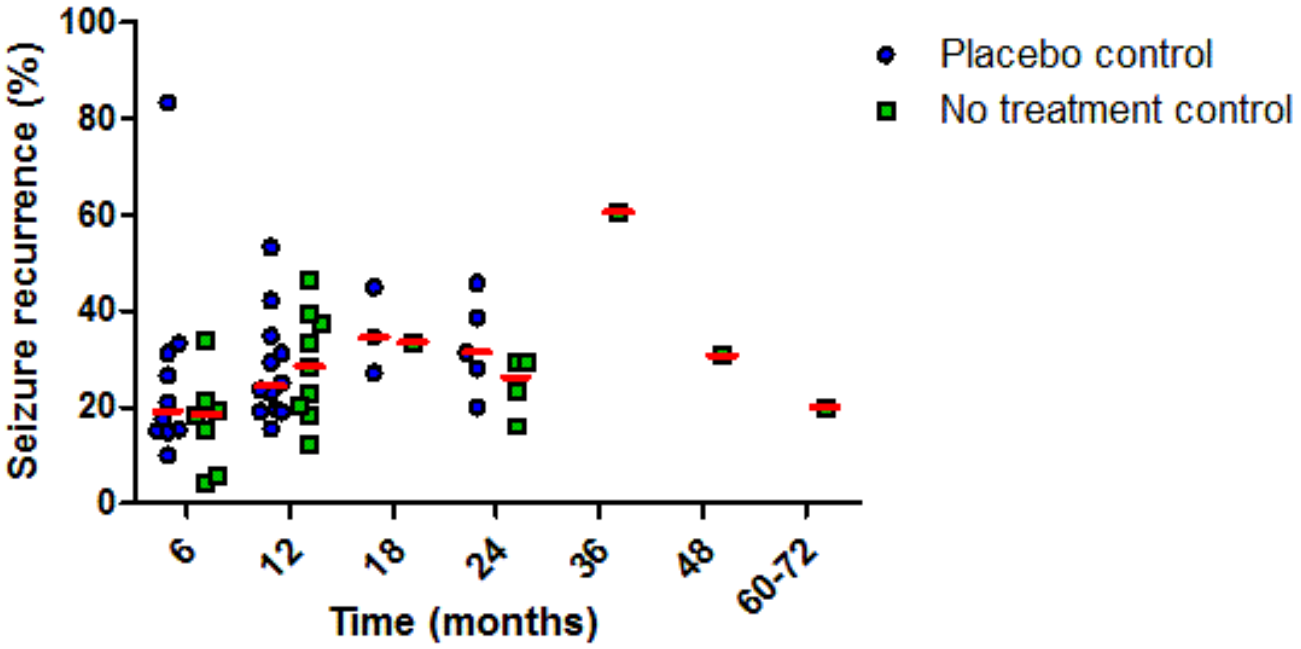
13. Intermittent diazepam versus intermittent clobazam (see Analysis 13.1).

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

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 5.

Figure 5. 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: these pooled data included the studies of Bajaj 2005; Camfield 1980; Farwell 1990; Heckmatt 1976; Knudsen 1985; Mackintosh 1970; McKinlay 1989; McKiernan 1981; Mosquera 1987; Pavlidou 2006; Rosman 1993; Strengell 2009; Thilothammal 1993; Uhari 1995; Van Stuijvenberg 1998; Verrotti 2004; Wolf 1977. A total of 259 (19.4%) of 1333 children had a recurrent febrile seizure within six months of study entry (placebo-controlled trials: 166/804 (20.6%); no-treatment controlled trials: 93/529 (17.6%)).

Recurrence risk at 12 months: pooled data at 12 months included 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: pooled data included the studies of Farwell 1990; Knudsen 1985; Mamelle 1984; Strengell 2009. One hundred and thirty-five (35.0%) of 386 children in these studies 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: pooled data included the studies from Farwell 1990; McKinlay 1989; Mosquera 1987; Rosman 1993; Strengell 2009; Uhari 1995; Van Stuijvenberg 1998; Verrotti 2004; Wolf 1977. Two hundred and seventy-nine (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 included only Pavlidou 2006: 43 (60.5%) recurrences among 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: analysis included data from only one study (Ramakrishnan 1986); 6 (20.0%) of 30 children receiving no treatment had a recurrent seizure at this point in time.

Treatment adherence

Fifteen of 30 trials assessed treatment adherence using various approaches. Their results are summarised in Table 1. Some measures were relatively crude, e.g. Camfield 1980 reported the presence or absence of the drug in serum samples. Others, e.g. 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 know for frequent and sometimes severe side effects in children. A variety of adverse effects were reported in some studies. Some 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 in so far as was possible from the information provided in the articles, is given in Table 2 'Unwanted medication effects'. We consider the fact that adverse effects were not addressed at all in eight included studies and only in one arm of the study in a further two as a measure of the generally poor quality of these studies.

Camfield 1980 was the only one to address behavioural change in a focused way. The authors recorded the incidence of behavioural changes in those allocated to the active phenobarbitone treatment group, comparing them to those in the placebo group, at 12-month follow-up. Fifteen of 35 (42.8%) allocated to phenobarbitone 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). More detail on the adverse effects in this study is given in the summary table under 'adverse effects', see below.

DISCUSSION

Summary of main results

We note no significant benefit for intermittent phenobarbitone, phenytoin, valproate, pyridoxine, ibuprofen or zinc sulfate versus placebo or no treatment; nor for diclofenac versus placebo followed by ibuprofen, acetaminophen or placebo; nor for continuous phenobarbitone versus diazepam, intermittent rectal diazepam versus intermittent valproate, or oral diazepam versus clobazam. 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 a risk ratio (RR) ranging from 0.37 to 0.73 and a number needed to treat (NNT) from 5 to 14 patients (rounded to integer). A significant reduction in febrile seizure recurrence risk was also seen in continuous phenobarbitone versus placebo or no treatment in each meta-analyses 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 a NNT of 8 to 10.

Another significant reduction in febrile seizure recurrence was seen in the intermittent clobazam group compared to placebo at six months follow-up: the risk ratio was 0.36, with a NNT 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 included trials was approximately 20% at six months (Figure 5), indicating how potentially misleading this study's findings are likely to be.

As has been indicated, the recording of adverse effects in these studies was very variable and often non-existent. Camfield 1980 documented lower comprehension scores in phenobarbitone-treated children (yet with small numbers), which correlated with length of phenobarbitone 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 phenobarbitone-treated group, although notably the studies by Bacon 1981 and Camfield 1980 (the latter for behavioural change or sleep disturbance) observed no difference with control groups. Knudsen 1985 noted mild transient adverse effects in up to 36% of children in the diazepam-treated groups.

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 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 increasing 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, it conferred no significant benefit over placebo (RR 0.58, 95% CI 0.31 to 1.09).

Figure 5 offers useful data when counselling parents on the natural history of the condition. As one might predict, there was no significant difference in recurrence rate in those treated with placebo or those who had no treatment. For each follow-up epoch recurrence rates stay remarkably similar at between 20% and 35%, except for the remarkable 36-month follow-up rate in Pavlidou 2006 of 60.5%, an outlier unlikely to be repeated. This continuing risk serves to emphasise the importance of conveying appropriate supportive advice to parents (see below).

In summary, we found reduced recurrence rates in children treated with intermittent diazepam or continuous phenobarbitone. Both drugs lead to the advent of mild to moderate adverse effects in up to 30% of its recipients. However, since 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 we should bear in mind we would need to treat 100 children with either intermittent diazepam or phenobarbitone to save up to 10 children from a recurrence, while giving 33 children unwanted effects. The mainstay of intervention should be the provision of information for 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 ser-

vices 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 nine (intermittent diazepam) and 10 (continuous phenobarbitone) 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 phenobarbitone (which had two trials favouring control). The majority of these trials included children after their first simple febrile seizure. Thus there is reasonable evidence to conclude their effectiveness to prevent a recurrent seizure in this population with a NNT 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 have 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 phenobarbitone. 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 are of a methodological quality which nowadays would 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 does allow 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 selected 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 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 for intermittent diazepam and continuous phenobarbitone. No benefit was demonstrated for phenytoin, valproate, pyridoxine, intermittent phenobarbitone or antipyretics in the form of intermittent ibuprofen, acetaminophen 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. 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 of justification 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

Methods	Double-blind RCT
Participants	185, age 8 - 36 months, first FS, < 2 RF

Autret 1990 *(Continued)*

Interventions	Intermittent oral diazepam, 0.5 mg load, 0.2 mg maintenance per kilo, or placebo
Outcomes	RS @ 12 months, adverse effects @ 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) All outcomes	Low risk	Double-blind
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

Methods	RCT
Participants	207, after first FS
Interventions	Phenytoin, 8 mg per kilo, or phenobarbitone 5 mg per kilo, or placebo
Outcomes	RS @ 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.

Bacon 1981 *(Continued)*

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
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

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
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 patients originally
Selective reporting (reporting bias)	Low risk	Stated outcome objective met
Other bias	Low risk	No bias identified

Bajaj 2005 *(Continued)*

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

Camfield 1980

Methods	Double-blind RCT
Participants	79, 6 - 36 months, first simple FS
Interventions	Phenobarbitone 4 - 5 mg per kilo, or placebo, both with antipyretics
Outcomes	RS @ 6 months, RS @ 12 months, behavioural changes @ 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
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	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Daugbjerg 1990

Methods	RCT, open label

Daugbjerg 1990 *(Continued)*

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

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

Methods	Single-centre randomised single-blind clinical study
Participants	Children aged 1½ - 5 years, with first simple FS, with weight and height above the third percentile and with 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

Fallah 2015 *(Continued)*

Allocation concealment (selection bias)	Low risk	Computer-generated equal simple randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blind design
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 Meijer 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 was 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 was 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

Methods	Double-blind RCT
Participants	217, first FS, > 1 RF
Interventions	Phenobarbitone 4 - 5 mg per kilo, or placebo
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 18 months, RS @ 24 months. IQ after 2 and 3 - 5 years, sleep disturbances
Notes	Attrition 26, 10 PB, 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 phenobarb levels
Incomplete outcome data (attrition bias) All outcomes	Low risk	86% of placebo, 77% phenobarb completed
Selective reporting (reporting bias)	Low risk	Stated outcome objective met

Farwell 1990 *(Continued)*

Other bias	Low risk	No bias identified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding maintained with fake phenobarb levels
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding maintained with fake phenobarb levels

Garcia 1984

Methods	RCT
Participants	100. 6 - 60 months, first FS
Interventions	During fever: either rectal diazepam 0.5 mg/kg/dose x 8-hourly or phenobarbitone 5 mg/kg/day plus antipyretics for both groups
Outcomes	RS @ 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

Methods	Single-centre randomised open-label trial
Participants	Children 6 - 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 patient's weight (daily 5 mg when weight ≤ 5 kg, twice daily 5 mg when 6 - 10 kg, twice daily 7.5 mg when 11 - 15 kg, and twice daily 10 mg when > 15 kg)
Outcomes	RS @ 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
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

Methods	Quasi-RCT
Participants	165, first FS, mean age 20 months
Interventions	Phenobarbitone 4 - 5 per kilo, or no treatment
Outcomes	RS @ 6 months
Notes	Attrition 4, 2 per arm, unblinded study

Risk of bias

Bias	Authors' judgement	Support for judgement

Heckmatt 1976 *(Continued)*

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

Khosroshahi 2011

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 – 10 kg; 7.5 mg, twice daily in children 11 – 15 kg; and 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.
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)

Khosroshahi 2011 *(Continued)*

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

Methods	Quasi-RCT
Participants	289, first FS
Interventions	Intermittent rectal diazepam 5 for children < 3 years, 7.5 for > 3 years, or no treatment
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 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
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

Methods	Double-blind RCT
Participants	32, 6 - 60 months, first simple FS
Interventions	Phenobarbitone 30 with ASA 150, or placebo
Outcomes	RS @ 6 months, RS @ 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

Methods	Single-blind RCT
Participants	69, 6 - 48 months, first FS, excluded focal and neuropsychiatric disorders
Interventions	Phenobarbitone 3 - 4 per kilo, or valproate 30 - 40 per kilo, or placebo
Outcomes	RS @ 18 months, length of follow-up differed (mean > 20 months)
Notes	Attrition: 4

Risk of bias

Mamelle 1984 *(Continued)*

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

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

McKiernan 1981 *(Continued)*

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

Methods	Quasi-RCT
Participants	151, 6 - 72 months, > one previous FS, or complicated FS
Interventions	Phenobarbitone 5 per kilo, or valproate 30 per kilo, or no treatment
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 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
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

Methods	RCT
Participants	69, first FS
Interventions	Intermittent rectal diazepam 0.5 mg/kg every 8 hours during fever, valproate 30 per kilo, or no treatment
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 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
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

Methods	Quasi-RCT, included were randomised in the 2 treatment arms, the participants that refused or were otherwise not included but eligible were considered the 'nothing arm'
Participants	64, 6 - 18 months, first simple FS
Interventions	Phenobarbitone 3 - 6 per kilo, or valproate 30 - 60 per kilo, or no treatment
Outcomes	RS @ 12 months, adverse effects
Notes	

Ngwane 1980 *(Continued)*

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 nor 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 nor 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 nor 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 nor blinding was used for the 'no treatment' control group.

Pavlidou 2006

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 (checked!)
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)	Low risk	Attrition of 6 of 145

Pavlidou 2006 *(Continued)*

All outcomes		
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

Methods	RCT
Participants	120, 2 - 72 months, first FS
Interventions	Phenobarbitone 3 - 5 per kilo, or intermittent phenobarbitone same dose, or intermittent diazepam 0.6 per kilo, or no treatment
Outcomes	RS @ 60 - 72 months
Notes	No attrition reported, unblinded study

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)	High risk	No blinding

Ramakrishnan 1986 *(Continued)*

All outcomes

Rosman 1993

Methods	Double-blind RCT
Participants	406, 6 - 60 months, at least 1 FS
Interventions	Intermittent oral diazepam 1 per kilo per day, or placebo
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 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
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

Methods	Single-centre RCT
Participants	Children 6 - 60 months of age with ≥ 3 simple FS or with complex FS
Interventions	Continuous phenobarbitone 3 - 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 @ 12 months, adverse effects

Salehiomran 2016 *(Continued)*

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
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

Strengell 2009

Methods	Randomised, placebo-controlled, double-blind trial
Participants	231, 4 - 48 months, first febrile seizure; 63 of these 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 acetaminophen (15 mg/kg) versus ibuprofen (10 mg/kg)) - each up to four times per day for as long as temp. > 38 °C
Outcomes	Actuarial analysis of seizure recurrence up to 24 months
Notes	Participants included in analyses for as long as they participated 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

Strengell 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition: 50 of 231: 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) All outcomes	Low risk	Special preparations made for drugs/placebos by pharmaceutical companies

Taghdiri 2011

Methods	Quasi-RCT
Participants	80 children, aged 9 months to 5 years, simple seizure
Interventions	Rectal diazepam (0.5 mg/kg) and acetaminophen versus acetaminophen only
Outcomes	RS @ 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	
Other bias	Low risk	
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

Methods	Double-blind RCT
Participants	90 but only 60 used in randomisation, 6 - 72 months, 2 or more simple seizure, 60 simple FS (30 placebo, 30 phenobarbitone), 30 atypical (phenobarbitone)
Interventions	Phenobarbitone 5 per kilo, or placebo
Outcomes	RS @ 6 months, RS @ 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

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

Risk of bias

Uhari 1995 *(Continued)*

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

Methods	Double-blind RCT
Participants	230, 12 - 48 months, FS at least 1 risk factor
Interventions	Intermittent oral ibuprofen 5 per kilo per day, or placebo
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 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 randomization schedule, stratified by center. "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

Van Stuijvenberg 1998 *(Continued)*

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

Verrotti 2004

Methods	RCT
Participants	110, 6 - 60 months, 1 simple febrile seizure, no risk factors
Interventions	Oral with diazepam, 0.35 mg/kg every 8 hours, during each episode of fever higher than 38 °C, continuing until child afebrile for 24 hours or no treatment
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 24 months and RS @ 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 and 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

Methods	RCT
Participants	58, 6 - 72 months, 2 or more simple FS
Interventions	Valproate 40 per kilo, or no treatment
Outcomes	RS @ 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	
Blinding of outcome assessment (detection bias) All outcomes	High risk	None

Wolf 1977

Methods	Quasi-RCT
Participants	355, 6 - 48 months, first FS
Interventions	Phenobarbitone 3 - 4 per kilo, or intermittent phenobarbitone 5 per kilo, or no treatment
Outcomes	RS @ 6 months, RS @ 12 months, RS @ 24 months, late cognition and behaviour, and adverse effects
Notes	Kaplan Meier used in estimations. Duration of follow-up differed: 28 (6 - 70) months

Risk of bias

Wolf 1977 *(Continued)*

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
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.
Antony 1983	72 children randomised, 36 to phenobarbital and 36 to carbamazepine, but 32 not included in final analysis. In 15 there was no follow-up, 5 were excluded because of low or no anti-epileptic drug level, 9 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%!).
Frehlih 1997	No data reported to estimate the occurrence of any of the prespecified outcomes.
Galli 1977	Could not get hold of a copy of paper.
Kazemi 2013	Publishes in Iranian
Knudsen 1978	Further exclusions from analysis 16 children in phenobarbitone group due to adverse effects or parents' "dislike to it". No follow-up data given for these 16 (+ 24 lost to follow-up) children.
Lahat 2000	Not a recurrence study - acute treatment only.

Study	Reason for exclusion
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.
Rose 2005	RCT but with inadequate follow-up range of 0 - 14 months; data interpretation at 6 months impossible.
Rosman 2001	Research question asking parental experiences.
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 on effect on temperature, not on recurrences.
Vining 1987	Side effects study not on FC children.
Winsley 2005	No data reported to estimate the occurrence of any of the prespecified outcomes.

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

JPRN-UMIN000004291

Trial name or title	A randomised, multicentre, controlled trial of prophylactic use of diazepam for recurrence of febrile seizures during a single febrile episode
Methods	Multicentre open-label dose-comparing RCT
Participants	Children with a simple febrile seizure
Interventions	(1) Single dose of diazepam 0.5 mg/kg, or (2) 2 sequential doses of diazepam 0.5 mg/kg with 8 hours interval, or (3) diazepam 0.3 mg/kg/dose 3 times a day during febrile period (terminated after confirmation that fever-free status maintains at least 24 hours)
Outcomes	Febrile seizure recurrence, adverse events
Starting date	2010/09/29
Contact information	Yoshihiko Morikawa (masaru_miura@tmhp.jp)
Notes	

DATA AND ANALYSES

Comparison 1. Intermittent oral or rectal diazepam versus placebo or no treatment

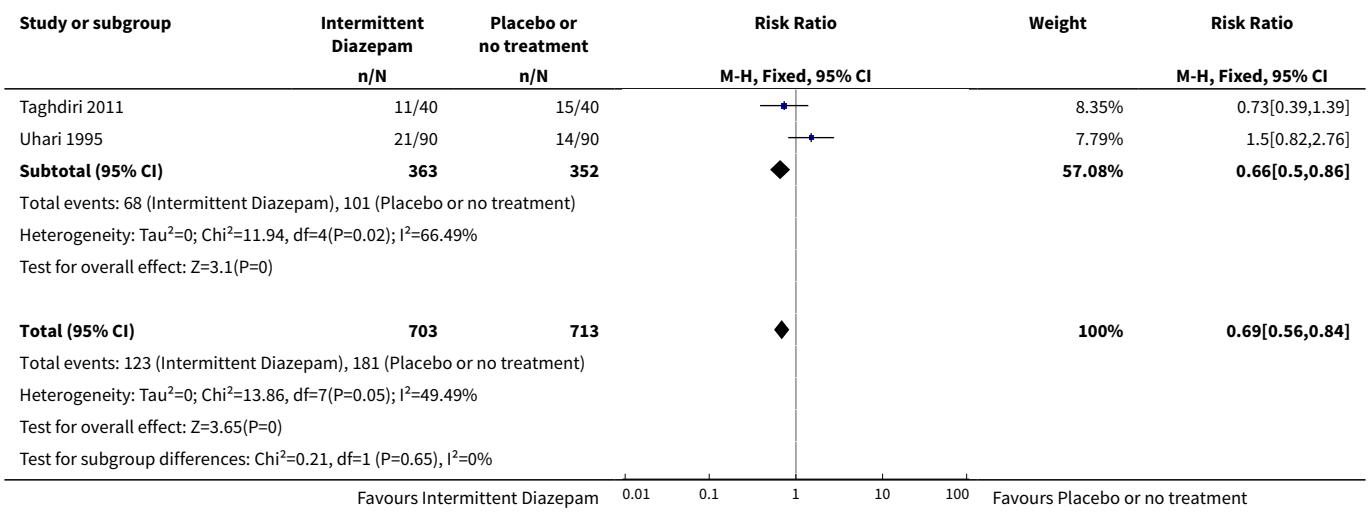
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent seizure @ 6 months	6	1151	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.85]
1.1 Intermittent oral diazepam	2	516	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.45, 1.11]
1.2 Intermittent rectal diazepam	4	635	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.41, 0.86]
2 Recurrent seizure @ 12 months	8	1416	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.56, 0.84]
2.1 Intermittent oral diazepam	3	701	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.53, 0.99]
2.2 Intermittent rectal diazepam	5	715	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.50, 0.86]
3 Recurrent seizure @ 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Intermittent rectal diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Recurrent seizure @ 24 months	4	739	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.95]
4.1 Intermittent oral diazepam	2	516	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.45, 0.85]
4.2 Intermittent rectal diazepam	2	223	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.67, 1.90]
5 Recurrent seizure @ 36 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Intermittent rectal diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Recurrent seizure @ 48 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Intermittent oral diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Recurrent seizure @ 60-72 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Intermittent oral diazepam	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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

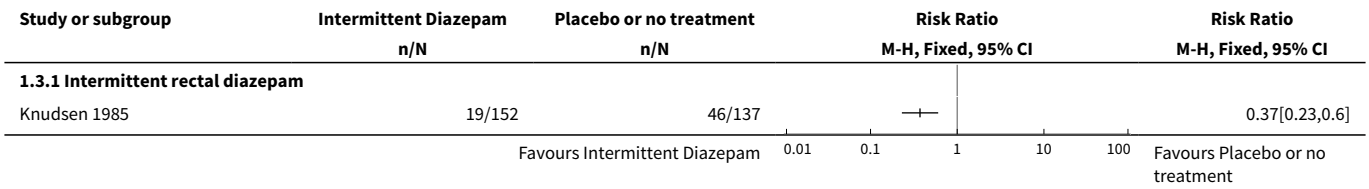
Study or subgroup	Intermittent diazepam n/N	p lacebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Intermittent oral diazepam					
Rosman 1993	25/202	31/204		29.81%	0.81[0.5,1.33]
Verrotti 2004	3/45	12/65		9.49%	0.36[0.11,1.21]
Subtotal (95% CI)	**247**	**269**		**39.29%**	**0.7[0.45,1.11]**
Total events: 28 (Intermittent diazepam), 43 (p lacebo or no treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.51, df=1(P=0.22); I^2=33.97%					
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[0.1,0.49]
Mosquera 1987	0/18	1/25		1.22%	0.46[0.02,10.6]
Pavlidou 2006	15/68	24/71		22.69%	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**		**60.71%**	**0.59[0.41,0.86]**
Total events: 37 (Intermittent diazepam), 61 (p lacebo or no treatment)					
Heterogeneity: Tau^2=0; Chi^2=12.83, df=3(P=0.01); I^2=76.62%					
Test for overall effect: Z=2.77(P=0.01)					
Total (95% CI)	**570**	**581**		**100%**	**0.64[0.48,0.85]**
Total events: 65 (Intermittent diazepam), 104 (p lacebo or no treatment)					
Heterogeneity: Tau^2=0; Chi^2=14.52, df=5(P=0.01); I^2=65.57%					
Test for overall effect: Z=3.09(P=0)					
Test for subgroup differences: Chi^2=0.33, df=1 (P=0.57), I^2=0%					

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

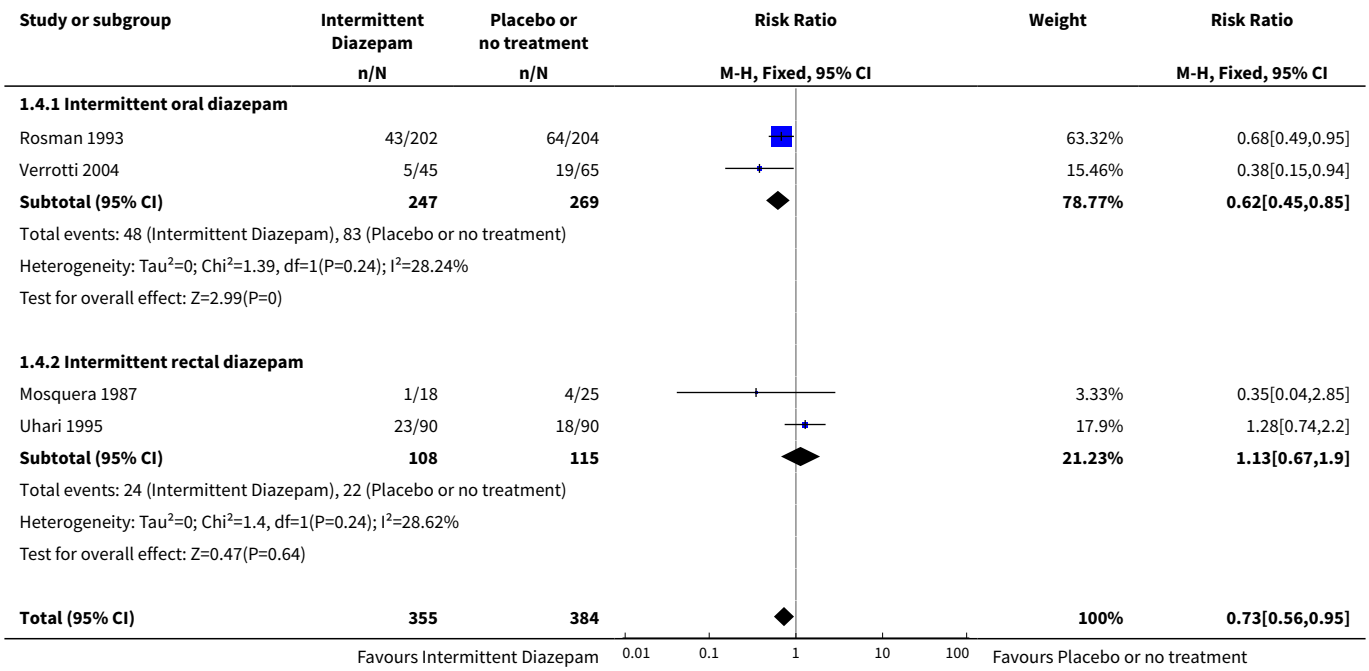
Study or subgroup	Intermittent Diazepam n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Intermittent oral diazepam					
Autret 1990	15/93	18/92		10.07%	0.82[0.44,1.53]
Rosman 1993	36/202	47/204		26.02%	0.77[0.52,1.14]
Verrotti 2004	4/45	15/65		6.83%	0.39[0.14,1.08]
Subtotal (95% CI)	**340**	**361**		**42.92%**	**0.72[0.53,0.99]**
Total events: 55 (Intermittent Diazepam), 80 (Placebo or no treatment)					
Heterogeneity: Tau^2=0; Chi^2=1.71, df=2(P=0.43); I^2=0%					
Test for overall effect: Z=2.03(P=0.04)					
1.2.2 Intermittent rectal diazepam					
Knudsen 1985	15/147	36/126		21.57%	0.36[0.21,0.62]
Mosquera 1987	1/18	3/25		1.4%	0.46[0.05,4.1]
Pavlidou 2006	20/68	33/71		17.97%	0.63[0.41,0.99]

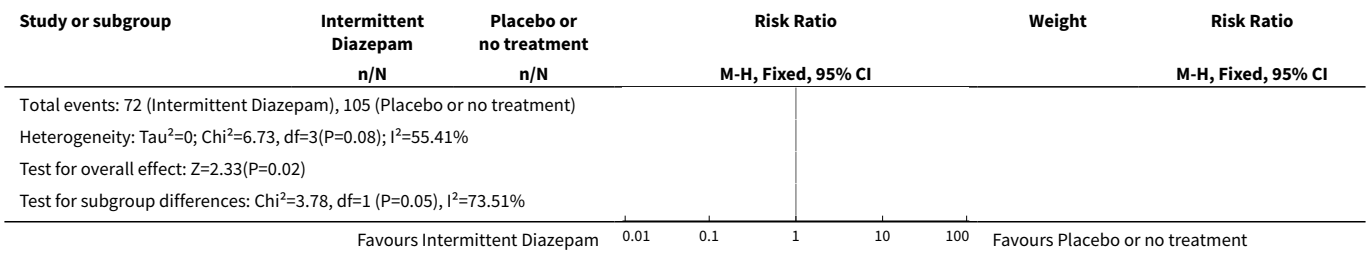


Analysis 1.3. Comparison 1 Intermittent oral or rectal diazepam versus placebo or no treatment, Outcome 3 Recurrent seizure @ 18 months.

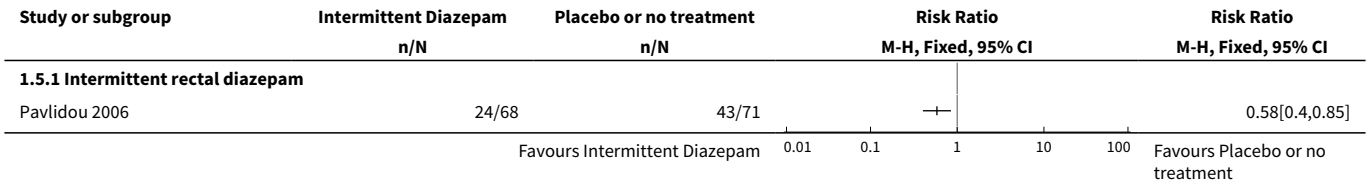


Analysis 1.4. Comparison 1 Intermittent oral or rectal diazepam versus placebo or no treatment, Outcome 4 Recurrent seizure @ 24 months.

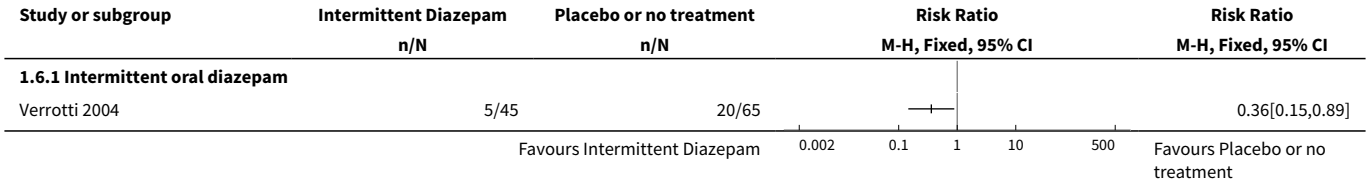




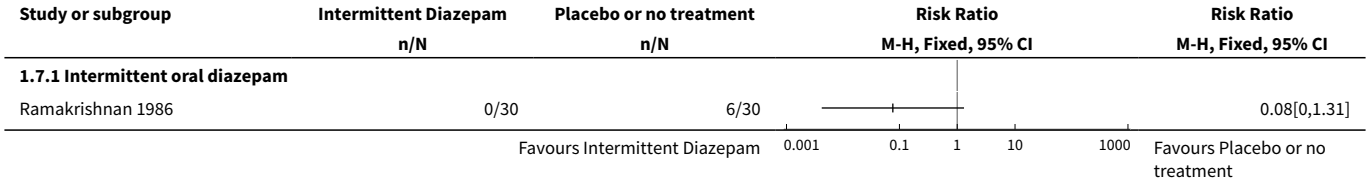
Analysis 1.5. Comparison 1 Intermittent oral or rectal diazepam versus placebo or no treatment, Outcome 5 Recurrent seizure @ 36 months.



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



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



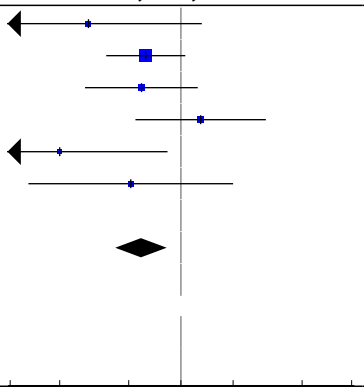
Comparison 2. Continuous phenobarbitone versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Recurrent seizure @ 6 months	6	833	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.83]
2 Recurent seizure @ 12 months	7	807	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.42, 0.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Recurent seizure @ 18 months	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.05]
4 Recurent seizure @ 24 months	3	533	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.89]
5 Recurrent seizure @ 60-72 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Behavioural changes	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.79, 3.26]

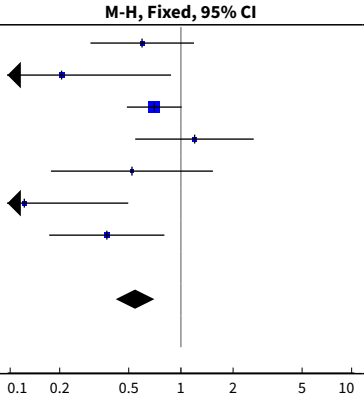
Analysis 2.1. Comparison 2 Continuous phenobarbitone versus placebo or no treatment, Outcome 1 Recurrent seizure @ 6 months.

Study or subgroup	Continuous Phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	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		38.85%	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		9.83%	1.3[0.55,3.09]
Thilothammal 1993	2/30	10/30		13.46%	0.2[0.05,0.84]
Wolf 1977	3/106	6/109		7.96%	0.51[0.13,2]
Total (95% CI)	**412**	**421**		**100%**	**0.59[0.42,0.83]**
Total events: 43 (Continuous Phenobarbitone), 75 (Placebo or no treatment)					
Heterogeneity: $Tau^2=0$; $Chi^2=6.32$, df=5(P=0.28); $I^2=20.93\%$					
Test for overall effect: Z=3.04(P=0)					



Analysis 2.2. Comparison 2 Continuous phenobarbitone versus placebo or no treatment, Outcome 2 Recurent seizure @ 12 months.

Study or subgroup	Continuous Phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bacon 1981	10/48	15/43		12.62%	0.6[0.3,1.19]
Camfield 1980	2/39	10/40		7.87%	0.21[0.05,0.88]
Farwell 1990	32/108	46/109		36.51%	0.7[0.49,1.01]
McKinlay 1989	9/41	11/60		7.12%	1.2[0.55,2.63]
Ngwane 1980	4/23	7/21		5.83%	0.52[0.18,1.53]
Thilothammal 1993	2/30	16/30		12.76%	0.13[0.03,0.5]
Wolf 1977	8/106	22/109		17.3%	0.37[0.17,0.8]
Total (95% CI)	**395**	**412**		**100%**	**0.54[0.42,0.7]**
Total events: 67 (Continuous Phenobarbitone), 127 (Placebo or no treatment)					

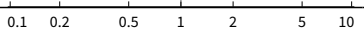


Study or subgroup	Continuous Phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=12.84, df=6(P=0.05); I²=53.28%					
Test for overall effect: Z=4.65(P<0.0001)					

Favours Continuous Phenobarbitone — Favours Placebo or no treatment

Analysis 2.3. Comparison 2 Continuous phenobarbitone versus placebo or no treatment, Outcome 3 Recurent seizure @ 18 months.

Study or subgroup	Continuous Phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Farwell 1990	39/108	49/109		85.84%	0.8[0.58,1.11]
Mamelle 1984	4/21	9/26		14.16%	0.55[0.2,1.54]
Total (95% CI)	**129**	**135**		**100%**	**0.77[0.56,1.05]**
Total events: 43 (Continuous Phenobarbitone), 58 (Placebo or no treatment)					
Heterogeneity: Tau²=0; Chi²=0.48, df=1(P=0.49); I²=0%					
Test for overall effect: Z=1.67(P=0.1)					



Favours Continuous Phenobarbitone — Favours Placebo or no treatment

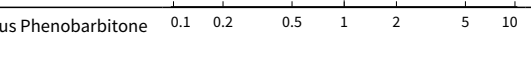
Analysis 2.4. Comparison 2 Continuous phenobarbitone versus placebo or no treatment, Outcome 4 Recurent seizure @ 24 months.

Study or subgroup	Continuous Phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Farwell 1990	41/108	50/109		53.7%	0.83[0.6,1.13]
McKinlay 1989	12/41	14/60		12.26%	1.25[0.65,2.43]
Wolf 1977	8/106	32/109		34.04%	0.26[0.12,0.53]
Total (95% CI)	**255**	**278**		**100%**	**0.69[0.53,0.89]**
Total events: 61 (Continuous Phenobarbitone), 96 (Placebo or no treatment)					
Heterogeneity: Tau²=0; Chi²=11.56, df=2(P=0); I²=82.7%					
Test for overall effect: Z=2.8(P=0.01)					

Favours Continuous Phenobarbitone — Favours Placebo or no treatment

Analysis 2.5. Comparison 2 Continuous phenobarbitone versus placebo or no treatment, Outcome 5 Recurrent seizure @ 60-72 months.

Study or subgroup	Continuous Phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Ramakrishnan 1986	9/30	6/30		1.5[0.61,3.69]



Favours Continuous Phenobarbitone | Favours Placebo or no treatment

Analysis 2.6. Comparison 2 Continuous phenobarbitone versus placebo or no treatment, Outcome 6 Behavioural changes.

Study or subgroup	Continuous Phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Camfield 1980	15/35	8/30		100%	1.61[0.79,3.26]
Total (95% CI)	**35**	**30**		**100%**	**1.61[0.79,3.26]**
Total events: 15 (Continuous Phenobarbitone), 8 (Placebo or no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.32(P=0.19)					

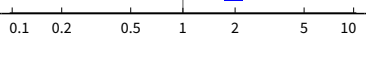
Favours Continuous Phenobarbitone | Favours Placebo or no treatment

Comparison 3. Intermittent phenobarbitone versus placebo or no treatment

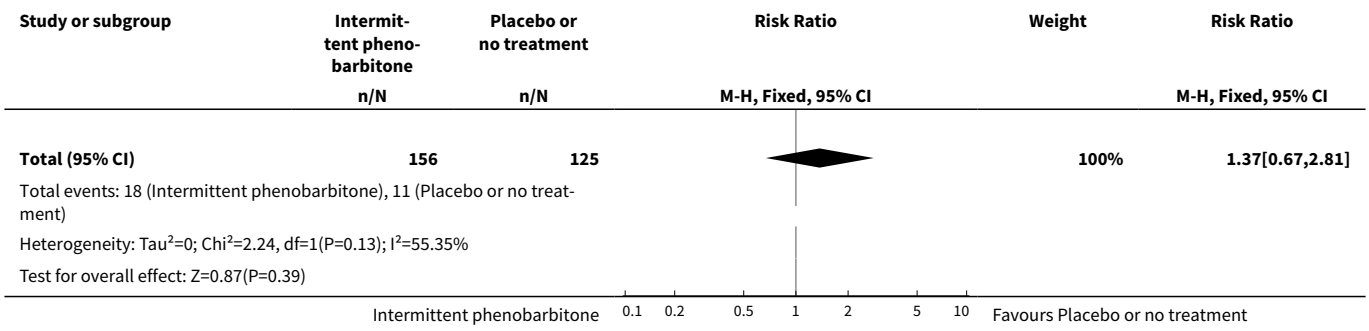
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent seizure @ 6 months	2	281	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.67, 2.81]
2 Recurent seizure @ 12 months	2	281	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.65, 1.59]
3 Recurent seizure @ 24 months	1		Risk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

Analysis 3.1. Comparison 3 Intermittent phenobarbitone versus placebo or no treatment, Outcome 1 Recurrent seizure @ 6 months.

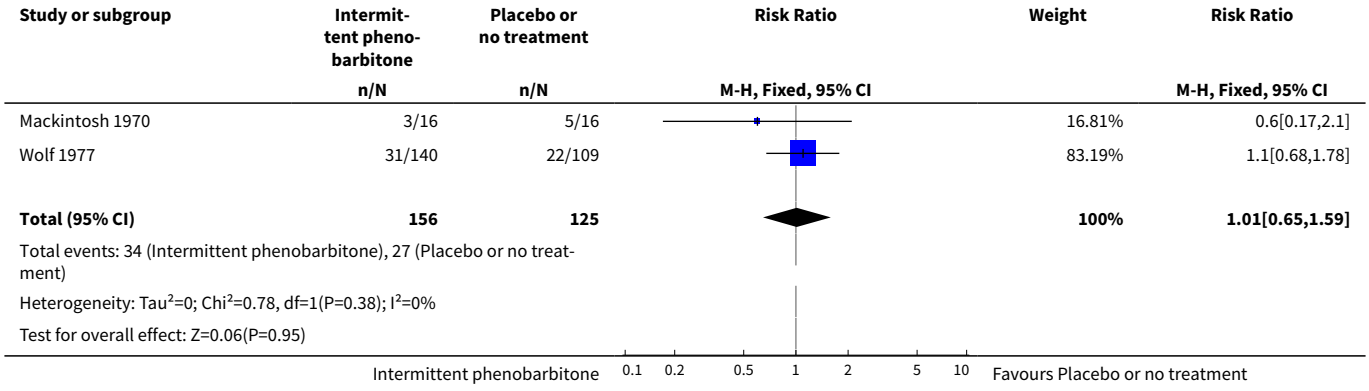
Study or subgroup	Intermittent phenobarbitone n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mackintosh 1970	3/16	5/16		42.56%	0.6[0.17,2.1]
Wolf 1977	15/140	6/109		57.44%	1.95[0.78,4.85]



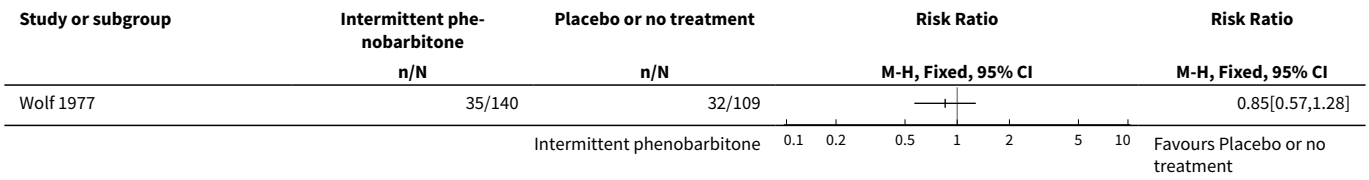
Intermittent phenobarbitone | Favours Placebo or no treatment



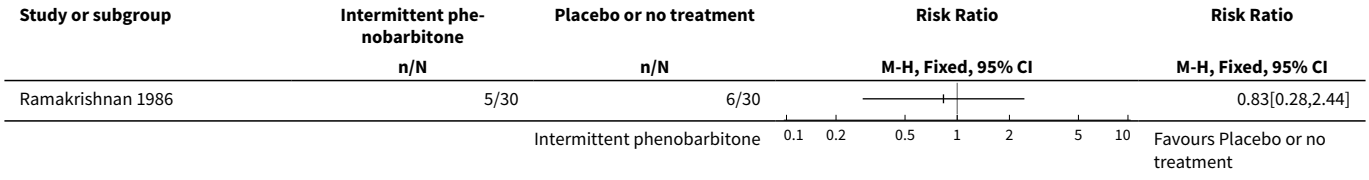
Analysis 3.2. Comparison 3 Intermittent phenobarbitone versus placebo or no treatment, Outcome 2 Recurent seizure @ 12 months.



Analysis 3.3. Comparison 3 Intermittent phenobarbitone versus placebo or no treatment, Outcome 3 Recurent seizure @ 24 months.



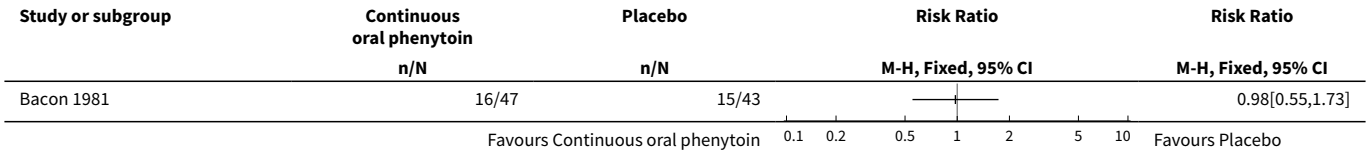
Analysis 3.4. Comparison 3 Intermittent phenobarbitone versus placebo or no treatment, Outcome 4 Recurrent seizure @ 60-72 months.



Comparison 4. Continuous oral phenytoin versus placebo

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

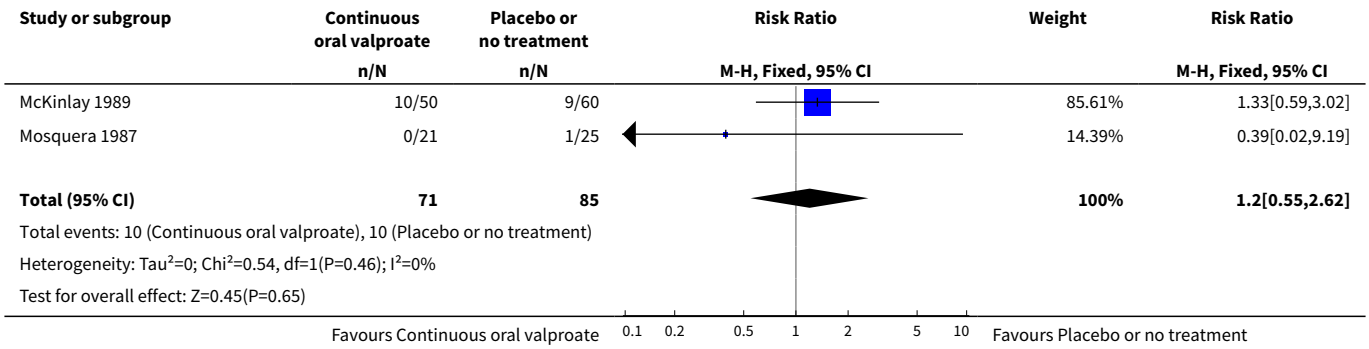
Analysis 4.1. Comparison 4 Continuous oral phenytoin versus placebo, Outcome 1 Recurent seizure @ 12 months.



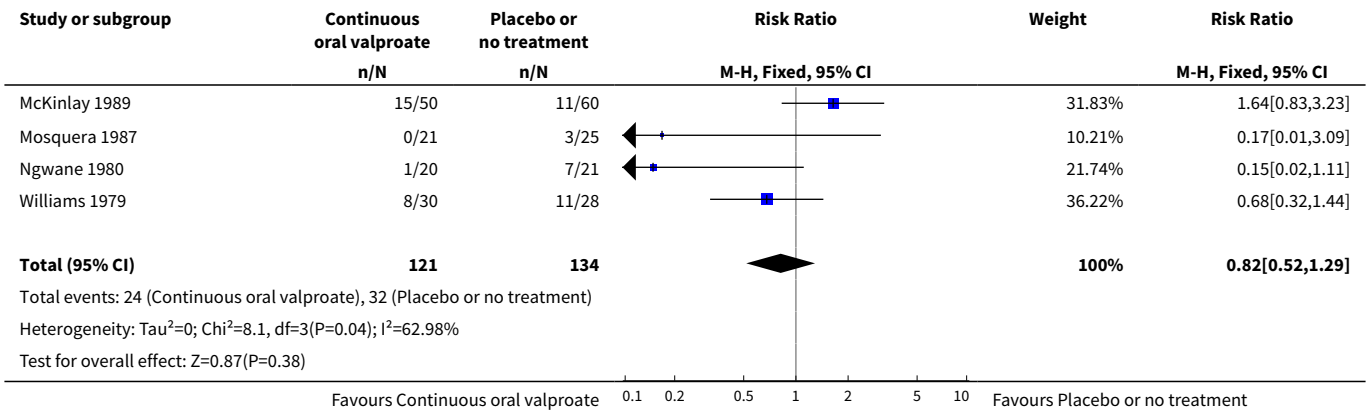
Comparison 5. Continuous oral valproate versus placebo or no treatment

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

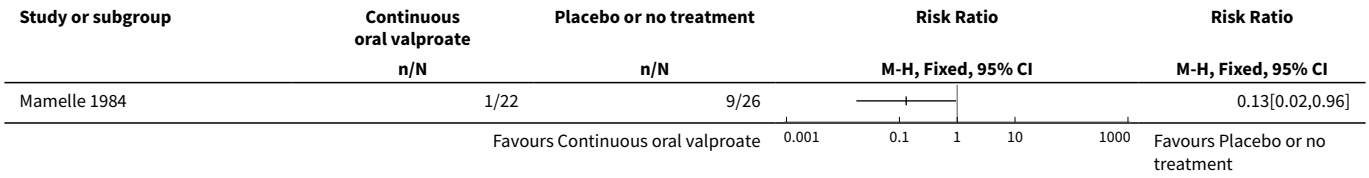
Analysis 5.1. Comparison 5 Continuous oral valproate versus placebo or no treatment, Outcome 1 Recurrent seizure @ 6 months.



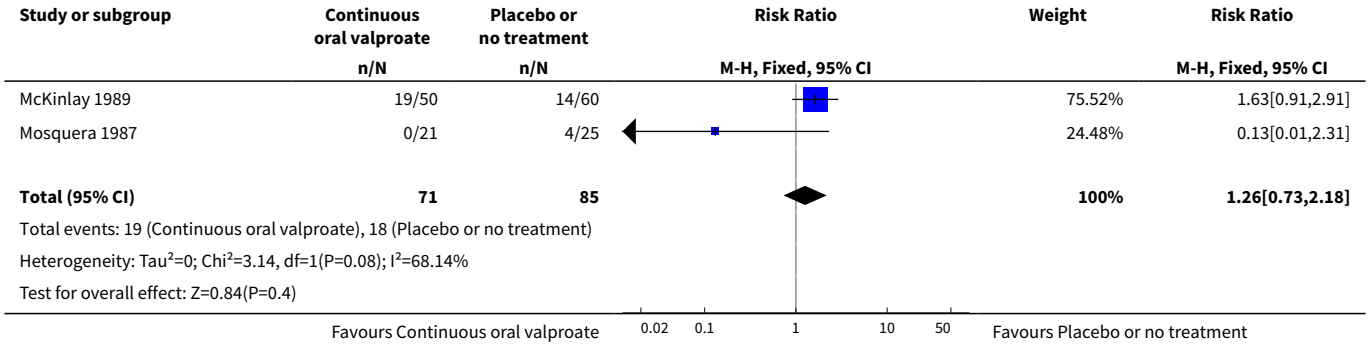
Analysis 5.2. Comparison 5 Continuous oral valproate versus placebo or no treatment, Outcome 2 Recurrent seizure @ 12 months.



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



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



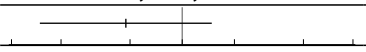
Comparison 6. Continuous oral pyridoxine versus placebo

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

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

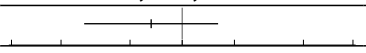
Analysis 6.1. Comparison 6 Continuous oral pyridoxine versus placebo, Outcome 1 Recurrent seizure @ 6 months.

Study or subgroup	Continuous oral pyridoxine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
McKiernan 1981	4/55	8/52		0.47[0.15,1.48]



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

Study or subgroup	Continuous oral pyridoxine n/N	Placebo n/N	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 versus placebo

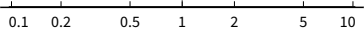
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent seizure @ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Recurrent seizure @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Recurrent seizure @ 24 months	1		Risk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

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

Study or subgroup	Intermittent oral ibuprofen n/N	Placebo n/N	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 versus placebo, Outcome 2 Recurrent seizure @ 12 months.

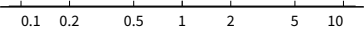
Study or subgroup	Intermittent oral ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Van Stuijvenberg 1998	31/111	35/119		0.95[0.63,1.43]



Favours Intermittent oral ibuprofen | Favours Placebo

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

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



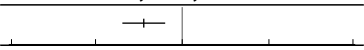
Favours Intermittent oral ibuprofen | Favours Placebo

Comparison 8. Intermittent oral clobazam versus placebo

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

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

Study or subgroup	Clobazam n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bajaj 2005	9/30	25/30		0.36[0.2,0.64]



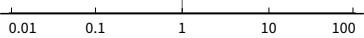
Favours intervention | Favours control

Comparison 9. Continuous zinc sulfate for 6 months versus placebo

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

Analysis 9.1. Comparison 9 Continuous zinc sulfate for 6 months versus placebo, Outcome 1 Recurrent seizures @ 12 months.

Study or subgroup	Continuous zinc sulfate n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah 2015	11/50	19/50		0.58[0.31,1.09]



Favours Continuous zinc sulfate | Favours Placebo

Comparison 10. Intermittent rectal diclofenac versus placebo followed after 8 hours by oral ibuprofen, acetaminophen or placebo

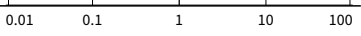
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent seizures @ 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Recurrent seizures @ 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Recurrent seizures @ 18 months	1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

Analysis 10.1. Comparison 10 Intermittent rectal diclofenac versus placebo followed after 8 hours by oral ibuprofen, acetaminophen or placebo, Outcome 1 Recurrent seizures @ 6 months.

Study or subgroup	Intermittent rectal diclofenac n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Strengell 2009	14/117	17/114		0.8[0.42,1.55]

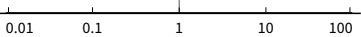
Analysis 10.2. Comparison 10 Intermittent rectal diclofenac versus placebo followed after 8 hours by oral ibuprofen, acetaminophen or placebo, Outcome 2 Recurrent seizures @ 12 months.

Study or subgroup	Intermittent rectal diclofenac n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Strengell 2009	19/117	27/114		0.69[0.4,1.16]



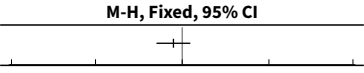
Analysis 10.3. Comparison 10 Intermittent rectal diclofenac versus placebo followed after 8 hours by oral ibuprofen, acetaminophen or placebo, Outcome 3 Recurrent seizures @ 18 months.

Study or subgroup	Intermittent rectal diclofenac n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio 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 versus placebo followed after 8 hours by oral ibuprofen, acetaminophen or placebo, Outcome 4 Recurrent seizures @ 24 months.

Study or subgroup	Intermittent rectal diclofenac n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Strengell 2009	26/117	32/114		0.79[0.51,1.24]



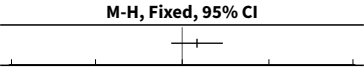
Favours Intermittent rectal diclofenac | Favours Placebo

Comparison 11. Continuous phenobarbitone versus intermittent rectal/oral diazepam

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

Analysis 11.1. Comparison 11 Continuous phenobarbitone versus intermittent rectal/oral diazepam, Outcome 1 Recurrent seizure @ 12 months.

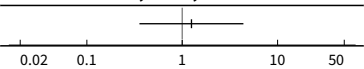
Study or subgroup	Continuous phenobarbitone n/N	intermittent rectal/oral diazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Salehiomran 2016	17/74	11/71		1.48[0.75,2.94]



Favours Continuous phenobarbitone | Favours intermittent rectal/oral diazepam

Analysis 11.2. Comparison 11 Continuous phenobarbitone versus intermittent rectal/oral diazepam, Outcome 2 Recurrent seizure @ 18 months.

Study or subgroup	Continuous phenobarbitone n/N	intermittent rectal/oral diazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Garcia 1984	5/50	4/50		1.25[0.36,4.38]

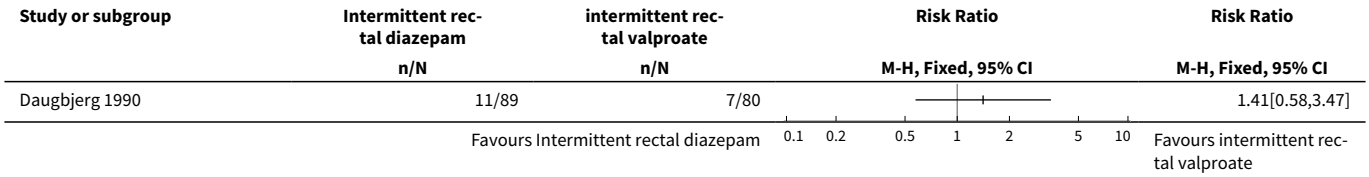


Favours Continuous phenobarbitone | Favours intermittent rectal/oral diazepam

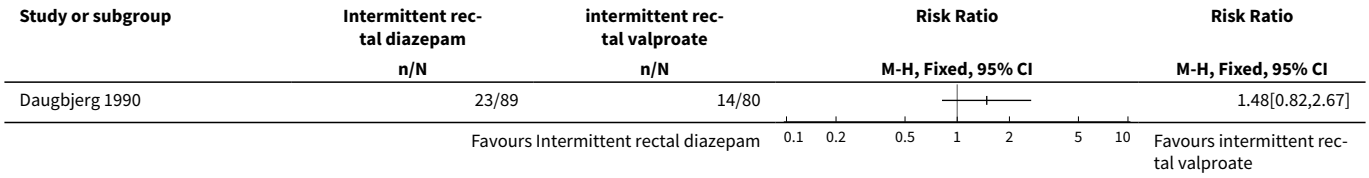
Comparison 12. Intermittent rectal diazepam versus intermittent rectal valproate

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

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



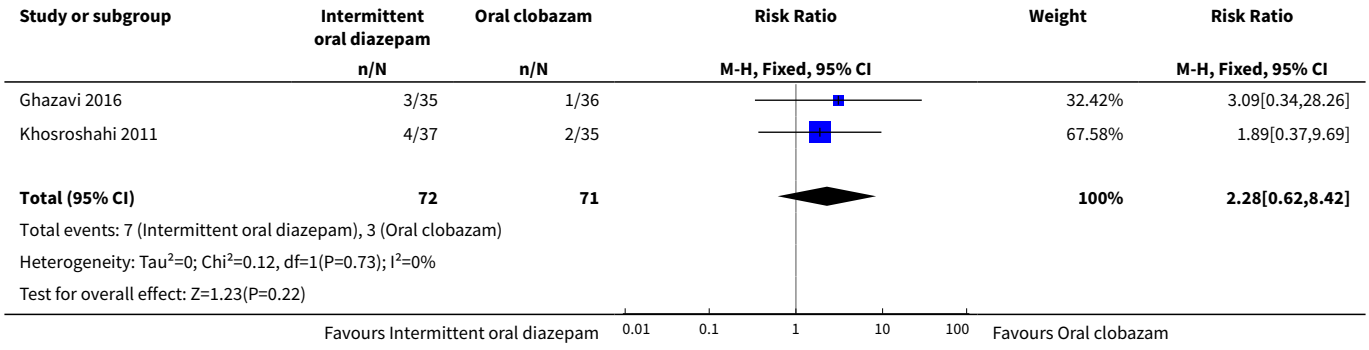
Analysis 12.2. Comparison 12 Intermittent rectal diazepam versus intermittent rectal valproate, Outcome 2 Recurrent seizure @ 12 months.



Comparison 13. Intermittent oral diazepam versus oral clobazam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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 versus oral clobazam, 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 the patients 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 - 8 mg/l; 5/25 (20%) at > 8 mg/l PT: 3/9 (33%) at < 0.5 mg/l, 9/19 (47%) at 0.5 - 1.0 mg/l, 4/19 (21% 0 at > 1.0 mg/l	Yes
Bajaj 2005	-CBZ -PCB	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 - 1.5 mg/dl, 70% - 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 micromole/l or 15 microgram/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 micromole/l. All 4 recurrences in the PB group occurred in children with levels above 65 micromole/l	Yes

Table 1. Treatment adherence *(Continued)*

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." Origin of the denominator is unclear as 21 recurrences occurred in DZP and 77 in NT	No
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 measure 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	No

Table 1. Treatment adherence *(Continued)*

				982 PCB samples, 95% of all reported fever days, 95% of samples tested positive	
Salehiomran 2016	-DZP (oral) -PB (cont.)	No			
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; NT = no treatment; PB = phenobarbitone; 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". One sudden unexpected death in placebo group.
Bacon 1981	138, 43 control, 48 phenobarbitone, 48 phenytoin	Rash in 1 child on phenobarbitone, ataxia in 5 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

Table 2. Unwanted medication effects *(Continued)*

		of these items between phenobarbitone/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)
Camfield 1980	79	At 12 months no difference between phenobarbitone and placebo groups for behavioural change or sleep disturbance. Placebo group, transient adverse effects in 7 of 30. Phenobarbitone group, transient adverse effects 15 of 35. Significant negative correlation between phenobarbitone serum level and memory concentration subscores on Binet scores. Lower comprehension scores showed significant correlation with length of phenobarbitone treatment (but n = 7 at 8 months and 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 wks 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 phenobarbitone to a group randomly assigned to placebo. After 2 years mean IQ 8.4 points lower in phenobarbitone group (95% CI ?13.3 to -3.5, P + 0.006). 6 months later after discontinuing medication IQ 5.2 points lower in phenobarbitone 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 in phenobarbitone and placebo groups. No difference noted between groups except subset of predisposed children did experience an increase in night awakenings, (that is, those already recorded to have frequent sleep disturbances at study entry). 35: Retesting of group after school entry. Phenobarbitone treated group had Wide Range Achievement Test (WRAT-R) reading achievement score significantly lower than placebo group: 87.6 v 95.6; P = 0.007. No significant difference for IQ on Stamford Binet.
Garcia 1984	100	Adverse effects: Diazepam 5 (10%), phenobarbitone 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 (over-activity, unpleasant behaviour, temper, not sleeping) 12 improved; 23 for a variety of reasons, e.g. drowsy/unsteady. 3 in control group reported behaviour problems.
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.
Khosroshahi 2011	72	The adverse effects of clobazam were noted to be lower than with diazepam. Sedation was noted more often with diazepam compared to clobazam (P < 0.0001) - further details are not given.
Mamelle 1984		Adverse effects not addressed.
Mackintosh 1970	32	Adverse effects not addressed.

Table 2. Unwanted medication effects *(Continued)*

McKiernan 1981	107	Adverse effects not addressed.
McKinlay 1989	151	13 of 41 on phenobarbitone had disturbed behaviour and/or drowsiness; 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 phenobarbitone had adverse effects within 72 hours; 2 of these drug withdrawn (details not given). 4 of 20 on Valproate, 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.153 on diazepam with 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 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 phenobarbitone 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 children	Adverse effects not addressed.
Verrotti 2004	110	Adverse effects were only reported from the treatment group, including 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.
Wolf 1977	355	Phenobarbitone 34 of 109 (32%) discontinued continuous phenobarbitone, reasons as follows:16% hyperactivity; 1% irritability; 3% rash; 2% lethargy; 10% parental non-compliance. Long-term effect of phenobarbitone on cognitive function: Group of 50 matched for age, sex, rash and socio-economic status for difference cognitive function to median age of 57.5 months (phenobarbitone-treated children) and 59.6 months (children not receiving phenobarbitone).

APPENDICES

Appendix 1. Search strategies

CENTRAL search strategy

#1 (febrile seizure*) or (febrile convulsion*)

#2 MeSH descriptor Seizures, Febrile explode all trees

#3 (anticonvulsant*) OR (antiepilep*)

#4 MeSH descriptor Anticonvulsants explode all trees

#5 (acetaminophen OR paracetamol OR aspirin)

#6 MeSH descriptor Ibuprofen explode all trees

#7 MeSH descriptor Acetaminophen explode all trees

#8 (#1 OR #2)

#9 (#3 OR #4 OR #5 OR #6 OR #7)

#10 (#8 AND #9)

MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2009).

1. randomised controlled trial.pt.

2. controlled clinical trial.pt.

3. randomised.ab

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp animals/ not humans.sh.

10. 8 not 9

11. febrile seizure$.tw.

12. febrile convulsion$.tw.

13. exp Seizures, Febrile/

14. 11 or 12 or 13

15. exp Anticonvulsants/

16. anticonvulsant$.tw.

17. antiepilep$.tw.

18. exp Acetaminophen/

19. (acetaminophen or paracetamol).tw.

20. exp Ibuprofen/

21. ibuprofen.tw.

22. 15 or 16 or 17 or 18 or 19 or 20 or 21

23. 10 and 14 and 22

WHAT'S NEW

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, and Martinus Cozijnsen joined for the 2016 update. They independently assessed trials for inclusion, appraised papers, and extracted data. They jointly prepared the report. Sarah Nevitt provided support with the creation of the 'Summary of findings' tables.

DECLARATIONS OF INTEREST

Martin Offringa: none known.

Richard Newton: none known.

Martinus Cozijnsen: none known.

Sarah Nevitt: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In a post-hoc change from protocol, in line with current Cochrane recommendations, we report 13 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]; Randomized Controlled Trials as Topic; Recurrence; Seizures, Febrile [*prevention & control]

MeSH check words

Child; Child, Preschool; Humans; Infant