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Febrile seizures

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ABSTRACT

INTRODUCTION: Simple febrile seizures are generalised in onset, last <15 minutes, and do not occur more than once in 24 hours. Complex febrile seizures are longer lasting, have focal symptoms, and can recur within 24 hours. This review only deals with simple febrile seizures. About 2% to 5% of children in the USA and Western Europe, and 6% to 9% of infants and children in Japan will have experienced at least one febrile seizure by the age of 5 years. Simple febrile seizures may slightly increase the risk of developing epilepsy, but have no known adverse effects on behaviour, scholastic performance, or neurocognition. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments given during episodes of fever in children with one or more previous simple febrile seizures? What are the effects of long-term (daily, for >1 month) anticonvulsant treatment in children with a history of simple febrile seizures? What are the effects of treatments on reducing the risk of subsequent epilepsy in children with a history of simple febrile seizures? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 18 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: anticonvulsants (intermittent or continuous) and antipyretic treatments (physical antipyretic measures, paracetamol, ibuprofen).

QUESTIONS

INTERVENTIONS

Key points

- Febrile seizures are defined as events in infancy or childhood usually occurring between 3 months and 5 years of age associated with a fever, but without evidence of intracranial infection or defined cause for the seizure.

  Simple febrile seizures are generalised in onset, last <15 minutes, and do not occur more than once in 24 hours. Complex seizures are longer lasting, have focal symptoms, and can recur within 24 hours. This review only deals with simple febrile seizures.

  About 2% to 5% of children in the USA and Western Europe, and 6% to 9% of infants and children in Japan will have experienced at least one febrile seizure by age 5 years.

  Simple febrile seizures may slightly increase the risk of developing epilepsy, but have no known adverse effects on behaviour, scholastic performance, or neurocognition.

- So far evidence showing whether antipyretic drug treatments or physical methods of temperature reduction are useful in treating episodes of fever to prevent seizure recurrence in children with one or more previous simple febrile seizures is lacking.

  Intermittent anticonvulsants used in treating episodes of fever to prevent seizure recurrence in children are associated with adverse effects, including hyperactivity, irritability, and difficulties with speech, activity level, or sleep.

- Continuous anticonvulsant treatment may be effective for reducing recurrence in children with a history of simple febrile seizures, but is associated with adverse effects; for example, phenobarbital may be associated with cognitive impairments and behavioural adverse effects, including hyperactivity, irritability, and aggressiveness.

Serious adverse events that may be associated with sodium valproate include hepatotoxicity and haematological toxicity, both of which may occasionally be fatal.

Anticonvulsants do not seem to reduce the risk of epilepsy up to 12 years later in children with a history of simple febrile seizures.

DEFINITION

Febrile seizures are divided into three types: simple febrile seizures, complex febrile seizures, and febrile status epilepticus. **This review focuses on children with simple febrile seizures.** The National Institutes of Health (NIH) definition of a febrile seizure is "an event in infancy or childhood usually occurring between 3 months and 5 years of age associated with a fever, but without evidence of intracranial infection or defined cause for their seizure", [1] after having excluded children with previous afebrile seizures. Another definition from the International League Against Epilepsy (ILAE) is that of "a seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of the central nervous system (CNS), without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures". [2] In working practice, the lower age limit for febrile seizures is generally taken to be 6 months, given concerns regarding the possibility of an underlying serious but treatable infection in younger infants masquerading as a febrile seizure (e.g., meningitis). A simple febrile seizure is a generalised seizure, often tonic-clonic, lasting <15 minutes in duration, which does not occur more than once in 24 hours, and is followed by full recovery within 1 hour. Treatment for the actual seizure is generally not indicated, given the short duration. In >80% of children the duration of the febrile seizure is <10 minutes, and in only about 9% of children do they last >15 minutes. [3] Often, by the time the child presents to hospital, the seizure has already stopped. A febrile seizure may also be the presenting sign of a fever episode. **This review does not include children experiencing complex febrile seizures**, which are characterised by any of the following features: >15 minutes in duration, focal symptoms, recurrence within 24 hours, and not followed by full consciousness within 1 hour. Investigations including neuroimaging and lumbar puncture are often warranted. **Also excluded from this review are children experiencing febrile status epilepticus**, which lasts >30 minutes and requires treatment. Addressing parental anxiety forms a key part of the management of simple febrile seizures, because parents' (unspoken) worry with a first seizure is that their child might have died. However, there is little in the medical literature about this aspect of education and reassurance in management of simple febrile seizures.

INCIDENCE/ PREVALENCE

About 2% to 5% of children in the USA and Western Europe, and 6% to 9% of infants and children in Japan will have experienced at least one febrile seizure, simple or complex, by the age of 5 years. Elsewhere the incidence varies, being 5% to 10% in India, and as high as 14% in Guam. [2] There are no specific data available for simple febrile seizures.

AETIOLOGY/ RISK FACTORS

While the exact cause of simple febrile seizures is unknown, it is thought to be multifactorial, with both genetic and environmental factors having been shown to contribute to its pathogenesis. [4] [5] Increasingly, a genetic predisposition is recognised, with febrile seizures occurring in families. However, the exact mode of inheritance is not known, and seems to vary between families. While polygenic inheritance is likely, there is a small number of families identified with an autosomal-dominant pattern of inheritance of febrile seizures, leading to the description of a "febrile seizure susceptibility trait" with an autosomal-dominant pattern of inheritance with reduced penetrance. [6] [4] In addition, mutations in several genes have been found that account for enhanced susceptibility to febrile seizures. [5] [7] [8] [9] [10] [11] A familial epilepsy syndrome exists (Generalised Epilepsy with Febrile Seizures Plus [GEFS+]), in which patients can have classical febrile seizures, febrile seizures that persist beyond 5 years (hence FS+), and/or epilepsy. Similar genetic factors have been identified that are involved in both febrile seizures and GEFS+. [5] [12] Although the exact molecular mechanisms of febrile seizures are yet to be understood, underlying mutations have been found in genes encoding the sodium channel and the gamma-aminobutyric acid A receptor. [12] [13] Both of these channels are also associated with another early epilepsy syndrome, Severe Myoclonic Epilepsy of Infancy (SMEI), which often begins with prolonged febrile seizure (either complex febrile seizure or febrile status) with subsequent seizures precipitated by fever. [12] With regards to risk factors, febrile seizures are more frequent in children attending day-care centres, and in those with a first- or second-degree relative with a history of febrile seizures. [14] The risk of another child having febrile seizures is 1 in 5ive if one sibling is affected, and 1 in 3 if both parents and a previous child have had febrile seizures. [15] Other risk factors associated with an increased rate of febrile seizure recurrence include young age at onset (<12 months), history of simple or complex febrile seizures, and body temperature at onset of <40 °C. [14] [16] Among these, age at onset seems the most constant predictive factor, with 50% of children aged <12 months and 30% of children aged >12 months presenting with a recurrent febrile seizure. Positive family history of epilepsy is not consistently associated with increased simple febrile seizure recurrence. [16]

PROGNOSIS

Simple febrile seizures may slightly increase the risk of developing epilepsy, [17] but have no adverse effects on behaviour, scholastic performance, or neurocognition. The risk of developing epilepsy is increased further in children with a history of complex febrile seizures. [18] [19] [20] [21] A strong association exists between febrile status epilepticus or febrile seizures characterised by focal symptoms and later development of temporal lobe epilepsy. [17] [22]

AIMS OF INTERVENTION

To reduce febrile seizures and prevent recurrence, and to prevent the development of epilepsy, with minimal adverse effects.

OUTCOMES

In the questions on treatments given during fever and the effects of long-term anticonvulsant treatment: **recurrence of febrile seizures** and **adverse effects**. In the question on reducing the risk of subsequent epilepsy: **incidence of epilepsy** and **adverse effects**.

METHODS

Clinical Evidence search and appraisal March 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2010, Embase 1980 to March 2010, and The Cochrane Database of Systematic Reviews 2010, March Issue (online)(1966 to date of issue). When editing this review we used the Cochrane Database of Systematic Reviews 2010, Issue 2. An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We included all studies described as "blinded", "open", or "open label". We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. We did an observational harms search for specific harms as highlighted by the contributor, peer reviewer, and editor. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. Some systematic reviews meta-analysed RCTs of children with both simple febrile seizures and complex febrile seizures, and in some RCTs the type of febrile seizure is unspecified; we have reported this throughout the text. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 16). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION

What are the effects of treatments given during episodes of fever in children with one or more previous simple febrile seizures?

OPTION

ANTIPYRETIC DRUG TREATMENTS (PARACETAMOL, IBUPROFEN)

- For GRADE evaluation of interventions for Febrile seizures, see table, p 16 .
- We do not know whether antipyretic drug treatments are useful in treating episodes of fever to prevent seizure recurrence in children with one or more previous simple febrile seizures.

Benefits and harms

Antipyretic drugs versus placebo:

We found one systematic review (search date 2003), [23] which identified two RCTs. We also found one systematic review (search date 2004) assessing the adverse effects of paracetamol in children with fever (see comment). [24]

Recurrence of febrile seizures

Antipyretic drugs compared with placebo Antipyretic drugs (ibuprofen or paracetamol) may be no more effective at 1 to 2 years at reducing the proportion of children (who have previously had one febrile seizure) with recurrence of febrile seizures (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[23] Systematic review	230 children with one previous simple febrile seizure Data from 1 RCT	**Proportion of children who had recurrence of febrile seizures , 1 year** 31/111 (28%) with ibuprofen given during episodes of fever 36/119 (30%) with placebo	Reported as not significant P value not reported Results should be interpreted with caution (the review used inadequate search methods that are difficult to replicate, and had no specific inclusion/exclusion criteria)	⟷	Not significant
[23] Systematic review **4-armed trial**	180 children with one previous simple febrile seizure Data from 1 RCT The remaining arms evaluated paracetamol plus diazepam and diazepam plus placebo	**Number of recurrent febrile seizures , 2 years** 5% with paracetamol (given during episodes of fever) plus placebo 8% with placebo plus placebo Absolute numbers not reported	Reported as not significant for paracetamol *v* placebo P value not reported Results should be interpreted with caution (the review used inadequate search methods that are difficult to replicate, and had no specific inclusion/exclusion criteria)	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [23]

Paracetamol versus physical methods of temperature reduction:

See benefits and harms of conservative measures (physical methods of temperature reduction), p 4 .

Further information on studies

Comment: **Adverse effects:** We found one systematic review (search date 2004), which identified 7 RCTs comparing paracetamol versus placebo in children with fever. The review found no significant difference in adverse effects between paracetamol and placebo (3 RCTS: 9/130 [7%] with paracetamol *v* 4/124 [3%] with placebo; RR 1.84, 95% CI 0.65 to 5.18). Because this review focused on children with fever and not those with simple febrile seizures, we have not reported it in the previous section. [24]

OPTION CONSERVATIVE MEASURES (E.G., WATCHFUL WAITING, PHYSICAL ANTIPYRETIC MEASURES [SUCH AS TEPID SPONGING, REMOVING CLOTHING])

- For GRADE evaluation of interventions for Febrile seizures, see table, p 16 .
- We found no direct information from RCTs about physical methods of temperature reduction in the treatment of children with simple febrile seizures.

Benefits and harms

Physical methods of temperature reduction:

We found no systematic review or RCTs in children with febrile seizures (see comments section below).

Further information on studies

Comment: **Physical methods of temperature reduction in children with high temperature:** We found one systematic review (search date 2004), which identified 6 RCTs comparing tepid sponging versus paracetamol in children with fever. One of the RCTs (80 children) assessed febrile seizures. [24] It found no significant difference in febrile seizures at 2 hours between sponging and paracetamol (1/40 [3%] with tepid sponging *v* 0/40 [0%] with paracetamol; RR 0.33, 95% CI 0.01 to 7.95). The review found no significant difference in adverse effects, including shivering, goose pimples, and discomfort, between sponging and paracetamol (2 RCTs: 6/55 [11%] with tepid sponging *v* 2/65 [3%] with paracetamol; RR 0.26, 95% CI 0.07 to 1.01). Because this review excluded children with previous simple febrile seizures, we have not reported it in the previous section. [24]

OPTION ANTICONVULSANTS (INTERMITTENT)

- For GRADE evaluation of interventions for Febrile seizures, see table, p 16 .
- Diazepam has been associated with increased hyperactivity, lethargy, irritability, and with difficulties with speech, activity level, or sleep.
- We found no clinically important results from RCTs about intermittent compared with continuous anticonvulsants for treating children with febrile seizures.

Benefits and harms

Intermittent anticonvulsants versus placebo or no treatment :

We found two systematic reviews (search dates not reported) [25] [26] assessing intermittent diazepam given during a febrile episode versus placebo or no treatment in children with a history of febrile seizures (see further information on studies for more details on search criteria of the reviews). The second review [26] identified three of the same RCTs as the first systematic review. [25] We report from both reviews because they reached different conclusions on the effectiveness of intermittent diazepam (see further information on studies for possible explanation). [26] [25] The first review also identified two RCTs assessing intermittent phenobarbital versus placebo or no treatment. We found two subsequent RCTs comparing intermittent clobazam versus placebo. [27] [28] For further general information on harms of anticonvulsants see review on epilepsy (partial).

Recurrence of febrile seizures

Intermittent anticonvulsants compared with placebo We don't know whether intermittent diazepam or intermittent phenobarbital given to children during a febrile episode is more effective than placebo or no treatment at reducing the risk of febrile seizure recurrence. Clobazam given during a febrile episode may be more effective at reducing the risk of recurrence of febrile seizures (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[26] Systematic review	791 children with febrile seizures, unclear how many had simple febrile seizures 4 RCTs in this analysis	**Proportion of children with febrile seizure recurrence** 44/393 (11%) with intermittent diazepam (given during a febrile episode) 68/398 (17%) with placebo	OR 0.60 95% CI 0.40 to 0.90 Results should be interpreted with caution (most of the RCTs identified by the review had weak methods; see further information on studies)	●○○	intermittent diazepam

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] Systematic review	1060 children with febrile seizures, unclear how many had simple febrile seizures 4 RCTs in this analysis	**Proportion of children with febrile seizure recurrence** 92/537 (17%) with intermittent diazepam (given during a febrile episode) 134/523 (26%) with placebo or no treatment	RR 0.71 95% CI 0.44 to 1.13 P = 0.20 Results should be interpreted with caution (most of the RCTs identified by the review had weak methods; see further information on studies)	⟷	Not significant
[27] RCT	40 children with one or more episodes of febrile seizure, unclear how many had simple febrile seizures The children had 108 episodes of fever over a mean of 9.9 months; 60 episodes were treated with clobazam and 48 with placebo	**Rate of seizure recurrence** 1/60 (2%) episodes with clobazam (given during episodes of fever) 6/48 (12%) episodes with placebo	P = 0.01 The RCT randomised children and analysed episodes of fever; it is unclear whether adjustments were made to allow for this, but it is likely that results would remain significant even with adjustment	○○○	clobazam
[28] RCT	60 children who completed the study, aged 6 months to 5 years, presenting with one or more episodes of febrile seizure, unclear how many had simple febrile seizures The children had 312 episodes of fever over a period of 6 months; 151 episodes were treated with clobazam and 161 with placebo	**Recurrence of seizures** 9/30 (30%) with clobazam (given during febrile episodes) 25/30 (83%) with placebo In both groups, parents were advised to treat temperatures above 38 °C with antipyretic (paracetamol) and cold sponging	P <0.001 Results should be interpreted with caution (the RCT had several methodological issues; see further information on studies for more details)	○○○	clobazam
[25] Systematic review	281 children with febrile seizures, unclear how many had simple febrile seizures 2 RCTs in this analysis	**Proportion of children with febrile seizure recurrence** 41/156 (26%) with intermittent phenobarbital (given during a febrile episode) 41/125 (33%) with placebo or no treatment	RR 0.80 95% CI 0.55 to 1.15 P = 0.22	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT	185 children with one previous febrile seizure, unclear how many had simple febrile seizures	**Number of days that children were hyperactive (defined as agitation and inability to keep still)** 138 days with diazepam	P <0.0003	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [26] [25]	34 days with placebo			
[30] RCT	406 children aged 6 months to 5 years; approximately 60% had simple febrile seizures In review [26] [25]	**Adverse effects** with diazepam with placebo Absolute results not reported 59/153 (39%) children taking intermittent diazepam had adverse effects, including: ataxia; lethargy; irritability; or difficulties with speech, activity level, or sleep. One child taking placebo had a rash			
[27] RCT	40 children with one or more episodes of febrile seizure, unclear how many had simple febrile seizures The children had 108 episodes of fever over a mean of 9.9 months; 60 episodes were treated with clobazam and 48 with placebo	**Ataxia** 5/60 (8%) episodes with clobazam (given during episodes of fever) 0/48 (0%) episodes with placebo	P = 0.04 The RCT randomised children and analysed episodes of fever; it is unclear whether adjustments were made to allow for this, but it is likely that results would remain significant even with adjustment	○○○	placebo
[28] RCT	60 children who completed the study, aged 6 months to 5 years, presenting with one or more episodes of febrile seizure, unclear how many had simple febrile seizures The children had 312 episodes of fever over a period of 6 months; 151 episodes were treated with clobazam and 161 with placebo	**Irritability** 4/30 (13%) with clobazam (given during febrile episodes) 1/30 (3%) with placebo In both groups, parents were advised to treat temperatures above 38 °C with antipyretic (paracetamol) and cold sponging	Significance not assessed RCT reported that "no significant difference in adverse drug-reaction profile was observed except irritability, which was occasionally more in clobazam group" Results should be interpreted with caution (the RCT had several methodological issues; see further information on studies for more details)		
[31] Cohort study Prospective study design	139 children who entered the study after their first febrile seizure Children with complex febrile seizures (approximately 19%) and febrile status epilepticus (approximately 3%) were also included. Treatments were allocated by odd and even dates (further details not reported)	**Adverse effects , 3 years** with intermittent rectal diazepam (given during first 2 days of fever) with no diazepam Absolute results not reported The study reported that adverse effects with diazepam were mild and transient, and no long-term adverse effects were recorded	Significance not assessed		

No data from the following reference on this outcome. [26] [25]

Intermittent anticonvulsants versus continuous anticonvulsants:

We found no systematic review or RCTs comparing intermittent anticonvulsants versus continuous anticonvulsants.

Further information on studies

[26] [25] One review included only studies written in Spanish, Portuguese, and English language. [26] Another review restricted inclusion to English language RCTs. [25] Both reviews stated inclusion criteria and reported methods of data extraction. One RCT [30] identified by both reviews was reported differently in each review: the RCT compared diazepam versus placebo. One review reported recurrence rates for the RCT as 7/202 (3.5%) in children taking diazepam and 29/204 (14.2%) in children taking placebo; [26] however, the second review reported recurrence rates as 37/202 (18.3%) in children taking diazepam compared with 53/204 (30%) in children taking placebo. [25] This may explain how reviews with predominantly the same included RCTs came to different conclusions. The mode, dose, and frequency of administration of diazepam varied in each RCT. Most of the RCTs identified by the reviews had weak methods. The first RCT was small. In the second RCT, 50 children (25%) taking diazepam and 55 children (27%) taking placebo were lost to follow-up. The third RCT reported poor compliance in children taking diazepam, which was significantly different from those taking placebo.

[28] Both arms were treated with an antipyretic if the temperature exceeded 38 °C, however it is unclear how many children actually received antipyretics. Since both groups had the same instructions the significant results in the treatment group may be attributable to clobazam. However, method of randomisation used was not reported, and it was stated that the analysis was not by intention to treat; in addition, the number of children lost to follow-up after randomisation is unclear.

Comment: None.

QUESTION **What are the effects of long-term (daily, >1 month) anticonvulsant treatment in children with a history of simple febrile seizures?**

OPTION **ANTICONVULSANTS (CONTINUOUS)**

- For GRADE evaluation of interventions for Febrile seizures, see table, p 16 .
- Continuous anticonvulsant treatment may be effective for reducing recurrence in children with a history of simple febrile seizures, but is associated with adverse effects.
- Phenobarbital may be associated with cognitive impairment, and with behavioural problems including hyperactivity, irritability, and aggression.
- Serious adverse events that may be associated with sodium valproate include hepatotoxicity and haematological toxicity, both of which may occasionally be fatal.

Benefits and harms

Continuous phenobarbital versus placebo or no treatment:

We found two systematic reviews (search dates not reported), which between them identified 8 RCTs assessing continuous phenobarbital given during a febrile episode in children with a history of febrile seizures (see further information on studies for details on search criteria of the reviews). [25] [26] The first review [25] identified all 6 of the RCTs included in the second review. [26] Doses of phenobarbital differed across RCTs. For general information on harms of anticonvulsants see review on epilepsy (partial).

Recurrence of febrile seizures

Continuous phenobarbital compared with placebo/no treatment Phenobarbital may be more effective at reducing febrile seizure recurrence in children with a history of febrile seizures (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[26] Systematic review	598 children with febrile seizures, unclear how many had simple febrile seizures 6 RCTs in this analysis	**Proportion of children with febrile seizure recurrence** 71/290 (24%) with continuous phenobarbital 114/308 (37%) with placebo	OR 0.54 95% CI 0.38 to 0.76 NNT 17 95% CI 10 to 85 There was significant statistical heterogeneity among the RCTs (P <0.01)	●○○	continuous phenobarbital
[25] Systematic review	975 children with febrile seizures, unclear how many had simple febrile seizures 8 RCTs in this analysis	**Proportion of children with febrile seizure recurrence** 90/483 (19%) with continuous phenobarbital 184/492 (37%) with placebo or no treatment	RR 0.51 95% CI 0.32 to 0.82 P <0.01 There was significant statistical heterogeneity among the RCTs	●○○	continuous phenobarbital

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] RCT	217 children with at least one previous simple febrile seizure In review [26] [25]	**Negative effect on cognition (mean IQ) , 6 months after weaning and discontinuation of phenobarbital** with phenobarbital with placebo Absolute results not reported	Difference in mean IQ score: –5.2 points 95% CI –10.5 points to +0.04 points P = 0.052	⟷	Not significant
[32] RCT	217 children with at least one previous simple febrile seizure In review [26] [25]	**Negative effect on cognition (mean IQ) , 2 years** with phenobarbital with placebo Absolute results not reported	Difference in mean IQ score: –8.4 points 95% CI –13.3 points to –3.5 points P = 0.0057	○○○	placebo
[33] RCT	90 children with two or more previous simple febrile seizures (60 taking phenobarbital and 30 taking placebo) In review [26] [25]	**Adverse effects necessitating withdrawal** 3/60 (5%) with phenobarbital 1/30 (3%) with placebo In the phenobarbital group, children withdrawing from the study had "intolerable" adverse effects (defined as effects persistent for >1 month), which included hyperkinetic behaviour, extreme irritability, fussiness, and aggressiveness The child who withdrew from the placebo arm withdrew for unknown reasons	Significance not assessed		
[34] RCT	138 children with one previous simple febrile seizure In review [26] [25]	**Negative effects on behaviour** with phenobarbital with placebo Absolute results not reported			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Many parents of children taking phenobarbital reported deterioration in behaviour, as did many parents of children taking placebo (significance not assessed); 20% reported slight improvement in some aspects of behaviour when phenobarbital treatment was stopped			
[35] RCT	79 children with one previous simple febrile seizure In review [26] [25]	**Adverse effects necessitating withdrawal** 4/39 (10%) with phenobarbital 4/39 (10%) with placebo	Significance not assessed		
[36] RCT	371 children with one previous simple febrile seizure (109 taking continuous phenobarbital *v* 142 intermittent phenobarbital *v* 120 no treatment) In review [26] [25]	**Negative effects on behaviour** 46/109 (42%) with continuous phenobarbital 22/120 (18%) with no treatment Hyperactivity was the most common behavioural disorder. Hyperactivity spontaneously disappeared in 52% of children. Continuous phenobarbital was prematurely discontinued in 25/46 (54%) of the children with behaviour abnormality (20% of those treated)	Significance not assessed		
[37] RCT	65 children with one previous simple febrile seizure	**Negative effects on behaviour (increased fussiness and sleep disturbance; transient)** 8/35 (23%) with continuous phenobarbital 7/30 (23%) with placebo	Significance not assessed		
[37] RCT	65 children with one previous simple febrile seizure	**Negative effects on behaviour (increased fussiness and sleep disturbance; dose related)** 4/35 (11%) with continuous phenobarbital 0/30 (0%) with placebo	Significance not assessed		
[37] RCT	65 children with one previous simple febrile seizure	**Negative effects on behaviour (increased fussiness and sleep disturbance; unacceptable)** 3/35 (9%) with continuous phenobarbital 1/30 (3%) with placebo	Significance not assessed		
[37] RCT	65 children with one previous simple febrile seizure	**Decreased comprehension** with continuous phenobarbital with placebo Absolute results not reported Children taking phenobarbital had lower scores on memory concentration items on the Stanford–Binet Intelligence scale at 8-month to 12-month follow-up compared with children taking placebo, although the difference between groups was not significant	P = 0.07	⟷	Not significant

No data from the following reference on this outcome. [26] [25]

Continuous sodium valproate versus placebo or no treatment:

We found one systematic review (search date not reported; see further information on studies for details on search criteria of the review), which identified three RCTs comparing sodium valproate versus placebo or no treatment. [25] For further information on hepatological and haematological toxicity of sodium valproate from case studies, see comment. For further general information on harms of anticonvulsants see review on epilepsy (partial).

Recurrence of febrile seizures

Continuous sodium valproate compared with placebo/no treatment Continuous sodium valproate may be no more effective at reducing febrile seizure recurrence in children with a history of febrile seizures (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[25] Systematic review	216 children with a history of febrile seizure 3 RCTs in this analysis	**Proportion of children with recurrence of febrile seizures** 29/102 (28%) with sodium valproate 34/114 (30%) with placebo or no treatment	RR 0.74 95% CI 0.24 to 2.23 P = 0.59 Analysis of one small, placebo-controlled RCT included in this meta-analysis found the difference between groups to be significant in favour of sodium valproate (see further information about studies for more details) There was significant statistical heterogeneity among RCTs	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [25]

Continuous anticonvulsants versus each other:

We found one systematic review (search date not reported; see further information on studies for details on search criteria of the review), [26] which identified one RCT. [38] For further general information on harms of anticonvulsants see review on epilepsy (partial).

Recurrence of febrile seizures

Continuous anticonvulsants compared with each other We don't know whether phenobarbital is more effective than sodium valproate at reducing the proportion of children with recurrence of febrile seizures (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[38] RCT **3-armed trial**	69 children with one previous febrile seizure, type not reported In review [26] The third arm evaluated placebo	**Proportion of children with febrile seizure recurrence** 1/22 (4%) with sodium valproate (daily) 4/21 (19%) with phenobarbital (daily)	Reported as not significant for sodium valproate *v* phenobarbital P value not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [26] [38]

Further information on studies

[26] The review included only RCTs written in Spanish, Portuguese, and English language. The review stated inclusion criteria and reported methods of data extraction.

[25] The review restricted inclusion to English language RCTs. The review stated inclusion criteria and reported methods of data extraction. In the comparison of continuous sodium valproate versus placebo or no treatment, the authors of the review suggest that, if only the small (48 children), placebo-controlled RCT is considered, there is a significant decrease in recurrent febrile seizures with sodium valproate compared with placebo (1/22 [4%] with sodium valproate *v* 9/26 [35%] with placebo; RR 0.13, 95% CI 0.02 to 0.96, P = 0.01).

Comment:

Known rare, serious adverse effects of sodium valproate include hepatological and haematological toxicity. Although valproate hepatotoxicity may be dose dependent, it can, more rarely, be an idiosyncratic phenomenon — which means that it is often irreversible and difficult to predict on the basis of laboratory monitoring. [39] Blood disturbances can also be dose dependent, with direct bone marrow suppression leading to aplastic anaemia or peripheral cytopenia affecting one or more cell lines, or even fatal bone marrow failure. [40]

One cohort study (61 children, 55 with epilepsy, 6 with complex febrile seizures, mean age 81 months) assessed the effects of valproate on bone mineral density after 1 year. It found no significant difference in bone mineral density or fracture risk between groups, however it recommended bone mineral density monitoring in children taking valproate. It also found that valproate was associated with a significant increase in BMI (body mass index). [41]

Clinical guide:
Most RCTs did not assess compliance and, although the adverse effects associated with anticonvulsants are well known, potential adverse events associated with their use were not routinely monitored or investigated. Despite this lack of formal monitoring of adverse effects, the authors of the individual RCTs and the reviews often concluded that the benefit:harm ratios for phenobarbital and sodium valproate were unfavourable.

The authors of the second review concluded that the effectiveness of phenobarbital could not be shown. [26] This is not quite in keeping with the findings of the review of a significantly lower recurrence of febrile seizures in children taking phenobarbital. The first review found that, even taking the heterogeneity of the trials of phenobarbital into account, the overall effect remained positive, with inconsistencies in effect among RCTs being ascribed to the differing degree of seizure severity. [25]

QUESTION What are the effects of treatments on reducing the risk of subsequent epilepsy in children with a history of simple febrile seizures?

OPTION ANTICONVULSANTS (INTERMITTENT AND CONTINUOUS)

- For GRADE evaluation of interventions for Febrile seizures, see table, p 16 .
- Anticonvulsants do not seem to reduce the risk of epilepsy up to 12 years later in children with a history of simple febrile seizures.

Benefits and harms

Intermittent diazepam versus no prophylaxis:

We found one quasi-randomised RCT. [42]

Incidence of epilepsy

Intermittent diazepam compared with no prophylaxis Intermittent diazepam given during a febrile episode may be no more effective at reducing the incidence of epilepsy at 12 years in children with one previous simple or complex febrile seizure (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of epilepsy					
[42] RCT	289 children with one previous simple or complex febrile seizure Quasi-randomised RCT that assigned groups alternatively, depending on whether the child was admitted on an odd or even date	**Incidence of epilepsy , 12 years** 0.8% with intermittent diazepam (given during a febrile episode) 0.7% with no prophylaxis Absolute numbers not reported In the no prophylaxis arm, diazepam was given only in case of febrile seizure	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[42] RCT	289 children with one previous simple or complex febrile seizure Quasi-randomised RCT that assigned groups alternatively, depending on whether the child was admitted on an odd or even date	**Adverse effects** with intermittent diazepam (given during a febrile episode) with no prophylaxis The quasi-randomised RCT found no significant difference in full scale, verbal, or performance intelligence quotients (IQ; measured by the Wechsler Intelligence Scale for Children [WISC] general intelligence test), memory, reading tests, and overall scholastic performance at 12 years between intermittent diazepam and diazepam during seizures (absolute results tabulated) In the no prophylaxis arm, diazepam was given only in case of febrile seizure	Difference between groups reported as not significant for all outcomes P values not reported	⟷	Not significant

Phenobarbital (daily or intermittent) versus no treatment:

We found one RCT. [43] For further general information on harms of anticonvulsants see review on epilepsy (partial) and comments below.

Incidence of epilepsy

Phenobarbital (daily or intermittent) compared with no treatment Phenobarbital given daily or intermittently may be no more effective at reducing the proportion of children who develop epilepsy at 6.3 years (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of epilepsy					
[43] RCT **3-armed trial**	400 children with one previous simple or complex febrile seizure	**Proportion of children who developed epilepsy , mean follow-up of 6.3 years** 7/116 (6%) with daily phenobarbital 6/158 (4%) with intermittent phenobarbital 1/126 (1%) with no treatment	Reported as not significant (for both comparisons of phenobarbital *v* no treatment) P values not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [43]

Continuous sodium valproate versus placebo/no treatment:

We found no systematic review or RCTs assessing the effects of sodium valproate on preventing epilepsy in children with simple febrile seizures. For further general information on harms including the effects on bone mineral density of anticonvulsants see review on epilepsy (partial).

Further information on studies

[42] The RCT found that the risk of having epilepsy at the mean age of 14 years was 1/250 (0.4%) after simple febrile seizures and 1/40 (2.5%) after complex febrile seizures. There was no significant difference in the incidence of epilepsy with different types of seizure (reported as not significant, P value not reported).

Comment: The RCT assessing children who had taken phenobarbital for febrile seizures suggested that children who subsequently developed epilepsy differed from those who did not in the frequency of neonatal abnormality, family history of mental retardation, focal initial febrile seizures, and delay in psychomotor milestones before the initial febrile seizure. It also suggested that half of the children who developed mental retardation had histories of delay in psychomotor milestones before the initial febrile seizure. [43]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Anticonvulsants (intermittent) One previously included systematic review re-evaluated. [25] Additional data added on intermittent phenobarbital versus placebo. The review found no significant difference in febrile seizure recurrence between intermittent phenobarbital and placebo. Categorisation unchanged (Likely to be ineffective or harmful)

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Disclaimer

GRADE **Evaluation of interventions for Febrile seizures.**

Important outcomes			Incidence of epilepsy, Recurrence of febrile seizures						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments given during episodes of fever in children with one or more previous simple febrile seizures?									
2 (at least 230) [23]	Recurrence of febrile seizures	Antipyretic drugs versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results and methodological weaknesses (inadequate search methods in systematic review and unclear inclusion criteria)
6 (at least 1441) [26] [25] [27] [28]	Recurrence of febrile seizures	Intermittent anticonvulsants versus placebo or no treatment	4	–1	0	–2	0	Very low	Quality point deducted for methodological issues. Directness points deducted for differences in doses, methods of administration and compliance
What are the effects of long-term (daily, >1 month) anticonvulsant treatment in children with a history of simple febrile seizures?									
8 (975) [26] [25]	Recurrence of febrile seizures	Continuous phenobarbital versus placebo or no treatment	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among studies. Directness point deducted for differences in doses used
3 (216) [25]	Recurrence of febrile seizures	Continuous sodium valproate versus placebo or no treatment	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among studies. Directness point deducted for differences in doses used
1 (43) [38]	Recurrence of febrile seizures	Continuous anticonvulsants versus each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of treatments on reducing the risk of subsequent epilepsy in children with a history of simple febrile seizures?									
1 (290) [42]	Incidence of epilepsy	Intermittent diazepam versus no prophylaxis	4	–2	0	0	0	Low	Quality points deducted for quasi-randomisation and incomplete reporting of results
1 (400) [43]	Incidence of epilepsy	Phenobarbital (daily or intermittent) versus no treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for underlying differences in risk of developing epilepsy

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.