Febrile seizures

Search date July 2013

Leena D Mewasingh

ABSTRACT

INTRODUCTION: Simple febrile seizures are generalised in onset and have a brief duration. The American Academy of Pediatrics defines this brief duration to be <15 minutes; whereas, in the UK, a maximum duration of 10 minutes is used. Simple febrile seizures do not occur more than once in 24 hours and resolve spontaneously. Complex febrile seizures are longer lasting, have focal symptoms (at onset or during the seizure), and can recur within 24 hours or within the same febrile illness. This review only deals with simple febrile seizures. About 2% to 5% of children in the US 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. A very small number of children with simple febrile seizures may develop afebrile seizures, but simple febrile seizures are not associated with any permanent neurological deficits. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments given during episodes of fever in children (aged 6 months to 5 years) with one or more previous simple febrile seizures? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2013 (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 4 RCTs or systematic reviews of RCTs 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: intermittent anticonvulsants (clobazam, diazepam, lorazepam), antipyretic drug treatments (paracetamol, ibuprofen), and conservative measures (watchful waiting, physical antipyretic measures [tepid sponging, removing clothes, cooling room, direct fanning of child]).

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. [1]

  Simple febrile seizures are generalised in onset and have a brief duration. They do not occur more than once in 24 hours and resolve spontaneously. Complex seizures are longer lasting, have focal symptoms (at onset or during the seizure), and can recur within 24 hours or within the same febrile illness. This review only deals with simple febrile seizures.

  About 2% to 5% of children in the US 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.

  A very small number of children with simple febrile seizures may develop afebrile seizures, but simple febrile seizures are not associated with any permanent neurological deficits.

- Evidence is lacking on whether antipyretic drug treatments (paracetamol, ibuprofen) or physical methods of temperature reduction (tepid sponging, removing clothing, cooling room, direct fanning of child) are useful in treating episodes of fever to prevent seizure recurrence in children with one or more previous simple febrile seizures.

- Intermittent anticonvulsants (clobazam, diazepam) may be effective in reducing seizure recurrence at some time points, but the lack of consistency of results over time and weak methods of RCTs make it difficult to draw any definitive conclusions on their effectiveness, and any long-term clinical benefits are unclear.

  Also, adverse effects, such as hyperactivity, lethargy, ataxia, and sedation, may often be associated with the use of intermittent anticonvulsants (clobazam, diazepam, lorazepam).

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 addition, following updates to ILAE classification and terminology, febrile seizures are now categorised under "conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se". [3] 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 that has a brief duration. The American Academy of Pediatrics has defined this brief duration to be <15 minutes; [4] whereas, in the UK, a maximum duration of 10 minutes is used. A simple febrile seizure does not occur more than once in 24 hours and resolves spontaneously. 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. [5] 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: >10 or 15 minutes in duration (depending on the definition used), focal symptoms (at onset or during the seizure), and recurrence within 24 hours or within the same febrile illness. Investigations, including neuro-imaging 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 febrile seizures because parents' (unspoken) worry with a first seizure is often that their child might have died. [6] It is good practice to support families with information on simple febrile seizures and contact details of medical services, and reassure them of the benign nature of simple febrile seizures. [7]

INCIDENCE/ PREVALENCE

About 2% to 5% of children in the US 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, it is between 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. [8] [9] 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. [10] [8] In addition, mutations in several genes have been found that account for enhanced susceptibility to febrile seizures. [9] [11] [12] [13] [14] [15] A familial epilepsy syndrome exists (generalised epilepsy with febrile seizures plus [GEFS+]), in which people can have classical febrile seizures, febrile seizures that persist beyond 5 years (hence FS+), and/or epilepsy. The revised ILAE classification refers to FS+ as an 'electroclinical syndrome' that usually starts in childhood but can occasionally have its onset in infancy. [3] Similar genetic factors have been identified that are involved in both febrile seizures and FS+. [9] [16] Although the exact molecular mechanisms of febrile seizures are yet to be understood, underlying mutations have been found in genes encoding the gamma-aminobutyric acid A receptor and the sodium channel (e.g., sodium channel, voltage-gated, type I, alpha subunit [SCN1A]). [16] [17] The latter, in particular, is associated with an early epilepsy syndrome and epileptic encephalopathy called Dravet syndrome (also known as severe myoclonic epilepsy of infancy [SMEI]), which often begins with prolonged seizures triggered by fever or the first presentation of epilepsy. [3] [16] Certain SCN1A mutations have also been associated with increased susceptibility to febrile seizures and FS+. [18] [19] As most of the mutations in SCN1A-related epilepsies occur de novo, when an infant presents initially with febrile seizures, there is uncertainty as to whether they will have simple febrile seizures only, develop FS+, or develop severe epilepsy, such as Dravet syndrome. [20] In the UK, genetic testing for SCN1A mutations is currently not routinely carried out in clinical practice for infants and children with simple febrile seizures, but it is increasingly being considered and performed in infants and children with complex febrile seizures, febrile status, and FS+. 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. [21] The risk of another child having febrile seizures is 1 in 5 if one sibling is affected, and 1 in 3 if both parents and a previous child have had febrile seizures. [22] 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. [21] [23] 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. [23]

PROGNOSIS

A very small number of children with simple febrile seizures may develop afebrile seizures, [24] but simple febrile seizures are not associated with any permanent neurological deficits. Furthermore, simple febrile seizures do not appear to have any known long-term adverse effects or sequelae. [25] Whereas traditionally understood to be a 'benign' condition, the ILAE cautions against this terminology, stating that 'benign' can be misleading and leave physicians, patients, and families unaware of and unprepared to address the wide variety of brain disorders that may be associated with febrile seizures, such as cognitive, behavioural, and psychiatric illnesses, as well as sudden death and suicide. [3] Nonetheless, there is very little evidence to suggest that simple febrile seizures have any adverse effects on behaviour or learning. [26] [25] The risk of developing epilepsy is increased further in children with a history of complex febrile seizures. [27] [28] [29] [26] A strong association exists between febrile status epilepticus or febrile seizures characterised by focal symptoms and later development of temporal lobe epilepsy. [24] [30]

AIMS OF INTERVENTION

To prevent seizure recurrence with minimal adverse effects in children with one or more previous simple febrile seizures.

OUTCOMES

Recurrence of febrile seizures and **adverse effects**.

METHODS

Clinical Evidence search and appraisal July 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2013, Embase 1980 to July 2013, and The Cochrane Database of Systematic Reviews 2013, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in English (including open studies) and containing more than 20 individuals (at least 10 per arm), of whom more than 80% were followed up. There was no minimum length of follow-up. A regular surveillance protocol was used 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 were added to the review as required. 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 12). 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 (aged 6 months to 5 years) 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 12 .
- We do not know whether antipyretic drug treatments (paracetamol, ibuprofen) 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 (paracetamol, ibuprofen) versus placebo:

We found two systematic reviews. [31] [7] The first systematic review (search date 2003) identified two RCTs; one assessing ibuprofen versus placebo and the other assessing paracetamol versus placebo. [31] The second systematic review (search date 2011) was a higher quality review which identified one of the RCTs found in the first review (ibuprofen versus placebo). [7] We also found one further systematic review (search date 2004) assessing the adverse effects of paracetamol in children with fever (see Comment). [32]

Recurrence of febrile seizures

Antipyretic drugs (paracetamol, ibuprofen) compared with placebo We don't know whether paracetemol or ibuprofen are more effective than placebo at reducing the proportion of children with recurrence of febrile seizures in children with one or more previous simple febrile seizures (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[7] Systematic review	230 children (12 months–4 years) with febrile seizures and at least 1 risk factor for recurrence Data from 1 RCT	**Proportion of children who had recurrence of febrile seizures , 6 months** 27/111 (24%) with ibuprofen given during episodes of fever 25/119 (21%) with placebo	RR 1.16 95% CI 0.72 to 1.87 P = 0.55	⟷	Not significant
[7] Systematic review	230 children (12 months–4 years) with febrile seizures and at least 1 risk factor for recurrence Data from 1 RCT	**Proportion of children who had recurrence of febrile seizures , 12 months** 32/111 (29%) with ibuprofen given during episodes of fever 38/119 (32%) with placebo	RR 0.90 95% CI 0.61 to 1.34 P = 0.61	⟷	Not significant
[7] Systematic review	230 children (12 months–4 years) with febrile seizures and at least 1 risk factor for recurrence Data from 1 RCT	**Proportion of children who had recurrence of febrile seizures , 24 months** 37/111 (33%) with ibuprofen given during episodes of fever 46/119 (39%) with placebo	RR 0.86 95% CI 0.61 to 1.22 P = 0.40	⟷	Not significant
[31] 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 , 24 months** 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) Number of children in each study arm not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [7] [31]

Paracetamol versus physical methods of temperature reduction:

See Benefits and harms of conservative measures (physical methods of temperature reduction), p 5 .

Comment: **Adverse effects:** We found one systematic review (search date 2004), which identified 7 RCTs comparing paracetamol versus placebo in children with fever. Because the review focused on children with fever and not those with simple febrile seizures, we have not reported the results in the Benefits and harms section. [32] 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).

Drug safety alert: paracetamol (acetaminophen) (August 2013)

The Food and Drug Administration (FDA) issued a drug safety alert on the risk of rare but serious skin reactions with paracetamol (acetaminophen). These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP) can be fatal. (www.fda.gov/)

OPTION CONSERVATIVE MEASURES (WATCHFUL WAITING, PHYSICAL ANTIPYRETIC MEASURES [TEPID SPONGING, REMOVING CLOTHING, COOLING ROOM, DIRECT FANNING OF CHILD])

- For GRADE evaluation of interventions for Febrile seizures, see table, p 12 .
- We found no direct information from RCTs about physical methods of temperature reduction (tepid sponging, removing clothing, cooling room, direct fanning of child) in the treatment of children with simple febrile seizures.

Benefits and harms

Physical methods of temperature reduction (tepid sponging, removing clothing, cooling room, direct fanning of child):

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

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. [32] However, the review excluded children with previous simple febrile seizures, so we have not reported the results in the Benefits and harms section. One of the RCTs (80 children) assessed febrile seizures. 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).

OPTION INTERMITTENT ANTICONVULSANTS (CLOBAZAM, DIAZEPAM, LORAZEPAM)

- For GRADE evaluation of interventions for Febrile seizures, see table, p 12 .
- Intermittent anticonvulsants (clobazam, diazepam) may be effective in reducing seizure recurrence at some time points, but the lack of consistency of results over time and weak methods of RCTs make it difficult to draw any definitive conclusions on their effectiveness, and any long-term clinical benefits are unclear.
- Also, adverse effects, such as hyperactivity, lethargy, ataxia, and sedation, may often be associated with the use of intermittent anticonvulsants.
- We found no RCTs evaluating intermittent lorazepam for treating children with one or more previous simple febrile seizure.

Benefits and harms

Intermittent anticonvulsants (clobazam, diazepam, lorazepam) versus placebo or no treatment:

We found one systematic review (search date 2011) assessing intermittent use of the anticonvulsants diazepam and clobazam versus placebo or no treatment in children with a history of febrile seizures. [7] It found no studies on lorazepam. The methods of the included RCTs were weak (see Further information on studies). For further general information on harms of anticonvulsants see review on Epilepsy (partial).

Recurrence of febrile seizures

Intermittent anticonvulsants (clobazam, diazepam, lorazepam) compared with placebo or no treatment We don't know whether intermittent oral diazepam given to children during a febrile episode is more effective than placebo or no treatment at reducing the risk of febrile seizure recurrence at 6 and 12 months. Intermittent oral diazepam may be more effective than placebo or no treatment at reducing the risk of febrile seizure recurrence at 24 and 48 months but we don't know whether it is more effective at 60 months or longer. Intermittent rectal diazepam given during a

febrile episode may be more effective than placebo or no treatment at reducing the risk of febrile seizure recurrence at 6, 12, 18, and 36 months, but not at 24 months. Clobazam given during a febrile episode may be more effective at reducing the risk of recurrence of febrile seizures at 6 months, but we don't know how effective it is longer-term. However, the overall evidence for intermittent anticonvulsants was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[7] Systematic review	406 children (6 months–5 years) with 1 or more febrile seizure Data from 1 RCT	**Proportion of children with febrile seizure recurrence , 6 months** 25/202 (12%) with oral diazepam 31/204 (15%) with placebo	RR 0.81 95% CI 0.50 to 1.33 P = 0.41	⟷	Not significant
[7] Systematic review	591 children (6 months–5 years) with febrile seizures 2 RCTs in this analysis	**Proportion of children with febrile seizure recurrence , 12 months** 49/289 (17%) with oral diazepam 67/293 (23%) with placebo	RR 0.74 95% CI 0.53 to 1.03 P = 0.076	⟷	Not significant
[7] Systematic review	406 children (6 months–5 years) with 1 or more febrile seizure Data from 1 RCT	**Proportion of children with febrile seizure recurrence , 24 months** 42/202 (21%) with oral diazepam 63/204 (31%) with placebo	RR 0.67 95% CI 0.48 to 0.94 P = 0.022 NNT = 10 95% CI 5 to 50	●○○	oral diazepam
[7] Systematic review	110 children (6 months–5 years) with 1 simple febrile seizure and no risk factors for recurrence Data from 1 RCT	**Proportion of children with febrile seizure recurrence , 48 months** 5/45 (11%) with oral diazepam 20/65 (31%) with no treatment	RR 0.36 95% CI 0.15 to 0.89 P = 0.027 NNT = 5 95% CI 3 to 20	●●○	oral diazepam
[7] Systematic review	60 children (2 months–6 years) with first febrile seizure Data from 1 RCT 4-armed trial The remaining arms evaluated intermittent and continuous phenobarbitone therapy	**Proportion of children with febrile seizure recurrence , 60–72 months** 5/30 (17%) with oral diazepam 6/30 (20%) with no treatment	RR 0.83 95% CI 0.28 to 2.44 P = 0.74	⟷	Not significant
[7] Systematic review	677 children with first febrile seizures 4 RCTs in this analysis	**Proportion of children with febrile seizure recurrence , 6 months** 37/308 (12%) with rectal diazepam 61/300 (20%) with no treatment or placebo	RR 0.60 95% CI 0.41 to 0.86 P = 0.0057 NNT = 12 95% CI 7 to 33 2 quasi-randomised RCTs included (odd/even date allocation; alternate day allocation); significant heterogeneity P = 0.01, I^2 = 77%	●○○	rectal diazepam
[7] Systematic review	677 children with first febrile seizures 4 RCTs in this analysis	**Proportion of children with febrile seizure recurrence , 12 months** 58/306 (19%) with rectal diazepam 86/296 (29%) with no treatment or placebo	RR 0.65 95% CI 0.49 to 0.87 P = 0.0037 NNT = 10 95% CI 6 to 25	●○○	rectal diazepam

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
			2 quasi-randomised RCTs included (odd/even date allocation; alternate day allocation); significant heterogeneity P = 0.004, I^2 = 77%		
[7] Systematic review	289 children with first febrile seizures Data from 1 RCT	**Proportion of children with febrile seizure recurrence , 18 months** 16/105 (15%) with rectal diazepam 43/90 (48%) with no treatment	RR 0.32 95% CI 0.19 to 0.53 P <0.00001 NNT = 3 95% CI 2 to 5 A quasi-randomised RCT (odd/even date allocation)	●●○	rectal diazepam
[7] Systematic review	249 children with first febrile seizures 2 RCTs in this analysis	**Proportion of children with febrile seizure recurrence , 24 months** 24/108 (22%) with rectal diazepam 22/115 (19%) with no treatment or placebo	RR 1.13 95% CI 0.67 to 1.90 P = 0.64	⟷	Not significant
[7] Systematic review	139 children (6 months–3 years) with first febrile seizures Data from 1 RCT	**Proportion of children with febrile seizure recurrence , 36 months** 24/68 (35%) with rectal diazepam 43/71 (61%) with no treatment	RR 0.58 95% CI 0.40 to 0.85 P = 0.0045 NNT = 4 95% CI 2 to 11 A quasi-randomised RCT (alternate day allocation)	●○○	rectal diazepam
[7] Systematic review	60 children (6 months–5 years) with 1 or more febrile seizure Data from 1 RCT Only the 60 children who completed the study duration of 6 months were considered. Total number of children included at the start of the study not known.	**Proportion of children with febrile seizure recurrence , 6 months** 9/30 (30%) with oral clobazam 25/30 (83%) with placebo	RR 0.36 95% CI 0.20 to 0.64 P = 0.00044 Note: very high recurrence rate in placebo group (see Comments section)	●●○	clobazam

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] RCT	185 children (8 months–3 years) with first febrile seizures and <2 risk factors for recurrence In review [7]	**Number of days that children were hyperactive (defined as agitation and inability to keep still)** 138 days with oral diazepam 34 days with placebo	P <0.0003	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[7] Systematic review	110 children (6 months–5 years) with 1 simple febrile seizure and no risk factors for recurrence Data from 1 RCT	**Proportion of children with lethargy , 48 months** 13/45 (29%) with oral diazepam 0/65 (0%) with no treatment Adverse effects did not last longer than 36 hours	Significance not reported		
[7] Systematic review	110 children (6 months–5 years) with 1 simple febrile seizure and no risk factors for recurrence Data from 1 RCT	**Proportion of children with ataxia , 48 months** 14/45 (31%) with oral diazepam 0/65 (0%) with no treatment Adverse effects did not last longer than 36 hours	Significance not reported		
[7] Systematic review	288 children (6 months–5 years) with 1 or more febrile seizure Data from 1 RCT	**Proportion of children with ataxia , 24 months** 30% of 59 patients with oral diazepam 0% with placebo Absolute numbers not reported	Significance not reported		
[7] Systematic review	288 children (6 months–5 years) with 1 or more febrile seizure Data from 1 RCT	**Proportion of children with lethargy , 24 months** 29% of 59 patients with oral diazepam 0% with placebo Absolute numbers not reported	Significance not reported		
[7] Systematic review	152 children with first febrile seizures Data from 1 RCT	**Proportion of children with ataxia , 18 months** 8% with rectal diazepam Absolute numbers not reported Unclear whether reported adverse effects refer to overall population	Significance not reported		
[7] Systematic review	139 children (6 months–3 years) with first febrile seizures Data from 1 RCT	**Adverse effects , 36 months** with rectal diazepam Absolute results not reported Adverse effects were reported only in diazepam group and described as mild and transient including somnolence and irritability	Significance not reported		
[7] Systematic review	60 children (6 months–5 years) with 1 or more febrile seizure Data from 1 RCT	**Proportion of children with weakness , 6 months** 1/30 (3%) with oral clobazam 11/30 (37%) with placebo	Significance not reported		
[7] Systematic review	60 children (6 months–5 years) with 1 or more febrile seizure Data from 1 RCT	**Proportion of children experiencing sedation , 6 months** 5/30 (17%) with oral clobazam 5/30 (17%) with placebo	Significance not reported		

Intermittent anticonvulsants (clobazam, diazepam, lorazepam) versus each other:

We found one systematic review (search date 2011) assessing intermittent oral diazepam versus intermittent oral clobazam in children with a history of febrile seizures. [7] For further general information on harms of anticonvulsants see review on Epilepsy (partial).

Recurrence of febrile seizures

Intermittent anticonvulsants (clobazam, diazepam, lorazepam) compared with each other We don't know whether intermittent oral diazepam given to children during a febrile episode is more effective at 12 months than intermittent oral clobazam at reducing the risk of febrile seizure recurrence (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of febrile seizures					
[7] Systematic review	72 children (6 months–5 years) with first simple febrile seizures Data from 1 RCT	**Proportion of children with febrile seizure recurrence , 12 months** 2/35 (6%) with oral diazepam 4/37 (11%) with oral clobazam	RR 0.53 95% CI 0.10 to 2.71 P = 0.44 Unblinded	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[7] Systematic review	72 children (6 months–5 years) with first simple febrile seizures Data from 1 RCT	**Proportion of children experiencing sedation , 12 months** with oral diazepam with oral clobazam A greater number of children receiving intermittent oral diazepam experienced sedation compared to those receiving intermittent oral clobazam – further details were not provided	P <0.0001	○○○	oral clobazam

Further information on studies

[7] The regimen and dose of administration of diazepam varied between the RCTs identified in the systematic review. Most of the RCTs identified by the systematic review had weak methods, such as lack of blinding and inadequate reporting of allocation concealment. The review noted that using no treatment as a comparator (rather than a placebo) in some studies was a source of potential bias. Also, many of the trials specified that children had febrile seizures, but did not further specify whether they were all simple or not.

Comment: This intervention only looked at the intermittent use of the following anticonvulsants: clobazam, diazepam, and lorazepam. In addition to categorising this option as 'unknown effectiveness', it should be noted that there is a potential for harm with this option.

The review noted that significant benefit with oral diazepam was found at 24 and 48 months, but not at 6, 12, or 60–72 months. [7] There was significant benefit with rectal diazepam at 6, 12, 18, and 36 months, but not at 24 months. The review noted that benefits did not seem to be stable over time. Although one RCT showed benefit with clobazam at 6 months, the review noted a very high recurrence in the placebo group (83%), and that this RCT needed replication. It also noted

that, although adverse effects reporting was variable, adverse effects were reported in up to a third of children in some trials.

After reviewing risk differences and NNTs for significant results, the review concluded that no clinically important benefits were found for intermittent oral and rectal diazepam, and that the apparent benefit in the clobazam trial needed to be repeated to be judged reliable. [7]

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

Antipyretic drug treatments (paracetamol, ibuprofen) One systematic review added (search date 2011). [7] Categorisation unchanged (unknown effectiveness)

Intermittent anticonvulsants (clobazam, diazepam, lorazepam) One systematic review added (search date 2011). [7] Categorisation changed from 'likely to be ineffective or harmful' to 'unknown effectiveness'.

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Leena D Mewasingh
Paediatric Neurology Consultant
Imperial College Healthcare NHS Trust
London
UK

Competing interests: LDM has been reimbursed by the pharmaceutical companies Janssen-Cilag and UCB Pharma for attending epilepsy congresses and epilepsy meetings.

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

Important outcomes			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 (aged 6 months to 5 years) with one or more previous simple febrile seizures?									
2 (at least 230) [7] [31]	Recurrence of febrile seizures	Antipyretic drugs (paracetamol, ibuprofen) versus placebo	4	-2	0	0	0	Low	Quality points deducted for incomplete reporting of results and unclear follow-up (no absolute numbers reported).
10 (at least 1429) [7]	Recurrence of febrile seizures	Intermittent anticonvulsants (clobazam, diazepam, lorazepam) versus placebo or no treatment	4	-2	0	-2	0	Very low	Quality points deducted for weak methods (blinding, treatment allocation, randomisation) and using no treatment as a comparator. Directness points deducted for inconsistent effects over time, unclear clinical importance, and significant heterogeneity.
1 (72) [7]	Recurrence of febrile seizures	Intermittent anticonvulsants (clobazam, diazepam, lorazepam) versus each other	4	-2	0	0	0	Low	Quality points deducted for methodological issues (treatment allocation and blinding not reported) and sparse data.

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.