National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

[P] Effectiveness of antiseizure therapies for infantile spasms

NICE guideline number tbc

Evidence reviews underpinning recommendations 6.3.1-6.3.11 in NICE guideline

November 2021

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

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ISBN:

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Evidence review for effectiveness of antiseizure therapies in the treatment of infantile spasms

Review question

What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

Introduction

Infantile spasms are a manifestation of an early onset infantile epileptic encephalopathy and most commonly occur as part of West syndrome in which spasms are associated with hypsarrythmia on an electroencephalogram (EEG) and with developmental stagnation or regression. Recognition and prompt treatment are essential to minimise the negative effects on the child's development. The aim of this review is to determine which antiseizure therapies are the most effective at improving outcomes for children with infantile spasms.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Children and young people with confirmed infantile spasms
Intervention	The following antiseizure therapies and their combinations will be considered: Injectable steroids (for example, ACTH) Ketogenic diet Levetiracetam Nitrazepam Oral steroids (for example, prednisolone, prednisone, hydrocortisone, tetracosactide) Pyridoxine Sodium valproate Topiramate Vigabatrin
Comparison	Any of the above (including their combinations, different doses, and different lengths of treatment) • No treatment/placebo
Outcomes	**Critical** Spasms freedom EEG resolution Side effects ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse events (dichotomous outcome only) **Important**

	Spasms relapse Ongoing seizures Neurodevelopmental outcomes, as assessed by validated developmental/IQ tools (for example, VABS)

ACTH: adrenocorticotropic hormone; EEG: electroencephalogram; IQ: intelligence quotient; VABS: Vineland Adaptive Behaviour Scale

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1). Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Twenty-five studies reporting 22 randomised controlled trials (RCTs) were identified for inclusion in this review (Appleton 1999, Askalan 2003, Baram 1996, Chellamuthu 2014, Chiron 1997, Dreifuss 1986, Dressler 2019, Elterman 2010, Fallah 2014, Gowda 2019, Hrachovy 1983, Hrachovy 1994, Kang 2011, Kapoor 2021, Kunnanayaka 2018, Lux 2004, Lux 2005, O'Callaghan 2017, O'Callaghan 2018, Omar 2002, Vigevano 1997, Wanigasinghe 2015, Wanigasinghe 2017, Yanagaki 1999, Yi 2019). Six of these studies provided data for the same RCT (Lux 2004 and Lux 2005; O'Callaghan 2017 and O'Callaghan 2018; Wanigasinghe 2015 and Wanigasinghe 2017).

One RCT compared vigabatrin with placebo (Appleton 1999); 3 RCTs compared injectable steroids to vigabatrin (Askalan 2003, Omar 2002, Vigevano 1997); 6 studies reporting on 5 RCTs compared oral steroids to injectable steroids (Baram 1996, Gowda 2019, Hrachovy 1983, Kapoor 2021, Wanigasinghe 2015, Wanigasinghe 2017); 1 RCT compared high-dose oral steroids to low-dose oral steroids (Chellamuthu 2014); 1 RCT compared vigabatrin to oral steroids (Chiron 1997); 1 RCT compared nitrazepam to injectable steroids (Dreifuss 1986); 1 RCT compared ketogenic diet to injectable steroids (Dressler 2019); 1 RCT compared high-dose vigabatrin to low-dose vigabatrin (Elterman 2010); 1 RCT compared nitrazepam to topiramate (Fallah 2014); 2 RCTs compared high-dose injectable steroids to low-dose injectable steroids (Hrachovy 1994, Yanagaki 1999); 1 RCT compared short-term ketogenic diet to long-term ketogenic diet (Kang 2011); 1 RCT compared pyridoxine in combination with prednisolone with oral steroids (Kunnanayaka 2018); 2 studies reporting on 1 RCT compared prednisolone in combination with tetracosactide to vigabatrin (Lux 2004, Lux 2005); 2 studies reporting on 1 RCT compared vigabatrin in combination with oral steroids to oral steroids alone (O'Callaghan 2017, O'Callaghan 2018) and 1 RCT compared high-dose prednisone alone to high-dose prednisone in combination with topiramate (Yi 2019).

The included studies are summarised in Table 2 to Table 16.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2 to Table 16.

Table 2: Summary of included studies. Comparison 1: vigabatrin versus placebo

Study	Population	Intervention	Comparison	Outcomes
Appleton 1999 RCT Multicenter (Canada, Finland, France, Hungary, the Netherlands, Serbia, UK)	N=40 children with confirmed previously untreated infantile spasms Age, mean (range): intervention: 8 (5 to 20) Control: 6 (1 to 5)	Vigabatrin n=20 50 mg/kg/day for 5 days (administration route NR)	Placebo n=20 50 mg/kg/day for 5 days (administration route NR)	Spasms freedom EEG resolution % of patients with reported AEs

AEs: adverse events; EEG: electroencephalogram; kg: kilogram; mg: milligram; N: number of participants in study; NR: not reported; RCT: randomised controlled trial

Table 3. Summary of included studies. Comparison 2: injectable steroids versus vigabatrin

Study	Population	Intervention	Comparison	Outcomes
Askalan 2003 RCT Canada	N=9 children with confirmed infantile spasms who had not previously received vigabatrin or corticosteroids. Age was not reported	Injectable steroids n=3 ACTH divided in 2 doses: 150 IU/m^2/ day for 1 week, then 75 IU/m^2/day for a second week	Vigabatrin PO n=6 Vigabatrin divided in 2 doses: 100 mg/kg/day for 1 week, then 150 mg/kg/day for a second week	Spasms freedom EEG resolution
Omar 2002 RCT Saudi Arabia	N=36 children with newly diagnosed infantile spasms. Only 32 are included in analysis. Age, months, range (mean): 3 – 10 (5.2)	Injectable steroids n=16 ACTH – average dose of 20 IU intramuscular daily	Vigabatrin n=16 Average dose of 87mg/ kg /day	Spasms freedom Side effects
Vigevano 1997 RCT Italy	N=42 children with confirmed previously untreated infantile spasms. Age at onset, months, mean (range): Intervention: 5.3 (2-9)	Depot ACTH n=19 10 IU/day for 20 days (administration route NR)	Vigabatrin n=23 100 to 150 mg/kg/day for 20 days (administration route NR)	Spasms freedom EEG resolution Treatment cessation due to AEs

Study	Population	Intervention	Comparison	Outcomes
	Control: 5.8 (2.5-9)			

ACTH: adrenocorticotropic hormone; AEs: adverse events; EEG: electroencephalogram; IU: international units; kg: kilogram; m2: body surface; mg: milligram; N: number of participants in study; NR: not reported; PO: per oral; RCT: randomised controlled trial.

Table 4: Summary of included studies. Comparison 3: oral steroids versus injectable steroids

Study	Population	Intervention	Comparison	Outcomes
Baram 1996 RCT US	N=29 children with confirmed infantile spasms who had not previously received steroids Age, months, mean (SD not reported): Intervention: 7.5 Control: 5.1	Oral steroids n= 14 prednisone 1 mg/kg twice a day for 2 weeks	Injectable steroids n= 15 ACTH 75 U/m^2 twice a day for 2 wees	Spasms freedom EEG resolution Spasms relapse
Gowda 2019 RCT India	N=34 children with confirmed infantile spasms who had not previously receive corticosteroids or those in whom these were contraindicated Children with TS were excluded Age, years, mean (SD): Intervention: 13.9 (9.2) Control: 9.4 (5.32)	Oral steroids n=16 prednisolone 4 mg/kg/day, up to 60 mg/kg/day for 2 weeks	Injectable steroids n=18 ACTH 100 U/m^2/day for 2 weeks	Spasms freedom Time taken to spasms freedom EEG resolution % of patients with reported AEs Spasms relapse
Hrachovy 1983 RCT US	N=24 children with confirmed infantile spasms (no information about previous ASMs was reported) Age was not reported	Prednisone gel n=12 2 mg/kg/day + ACTH placebo gel for 2 weeks	ACTH gel n=12 20 U/day + prednisone placebo for 2 weeks	Spasms freedom Spasms relapse
Kapoor 2021 RCT India	N=60 consecutive children aged 2 to 30 months presenting with newly diagnosed epileptic spasms with hypsarrhythmia or its variants on EEG.	Intravenous methylprednisolone n=31 30 mg/kg/day for 3 days followed by oral	Oral prednisolone n=29 4 mg/kg/day for two weeks followed by taper	Spasms freedom EEG resolution Spasms relapse

Study	Population	Intervention	Comparison	Outcomes
	Age at onset, months, median (IQR): Intervention group 5 (3–7); control group 5 (3–8).	prednisolone taper		
Wanigasinghe 2015 RCT Sri Lanka	N=97 children with confirmed previously untreated infantile spasm Children with TS were excluded Age, months, mean (SD): Intervention: 8.31 (6.19) Control: 9.93 (8.67)	<u>Oral steroids prednisolone</u> n=48 40 to 60 mg divided into 4 doses per day for 14 days	<u>Injectable steroids</u> n=49 synthetic ACTH 40-60 IU (0.5 to 0.75 mg) every other day for 14 days	Spasms freedom (short term, medium term) Time taken to spasms freedom EEG resolution Treatment cessation due to AEs
Wanigasinghe 2017 RCT Sri Lanka	See Wanigasinghe 2015	See Wanigasinghe 2015	See Wanigasinghe 2015	Spasms freedom (long term)

ASMs:antiseizure medications; EEG: electroencephalogram; kg: kilogram; m^2: body surface; mg: milligram; N: number of participants in study; RCT: randomised controlled trial; SD: standard deviation; TS: tuberous sclerosis; U: units; US: United States.

Table 5: Summary of included studies. Comparison 4: high-dose oral steroids versus low-dose oral steroids

Study	Population	Intervention	Comparison	Outcomes
Chellamuthu 2014 RCT India	N=63 children with confirmed infantile spasms (no information about previous ASMs was reported) Age, months, median (IQR): Intervention: 12 (9 to 18) Control: 10.5 (8 to 14.5) *Children with TS were excluded*	<u>High-dose oral steroids</u> n=31 prednisolone 4mg/kg/day for 2 weeks	<u>Low-dose oral steroids</u> n=32 prednisolone 2 mg/ kg/day for 2 weeks	• Spasms freedom • EEG resolution • Treatment cessation due to AEs • Spasms relapse • Ongoing seizures

ASMs: antiseizure medications; AEs: adverse events; EEG: electroencephalogram; mg: milligram; N: number of participants in study; RCT: randomised controlled trial.

Table 6: Summary of included studies. Comparison 5: vigabatrin versus oral steroids

Study	Population	Intervention	Comparison	Outcomes
Chiron 1997 RCT France	N=22 children with confirmed infantile spasms *due to TS* who had not previously received ACTH, vigabatrin or oral corticosteroids. Age at onset of infantile spasms, months, mean (SD): Intervention: 5.8 (1.8) Control: 5.9 (3.2)	Vigabatrin n=11 150 mg/kg per day for 1 month (administration route NR)	Oral steroids n=11 hydrocortisone 15 mg/kg per day for 1 month (administration route NR)	• Spasms freedom • % of patients with reported AEs • Spasms relapse

ACTH: adrenocorticotropic hormone; AEs: adverse events; kg: kilogram; mg: milligram; N: number of participants in study; RCT: randomised controlled trial.

Table 7: Summary of included studies. Comparison 6: nitrazepam versus injectable steroids

Study	Population	Intervention	Comparison	Outcomes
Dreifuss 1986 RCT US	N=48 children with confirmed infantile spasms who had not previously received ACTH, steroids or nitrazepam Age, months, mean (range): Intervention: 8.70 (2 to 23) Control: 8.04 (3 to 21)	Nitrazepam PO n=27 Starting dose: 0.2 mg/kg/day in 2 divided doses or 1 mg twice daily, whichever was greater Final dose: 4.80 to 9 mg/day	Injectable steroids n=21 ACTH gel at a dose of 40 U/day	• Spasms freedom • Treatment cessation due to AEs

AEs: adverse events; mg: milligram; N: number of participants in study; PO: per oral; RCT: randomised controlled trial; U: units

Table 8: Summary of included studies. Comparison 7: ketogenic diet versus injectable steroids

Study	Population	Intervention	Comparison	Outcomes
Dressler 2019 RCT Austria	N=32 children with confirmed infantile spasms who did not previously receive KD or steroids Age at epilepsy onset, months, median (range):	Ketogenic diet n=16 Introduced at a 1:1 ratio and increased to 3:1	Injectable synthetic steroids n=16 ACTH 150 IU/m^2/day (administration route NR)	• Spasms freedom • % of patients with reported AEs • Spasms relapse • Neurodevelopmental outcomes (TINE, Hempel Neurological Examination, VABS)

Study	Population	Intervention	Comparison	Outcomes
	Intervention: 4.9 (0-12) Control: 5.0 (0.2-27).			

ACTH: adrenocorticotropic hormone; AEs: adverse events; m^2: body surface; N: number of participants in study; NR: not reported; RCT: randomised controlled trial; TINE: Touwen Infant Neurological Examination; VABS: Vineland Adaptive Behavior Scale.

Table 9: Summary of included studies. Comparison 8: high-dose vigabatrin versus low-dose vigabatrin

Study	Population	Intervention	Comparison	Outcomes
Elterman 2010 RCT US	N=221 children with confirmed infantile spasms who did not previously received corticosteroids, ACTH or valproic acid Age, years, mean (SD): Intervention: 0.6 (0.3) Control: 0.6 (0.3)	High-dose vigabatrin PO n=107 100 to 148 mg/kg/day for 14 days	Low-dose vigabatrin PO n=114 18 to 36 mg/kg/day for 14 days	• Spasms freedom • % of patients with reported AEs • Spasms relapse

AEs: adverse events; PO: per oral; RCT: randomised controlled trial; SD: standard deviation.

Table 10: Summary of included studies. Comparison 9: nitrazepam versus topiramate

Study	Population	Intervention	Comparison	Outcomes
Fallah 2014 RCT Iran	N=50 children with confirmed infantile spasms who were not taking any ASMs at the time of the study Age, months, mean (SD): Intervention: 9.82 (3.76) Control: 9.01 (3.96)	Nitrazepam PO n=25 0.5 mg/kg/day, up to 1 mg/kg/day for 2 weeks	Topiramate PO n=25 3 mg/kg/day, up to 3 mg/kg/day for 2 weeks	• Spasms freedom • % of patients with reported AEs • Treatment cessation due to AEs

ASMs: antiseizure medications; AEs: adverse events; kg: kilogram; mg: milligram; N: number of participants in study; PO: per oral; RCT: randomised controlled trial.

Table 11: Summary of included studies. Comparison 10: high-dose injectable steroids versus low-dose injectable steroids

Study	Population	Intervention	Comparison	Outcomes
Hrachovy 1994 RCT US	N=59 children with confirmed infantile spasms who had not previously received ACTH or corticosteroids	High-dose injectable steroids n=30 ACTH 150U/m2/day for 3 weeks, then	Low-dose injectable steroids n=29 ACTH	Spasms freedom EEG resolution Spasms relapse

Study	Population	Intervention	Comparison	Outcomes
	Age was not reported	80 U/m^2/day for 2 weeks, then 50 U/m2 every other data for 1 week	20U/m^2/day for 2 weeks	
Yanagaki 1999 RCT Japan	N=25 children with confirmed infantile spasms who had not previously received ACTH, corticosteroids or IV gammaglobulin Age at onset, months, mean (SD): Intervention: 4.89 (2.59) Control: 5.80 (3.77)	High-dose IM synthetic steroids n=13 ACTH 0.025 mg/kg/day (= 1 U/kg/day) for 2 weeks	Low-dose IM synthetic steroids n=12 ACTH 0.005 mg/kg/day (= 0.2 U/kg/day) for 2 weeks	Spasms freedom Spasms relapse

ACTH: adrenocorticotropic hormone; EEG: electroencephalogram; kg: kilogram; m2: body surface; mg: milligram; N: number of participants in study; RCT: randomised controlled trial; U: units; US: United States.

Table 12: Summary of included studies. Comparison 12: short-term ketogenic diet versus long-term ketogenic diet

Study	Population	Intervention	Comparison	Outcomes
Kang 2011 RCT Korea	N=40 children previously diagnosed with intractable spasms (on a combination of vigabatrin, topiramate, and/or additional ASMs) who became spasms free after using the KD for 6 months as an add-on treatment Age, months, median (range): Intervention: 13.5 (6.0 to 30) Control: 15.0 (9-30)	Continuation on a short- term ketogenic diet as an add-on treatment n=16 KD ratio of 3:1 fat: non-fat during 8 months (additional interventions were not reported)	Continuation on a-on long-term ketogenic diet as an add-on treatment n=24 KD ratio of 3:1 fat: non-fat during 2 years (additional interventions were not reported)	• Duration until spasms freedom • EEG resolution • Treatment cessation due to adverse events • Spasms relapse • Neurodevelopmental outcomes (VABS)

ASMs: antiseizure medications; EEG: electroencephalogram; KD: ketogenic diet; kg: kilogram; RCT: randomised controlled trial; VABS: Vineland Adaptive Behavior Scale.

Table 13: Summary of included studies. Comparison 12: pyridoxine in combination with prednisolone versus oral steroids

Study	Population	Intervention	Comparison	Outcomes
Kunnanayaka 2018 RCT	N=62 children with confirmed infantile spasms who	Pyridoxine PO + oral steroids n=30	Oral steroids n=32 prednisolone	• Spasms freedom • EEG resolution • Spasms relapse

Study	Population	Intervention	Comparison	Outcomes
India	had not previously received pyridoxine, steroids or ACTH *Children with TS were excluded* Age, months, median (IQR): Intervention: 12.5 (8-18) Control: 9.5 (8-15)	Pyridoxine 30 mg/kg/day pyridoxine + prednisolone 4 mg/kg/day for 2 weeks	4 mg/kg/day for 2 weeks	

ACTH: adrenocorticotropic hormone; EEG: electroencephalogram; RCT: randomised controlled trial; TS: tuberous sclerosis; VABS: Vineland Adaptive Behavior Scale.

Table 14: Summary of included studies. Comparison 13: prednisolone in combination with tetracosactide versus vigabatrin

Study	Population	Intervention	Comparison	Outcomes
Lux 2004 UKISS trial RCT UK	N=110 children with confirmed infantile spasms who had not previously received vigabatrin or a hormonal treatment in the previous 28 days Children with TS were excluded Age, months, median (IQR): Intervention: 6 (4-8) Control: 6 (4-9)	Combination <u>hormonal treatments</u> n=55 Prednisolone PO: 40mg/day for 2 weeks Tetracosactide depot IM: 0.5 mg (40 IU) on alternate days for 2 weeks	<u>Vigabatrin PO</u> n=55 50 mg/kg/day for the first 2 doses, then 100 mg/kg/day after 24 h	Spasms freedom (short term) EEG resolution Treatment cessation due to AEs Spasms relapse
Lux 2005 UKISS trial RCT UK	See Lux 2004	See Lux 2004	See Lux 2004	Spasms freedom (long term) Neurodevelopmental outcomes (VABS)

AEs: adverse events; EEG: electroencephalogram; IM: intramuscular; ICISS: International Collaborative Infantile Spasms Study; IU: international units; RCT: randomised controlled trial; VABS: Vineland Adaptive Behavior Scale.

Table 15: Summary of included studies. Comparison 14: vigabatrin in combination with oral steroids versus oral steroids

Study	Population	Intervention	Comparison	Outcomes
O'Callaghan 2018 ICISS trial RCT Multicenter (Australia, Germany, New Zealand, Switzerland, UK)	N=377 children with confirmed previously untreated infantile spasms *Children with TS were excluded* Children were >2 months and <14 months of age	Combination therapy (vigabatrin with tetracosactide depot OR vigabatrin with prednisolone): n=186 Vigabatrin PO: 50 mg/kg per day for the first 2 doses, then 100 mg/day after 24 hours Tetracosactide depot IM: 0.5 mg [40 IU] on alternate days for 2 weeks OR Prednisolone PO: 40 mg/day for 2 weeks	Hormonal therapy alone (tetracosactide depot or prednisolone) n=191 Tetracosactide depot IM: 0.5 mg [40 IU] on alternate days for 2 weeks OR Prednisolone PO: 40 mg/day for 2 weeks	• Spasms freedom • Neurodevelopmental outcomes (VABS)
O'Callaghan 2017 ICISS trial RCT Multicenter (Australia, Germany, New Zealand, Switzerland, UK)	See O'Callaghan 2018	See O'Callaghan 2018	See O'Callaghan 2018	• EEG resolution • % of patients with reported AEs • Spasms relapse

EEG: electroencephalogram; PO: per oral; RCT: randomised controlled trial; IM: intramuscular; VABS: Vineland Adaptive Behavior Scale.

Table 16: Summary of included studies. Comparison 15: high-dose prednisone alone versus high-dose prednisone in combination with topiramate

Study	Population	Intervention	Comparison	Outcomes
Yi 2019 RCT China	N=77 children with infantile spasms or late-onset epileptic spasms (age at onset > 2 years) in clusters or single attacks with hypsarrhythmia or its variants on EEG.	High-dose prednisone only n=39 Prednisone administered orally as follows: 10 mg, four times daily for 14 days. If spasms continued at day 7, the dose was increased to 15 mg, four times	High-dose prednisone + add-on topiramate n=38 Prednisone administered as in the prednisone only group and topiramate was administered as follows: 1 mg/kg/day, two times a day, and	Spasms freedom EEG resolution Treatment cessation due to adverse events Spasms relapse

Study	Population	Intervention	Comparison	Outcomes
	Age at onset, median, months (range): Monotherapy 6 (2-39); combination therapy 5.7 (0.4-46), p=0.443.	daily for a further 7 days. After 14 days of treatment, whether spasms had completely ceased or not, prednisone was reduced weekly to complete a 49 day or 56 day course (for example, 40 mg once daily for 1 week or 30 mg once daily for 1 week, 20 mg once daily for 1 week, 10 mg daily for 1 week, 5 mg daily for 1 week, then 5 mg alternate days for 1 week). After 14 days, non-responders in the prednisone only group received other treatments such as ASMs (including topiramate) and ketogenic diet.	then gradually titrated to 3 mg/kg/day in the 7th day and 5 mg/kg/day in the 14th day. After 14 days, topiramate was administered at 5 mg/kg/day on a bodyweight basis for 35 or 42 days. Non-responders received other treatments after 56 days (for example, Ketogenic diet).	

ASMs: antiseizure medications; EEG: electroencephalogram; kg: kilogram; mg: milligram; N: number of participants in study; RCT: randomised controlled trial.

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Across all the interventions identified in this review, vigabatrin alone or in combination with other antiseizure medications was shown to be the most effective antiseizure therapy. Vigabatrin combined with prednisolone showed a clinically important benefit in terms of spasms freedom and EEG resolution when compared to vigabatrin alone. Vigabatrin alone also showed an important benefit for spasms freedom when compared to oral steroids.

Other comparisons showing an important benefit included: high-dose oral steroids versus low-dose oral steroids, nitrazepam versus topiramate, and prednisolone in combination with tetracosactide versus vigabatrin; where low-dose oral steroids, nitrazepam, and prednisolone in combination with tetracosactide all showed an important benefit in terms of spasms freedom.

There were various interventions assessing the effectiveness of different antiseizure therapies which showed no important differences in outcomes between the interventions compared; for example, vigabatrin versus placebo, nitrazepam versus injectable steroids, ketogenic diet versus injectable steroids, high-dose injectable steroids versus low-dose injectable

steroids, short-term ketogenic diet versus long-term ketogenic diet, pyridoxine in combination with prednisolone versus oral steroids, high-dose prednisone versus high-dose prednisone in combination with topiramate.

Typically, the comparisons where no difference between interventions was found included less participants and very imprecise findings, therefore they should not be taken as definitive evidence of no difference between the interventions.

No evidence was found which evaluated the effectiveness of sodium valproate or levetiracetam for infantile spasms.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See Supplement 2 for the literature search strategy and economic study selection flow chart.

Excluded studies

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Summary of the economic evidence

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Infantile spasms can have negative developmental consequences if not recognised and treated promptly. The main objective of treatment is to control seizures and the committee therefore agreed that seizure freedom should be included as a critical outcome for this review. As infantile spasms are characterised by a hypsarrhythmia pattern on EEG, the committee also agreed that EEG resolution should be included as a critical outcome. The committee discussed the importance of balancing the goal of effective seizure control with the need to minimise side effects associated with treatments and agreed that adverse events should also be included as a critical outcome.

The critical outcomes were amended after protocol registration to change 'short term seizure freedom' to 'spasm freedom at any time point', in order to reflect the importance of freedom from spasms.

As there is a high risk of spasms relapse and ongoing seizures of other types for children with infantile spasms these were included as important outcomes for this review. Children with infantile spasms are also likely to experience developmental delay and the committee

therefore agreed to include neurodevelopmental outcomes as treatment can sometimes lead to improvements in this area.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. The quality of the outcomes assessed ranged from very low to moderate quality evidence, indicating uncertainty in the data. The main reason for downgrading was imprecision; the trials had a small number of participants, and therefore the confidence around the estimate for each of the outcomes was low. Some of the trials were also downgraded because of high to very high risk of bias, as assessed by the Cochrane risk of bias tool (version 2). The main sources of potential bias were: lack of information regarding how the randomisation was performed or concealed; or because participants, clinicians and/or outcome assessors were aware of treatment allocation. Some trials had not registered the study protocol, therefore were downgraded for unclear reporting bias.

Benefits and harms

The committee considered the evidence presented within this review, and used this information alongside their expert opinion and clinical knowledge to make the recommendations.

Assessment and monitoring

Babies with infantile spasms are at an increased risk of neurodevelopmental problems, which is a serious safety concern. They may present with slow development, irritability and drowsiness, however, according to the committee's expertise, shorter duration between diagnosis and treatment, prompt response to treatment and shorter duration of EEG abnormalities are associated with an improved prognosis. Based on best practice, the committee agreed that, if a baby has infantile spasms, advice should be sought from a tertiary paediatric neurologist, followed by referral. As this is best practice, it is unlikely this recommendation would lead to increased costs or resource use.

Once the treatment has been started, and based on best practice, the committee agreed that these babies should be reviewed weekly as a minimum to monitor the relapse of spasms and the emergence of other seizure types, as well as for possible side-effects related to treatment.

The committee noted that infantile spasms present with a very distinct EEG pattern, which may only show when the infant is asleep. Hence, based on best practice and the committee's experience, a sleep EEG should be done in babies with infantile spasms at 2 weeks after starting treatment. This timeframe was based the most recent and largest trial included in the review (ICISS trial, O'Callaghan 2017 and O'Callaghan 2018), which showed an electroclinical response and spasms resolution in babies who received high-dose oral prednisolone and vigabatrin between days 15 and 42 of treatment. Based on this, the committee agreed that babies need to continue to be reviewed monthly and the sleep EEG should be repeated if spasms recur or if there are concerns.

First-line treatment

The evidence included showed a benefit of high-dose oral prednisolone and vigabatrin when compared to oral steroids alone. This data was from a large multi-centre study which the committee agreed reflected UK practice.

The aetiology of infantile spasms may be infectious disorders, such as adenovirus or herpes simplex. For this reason, babies with infantile spasms are at risk of being immunosupressed. Based on clinical experience and expertise, the committee agreed that, for those at high risk of steroid-related side effects, such as those with underlying comorbidities or neurological impairments, vigabatrin should be offered.

Based on evidence, the committee agreed that babies with infantile spasms due to tuberous sclerosis should be offered vigabatrin as a first-line treatment. Tuberous sclerosis is a major cause of infantile spasms, and these babies are particularly refractory to treatment. Trials have shown spasms freedom in a short period of time with vigabatrin in babies with infantile spasms due to tuberous sclerosis, however, due to the high risk of neurodevelopmental problems in these babies, the committee agreed, based on evidence, that high-dose oral prednisolone should be added if vigabatrin is ineffective after 1 week. The study that assessed the effectiveness of high-dose oral prednisolone and vigabatrin did not include babies with tuberous sclerosis, however the committee agreed that it was appropriate to extrapolate from this study due to the similar pathophysiology between both groups.

Prednisolone lowers the immune system, therefore the committee agreed that the possible side effects of steroid treatment should be discussed with the parents or carers of the baby with infantile spasms. The risk of immunosupression continues up to 3 months after starting treatment, and parents and carers need to be made aware of the increased risk of infection. However, the committee were in agreement that, in the majority of cases, the risks of a short course of steroids do not outweigh the benefits. Babies should also be tested for antibodies for varicella zoster virus as, if they get infected while taking prednisolone, it can have severe and occasionally life threatening consequences due to the supressed immune system. In line with current clinical practice, the committee also noted that a steroid card and information about where to seek medical advice for side effects should be provided to parents or carers.

The committee agreed the dosage of prednisolone given should be in line with advice in the BNF for children, and they believed that reflecting the dosages of prednisolone for treating infantile spams in the recommendations would be helpful in clinical practice because these provide further clarity to the information already available in the BNF for children. Based on their experience and expertise, they also noted that monitoring blood pressure and urinary glucose weekly would help identify possible risks of infection in a timely manner.

The committee agreed the dosage of vigabatrin should be in line with advice in the BNF for children, and they noted that, in some cases, it may be necessary to go above these recommended doses if there is a sub-optimal response, in which case, any adjustment should be undertaken with guidance from a specialist, to ensure optimal treatment benefit.

Second-line treatment

The committee did not think the evidence for second-line therapy allowed them to make any firm recommendations. Based on their experience and expertise, the committee provided some treatments that are successfully used in clinical practice and emphasised that any treatment should be individually tailored and only prescribed in consultation with a tertiary paediatric epilepsy specialist. This is due to the long-term risk of adverse neurodevelopmental outcomes associated with treatment resistant cases of infantile spasms and the complexity of the presentation.

Given the lack of evidence on second line therapies, the committee decided to prioritise a recommendation for research on the effectiveness of antiseizure therapies (individually or in combination) in the treatment of infantile spasms when first-line therapy is unsuccessful or not tolerated (see Appendix L).

Cost effectiveness and resource use

The committee did not make any recommendations which changed current practice. Therefore, there will not be any impact upon resource use.

Recommendations supported by this evidence review

This evidence review supports recommendations 6.3.1-6.3.11 and the research recommendation on complex epilepsy syndromes.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What antiseizure therapies (monotherapy or add-o) are effective in the treatment of infantile spasms?

Table 17: Review protocol for effectiveness of antiepileptic therapies in the management of tonic or atonic seizures/drop attacks

Field	Content
PROSPERO registration number	CRD42019143392
Review title	Effectiveness of antiseizure therapies in the treatment of infantile spasms
Review question	What antiseizure therapies (individually or in combination) are effective in the treatment of infantile spasms?
Objective	The objective of this review is to determine which antiseizure therapies are the most effective at improving outcomes for children with infantile spasms. The review will look at interventions given alone or as an add-on.
Searches	The following databases will be searched: CDSR CENTRAL DARE HTA MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations Embase EMCare CINAHL Searches will be restricted by: Date: no date limits

Field	Content
	English language studies Human studies RCT and systematic review study design filter
Condition or domain being studied	Infantile spasms
Population	Inclusion children and young people with confirmed infantile spasms Exclusion: newborn babies (under 28 days) with acute symptomatic seizures studies including syndromes not classified as “infantile spasms”
Intervention	The following antiseizure therapies and their combinations will be considered: injectable steroids (for example, ACTH [adrenocorticotropic hormone]) ketogenic diet levetiracetam nitrazepam oral steroids (for example, prednisolone, prednisone, hydrocortisone, tetracosactide) pyridoxine sodium valproate topiramate vigabatrin
Comparator	any of the above (including their combinations, different doses, and different lengths of treatment) placebo/no treatment
Types of study to be included	Systematic review of RCTs RCTs Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	Studies with a mixed population (this is, including children, and young people with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported.

Field	Content
	Studies with a mixed population (this is, including children, and young people with infantile spasms and other syndromes) will be excluded, unless subgroup analysis for infantile spasms has been reported. Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias Studies including surgery as part of the interventions
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary care)
Primary outcomes (critical outcomes)	Spasms freedom (at any time point) Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants then all data will be extracted. For decision making priority will be given to data presented as "time to spasm freedom", (this is, time to event: HR or mean time) followed by "achievement of spasm freedom" (RR). EEG resolution Side effects, as assessed by: % of patients with reported side effects (trial defined adverse and serious adverse effects) treatment cessation due to adverse events (dichotomous outcome only) Outcomes are in line with those described in the core outcome set for epilepsy http://www.cometinitiative.org/studies/searchresults
Secondary outcomes (important outcomes)	Spasms relapse Ongoing seizures Neurodevelopment outcomes, as assessed by: Validated developmental/IQ tools (for example the VABS [Vineland Adaptive Behaviour Scale]) Health-related quality of life (only validated scales will be included)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and will include: study setting; design; aim; study dates; funding; sample size; participant demographics and baseline

Field	Content
	characteristics; inclusion and exclusion criteria; details of intervention and controls; study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias. All data extraction will be quality assured by a senior reviewer. Draft included and excluded studies tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: ROBIS tool for systematic reviews Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <u>Data synthesis</u> Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events in one arm. Mean differences or standardised mean differences will be presented for continuous outcomes. <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted: according to the risk of bias of individual studies by age (older people/adults/children) study location Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be

Field	Content	
	explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. Minimal important differences (MIDs): Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes For risk ratios: 0.8 and 1.25. For continuous outcomes: +/-0.5 times the baseline SD of the control arm. If there are 2 studies, the MID is calculated as +/- 0.5 times the mean of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
Analysis of sub-groups (stratification)	Stratification If data is available, separate analysis will be conducted on: those with and without developmental delay those with an identified underlying cause and non-identified underlying cause Recommendations will apply to all those with infantile spasms unless there is evidence of a difference in these strata	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)

Field	Content		
Language	English		
Country	England		
Anticipated or actual start date	6th August 2019		
Anticipated completion date	7th April 2021		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact National Guideline Alliance 5b. Named contact e-mail epilepsies@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	The National Guideline Alliance technical team		

Field	Content	
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112	
Other registration details	Not applicable	
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019143392	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Epilepsy, infantile spasms	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published

Field	Content	
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; RCT: Randomised Controlled Trial; RoB: Risk of Bias; SD: Standard Deviation.

Appendix B – Literature search strategies

Literature search strategies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

Clinical

Database(s): EMCare, MEDLINE and Embase (Multifile) – OVID
EMCare 1995 to 2021 March 03; Embase Classic+Embase 1947 to 2021 March 03; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2021 March 03, 2021
Date of last search: 03 March 2021

Multifile database codes: emcr=EMCare; emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
2	carbamazepine/ use emczd, emcr or exp carbamazepine/ use ppez or carbamazepin*.sh. or (amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol).ti,ab.
3	clobazam/ use emczd, emcr or clobazam/ use ppez or (chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl).ti,ab.
4	clonazepam/ use emczd, emcr or clonazepam/ use ppez or (aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril).ti,ab.
5	corticotropin/ use emczd, emcr or exp adrenocorticotropic hormone/ use ppez or adrenocorticotropic hormone*.sh. or (acethropan or acetophran or acortan or acorto or acth or acthar or acthelea or acthon or acton or actonar or actrope or adactan or (adrenal cortex adj (trophic or tropic) adj hormone) or adrenocorticaltrophormon or adrenocorticotrop* or adrenocorticotrop* or adrenocorticotrophin or adrenocorticotropic hormone or adrenocorticotropin* or adrenomone or adrenotropin or cibacthen or corticotrophin* or corticotropic or corticotropin* or cortigel or cortilin or cortiphyson or cortosyn or cortrophin * or cortropin or cortrosyn or cosyntropin* or cotrophin* or exactin or hp acthar gel or humacthid or humactid or porcine acth or porcine corticotropin or procortan or reacthin or s cortophin or solacthyl or synacthen retard or tetracosactide or tetracosactrin or tetracosapeptide).ti,ab.
6	ethosuximide/ use emczd, emcr or ethosuximide/ or (emeside or ethosuccimid* or ethosuccinimid* or ethosuximide or ethylmethylsuccimide or ethylsuximide or ethymal or etosuximida or mesentol or pemal or petimid or petinimid* or petnidan or pyknolepsin or pyknolepsinum or ronton or simatin or succinutin or sucsilep or suksilep or suxilep or suximal or suxinutin or zarondan or zarontin).ti,ab.
7	gabapentin/ use emczd, emcr or gabapentin/ use ppez or gabapentin*.sh. or (apogabapentin or convalis or dineurin or gabalept or gabaliquid or geriasan or gabapentin* or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or novogabapentin or nupentin).ti,ab.
8	hydrocortisone*.hw. use emczd, emcr or hydrocortisone/ use ppez or (17 hydroxycorticosterone or acticort or aeroseb hc or ala-cort or ala-scalp or alfacort or algicortis or alkindi or alpha derm or alphaderm or anucort-hc or anumed-hc or anutone-hc or aquanil hc or balneol-hc or barseb hc or beta-hc or biacort or cetacort or cobadex or colocort or compound f or cordicare lotion or coripen or cort dome or cortef or cortenema or cortibel or corticorenol or cortifair or cortifan or cortiphate or cortisol or cortisole or cortispray or cortoderm or cortril or cotacort or covocort or cremicort-h or cutaderm or dermacrin hc lotion or dermaid or derm-aid cream or dermaid soft cream or dermocare or dermocortal or dermolate or dioderm or eczacort or ef cortelan or efcortelan or egocort or eksalb or eldecort or emo-cort or epicort or epicortisol or ficortril or filocot or flexicort or glycort or gly-cort or h-cort or hebcort or hemorrhoidal hc or hemril-30 or hemril-hc uniserts or hi-cor or hidrotisona or hycor or hycort or hydracort or hydrasson or hydro ricortex or hydrocort or hydrocorticosteroid or hydrocortisate or hydrocortisone or hydrocortisone or hydrocortisonum or hydrocortisyl or hydrocortone or hydrogalen or hydrokort or hydrokortison or hydro-rx or hydrotopic or hysone or hytisone or hytone or incortin h or instacort 10 or kyypakkaus or lacticare hc or lemnis fatty cream hc or lenirit or medihaler cort or medihaler duo or

#	searches
	medrocil or mildison or mitocortyl demangeaisons or munitren or nogenic hc or novohydrocort or nutracort or optef or otosone f or penecort or plenadren or prepcort or prevex h or pro cort or procort or proctocort or procto-kit or proctosol-hc or proctosone or proctozone or procutan or rectasol-hc or recto-cort or rederm or sanatison or scalp-aid or schericur or scherosone or sistral hydrocort or skincalm or stie-cort or substance m or synacort or texacort or triburon-hc or unicort or vasocort).ti,ab.
9	fat intake/ or glycemic index/ or ketogenic diet/ or exp low carbohydrate diet/ or exp triacylglycerol/
10	9 use emczd, emcr
11	diet, carbohydrate-restricted/ or exp dietary fats/ or glycemic index/ or diet, ketogenic/ or exp triglycer-ides/
12	11 use ppez
13	((adequate adj3 protein*) or atkin* or keto* or kd* or (carbohydrate* adj5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) adj5 (index or treat* or modulat*)) or (high fat* adj5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or low carb* or lchf or low glyc* index treatment* or lgit or (medium chain adj (tryglyceride* or triglyceride*)) or mct*).ti,ab.
14	or/10,12-13
15	lacosamide/ use emczd, emcr or lacosamide/ use ppez or (erlosamide or harkoseride or lacosamide or vimpat).ti,ab.
16	lamotrigine/ use emczd, emcr or lamotrigine/ use ppez or (crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium).ti,ab.
17	levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
18	nitrazepam/ use emczd, emcr,ppez or (apodorm or atempol or benzalin or dormalon or dormo-puren or dumolid or eatan or eunoctin or hypnotex or imadorm or imeson or insomin or mogadan or nelbon or nirven or nitra zepam or nitrados or nitravet or nitrazadon or nitrazep or nitrazepam or nitrodiazepam or novanox or pacisyn or radedorm or remnos or restorem or rhoxal nitrazepam or rhoxal-nitrazepam or sedamon or serenade or somnased or somnibel n or somnite).ti,ab.
19	oxcarbazepine/ use emczd, emcr or oxcarbazepine/ use ppez or oxcarbazepin*.sh. or (apydan or car-bamazepine or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trilep-tin).ti,ab.
20	prednisolone*.hw. use emczd, emcr or exp prednisolone/ use ppez or (adelcort or antisolon* or apred-nislon* or benisolon* or berisolon* or caberdelta or capsoid or co hydeltra or codelcortone or compre-solon or cortadelton* or cortalone or cortelinter or cortisolone or cotolone or dacortin or decaprednil or decortril or dehydro cortex or dehydro hydrocortison* or dehydrocortex or dehydrocortisol* or dehydro-hydrocortison* or delcortol or delta cortef or delta cortril or delta ef cortelan or delta f or delta hycortol or delta hydrocortison* or delta ophticor or delta stab or delta1 dehydrocortisol or delta1 dehydrohydrocor-tisone or delta1 hydrocortisone or deltacortef or delta-cortef or deltacortenolo or deltacortil or deltacor-toil or deltacortril or deltaderm or deltaglycortril or deltahycortol or deltahydrocortison* or deltaophticor or deltasolone or deltastab or deltidrosol or deltisolon* or deltisolone or deltolasson or deltolassone or deltosona or deltosone or depo-predate or dermosolon or dhasolone or di adreson* or diadreson* or diadresonf or di-adreson-f or dicortol or domucortone or encortelon* or encortolon* or equisolon or fernisolone-p or glistelone or hefasolon or hostacortin or hydeltra or hydeltrone or hydrelta or hydrocor-tancyl or hydrocortidelt or hydrodeltalone or hydrodeltisone or hydroretrocortin* or inflanefran or inso-lone or keteocort h or key-pred or lenisolone or leocortol or liquipred or lygal or kopftinktur n or medi-asolone or meprisolon* or metacortalon* or metacortandralon* or metacortelone or meti derm or meti-cortelone or metiderm or meti-derm or morlone or mydrapred or neo delta or nisolon or nisolone or opredsone or panafcortelone or panafcortolone or panafort or paracortol or phlogex or pre cortisyl or preconin or precortalon or precortancyl or precortisyl or predacort 50 or predaject-50 or predalone 50 or predartrin* or predate or predeltilone or predisole or predisyr or pred-ject-50 or predne dome or predne-cort or prednedome or prednelan or predni coelin or predni h tablinen or prednicoelin or prednicort * or prednifor drops or predni-helvacort or predniment or predniretard or prednis or prednisil or prednisolon* or prednivet or prednorsolon* or predonine or predorgasolon* or prelon or prelone or prenilone or prenin or prenolone or preventan or prezolon or rubycort or scherisolon* or serilone or solondo or so-lone or solupren* or spiricort or spolotane or sterane or sterolone or supercortisol or taracortelone or walesolone or wysolone).ti,ab.
21	prednisone/ use emczd, emcr or prednisone/ use ppez or (ancortone or biocortone or colisone or cortan or cortancyl or cortidelt or cortiprex or cutason or dacorten or dacortin or de cortisyl or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitisone or dellacort a or delta 1 dehydrocorti-sone or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or deltacorten* or deltacortisone or delta-cortisone or deltacortone or delta-dome or deltasone or deltison or deltisona or deltra or di adreson or diadreson or drazone or encorton* or enkortolon or enkorton or fernisone or hos-tacortin or insone or kortancyl or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or orasone or orisane or panafcort or panasol or paracort or peha-cort or precort or precortal or predni tablinen or prednicen-m or prednicorm or prednicot or prednidib or

#	searches
	predniment or prednison* or prednisone or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or sone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.
22	pyridoxine/ use emczd, emcr,ppez or pyridoxine*.sh. or (adermine or becilan or beesix or benadon or bexivit or bonadon or bonasanit or campoviton 6 or esa b or gravidox or hexa betalin or hexabetalin or hexabione or hexavibex or hexermin or hexobion or pabroxin or piridoxin* or pyridipca or pyridosine or pyridoxin* or pyridoxin* or pyridoxinium or pyridoxol or pyrivel or pyroxin or rodex or uvimag b6 or viderma or vitamin* b6).ti,ab.
23	rufinamide/ use emczd, emcr or rufinamide*.sh. or (banzel or inovelon or rufinamid* or xilep).ti,ab.
24	exp steroid/ use emczd, emcr or steroids/ use ppez or steroid*.sh. or steroid*.ti,ab.
25	sultiame/ use emczd, emcr or (conadil or contravul or elisal or ospolot or riker or sulphenytame or sulthiame or sultiam* or trolone).ti,ab.
26	tetracosactide/ use emczd, emcr or cosyntropin/ use ppez or (acth or actholain or adrenocorticotropin or corticotropin or cortosyn or cortrosinta depot or cortrosyn or cosyntropin or depot tetracosactrin or nuvacthen or synacten or synacthen* or synacthin* or synathen or synthetic acth or tetracosactid* or tetracosactin* or tetracosapeptide).ti,ab.
27	topiramate/ use emczd, emcr,ppez or (epitomax or topamax or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi).ti,ab.
28	vagus nerve stimulation/ use emczd, emcr or vagus nerve stimulation/ use ppez or ((vagal or vagus) adj2 (activity or stimulat*)).ti,ab.
29	valproic acid/ use emczd, emcr,ppez or (convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetate sodium or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetate sodium or dipropylacetatic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim chrono or epilim chronosphere or epilim enteric or epilim or episenta or epival cr or ergenyl or ergenyl chrono or ergenyl chronosphere or ergenyl retard or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or myproic acid or n dipropylacetic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or semisodium valproate or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or sodium di n propylacetate or sodium dipropyl acetate or sodium dipropylacetate or sodium n dipropylacetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.
30	vigabatrin/ use emczd, emcr,ppez or (4 vinyl 4 aminobutyric acid or 4 vinylaminobutyric acid or 4 vinylgaba or gamma vinyl 4 aminobutyric acid or gamma vinyl gaba or gamma vinyl gamma aminobutyric acid or gamma vinylgaba or n vinyl 4 aminobutyric acid or n vinyl gaba or n vinyl gamma aminobutyric acid or sabril sabrilex or vigadrone or sabril or sabrilex or vigabatrin or gamma vinyl gaba or gamma vinyl gamma aminobutyric acid).ti,ab.
31	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.
32	clinical trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
33	32 use ppez
34	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
35	34 use ppez
36	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
37	36 use emczd, emcr
38	or/33,35,37
39	meta-analysis/
40	meta-analysis as topic/ or systematic reviews as topic/
41	"systematic review"/
42	meta-analysis/
43	(meta analy* or metanaly* or metaanaly*).ti,ab.
44	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
45	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
46	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48	(search* adj4 literature).ab.

#	searches
49	(Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50	cochrane.jw.
51	((pool* or combined) adj2 (data or trials or studies or results)).ab.
52	(or/39-40,43,45-51) use ppez
53	(or/41-44,46-51) use emczd, emcr
54	or/52-53
55	or/38,54
56	1 and 55 and or/2-8,14-31
57	limit 56 to english language
58	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
59	58 use emez
60	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.)
61	60 use mesz
62	59 or 61
63	57 not 62

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 03 of 12, March 2021; Cochrane Central Register of Controlled Trials, Issue 3 of 12, March 2021

Date of last search: 03 March 2021

#	searches
1	“spasms, infantile”:kw or (((early or infantile) near/2 myoclonic near/2 encephalopath*) or ((early or infantile) near/2 epileptic near/2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near/2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) near/1 (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”):ti,ab
2	(acethropan or acetophran or acortan or acorto or acth or acthar or acthelea or acthon or acton or actonar or actrope or adactan or (“adrenal cortex” near/1 (trophic or tropic) near/1 hormone) or adrenocorticaltrophormon or adrenocorticotrop* or adrenocorticotrop* or adrenocorticotrophin or “adrenocorticotropic hormone” or adrenocorticotropin* or adrenomone or adrenotropin or cibacthen or corticotrophin* or corticotropic or corticotropin* or cortigel or cortilin or cortiphyson or cortosyn or cortrophin * or cortropin or cortrosyn or cosyntropin* or cotrophin* or exactin or “hp acthar gel” or humacthid or humactid or “porcine acth” or “porcine corticotropin” or procortan or reacthin or “s cortophin” or solacthyl or “synacthen retard” or tetracosactide or tetracosactrin or tetracosapeptide)
3	(“17 hydroxycorticosterone” or acticort or “aeroseb hc” or “ala-cort” or “ala-scalp” or alfacort or algicortis or alkindi or “alpha derm” or alphaderm or “anucort-hc” or “anumed-hc” or “anutone-hc” or “aquanil hc” or “balneol-hc” or “barseb hc” or “beta-hc” or biacort or cetacort or cobadex or colocort or “compound f” or “cordicare lotion” or coripen or “cort dome” or cortef or cortenema or cortibel or corticorenol or cortifair or cortifan or cortiphate or cortisol or cortisole or cortispray or cortoderm or cortril or cotacort or covocort or “cremicort-h” or cutaderm or “dermacrin hc lotion” or dermaid or “derm-aid cream” or “dermaid soft cream” or dermocare or dermocortal or dermolate or dioderm or eczacort or ef cortelan or efcortelan or egocort or eksalb or eldecort or “emo-cort” or epicort or epicortisol or ficortril or filocot or flexicort or glycort or “gly-cort” or “h-cort” or hebcort or “hemorrhoidal hc “ or “hemril-30” or “hemril-hc uniserts” or “hi-cor” or hidrotisona or hycor or hycort or hydracort or hydrasson or “hydro ricortex” or hydrocort or hydrocorticosteroid or hydrocortisate or hydrocortisone or hydrocortisone or hydrocortisonum or hydrocortisyl or hydrocortone or hydrogalen or hydrokort or hydrokortison or “hydro-rx” or hydrotopic or hysone or hytisone or hytone or “incortin h” or “instacort 10” or kyypakkaus or “lacticare hc” or “lemnis fatty cream hc” or lenirit or “medihaler cort” or “medihaler duo” or medrocil or mildison or “mitocortyl demangeaisons” or munitren or “nogenic hc” or novohydrocort or nutracort or optef or “otosone f” or penecort or plenadren or prepcort or “prevex h” or “pro cort” or procort or proctocort or “procto-kit” or “proctosol-hc” or proctosone or proctozone or procutan or “rectasol-hc” or rectocort or rederm or sanatison or “scalp-aid” or schericur or scherosone or ”sistral hydrocort” or skincalm or “stie-cort” or “substance m” or synacort or texacort or “triburon-hc” or unicort or vasocort)

#	searches
4	mesh descriptor: [triglycerides] explode all trees
5	mesh descriptor: [diet, ketogenic] this term only
6	mesh descriptor: [glycemic index] explode all trees
7	mesh descriptor: [dietary fats] explode all trees
8	mesh descriptor: [diet, carbohydrate-restricted] explode all trees
9	((adequate near/3 protein*) or atkin* or keto* or kd or (carbohydrate* near/5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) near/5 (index or treat* or modulat*)) or (“high fat*” near/5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or ”low carb*” or lchf or “low glyc* index treatment*” or lgit or (“medium chain” near/1 (tryglyceride* or triglyceride*)) or mct*)
10	(elepsia or keppra or kopodex or levetiracetam* or matever or spritam)
11	(apodorm or atempol or benzalin or dormalon or “dormo-puren” or dumolid or eatan or eunoctin or hypnotex or imadorm or imeson or insomin or mogadan or nelbon or nirven or “nitra zepam” or nitrados or nitravet or nitrazadon or nitrazep or nitrazepam or nitrodiazepam or novanox or pacisyn or radedorm or remnos or restorem or “rhoxal nitrazepam” or “rhoxal-nitrazepam” or sedamon or serenade or somnased or “somnibel n” or somnite)
12	(adelcort or antisolon* or aprednislon* or benisolon* or berisolon* or caberdelta or capsoid or “co hydeltra” or codelcortone or compresolon or cortadelton* or cortalone or cortelinter or cortisolone or cotolone or dacortin or decaprednil or decortril or “dehydro cortex” or “dehydro hydrocortison*” or dehydrocortex or dehydrocortisol* or dehydrohydrocortison* or delcortol or “delta cortef” or “delta cortril” or “delta ef cortelan” or “delta f” or “delta hycortol” or “delta hydrocortison*” or “delta ophticor” or “delta stab” or “delta1 dehydrocortisol” or “delta1 dehydrohydrocortisone” or “delta1 hydrocortisone” or deltacortef or “delta-cortef” or deltacortenolo or deltacortil or deltacortoil or deltacortril or deltaderm or deltaglycortril or deltahycortol or deltahydrocortison* or deltaophticor or deltasolone or deltastab or deltidrosol or deltisolon* or deltisolone or deltolasson or deltolassone or deltosona or deltosone or “depopredate” or dermosolon or dhasolone or “ di adreson*” or diadreson* or diadresonf or “di-adreson-f “or dicortol or domucortone or encortelon* or encortolon* or equisolon or “fernisolone-p” or glistelone or hefasolon or hostacortin or hydeltra or hydeltrone or hydrelta or hydrocortancyl or hydrocortidelt or hydrodeltalone or hydrodeltisone or hydroretrocortin* or inflanefran or insolone or “keteocort h” or “keypred” or lenisolone or leocortol or liquipred or lygal or “kopftinktur n” or mediasolone or meprisolon* or metacortalon* or metacortandralon* or metacortelone or “meti derm” or meticortelone or metiderm or ” meti-derm” or morlone or mydrapred or “neo delta” or nisolon or nisolone or opredsone or panafcortelone or panafcortolone or panafort or paracortol or phlogex or “pre cortisyl” or preconin or precortalon or precortancyl or precortisyl or “predacort 50” or “predaject-50” or “predalone 50” or predartrin* or predate or predeltilone or predisole or predisyr or “pred-ject-50” or” “predne dome”” or prednecort or prednedome or prednelan or “predni coelin” or “predni h tablinen” or prednicoelin or prednicort * or “prednifor drops” or “predni-helvacort” or predniment or predniretard or prednis or prednisil or prednisolon* or prednivet or prednorsolon* or predonine or predorgasolon* or prelon or prelone or prenilone or prenin or prenolone or preventan or prezolon or rubycort or scherisolon* or serilone or solondo or solone or solupren* or spiricort or spolotane or sterane or sterolone or supercortisol or taracortelone or walesolone or wysolone)
13	(ancortone or biocortone or colisone or cortan or cortancyl or cortidelt or cortiprex or cutason or dacorten or dacortin or “de cortisyl” or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitisone or “dellacort a” or “delta 1 dehydrocortisone” or “delta cortelan” or “delta cortisone” or “delta dome” or “delta e” or “delta prenovis” or deltacorten* or deltacortisone or “delta-cortisone” or deltacortone or “delta-dome” or deltasone or deltison or deltisona or deltra or “di adreson” or diadreson or drazone or encorton* or enkortolon or enkorton or fernisone or hostacortin or insone or kortancyl or ”liquid pred” or lodotra or “me-korti” or meprison or metacortandracin or meticorten or meticortine or nisona or orasone or orisane or panafcort or panasol or paracort or pehacort or precort or precortal or predni tablinen or “prednicen-m” or prednicorm or prednicot or prednidib or predniment or prednison* or prednisone or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or sone or steerometz or sterapred or ultracorten or urtilone or winpred)
14	(adermine or becilan or beesix or benadon or bexivit or bonadon or bonasanit or “campoviton 6” or “esa b” or gravidox or “hexa betalin” or hexabetalin or hexabione or hexavibex or hexermin or hexobion or pabroxin or piridoxin* or pyridipca or pyridosine or pyridoxin* or pyridoxin* or pyridoxinium or pyridoxol or pyrivel or pyroxin or rodex or “uvimag b6” or viderma or “vitamin* b6”)
15	steroid*
16	(acth or actholain or adrenocorticotropin or corticotropin or cortosyn or “cortrosinta depot “or cortrosyn or cosyntropin or “depot tetracosactrin” or nuvacthen or synacten or synacthen* or synacthin* or synathen or “synthetic acth” or tetracosactid* or tetracosactin* or tetracosapeptide)
17	(epitomax or topamax or topiramate or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi)

#	searches
18	(convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetate sodium" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetate sodium" or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or "epilim chrono" or "epilim chronosphere" or "epilim enteric" or epilim or episenta or "epival cr" or ergenyl or "ergenyl chrono" or "ergenyl chronosphere" or "ergenyl retard" or ergenyl or "espa valept "or everiden or goilim or hexaquin or labazene or leptilan or leptilanil or micropakine or mylproin or "myproic acid" or "n dipropylacetic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "semisodium valproate" or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or "sodium di n propylacetate" or "sodium dipropyl acetate" or "sodium dipropylacetate" or "sodium n dipropylacetate" or stavzor or "valberg pr" or valcote or valepil or valeptol or valerin or "valhel pr" or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral)
19	("gamma vinyl gaba" or "gamma vinyl gamma aminobutyric acid" or "gamma vinylgaba" or "n vinyl 4 aminobutyric acid" or "n vinyl gaba" or "n vinyl gamma aminobutyric acid" or "sabril sabrilex " or vigadrone or sabril or sabrilex or vigabatrin or "gamma vinyl gaba" or "gamma vinyl gamma aminobutyric acid")
20	{or #2-#19}
21	#1 and #20

Database(s): DARE; HTA database - CRD Date of last search: 03 March 2021

#	searches
1	mesh descriptor spasms, infantile this term only
2	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or "epileptic spasm*" or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or "generali?ed flexion epileps*" or hypsarrhythmia* or ((jacknife or "jack nife" or lightening or nodding or salaam) near1 (attack* or convulsion* or seizure* or spasm*)) or "massive myoclonia" or "minor motor epilepsy" or "propulsive petit mal" or "spasm in* flexion" or "spasmus nutans" or "west syndrome*")
3	#1 or #2

Economic

Database(s): MEDLINE & Embase (Multifile) - OVID
Embase Classic+Embase 1947 to 2021 March 31; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 31, 2021
Date of last search: 31 March 2021

Multifile database codes: emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	exp epilepsy/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(epilep* or seizure* or convuls*).ti,ab. or (continous spike wave of slow sleep or infant* spasm*).ti,ab.
6	(seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab.
7	(atonic seizure or tonic seizure).sh. use emczd, emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)).ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)).ti,ab.
8	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.

#	searches
9	exp generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez
10	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab.
11	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hyp-sarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
12	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab.
13	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epi-lepsy/ use emczd, emcr or epileptic syndromes/ use ppez
14	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
15	myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab.
16	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
17	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab.
18	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez
19	(dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
20	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
21	or/2,4-20
22	exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to engish language

Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD

Date of last search: 31 March 2021

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees

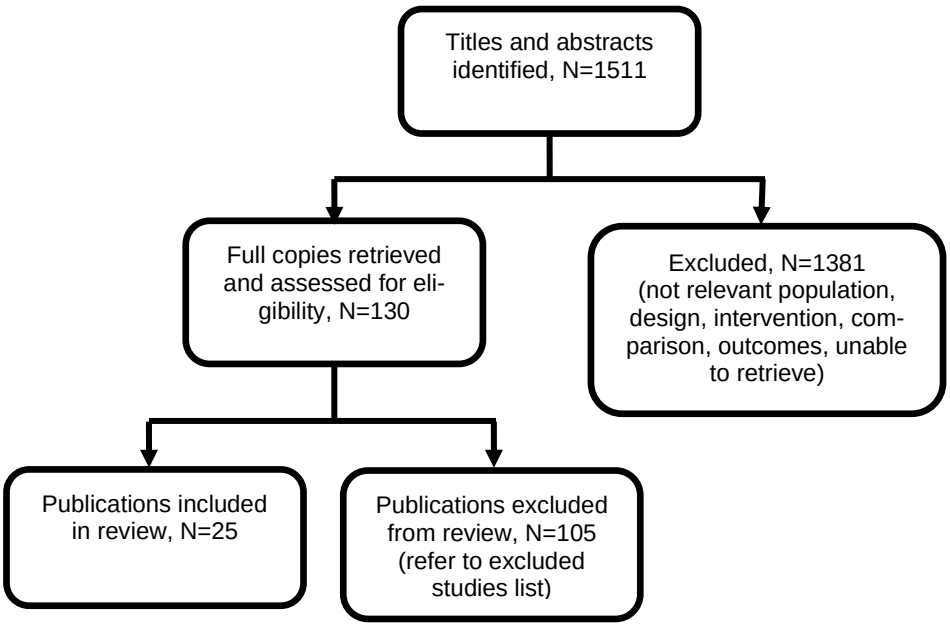
#	searches
5	(epilep* or seizure* or convuls*) or ("continous spike wave of slow sleep" or "infant* spasm*")
6	((absence near2 (convulsion* or seizure*)) or ((typical or atypical) next absenc*) or "petit mal*" or pyknolepsy or "typical absence*")
7	mesh descriptor seizures explode all trees
8	((drop or akinetic or atonic or tonic) near2 (attack* or epileps* or seizure* or convulsion*)) or "brief seizure" or (tonic near3 atonic near3 (attack* or epileps* or seizure* or convulsion*))
9	mesh descriptor epilepsy, rolandic this term only
10	(bcects or bects or brec or "benign epilepsy" or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or "temporal-central focal") near (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
11	mesh descriptor epilepsy, generalized this term only
12	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near3 (epilep* or seizure*)) or (("childhood absence" or "juvenile absence" or myoclonic or myoclonia or "myoclonic astatic" or myoclonus or gtcs) near2 epilep*) or (epilepsy near2 "eyelid myoclonia") or (ige near2 phantom absenc*) or "impulsive petit mal" or (janz near3 (epilep* or "petit mal")) or "jeavons syndrome*" or ((janz or lafora or "lafora body" or lundborg or unverricht) near2 (disease or syndrome)) or ((jme or jmes) and epilep*) or "perioral myoclon*")
13	mesh descriptor spasms, infantile this term only
14	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or "epileptic spasm*" or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or "generali?ed flexion epileps*" or hypsarrhythmia* or ((jacknife or "jack nife" or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or "massive myoclonia" or "minor motor epilepsy" or "propulsive petit mal"or "spasm in* flexion" or "spasmus nutans" or "west syndrome*")
15	mesh descriptor landau kleffner syndrome this term only
16	(dravet or "lennox gastaut" or lgs or (landau near2 kleffner) or smei)
17	mesh descriptor lennox gastaut syndrome this term only
18	mesh descriptor epileptic syndromes this term only
19	("child* epileptic encephalopath*" or gastaut or lennox or lgs)
20	((myoclon* near2 (absence* or epileps* or seizure* or jerk* or "progressive familial epilep*" or spasm* or convulsion*)) or ((lafora or unverricht) near2 disease) or "muscle jerk")
21	mesh descriptor epilepsies, myoclonic explode all trees
22	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or "doose* syndrome" or mae or "generali?ed idiopathic epilepsy") or ((absence or astatic or atonic or tonic or "tonic clonic") near2 (seizure* or spasm*))
23	mesh descriptor epilepsies, partial explode all trees
24	((focal or "focal onset" or local or partial or "simple partial") near3 (epileps* or seizure*))
25	mesh descriptor epilepsies, myoclonic this term only
26	(dravet*1 or ("intractable childhood epilepsy" near2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei)
27	mesh descriptor epilepsy, tonic-clonic this term only
28	mesh descriptor epilepsy, generalized this term only
29	(((clonic or "grand mal" or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*)))
30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

1

Appendix C – Clinical evidence study selection

Clinical study selection for: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

Table 18: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Appleton, R. E., Peters, A. C., Mumford, J. P., Shaw, D. E., Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms, Epilepsia, 40, 1627-1633, 1999 **Ref Id** 1078663 **Country/ies where the study was carried out** Canada, Finland, France, Hungary, the Netherlands, Serbia, and the UK. **Study type** Multicentre, double blind, randomised,	**Sample size** Total recruited: N=40 Intervention group (vigabatrin): n=20 Control group (placebo): n=20 **Characteristics** Age, months, mean (range) Intervention: 8 (5 to 20) Control: 6 (1 to 15) Males, n (%) Intervention: 11 (55) Control: 8 (40) Cryptogenic and idiopathic aetiology, n (%) Intervention: 6 (30) Control: 6 (30) Symptomatic aetiology, n (%) Intervention: 14 (70) Control: 14 (70)	**Interventions** Intervention group Vigabatrin 50 mg/kg/day, up to of 150 mg/kg/ day if the participant's spasms did not cease with the starting dose (administration route not reported) Control group Placebo 50 mg/kg/day, up to of 150 mg/kg/ day if the participant's spasms did not cease with the starting dose (administration route not reported)	**Details** Treatment duration: 5 days Follow-up: 5 days. Outcome measurement: EEG recordings (waking and sleeping) were recorded at the end of the 5-day double-blind trial. Classic hypsarrhythmia was defined by using the criteria by Gibbs and Gibbs and modified hypsarrhythmia by using the criteria by Hrachovy. Adverse effects recorded at the end of the 5-day double-blind trial were: neurologic, physical, biochemical, and hematologic examinations Data analysed according to per protocol	**Results** *Critical outcomes* Spasms freedom within 5 days of the start of treatment (spasm control on the final day of assessment; assessed with the 24 hour monitoring method) Intervention group: n= 7/20 Control group: n= 2/20 EEG resolution within 5 days of the start of treatment amongst those who were spasm free (resolution of hypsarrhythmia on EEG) Intervention group: n=5/7 Control group: n=1/2	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, a predetermined randomisation code was used 1.2: Yes, a remote method to allocate interventions to participants was used 1.3: No, no significant differences between groups at baseline **Domain 2:** Deviations from intended interventions: Some concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
placebo-controlled trial **Aim of the study** To determine the efficacy and safety of vigabatrin in children with infantile spasms **Study dates** Not reported (publication date 1999) **Source of funding** Not reported	No statistically significant differences seen between the treatment groups (p-values not provided) **Inclusion criteria** Aged between 1 and 20 months Newly diagnosed and previously untreated infantile spasms EGG demonstrating either classic or modified hypsarrhytmia Children whose parents were able to provide informed consent, were considered capable of completing a seizure diary and attending the clinic when needed **Exclusion criteria** Use of any AED within 2 months prior the start of the study			% of patients with reported side effects within 5 days of the start of treatment (total number with one or more trial defined AEs) Intervention group: n=12/20 Control group: n=6/20	2.1: No, double blind study 2.2: No, double blind study 2.6: no, analysis was done per protocol 2.7: none of the participants drop out from the double blind phase **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data was available for all participants randomised **Domain 4:** Measurement of the outcome: Low risk 4.1: Probably no, outcomes have been well defined, although there is no information as to how they were assessed or by whom 4.2: Probably no, outcomes included EEG resolution and side effects, and these are unlikely to differ between treatment arms 4.3: No, double blind study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Domain 5: Selection of the reported result: Some concerns 5.1: Probably no, the study authors do not make reference to any study protocol 5.2: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured 5.3: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured **Domain 6:** Overall judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					This study had a double-blind phase (lasting 5 days) and an open phase (lasting a minimum of 24 weeks). During the open phase, and at the discretion of the trial investigators, all participants were switched to vigabatrin monotherapy or as an add-on therapy to ACTH, sodium valproate, or prednisolone. Results have only been reported for the double-blind phase
Full citation Askalan, R., Mackay, M., Brian, J., Otsubo, H., McDermott, C., Bryson, S., Boyd, J., Snead Iii, C., Roberts, W., Weiss, S., Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms, Journal of Child Neurology, 18, 165-170, 2003	**Sample size** Total recruited: N=9 Intervention group (injectable steroids [ACTH]): n=3 Control group (vigabatrin): n=6 **Characteristics** Not reported **Inclusion criteria** Aged between 3 and 16 months at the onset of spasms	**Interventions** <u>Intervention group</u> ACTH IM was divided in 2 doses: 150 IU/ m^2/ day for 1 week, then 75 IU/m^2/day for a second week <u>Control group</u> Vigabatrin PO was divided in 2 doses: 100 mg/kg/day for 1 week, then increased to 150 mg/kg/day for a second week	**Details** Treatment duration: 3 weeks in phase 1, 2 weeks in phase 2 + 12 or 18 months (depending on the drug allocated to, see further details in interventions section). Follow-up: 24 months. Data analysed according to per protocol	**Results** *Critical outcomes* <u>Spasms freedom at 2 weeks</u> ACTH group: n=3/3 Vigabatrin group: n=6/6 <u>EEG resolution at 2 weeks</u> ACTH group: n=2/3 Vigabatrin group: n=3/6	**Limitations** <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u> **Domain 1:** <u>Randomisation:</u> Some concerns 1.1: No information was provided to assess whether the allocation sequence was random

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 1078673 **Country/ies where the study was carried out** Canada **Study type** Open-label, randomised, single-centre randomised controlled trial **Aim of the study** To assess the safety and effectiveness of ACTH as compared to vigabatrin in infants with infantile spasms **Study dates** January 1999 to January 2001 **Source of funding** Bloorview Children's Hospital Foundation	Had not previously taken and were not allergic to vigabatrin or corticosteroids No known visual disturbance Parents and carers able to comply with follow-up visits **Exclusion criteria** Medical condition by which corticosteroids were contra-indicated				1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: No baseline demographic baseline information was provided **Domain 2:** Deviations from intended interventions: Low risk 2.1: Yes, participants were aware of their assigned intervention during the trial 2.2: Yes, for neurodevelopmental outcomes (psychologists were blinded to treatment allocation) and no for spasm freedom and EEG resolution (no information was provided to assess whether assessors were blinded to treatment allocation) 2.3: No information was provided to assess if there were deviations from the intended intervention that arose because of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the experimental context **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data available for all participants randomised **Domain 4:** Measurement of the outcome: High risk 4.1: No, the method for measuring the outcome was appropriate 4.2: Yes, outcomes could have differed between intervention groups 4.3: Some outcome assessors were aware of the intervention received by study participants 4.4: Probably yes. Assessment of the outcome could have been influenced by knowledge of intervention received 4.5: Probably no. There is no reason to believe that assessment of the outcome was influenced by

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					knowledge of the intervention received **Domain 5:** Selection of the reported result: High risk 5.1: No information. Trial protocol was not available 5.2: No information. Trial protocol was not available 5.3: No information. Trial protocol was not available **Domain 6:** Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain
Full citation Baram, T. Z., Mitchell, W. G., Tournay, A., Snead, O. C., Hanson, R. A., Horton, E. J., High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study, Pediatrics, 97, 375-379, 1996	**Sample size** Total recruited: N=34; total included N=29 Intervention group (prednisone): n=14 Control group (ACTH): n=15 **Characteristics** Age, months, mean (SD not reported) Intervention: 7.5 Control: 5.1	**Interventions** Intervention group Prednisone PO 1 mg/kg twice a day for 2 weeks Control group ACTH IM 75 U/m^2 twice a day for 2 weeks	**Details** Treatment duration: 2 weeks. Follow-up: 2 weeks. Outcome measurement: 2 weeks after the intervention, EEG response was assessed through video. These lasted 4 to 24 hours and always included a full sleep-wake	**Results** *Critical outcomes* Spasms freedom at 2 weeks Intervention group: n=4/14 Control group: n=14/15 Spasms freedom at 2 weeks by aetiology Intervention group Symptomatic: n=3/14	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Some concerns 1.1: Yes, done according to a computer

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 1078691 **Country/ies where the study was carried out** US **Study type** Prospective, randomised, single blind controlled trial **Aim of the study** To assess the effectiveness of prednisone compared with ACTH in infants with infantile spasms **Study dates** Not reported (publication date 1996). **Source of funding** Not reported.	<u>Males, n (%)</u> Intervention: 4 (26.66) Control: 8 (57.14) <u>Aetiology: symptomatic, n (%)</u> Intervention: 10 (71.42) Control: 12 (80) <u>Aetiology: cryptogenic, n (%)</u> Intervention: 4 (28.58) Control: 3 (20) **Inclusion criteria** Presence of infantile spasms with hypsarrhythmia No prior steroid/ACTH treatment **Exclusion criteria** Not reported	Infants with persistent spasms or hypsarrhythmia were offered the alternative drug, although these results have not been reported here. Responders were tapered off their treatments as follows: those in prednisone received for 3 days 1 mg/kg, for 6 days 0.5 mg/kg and for 6 days 0.5 mg/ kg every other morning. Infants on ACTH received: for 3 days 30 U/m2, for 3 days 15 U/m2, for 3 days 10 U/m2 and for 6 days 10 U/m2 every other morning.	cycle. EEG response consisted of resolution of hypsarrhythmic pattern on both sleep and wake EEG. How data was analysed was not reported	Cryptogenic: n=1/14 Control group Symptomatic: n=11/15 Cryptogenic: n=3/15 <u>EEG resolution at 2 weeks</u> Intervention group: n=4/14 Control group: n=13/15 <u>EEG resolution at 2 weeks by aetiology</u> Intervention group Symptomatic: n=3/14 Cryptogenic: n=1/14 Control group Symptomatic: n=11/15 Cryptogenic: n=2/15 *Important outcomes* <u>Spasms relapse by end of treatment</u> Intervention group: n=0/4 Control group (symptomatic): n=2/15	generated random number list 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: No, any observed imbalances are compatible with chance **Domain 2:** <u>Deviations from intended interventions:</u> Low risk 2.1: Yes, participants were aware of their assigned intervention during the trial 2.2: Yes, carers and people delivering the interventions were aware of treatment allocation 2.3: No, there were no deviations from the intended intervention **Domain 3:** <u>Missing outcome data:</u> Low risk 3.1: Yes, data was available for all participants

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Domain 4: Measurement of the outcome: Low risk 4.1: No, the method for measuring the outcome was appropriate 4.2: No, measurement or ascertainment of the outcome could not have difference between intervention group 4.3: No, outcome assessors blinded to intervention status **Domain 5:** Selection of the reported result: High risk 5.1: No, there was no reference to a study protocol, therefore is not possible to know whether data was produced in accordance with a pre-specified plan 5.2: No, there was no reference to a study protocol, therefore is not possible to know whether the numerical results were selected on the basis of multiple eligible outcome measurements

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					5.3: No, there was no reference to a study protocol, therefore is not possible to know whether the results were selected on the basis of multiple eligible analyses of the data **Domain 6:** Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain
Full citation Chellamuthu, P., Sharma, S., Jain, P., Kaushik, J. S., Seth, A., Aneja, S., High dose (4mg/kg/day) versus usual dose (2mg/kg/day) oral prednisolone for treatment of infantile spasms: An open-label, randomized controlled trial, Epilepsy Research, 108, 1378-1384, 2014 **Ref Id** 1078763	**Sample size** Total recruited: N=71; total included: N=63 Intervention group (high-dose prednisolone [4 mg/kg/day]): n=31 Control group (low-dose prednisolone [2 mg/kg/day]): n=32 **Characteristics** Age, months, median (IQR) Intervention: 12 (9 to 18) Control: 10.5 (8 to 14.5)	**Interventions** Intervention group High-dose prednisolone PO 4mg/kg/day for 2 weeks Control group Low-dose prednisolone PO 2 mg/kg/day for 2 weeks Once the clinical resolution was achieved, prednisolone was tapered over 2 weeks and stopped. In children with persisting spasms after 2	**Details** Treatment duration: 2 weeks Follow-up: 6 months (14 days for EEG resolution and side effects and 6 months for spasms relapse and ongoing seizures). Outcome measurement: children were reviewed once weekly as outpatients during the trial period. A 1 hour video EEG recording at least one sleep-wake cycle was repeated between	**Results** *Critical outcomes* Spasms freedom at 2 weeks Intervention group: 16/31 Control group: 8/32 EEG resolution at 2 weeks: normal EEG with complete resolution of hypsarrhythmia in those with spasms freedom Intervention group: n=9/16 Control group: n=4/8	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, participants were randomised using computer-generated random number tables 1.2: Yes, allocation sequence was done by independent personnel

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out India **Study type** Open label, randomised controlled trial. **Aim of the study** To determine the efficacy and tolerability of high dose prednisolone as compared to usual dose in children with infantile spasms **Study dates** February 2012 to March 2013 **Source of funding** None	Number of spasms per cluster at study entry, median (IQR) Intervention: 5 (4 to 10) Control: 5 (3 to 7) Males, n (%) Intervention: 21 (67.7) Control: 23 (71.9) Aetiology: perinatal asphyxia, n (%) Intervention: 17 (54.8) Control: 18 (56.2) Aetiology: neonatal hypoglycaemia, n (%) Intervention: 3 (9.7) Control: 7 (21.9) Aetiology: cortical malformations, n (%) Intervention: 4 (12.9) Control: 0 (0) Aetiology: post-meningitic sequalae, n (%) Intervention: 1 (3.2) Control: 1 (3.1) Aetiology: inborn errors of metabolism, n (%) Intervention: 1 (3.2) Control: 1 (3.1)	weeks, other anti-epileptic agents were added. These children were reviewed once per month for the initial 6 months. The frequency of spasms in these children was based on a parental report	day 14 and day 21 (at the end of 2 weeks); during each visit side effects were recorded and parental concerns were also noted. The spasm frequency was noted in diaries completed by parents. Data analysed according to intention to treat	Treatment cessation due to adverse events at 2 weeks Intervention group: n=0/31 Control group: n=0/32 *Important outcomes* Spasms relapse at 6 months Intervention group: n=5/16 Control group: n=4/8 Ongoing seizures at 6 months Intervention group: n=1/31 Control group: n=0/32	1.3: No, there were no imbalances at baseline (p-values were reported) **Domain 2:** Deviations from intended interventions: Low risk 2.1: Yes, the study was open label 2.2: Yes, the study was open label 2.3: Probably no, no deviations from the intended protocol were reported **Domain 3:** Missing outcome data: Low risk 3.1: Yes, only data for one participant was not included in the analysis **Domain 4:** Measurement of the outcome: Some concerns 4.1: Probably no, outcomes were well defined, but no information was provided on how they were assessed, or by whom

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Aetiology: unknown cause, n (%) Intervention: 5 (16.1) Control: 5 (15.6) **Inclusion criteria** Children aged between 3 months and 2 years presented with at least 1 cluster of infantile spasms per day EEG evidence of hypsarrhythmia or its variants **Exclusion criteria** Those with chronic systemic illness Tuberculosis or severe acute malnutrition as defined by WHO criteria				4.2: Probably no, outcomes are unlikely to differ between treatment arms 4.3: Yes, the study was open label 4.4: Probably yes, the outcomes reported involve some judgement 4.5: Probably no, the study was comparing a usual dose versus a higher dose of the same medication, so there is no reason to believe that the knowledge of the intervention status may have influenced the outcome assessment **Domain 5:** Selection of the reported result: Low risk 5.1: Yes, the authors published a study protocol before starting the trial 5.2: No, there is clear evidence that the results correspond with all the intended outcome measurements

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					5.3: No, there is clear evidence that the results correspond with all the intended outcome measurements **Domain 6:** Overall judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation Chiron, C., Dumas, C., Jambaqué, I., Mumford, J., Dulac, O., Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis, Epilepsy Research, 26, 389-395, 1997 **Ref Id** 1078778 **Country/ies where the study was carried out** France	**Sample size** Total recruited: N=22 Intervention group (vigabatrin): n=11 Control group (hydrocortisone): n=11 **Characteristics** Age at onset of infantile spasms, months, mean (SD) Intervention: 5.8 (1.8) Control: 5.9 (3.2) Males, n (%) Intervention: 5 (45.45) Control: 6 (54.54)	**Interventions** Intervention group Vigabatrin 150 mg/kg per day during 1 month (administration route not reported) Control group Hydrocortisone 15 mg/kg per day during 1 month (administration route not reported)	**Details** Treatment duration: 1 month. Follow-up: 1 month. Method for data analysis was not reported.	**Results** *Critical outcomes* Spasms freedom at 1 month Intervention group: n=11/11 Control group: n=5/11 % of patients with reported side effects (trial defined adverse and serious adverse effects) at 1 month Intervention group: n=3/11 Control group: n= 8/11 *Important outcomes* Spasms relapse at 2 months	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Some concerns 1.1: Randomisation method was not reported 1.2: Whether the allocation sequence was concealed was not reported 1.3: There were no baseline differences

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial **Aim of the study** To assess the efficacy and safety of vigabatrin compared to hydrocortisone **Study dates** Not reported (study published in 1997) **Source of funding** Not reported	**Inclusion criteria** Infants with spasms and tuberous sclerosis recorded on EEG or seen by an experienced clinician Aged between 1 month and 2 years **Exclusion criteria** Previously received ACTH, vigabatrin or oral corticosteroids but not with other anticonvulsant medication (as long as they were treatment free for at least 1 week)			Intervention group: n=1/11 Control group: n=0/5	for the demographic characteristics reported **Domain 2:** Deviations from intended interventions: Some concerns 2.1: yes, participants were aware of their assigned intervention during the trial 2.2: Yes, carers were aware of participant's assigned intervention during trial 2.3: No information, trialists do not report whether deviations arose from the experimental context **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data available for all participants randomised **Domain 4:** Measurement of the outcome: Some concerns 4.1: There was no information was provided regarding the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					method of measuring the outcome 4.2: No, measurement or ascertainment could not have differed between intervention groups 4.3: Yes, outcome assessors were aware of the intervention received 4.4: Yes, assessment of the outcome could have been influenced by knowledge of the intervention received as there is some judgement involved for assessing the outcomes reported 4.5: No, it is not likely that assessment of the outcome could have been influenced by knowledge of the intervention received **Domain 5:** Selection of the reported result: High risk 5.1: No, there was no reference to a study protocol, therefore is not possible to know whether data was produced in accordance

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					with a pre-specified plan 5.2: No, there was no reference to a study protocol, therefore is not possible to know whether the numerical results were selected on the basis of multiple eligible outcome measurements 5.3: No, there was no reference to a study protocol, therefore is not possible to know whether the results were selected on the basis of multiple eligible analyses of the data **Domain 6:** Overall judgment of bias: High risk The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result
Full citation Dreifuss, F., Farwell, J., Holmes, G., Joseph, C., Lockman, L., Madsen, J. A., Minarcik, C. J.,	**Sample size** Total recruited: N= 52; total included N=48 Intervention group (nitrazepam): n=27	**Interventions** Intervention group Nitrazepam PO Starting dose: 0.2 mg/kg/day in 2 divided doses or 1 mg	**Details** Treatment duration: 1 month. Follow-up: 1 month	**Results** *Critical outcomes* Spasms freedom (number of patients who were 75% to 100%	**Limitations** Methodological limitations assessed using the Cochrane risk of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Rothner, A. D., Shewmon, D. A., Infantile spasms. Comparative trial of nitrazepam and corticotropin, Archives of Neurology, 43, 1107-1110, 1986 **Ref Id** 1078856 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of nitrazepam compared to ACTH in children with infantile spasms **Study dates** Not reported (study published in 1986) **Source of funding** Not reported	Control group (ACTH): n=21 **Characteristics** Age, months, mean (range) Intervention: 8.70 (2 to 23) Control: 8.04 (3 to 21) Number of seizures before study entry, mean (range) Intervention: 174.3 (6 to 542) Control: 17.1 (10 to 1616) Males, n (%) Intervention: 14 (51.85) Control: 15 (60) **Inclusion criteria** 1 to 24 months of age Diagnosis of infantile spasms, documented on EEG No previous treatment with ACTH, steroids or nitrazepam **Exclusion criteria** Those currently taking other medications, such as valproic acid or benzodiazepines. The administration of phenobarbital, phenytoin, carbamazepine or succinimides was permitted	twice daily, whichever was greater. The dose was adjusted weekly, with increments of 0.3 to 0.4 mg/kg/day Final dose: 4.80 to 9 mg/day Control group ACTH gel IM at a dose of 40 U/day	Outcome measurement: spasm frequency calculated from 24-hour EEG-videotape at baseline and end of treatment The principle according to which the data was analysed was not reported	spasm free after 1 month of starting treatment) (n=4 were excluded from the efficacy analysis due to AEs in the ACTH arm) Intervention group: n=14/27 Control group: n=12/21 Treatment cessation due to adverse events (2 within < than 1 week and 4 within 14 to 22 days of treatment) Intervention group: n=0/27 Control group: n=6/25	bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: No information, randomisation method was not reported 1.2: No information, no details were provided regarding treatment concealment 1.3: No, there were no baseline differences between interventions **Domain 2:** Deviations from intended interventions: Some concerns 2.1: No information was provided to assess whether participants were aware of their assigned intervention 2.2: No information was provided to assess whether carers were aware of the participant's assigned intervention 2.3: No information was provided to as-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					sess if there were deviations from the intended intervention that arose because of the experimental context **Domain 3:** Missing outcome data: High risk 3.1: Data was not available for all participants randomised 3.2: No evidence that the result was not biased 3.3: Yes, participants drop out because of side effects and one of the participants died, and not autopsy was done to assess the cause of death 3.4: There are differences between the intervention and control drop-out rates, which could be due to the intervention participants were allocated to **Domain 4:** Measurement of the outcome: Some concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					4.1: No, the method for measuring the outcome was appropriate 4.2: No, measurement or ascertainment of the outcome could not have differed between intervention groups 4.3: No information. It is unclear whether outcome assessors were aware of treatment allocation 4.4: Yes, assessment of the outcome could have been influenced by knowledge of intervention received 4.5: No, not likely that assessment of the outcome was influenced by knowledge of the intervention received **Domain 5:** Selection of the reported result: Some concerns 5.1: No information, the study authors do not make reference to any study protocol, and it is unclear whether the outcomes and procedures undertaken during the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					open phase were planned 5.2: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured 5.3: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured **Domain 6:** Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain for this result
Full citation Dressler, A., Benninger, F., Trimmel-Schwahofer, P., Groppel, G., Porsche, B., Abraham, K., Muhlebner, A., Samueli, S., Male, C., Feucht, M., Efficacy and tolerability of the ketogenic diet versus high-dose	**Sample size** Total recruited: N=130; N=32 children with confirmed infantile spasms who did not previously receive KD or steroids Intervention group (ketogenic diet): n=16 Control group (ACTH): n=16	**Interventions** Intervention group Ketogenic diet was introduced without fasting and fluid restriction. Initially it was at a 1:1 fat: non-fat ratio and then increased to 3:1 ratio. n=4 (25%) received vigabatrin before trial start	**Details** Treatment duration (follow-up): 28 days. Follow-up: 24 months. Follow-up visits were scheduled as follows: once per week during the first month, at 3 months, and at 12 months. The final visit took place at 24 months.	**Results** *Critical outcomes* Spasms freedom at last follow-up (at 6, 12 or 24 months) Intervention group: n=6/16 Control group: n=7/16	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, randomisation was computer

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
adrenocorticotropic hormone for infantile spasms: A single-center parallel-cohort randomized controlled trial, Epilepsia, 60, 441-451, 2019 **Ref Id** 1078857 **Country/ies where the study was carried out** Austria **Study type** Single centre, prospective, randomised controlled trial **Aim of the study** To assess the efficacy, safety and tolerability of ketogenic diet compared with ACTH in children with infantile spasms **Study dates** June 2008 to April 2017 **Source of funding** None	**Characteristics** Age at epilepsy onset, months, median (range) Intervention: 4.9 (0-12) Control: 5.0 (0.2-27) Time from epilepsy onset to trial treatment, days, median (range) Intervention: 22 (7-212) Control: 44 (0-256) Female, n (%) Intervention: 10 (63) Control: 6 (38) Aetiology known, n (%) Intervention: 7 (44) Control: 11 (69) **Inclusion criteria** Diagnosis of West Syndrome as per the ILAE criteria, based on video EEG monitoring Written consent from parents or carers **Exclusion criteria** Contraindications for either ketogenic diet or ACTH Previous treatment with ketogenic diet or steroids	Control group Synthetic ACTH was given at 150 IU/m2/day in 2 divided doses for 2 weeks and then tapered regularly. n=4 (25%) received vigabatrin before trial start (administration route not reported)	Outcome measurement: 24 hour EEG videos were performed to detect spasms and/or hypsarrhythmia. Parents and carers recorded adverse events in diaries. Data analysed according to intention to treat principle	% of patients with reported side effects (at 6, 12 or 24 months) Intervention group: n=14/16 Control group: n=16/16 *Important outcomes* Spasms relapse at last follow-up (at 6, 12 or 24 months) (note: reported as per the study; denominator was not those who were spasms free as not all of them may have been able at follow up) Intervention group: n=4/10 Control group: n=4/11 Neurodevelopment outcomes at last follow-up (at 6, 12 or 24 months): psychomotor development age-appropriate assessed by The Touwen Infant Neurological Examination in those <18 months and the Hempel Neurological Examination in those ≥18 months	generated using a web program 1.2: Yes, it was concealed 1.3: No, observed imbalances are compatible with chance and likely due to the low number of participants **Domain 2:** Deviations from intended interventions: Some concerns 2.1: Yes, participants were aware of their assigned interventions during the trial 2.2: Yes, parents and carers were aware of participant's assigned intervention during the trial 2.3: Yes, there were deviations from the interventions. Some infants who fulfilled the inclusion criteria were not finally randomised for different reasons, including lack of initial compliance, no consent to follow the intervention, or intervention not available. These characteristics

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Intervention group: 4/16 Control group: 5/16 <u>Neurodevelopment outcomes at last follow-up (at 6, 12 or 24 months): adaptive level age-appropriate assessed by VABS</u> Intervention group: 3/10 Control group: 6/11	are not listed as part of the inclusion criteria for the trial 2.4: Yes, these deviations are likely to have affected the outcome. Even though infants who did not follow the interventions as specified were not randomised, it is believed that this may have led to an over selection of those finally included in the randomised trial because the reasons by which these infants were not finally included are not listed in the inclusion criteria of the trial 2.5: Probably yes, these deviations seem to be balanced between groups 2.6: Yes, analysis was intention to treat **Domain 3:** <u>Missing outcome data</u>: Low risk 3.1: Yes, data was available for nearly all participants, although for the neurodevelop-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					mental outcomes (assessed by VABS), it was only available for a fraction of the total number of participants **Domain 4:** Measurement of the outcome: Low risk 4.1: No, the method for measuring the outcome was appropriate 4.2: No, measurement or ascertainment of the outcome could have not differed between treatment groups 4.3: No, outcome assessors were not aware of treatment allocation, however parents were and they were responsible for filling out a diary with the adverse events observed **Domain 5:** Selection of the reported result: Some concerns 5.1: No information. The study mentions the study protocol and provides a registration number, however it

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					has not been possible to access it. Not possible to assess whether data was analysed according to a pre-specified analysis plan or not 5.2: No information. Trial protocol was not available, therefore it was not possible to assess whether results could have been selected on multiple eligible outcome measurements 5.3: No information. Trial protocol was not available, therefore it was not possible to assess whether results could have been selected on multiple eligible analyses of the data **Domain 6:** Overall judgment of bias: Some concerns The study is judged to have some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Elterman, R. D., Shields, W. D., Bittman, R. M., Torri, S. A., Sagar, S. M., Collins, S. D., Vigabatrin for the treatment of infantile spasms: Final report of a randomized trial, Journal of Child Neurology, 25, 1340-1347, 2010 **Ref Id** 1078884 **Country/ies where the study was carried out** US **Study type** Randomised clinical trial **Aim of the study** To assess the efficacy and safety of high-dose vigabatrin as compared with low-dose vigabatrin **Study dates** Not reported (last subject completed in April 2002) **Source of funding**	Total randomised: N=227; total included N=221 Intervention group (high dose vigabatrin): n=107 Control group (low dose vigabatrin): n=114 **Characteristics** Age, years, mean (SD) Intervention: 0.6 (0.3) [based on n=102 participants] Control: 0.6 (0.3) [based on n=112 participants] Males, n (%) Intervention: 45 (42.1) [gender baseline characteristics were missing for n=1 in this group] Control: 63 (55.3) [gender baseline characteristics were missing for n=1 in this group] Aetiology: symptomatic-other, n (%) Intervention: 60 (56.1) Control: 66 (57.9) Aetiology: cryptogenic, n (%) Intervention: 27 (25.2) Control: 30 (26.3) Aetiology: symptomatic-tuberous sclerosis, n (%)	Intervention group High-dose vigabatrin PO 100 to 148 mg/kg/day for 14 to 21 days Control group Low-dose vigabatrin PO 18 to 36 mg/kg/day for 14 to 21days Those patients who were on stable medications prior to trial entry, were allowed to continue on them. Dose adjustments were not allowed during the first 21 days, and after then, adjustments or withdrawal of medication could be done at the investigator's discretion. Those achieving spasms freedom during the first 14 days of the study, remained for an additional 7 days on the medication they were initially allocated to. Those not achieving spasm freedom during the first 14 days,	Treatment duration: 14 to 21 days. Duration of vigabatrin exposure, mean (SD) – high-dose 423.3 (317.2); low-dose group 512 (372.1). Follow-up: 21 days (RCT phase only). Data analysed according to intention to treat	*Critical outcomes* Spasms freedom (free of spasms for 7 consecutive days at any time during the study and remained spasm free for the duration of the study based on caregiver assessment) Intervention group: n=73/107 Control group: n=59/114 % of patients with reported side effects at approximately 1.2 years Intervention group: n=52/107 (*trial reported 108 as a denominator, but assumed that a typo was made as 107 infants were randomised to the high-dose group) Control group: n=58/114 *Important outcomes* Spasms relapse at approximately 1.2 years Intervention group: n=2/17	Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: No information, randomisation method was not reported 1.2: No information, no details were provided regarding treatment concealment 1.3: No, there were no baseline differences between interventions **Domain 2:** Deviations from intended interventions: Low risk 2.1: No, participants were not aware of their assigned intervention 2.2: Carers were not aware of treatment allocation. No information was provided to specify whether people delivering the interventions were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aventis Pharmaceutical Inc (unrestricted grant), Hoecsht Marion Roussel and Rhone-Poulenc Rorer, National Institutes of Health General and Clinical Research Center, Lundbenk Inc	Intervention: 20 (18.7) Control: 18 (15.8) **Inclusion criteria** Diagnosis of infantile spasms of less than 3 months, confirmed by findings of hypsarrhythmia, modified hypsarrhythmia or multifocal spikes on EEG recording <2 years old <3.5 kg of weight Not previously treated with corticosteroids, adrenocorticotropic hormone or valproic acid, although infants could be on stable doses of spasms antiepileptic drugs **Exclusion criteria** Treatable or progressive cause of seizure Co-occurring medical condition that would interfere with the safe completion of the study Lennox-gastaut syndrome History of generalised tonic clonic status epilepticus Poor medication adherence Parents or carers unable to provide informed consent to participate in the study	were entered the open-label phase, where investigators were able to make adjustments to the medication participants were originally allocated to (they were not allowed to make a change > 25 to 50 mg/kg/day each week and were not able to exceed 200 mg/kg/day). Concomitant antiepileptic medications were allowed during the open label phase.		Control group: n=2/8	aware of participant's assigned intervention 2.3: Probably no, some participants were provided with the incorrect doses of medications, but this is unlikely to have arisen from the experimental context **Domain 3:** Missing outcome data: Low risk 3.1: Data was not available for all participants randomised 3.3: Yes, results were analysed according to the intention to treat principle **Domain 4:** Measurement of the outcome: Some concerns 4.1: No, the method for measuring the outcome was appropriate 4.2: No, measurement or ascertainment of the outcome could not have differed between intervention groups 4.3: No information. It is unclear whether outcome assessors

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					were aware of treatment allocation 4.4: Yes, assessment of the outcome could have been influenced by knowledge of intervention received 4.5: No, not likely that assessment of the outcome was influenced by knowledge of the intervention received **Domain 5:** Selection of the reported result: Some concerns 5.1: No information, the study authors do not make reference to any study protocol, and it is unclear whether the outcomes and procedures undertaken during the open phase were planned 5.2: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured 5.3: No information, analysis intentions are

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					not available and there is more than one way in which the outcomes could have been measured **Domain 6:** Overall judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation Fallah, R., Salor, F., Akhavan Karbasi, S., Motaghipisheh, H., Randomised clinical efficacy trial of topiramate and nitrazepam in treatment of infantile spasms, Iranian Journal of Child Neurology, 8, 12-19, 2014 **Ref Id** 436432 **Country/ies where the study was carried out** Iran.	**Sample size** Total randomised: N=50 Intervention group (nitrazepam): n=25 Control group (topiramate): n=25 **Characteristics** Age, months, mean (SD) Intervention: 9.82 (3.76) Control: 9.01 (3.96) Number of clusters in a week, mean (SD) Intervention: 26.16 (20.89) Control: 35.16 (28.27) Males, n (%) Intervention: 8 (32)	**Interventions** Intervention group Nitrazepam PO for 2 weeks Initial dose: 0.5 mg/kg/day Maximum dose: 1 mg/kg/day Control group Topiramate PO for 2 weeks Initial dose: 3 mg/kg/day Maximum dose: 12 mg/kg/day	**Details** Treatment duration: 4 weeks. Follow-up: 6 months. The principle according to which data was analysed was not reported	**Results** *Critical outcomes* Spasms freedom at 6 months Intervention group: n=4/25 Control group: n=12/25 % of patients with reported side effects at 6 months Intervention group: n=9/25 Control group: n=8/25 Treatment cessation due to adverse events at 6 months Intervention group: n=0/25 Control group: n=0/25	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, randomisation was computer generated 1.2: Probably yes, allocation concealment was done by someone not involved in the study, although how was it done has not been reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised, single blind, open label, parallel group controlled trial. **Aim of the study** To assess the safety and efficacy of nitrazepam compared with topiramate in infants with West Syndrome. **Study dates** Not reported (participants recruited between 2008 and 2010). **Source of funding** Shaheed Sadoughi University of Medical Sciences.	Control: 12 (48) Aetiology: symptomatic, n (%) Intervention: 20 (80) Control: 23 (92) Aetiology: cryptogenic, n (%) Intervention: 5 (20) Control: 2 (18) **Inclusion criteria** Children with infantile spasms based on the ILAE definition who were not taking any current antiepileptic medication, ACTHS and/or corticosteroids ≥ 2 months ≤ 2 years of age **Exclusion criteria** Presence of metabolic acidosis Kidney dysfunction Renal stone Those who had not completed 6 month of treatment period				1.3: No baseline differences were reported **Domain 2:** Deviations from intended interventions: Low risk 2.1: Yes, participants were aware of treatment allocation as study is single blind 2.2: Yes, carers and people delivering the interventions were aware of treatment allocation 2.3: No, there were no deviations from the intended intervention **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data was available for all participants randomised **Domain 4:** Measurement of the outcome: Low risk 4.1: Probably not, the study reports that video-EEG monitoring was not available in the city, therefore "cessation of clinical

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					seizures was indicative of successful management" 4.2: No, measurement or ascertainment of the outcome could have not differed between intervention groups 4.3: No, outcome assessors were not aware of the intervention received **Domain 5:** Selection of the reported result: High risk 5.1: Yes, data was analysed in accordance to a protocol 5.2: Yes, seizure freedom was measured in multiple ways (this is, improved, unchanged, worsened..) and the protocol does not specify that this outcome will be analysed according to these parameters 5.3: Yes, the numerical results are being assessed in multiple ways (this is, according to responders versus not responders

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					rather than treatment group) **Domain 6**: Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain
Full citation Gowda, V. K., Narayanaswamy, V., Shivappa, S. K., Benakappa, N., Benakappa, A., Corticotrophin-ACTH in Comparison to Prednisolone in West Syndrome - A Randomized Study, Indian Journal of Pediatrics, 86, 165-170, 2019 **Ref Id** 1078982 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial	**Sample size** Total recruited: N=58; total included N=34 Intervention group (oral steroids, prednisolone): n=16 Control group (injectable steroids, ACTH): n=18 **Characteristics** Age, years, mean (SD) Intervention: 13.9 (9.2) Control: 9.4 (5.32) Number with preceding/ concurrent seizures, n (%) Intervention: 7 (43.75) Control: 7 (38.8) Number of females, n (%) Intervention: 7 (43.75) Control: 6 (33.33) Aetiology: symptomatic, n (%) Intervention: 13 (81.25)	**Interventions** Intervention group Oral steroids (prednisolone) Starting dose: 4 mg/kg/day for 2 weeks Final dose: 60 mg/kg/day for 2 weeks Control group Injectable steroids (ACTH) Starting and final dose: 100 U/m^2/day 2 weeks The response was assessed at the end of the 2 weeks and drugs were tapered and stopped over a period of 3 to 4 weeks.	**Details** Treatment duration: 2 weeks. Follow-up:6 months. Data analysed according to intention to treat	**Results** *Critical outcomes* Spasms freedom on day 14 (no reported spasms for at least 48 hours including days 13 and 14 after randomisation) Intervention group: n=5/15 Control group: n=9/18 Spasms freedom on day 28 (no reported spasms for at least 48 hours including days 13 and 14 after randomisation) Intervention group: n=6/15 Control group: n=11/18 Time taken for spasms freedom (number of consecutive days free of spasms preceding	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Some concerns 1.1: Yes, randomisation was computer generated 1.2: No information was provided as to how the allocation sequence was concealed 1.3: No, no significant differences between groups at baseline **Domain 2:** Deviations from intended interventions: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the efficacy, safety and tolerability of prednisolone and ACTH in children with west syndrome **Study dates** October 2013 to October 2015 **Source of funding** Not reported	Control: 14 (77.77) Aetiology: idiopathic, n (%) Intervention: 0 (0) Control: 1 (5.55) Aetiology: cryptogenic, n (%) Intervention: 3 (18.75) Control: 3 (16.66) **Inclusion criteria** Children with infantile spasms aged 2 months to 5 years **Exclusion criteria** Those who had already received steroids or those in whom steroids were contraindicated Infantile spasms due to Tuberous sclerosis			and including day 14), mean days (SD) Intervention group: 8 (9.9); n=15 Control group: 6.9 (6.7); n=18 EEG resolution at 2 weeks Intervention group: n=4/15 Control group: n=7/18 % of patients with reported side effects at 2 weeks Intervention group: n=3/15 Control group: n= 3/18 *Important outcomes* Spasms relapse at 6 months (denominator provided by the study - unclear why this is lower than the total number of participants not lost to follow up and does not match with those who were spasms free within 2 weeks) Intervention group: n=3/6 Control group: n=2/11	2.1: Yes, the study was open label 2.2: Yes, the study was open label 2.3: No, there were no deviations reported from the intended intervention **Domain 3:** Missing outcome data: High risk 3.1: No, for some of the outcomes, data was not available for all participants. For example, in relapse rate, the study does not explain why the denominators are lower than the actual number of people the study lost to follow up 3.2: No evidence that the result was not biased 3.3: No information to assess whether missingness in the outcome depend on its true value 3.4: No information to assess if the differences between the intervention and control drop-out rates could

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					be due to the nature of the intervention or the participant's condition **Domain 4:** Measurement of the outcome: Some concerns 4.1: Probably no, outcomes have been well defined, although there is no information as to how they were assessed or by whom 4.2: Probably no, outcomes included cessation of spasms, EEG resolution, side effects, and spasms relapse. These are unlikely to differ between treatment arms 4.3: No information 4.4: Probably yes, the outcomes reported involved some judgement 4.5: Probably no, the study was comparing two types of steroids, so there is no reason to believe that the knowledge of the intervention status may have influenced the outcome assessment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Domain 5: Selection of the reported result: Some concerns 5.1: No information, the study authors do not make reference to any study protocol, and it is unclear whether the outcomes and procedures undertaken during the open phase were planned 5.2: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured 5.3: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured **Domain 6:** Overall judgment of bias: High risk of bias The study is judged to have some concerns for multiple domains

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					in a way that substantially lowers confidence in the result.
Full citation Hrachovy, R. A., Frost, J. D., Glaze, D. G., High-dose, long-duration versus low-dose, short-duration corticotropin therapy for infantile spasms, Journal of Pediatrics, 124, 803-806, 1994 **Ref Id** 1079050 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of high versus low dose ACTH in children with infantile spasms **Study dates** Not reported	**Sample size** Total recruited: N=59 Intervention group (high-dose ACTH): n=30 Control group (low-dose ACTH): n=29 **Characteristics** Not reported **Inclusion criteria** Recent diagnosis of infantile spasms Hypsarrhythmic EEG findings Not previously received ACTH or corticosteroids **Exclusion criteria** Not reported	**Interventions** Intervention group High-dose ACTH 150U/m^2/day for 3 weeks, then 80 U/m^2/day for 2 weeks, then 50 U/m^2 every other data for 1 week (administration route was not reported) Control group Low-dose ACTH 20U/m^2/day for 2 weeks (administration route was not reported)	**Details** Treatment duration: 3 months. Follow-up: 3 months in the high-dose group and 6 weeks in the low-dose group. Outcome measurement: Polygraphic and video monitoring were used to assess results objectively. Those assigned to the high-dose group were monitored 2 or 3 times during the treatment period. Those allocated to low-dose were reviewed 2 or 3 times during a period of 6 weeks. The principle according to which the data was analysed was not reported	**Results** *Critical outcomes* Spasm freedom at approximately 8 weeks Intervention group: n=13/26 Control group: n=14/24 Spasm freedom by aetiology at approximately 8 weeks Cryptogenic Intervention group: n=3/26 Control group: n=4/24 Symptomatic Intervention group: n=10/26 Control group: n=10/24 EEG resolution amongst responders at approximately 8 weeks Intervention group: n=3/13 Control group: n=3/14 *Important outcomes* Spasms relapse at approximately 8 weeks	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Some concerns 1.1: No information was provided regarding allocation sequence generation 1.2: No information was provided regarding allocation sequence concealment 1.3: No baseline characteristics were provided, but the authors reported these "were similar at baseline" **Domain 2:** Deviations from intended interventions: Some concerns 2.1: No information was provided regarding blinding of participants

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported				Intervention group: n=2/13 Control group: n=3/14	2.2: No information was provided regarding blinding of investigators 2.3: No information was provided to assess whether there were deviations from the intended intervention **Domain 3:** Missing outcome data: High risk 3.1: No, n=9 participants drop-out 3.2: Probably no, although there is no information regarding analysis methods that correct for bias or sensitivity analysis showing that results are little changed under a range of possible assumptions 3.3: Probably yes, reasons provided are related to compliance problems, moving out of the area, or development of medical problems unrelated to the use of ACTH (according to investigators)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					3.4: Probably yes, missingness in the outcome could depend on its true value **Domain 4:** Measurement of the outcome: High risk 4.1: No, the method for measuring the outcome was appropriate 4.2: Yes, because data was gathered at different time points **Domain 5:** Selection of the reported result: Some concerns 5.1: No information, protocol was not reported 5.2: No information, protocol was not reported 5.3: No information, protocol was not reported **Domain 6:** Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hrachovy, R. A., Frost, J. D., Kellaway, P., Zion, T. E., Double-blind study of ACTH vs prednisone therapy in infantile spasms, Journal of Pediatrics, 103, 641-645, 1983 **Ref Id** 1079055 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To assess the efficacy and safety of prednisone as compared to ACTH in infants with West Syndrome **Study dates** Not reported (study published in 1983) **Source of funding** Not reported	Total randomised: N=24 Intervention group (prednisone): n=12 Control group (ACTH): n=12 **Characteristics** Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	Intervention group Prednisone 2 mg/kg/day and ACTH placebo gel for 2 weeks Control group ACTH gel 20U/day and prednisone placebo for 2 weeks If a patient responded after 2 weeks, the dose was tapered until stopping it. Then the patient was evaluated at 2 weeks and 6 weeks after discontinuation of therapy. If a patient did not respond during the initial 2 weeks, the same doses were continued for an additional 4 weeks, after which the drug was tapered over a 2 week period.	Treatment duration: 2 weeks. Follow-up: 33 months.	*Critical outcomes* Spasms freedom at 2 weeks (total cessation of spasms and EEG cessation) Intervention group: 4/12 Control group: 5/12 *Important outcomes* Spasms relapse at 12 to 33 months follow up Intervention group: n=2/4 Control group: n=3/5	Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Some concerns 1.1: How randomisation was done has not been reported 1.2: How treatments were concealed has not been reported 1.3: Whether there were significant differences in baseline characteristics between treatment groups could not be assessed as baseline characteristics have not been reported **Domain 2:** Deviations from intended interventions: Low risk 2.1: Double blind trial 2.2: Double blind trial **Domain 3:** Missing outcome data: Low risk 3.1: No missing data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					3.2: No information to assess whether the result was not bias by missing outcome data **Domain 4:** Measurement of the outcome: Low risk 4.1: No, methods for assessing the outcome were appropriate 4.2: No, measurement of the outcome was similar between treatment groups 4.3: Double blind trial **Domain 5:** Selection of the reported result: Some concerns 5.1: No protocol reported 5.2: As above 5.3: As above **Domain 6: Overall judgment of bias:** Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
Kang, H. C., Lee, Y. J., Lee, J. S., Lee, E. J., Eom, S., You, S. J., Kim, H. D., Comparison of short-versus long-term ketogenic diet for intractable infantile spasms, Epilepsia, 52, 781-787, 2011
 	
Ref Id 1079141
 	
Country/ies where the study was carried out South Korea
 	
Study type A 2-arm, single centre, randomised comparative study
 	
Aim of the study
To assess the effectiveness of short-term (8 months) and conventional long-term (>2 years) in children who had become spasm free after using KD as an add-on treatment during 6 months
	Sample size
	Total recruited: N=40
	
	Intervention group (short-term KD trial:8 months): n=16
	
	Control group (long term KD trial:>2 years): n=24
	
	Characteristics
	Age, months, median (range)
	Intervention: 13.5 (6.0 to 30)
	Control: 15.0 (9-30)
	
	Number of seizures before study entry, (median +/-IQR, range)
	Intervention: n=3+/-1.0 (2-5)
	Control: n=3+/- 2.0 (2-5)
	
	Gender, n (%)
	Intervention: n=11 (male); n=5 (female)
	Control: n=12 (male; n=7 (female)
	
	Aetiology, n (%)
	Intervention: cryptogenic (n=6); symptomatic (n=10)
	Control: cryptogenic (n=9); symptomatic (n=10)
	
	Inclusion criteria
		Interventions
		Intervention group
		Add-on short term ketogenic diet: with a ratio of 3:1 fat: non-fat during 8 months
		
		Control group
		Add-on long term ketogenic diet: with a ratio of 3:1 fat: non-fat over 2 years
			Details
			Treatment duration, months, IQR (range):
			Short-term diet 8.0 ± 1.0 (8-9)
			Long-term diet 29.0 ± 2.0 (27-31).
			
			Follow-up (after discontinuation of diet): intervention=12-39 months (median=20.5 +/-11.5 IQR); control=13-11 months (median=15+/-2.0 IQR).
			
			Outcome measurement:
			Seizure relapse and frequency after successful completion of KD;
			EEG assessment were recorded at 1, 3 and 6 months after diet initiation and/or then every 6 months. Follow up tracing were graded as normal or mild abnormal background rhythms with or without multifocal sharp waves, mild-to-moderate abnormal background rhythms with generalized epileptiform discharges, modified hypsarrhythmic
				Results
				Critical outcomes
				
				Duration till seizure freedom, median (IQR)
				Intervention group (median+/- IQR, range):
				n=13: (5.0+/-20.3) 1-60 days -non-relapse
				Control group: n= (median+/- IQR, range):
				n=16: (11.0+/-15.5) 3-90 days -non-relapse
				
				EEG resolution (disappearance of hypsarrhythmia within 1 month to 6 months)
				Intervention group (median+/- IQR, range):
				n=13/13: (1.0+/-2.0) 1-6 months-non-relapse;
				n=3: (3.0+/-3.0) 3-6 months -relapse
				Control group (median+/- IQR, range):
				n=16/16: (2.0+/-2.0) 1-6 months-non-relapse;
				n=3: (6.0+/-3.0) 3-6 months –relapse
				
				Treatment cessation due to adverse events
				Intervention group:
				n=0/13
					Limitations
					Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)
					Domain 1: Randomisation: High risk
					1.1: Allocation was randomized with computer generated random numbers
					1.2: No information provided about allocation concealment
					1.3: No significant differences in the demographic data
					
					Domain 2: Deviations from intended interventions: High risk
					2.1: Probably yes, participants randomised into the intervention group were asked if they will accept the experimental therapy before determining which arm of they will participate in
					2.2: Probably yes, no information was provided about blinding

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 2005-2008 **Source of funding** Not reported	Patients who achieved seizure free outcomes Patients who showed an improvement in hypsarrhythmic patterns (including 8 patients with normalized EEG) within 6 months of the KD Patients with parents' or guardians' consent to participate **Exclusion criteria** Not reported		background with an improved nature, and no change in hypsarrhythmic background with an evolution to Lennox-Gastaut syndrome; Developmental assessments was rated by the Bayley Developmental Test (Version II) with results categorized as: <25 on the developmental index is profound retardation, 26–40 is severe retardation, 41–50 is moderate retardation, 51–70 is mild retardation, and 71–85 is borderline state. Measured at least 6 months interval. Data analysed according to per protocol	Control group: n=5/16 (n=3= [too restrictive]; n=2[ureteral stone]; n=1=[aspiration pneumonia]) *Important outcomes* Spasms relapse Intervention group: n= n=3/16 between 33-100 days [2 with clusters of spasm; 1 with focal seizures] Control group: n=3/19 between 35-70 days [2 evolved into Lennox-Gastaut syndrome; 1 with focal seizure with secondary generalization] Neurodevelopment outcomes (Bayley Developmental Test v.II); mean developmental quotient Intervention group: mean developmental quotient: (baseline) 41.88(SD+/-16.37) to (follow-up) 52.75(SD+/-17.76) (p=0.003), n=16 Control group: (baseline) 40.00(SD+/-16.80) to (follow-up)	of personnel or participants 2.6: No, per protocol analysis used 2.7: Probably yes, participants excluded from analysis could have substantial impact on result. **Domain 3:** Missing outcome data: Low risk 3.1: Yes, 5 participants dropped out of the study, but no missing data from the remaining participants **Domain 4:** Measurement of the outcome: High risk 4.1: No, method for measuring was appropriate 4.2: Probably yes, adverse events assessment involved repeated outpatients visits to report suspected events. **Domain 5:** Selection of the reported result: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				52.36(SD+/-17.86) (p=0.001), n=19	5.1: Yes, reported outcomes were analysed as per protocol 5.2: Yes, all reported results correspond to all intended outcome measurements 5.3: Yes, all reported results correspond to all intended outcome measurements **Domain 6:** Overall judgment of bias: High risk **Other information** Note: No statistically significant differences between demographic data of the 19 patients enrolled in the long term and those in the short term trial except for follow up duration after discontinuation of the KD.
Full citation Kapoor, D., Sharma, S., Garg, D., Samaddar, S., Panda, I., Patra, B., Mukherjee, S. B., Pemde, H. K., Intra-	**Sample size** N=60 randomised. Intervention group n=31 Control group n=29. **Characteristics**	**Interventions** Intervention group: Intravenous methylprednisolone (30 mg/kg/day for 3 days followed by oral prednisolone taper)	**Details** Treatment duration: 6 weeks. Follow-up: 6 weeks. Open label trial.	**Results** *Critical outcomes* Cessation of both clustered and individual spasms (no witnessed spasms for at least	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
venous Methylprednisolone Versus Oral Prednisolone for West Syndrome: A Randomized Open-Label Trial, Indian Journal of Pediatrics, 2021 **Ref Id** 1310571 **Country/ies where the study was carried out** India. **Study type** Randomised controlled trial. **Aim of the study** to "…to compare the efficacy of intravenous methylprednisolone (IVMP) with oral steroids taper versus OP in the treatment of IS." **Study dates** April 2019 – May 2020. **Source of funding** Not reported.	Consecutive children aged 2 to 30 months presenting with newly diagnosed epileptic spasms with hypsarrhythmia or its variants on EEG. Age at onset, months, median (IQR): Intervention group 5 (3–7); control group 5 (3–8). Age at presentation, months, median (IQR): Intervention group 11 (9–13); control group n=12 (7.5–18). Sex – male - intervention group n=22; control group n=19; female - intervention group n=9; control group n=10. **Inclusion criteria** Not reported. **Exclusion criteria** Children with single spasms only. Children with progressive neurological illness, renal, pulmonary, cardiac or hepatic dysfunction and/or severe malnutrition (weight for length and height less than 3	Control group: Oral prednisolone (4 mg/kg/day for two weeks followed by taper). Oral steroids administered in crushed form.	Terminated early due to Covid-19. Diagnosis confirmed by two pediatric neurologists on the basis of clinical and electrographic features. Patients were not on any antiseizure medications prior to enrolment. The critical outcome measure was spasms cessation on day 14. Secondary outcomes included time to response, electroclinical remission at 2 and 6 week, and frequency of adverse effects.	48 hours on day 14 from trial entry, as per parental reports): Intervention group n=17/31 Control group n=20/29. Proportion of patients with EEG resolution at 2 weeks: Intervention group n=16/31 Control group n=13/29. Proportion of patients with EEG resolution at 6 weeks: Intervention group n=14/31 Control group n=22/29. *Important outcomes* Recurrence of spasms within 6 weeks: Intervention group: 6/17 Control group: 0/20.	**Domain 1:** Randomisation: Low risk 1.1: Yes. Computerised randomisation. 1.2: Yes. Allocation concealment achieved using sequentially-numbered, opaque, sealed envelopes. 1.3: No. No significant differences detected at baseline. **Domain 2:** Deviations from intended interventions: Low risk 2.1: Yes. Participants were aware of their assigned intervention during the trial. 2.2: Yes. Participants and their parents/carers as well as investigators/clinicians were aware of assigned interventions. 2.3 Probably no. It is unlikely that there were deviations from the intended interventions that arose because of the trial context. 2.6: Yes, appropriate analyses conducted.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	SD for mean as per WHO growth charts).				2.7: Probably yes, participants excluded from analysis could have substantial impact on result. **Domain 3:** Missing outcome data: Low risk 3.1: Yes. Data available for all patients and outcomes. **Domain 4:** Measurement of the outcome: Low risk 4.1: No. Outcome measurement methods were appropriate in all cases. 4.2: No. Measurement or ascertainment of the outcome is unlikely to have differed between groups. 4.3 Yes. Outcome assessors were aware of assigned interventions (parental report used for some outcomes). 4.4: Yes. Assessment of some outcomes could have been influenced by knowledge

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					of the intervention received. 4.5: Probably no. It is unlikely that assessment of these outcomes was influenced by knowledge of the intervention received. **Domain 5:** Selection of the reported result: Some concerns. 5.1: No information. Analysis plans not available. 5.2: No information. Analysis plans not available. 5.3: No information. Analysis plans not available. **Domain 6:** Overall judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation Kunnanayaka, V., Jain, P., Sharma, S., Seth, A., Aneja,	**Sample size** Total recruited: N=71; total included N=62	**Interventions** Intervention group Pyridoxine PO 30 mg/kg/day pyridoxine	**Details** Treatment duration: 2 weeks.	**Results** *Critical outcomes*	**Limitations** Methodological limitations assessed using the Cochrane risk of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
S., Addition of pyridoxine to prednisolone in the treatment of infantile spasms: A pilot, randomized controlled trial, Neurology India, 66, 385-390, 2018 **Ref Id** 1079208 **Country/ies where the study was carried out** India **Study type** Pilot, randomised, open-label trial **Aim of the study** To assess the efficacy of pyridoxine as compared to prednisolone in infants with West Syndrome **Study dates** November 2012 to March 2014 **Source of funding** Not funded, done as part of a research project during the	Intervention group (pyridoxine + prednisolone): n=30 Control group (prednisolone): n=32 **Characteristics** Age, months, median (IQR) Intervention: 12.5 (8-18) Control: 9.5 (8-15) Number of clusters per day, median (IQR) Intervention: 2 (2-3) Control: 2 (2-3) Males, n (%) Intervention: 21 (70) Control: 23 (72) Known aetiology, n (%) Intervention: 26 (86.7) Control: 27 (84.4) **Inclusion criteria** >3 months < 3 years old Presence of epileptic spasms (> 1 cluster per day) with evidence of hypsarrhythmia on EEG **Exclusion criteria** Children with co-occurring conditions Children with evidence of active tuberculosis	+ prednisolone PO 4 mg/kg/day for 2 weeks Control group Prednisolone PO 4 mg/kg/day for 2 weeks	Follow-up: 2 weeks. Outcome measurement: Twice one-hour video-EEG record including at least one sleep-wake cycle Data analysed according to intention to treat	Spasms freedom at 2 weeks Intervention group: n=11/30 Control group: n=12/32 EEG resolution at 2 weeks within those with spasms resolution Intervention group: n=6/11 (*study reported n=10 as a denominator but a typo was assumed as there were 11 children with spasms resolution) Control group: n=9/12 *Important outcomes* Spasms relapse at 1 month Intervention group: n=1/11 Control group: n=4/12	bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, randomisation was performed with computer-generated random number tables 1.2: Yes, allocation concealment was done using sequentially-numbered opaque sealed envelopes 1.3: No, there were not baseline differences between treatment groups **Domain 2:** Deviations from intended interventions: Low risk 2.1: Probably no, although no information is provided to assess whether participants were blinded to treatment allocation 2.2: Yes, parents and people delivering the intervention were aware of treatment allocation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
residency of the first author	Severe acute malnutrition Those with recurrent illness or chronic systemic illness Previously received pyridoxine, steroid, or ACTH				2.3: No, no deviations from the intended intervention arose because of the experimental context **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data was available for all participants randomised **Domain 4:** Measurement of the outcome: Some concerns 4.1: No, the outcome was measured in an appropriate way 4.2: No, intervention groups had the same way of measuring outcomes and measurement was performed at comparable time points 4.3: No information was provided to say whether outcome assessors were aware of the intervention received by study participants

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					4.4: Yes, the outcomes assessed involved some judgement 4.5: No, knowledge of the intervention received is not likely to have influenced outcome assessment **Domain 5:** Selection of the reported result: Low risk 5.1: Yes, data was analysed in accordance with a pre-specified analysis plan 5.2: No, the outcome assessed is not likely to have been selected on the basis of results from multiple eligible outcome measurements 5.3: No, the outcome assessed is not likely to have been selected on the basis of results from multiple eligible analyses of the data **Domain 6:** Overall judgment of bias: Some concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation Lux, A. L., Edwards, S. W., Hancock, E., Johnson, A. L., Kennedy, C. R., Newton, R. W., O'Callaghan, F. J., Verity, C. M., Osborne, J. P., The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial, Lancet (london, england), 364, 1773-1778, 2004 **Ref Id** 1079267 **Country/ies where the study was carried out** UK **Study type** Open label, randomised,	**Sample size** Total recruited: N=208; total included N=110 Intervention group (hormonal treatments [prednisolone, tetracosactide]): n=55 Control group (vigabatrin): n=55 **Characteristics** Age, months, median (IQR) Intervention: 6 (4-8) Control: 6 (4-9) Males, n (%) Intervention: 32 (58.18) Control: 32 (58.18) Aetiology: prenatal, n (%) Intervention: 14 (25.45) Control: 15 (27.27) Aetiology: perinatal, n (%) Intervention: 8 (14.54) Control: 9 (16.36) Aetiology: postnatal, n (%) Intervention: 3 (5.45)	**Interventions** Intervention group Combination of the following hormonal treatments: Prednisolone PO: 40mg/day for 2 weeks, increasing to 60mg/a day for 1 week if spasms continued Tetracosactide depot IM: 0.5 mg (40 IU) on alternate days for 2 weeks, and increased to 0.75 mg (60 IU) on alternate days after 1 week if seizure control had not been achieved Infants randomised to this group were allocated to prednisolone with reductions of 10 mg every 5 days or, if in the higher dose, 40 mg per day, then 20 mg,	**Details** Treatment duration: 14 days. Follow-up: 14 days and then every 3 months until 14 months of age. Outcome measurement: a diary was given to record the treatment given, number of spasms, any treatments missed and the number of adverse events. The diaries were reviewed on day 14 Data analysed according to intention to treat principles	**Results** *Critical outcomes* Spasms freedom at 14 days (absence of spasms for a 48-hour period on days 13th and 14th) Intervention group: 40/55 Control group: 28/52 EEG resolution (hypsarrhythmia resolution) at 14 days (for those who were hypsarrhythmic at baseline and had an EEG done) Intervention group: n=26/32 Control group: n=20/36 Treatment cessation due to adverse events at 14 days Intervention group: n=2/55 Control group: n=0/52 *Important outcomes*	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, randomisation was computer generated 1.2: Yes, assignment was sequentially allocated and kept in sealed envelopes 1.3: No, no significant differences between groups at baseline **Domain 2:** Deviations from intended interventions: Low risk 2.1: Yes, the study was open label 2.2: Yes, as above 2.3: No, deviations from the intended protocol were justified as

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
parallel controlled trial **Aim of the study** To assess the efficacy, tolerability and safety of prednisolone or tetracosactide compared to vigabatrin in infants with infantile spasms **Study dates** Not reported (study published in 2004) **Source of funding** Bath Unit for Research in Paediatrics	Control: 0 (0) Other aetiology (uncertain classification), n (%) Intervention: 4 (7.27) Control: 6 (10.90) Not known aetiology (cranial imaging not reported), n (%) Intervention: 25 (45.45) Control: 21 (38.18) **Inclusion criteria** Clinical diagnosis of infantile spasms with hypsarrhythmia Aged > 2 months < 12 months **Exclusion criteria** Diagnosis of tuberous sclerosis Treated in the last 28 days with vigabatrin or a hormonal treatment Presence of a co-occurring lethal condition Inability of parents or carers to provide consent to participate in the study or to know when spasms stop Leaving the UK within 1 month of randomisation	then 10 mg for 5 day periods Control group Vigabatrin PO Vigabatrin 50 mg/kg/day for the first 2 doses and 100 mg/kg/day after 24 h. If spasms continued, it was increased to 150 mg/ kg per day after 96 h from the start of treatment		Spasms relapse within 3 months Intervention group: 18/40 Control group: 9/28	local investigators were allowed to change the treatment if considered to be on the infant's best interest **Domain 3:** Missing outcome data: Low risk 3.1: Nearly all, as no EEG data was available for some participants 3.2: No, there is no evidence that the results was not biased by missing outcome data 3.3: No, missing data is unrelated to the outcome **Domain 4:** Measurement of the outcome: Some concerns 4.1: Probably no, outcomes have been well defined, although there is no information as to how they were assessed or by whom 4.2: Probably no, outcomes included EEG resolution, and adverse events. These are unlikely to differ

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Participation in a concurrent trial that either used a treatment that might affect the outcome of the current trial or that was more labour-intensive for participants, guardians or clinicians				between treatment arms 4.3: No for EGG resolution and yes for adverse events as parents were aware of treatment allocation and were recording adverse events in a diary 4.4: Probably yes, the outcomes reported involved some judgement 4.5: Probably no, the study was comparing two types of steroids, so there is no reason to believe that the knowledge of the intervention status may have influenced the outcome assessment **Domain 5:** Selection of the reported result: Some concerns 5.1: No information. The study mentions the study protocol, but registration number is not provided, therefore it is not possible to assess whether data was analysed according to a pre-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					specified analysis plan 5.2: No information. Trial protocol was not available, therefore it was not possible to assess whether results could have been selected on multiple eligible outcome measurements 5.3: No information. Trial protocol was not available, therefore it was not possible to assess whether results could have been selected on multiple eligible analyses of the data **Domain 6:** Overall judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation Lux, A. L., Edwards, S. W., Hancock, E., Johnson, A. L., Kennedy, C. R.,	**Sample size** see Lux 2004 **Characteristics** see Lux 2004	**Interventions** see Lux 2004	**Details** Treatment duration14 days	**Results** *Critical outcomes* Free of spasms at final clinical assessment	**Limitations** see Lux 2004 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Newton, R. W., O'Callaghan, F. J., Verity, C. M., Osborne, J. P., The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: A multicentre randomised trial, Lancet Neurology, 4, 712-717, 2005 **Ref Id** 1079269 **Country/ies where the study was carried out** UK **Study type** see Lux 2004 **Aim of the study** see Lux 2004 **Study dates** see Lux 2004 **Source of funding** see Lux 2004	**Inclusion criteria** see Lux 2004 **Exclusion criteria** see Lux 2004		Follow-up: Follow-up: 14 days and then every 3 months until 14 months of age. See Lux 2004 for other details	(approximately 10 months after being enrolled in the study, when participants were between 12 and 14 months) Intervention group: n=41/55 Control group: n=39/51 Free of spasms at final clinical assessment - participants with known aetiology (approximately 10 months after being enrolled in the study, when participants were between 12 and 14 months) Intervention group: n=20/29 Control group: n=21/29 Free of spasms at final clinical assessment - participants with no identified aetiology (approximately 10 months after being enrolled in the study, when participants were between 12 and 14 months) Intervention group: n=21/26 Control group: n=18/22	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Important outcomes Neurodevelopment outcomes, VABS [Vineland Adaptive Behaviour Scale] mean composite scores (SD) Intervention group: 78.6 (16.8), n=55 Control group: 77.5 (12.7), n=51 Neurodevelopment outcomes, VABS [Vineland Adaptive Behaviour Scale] mean composite scores (SD) - participants with known aetiology Intervention group: 70.8 (11.1), n=29 Control group: 75.9 (11.3), n=29 Neurodevelopment outcomes, VABS [Vineland Adaptive Behaviour Scale] mean composite scores (SD) - participants with unknown aetiology Intervention group: 88.2 (17.3), n=26 Control group: 78.9 (14.3), n=26	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation O'Callaghan FJ, Edwards SW, Alber FD, et al., Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial, The Lancet Child and Adolescent Health, 2, 715-725, 2018 **Ref Id** 1079407 **Country/ies where the study was carried out** Australia, Germany, New Zealand, Switzerland, UK **Study type** Multicentre open-label,	**Sample size** Total screened: N=766; total randomised: N=377 Analysed at day 42 Intervention group (combination therapy [vigabatrin with tetracosactide depot OR vigabatrin with prednisolone]): n=186 Control group (hormonal therapy [tetracosactide depot OR prednisolone]): n=191 Analysed at 18 months follow-up Intervention group (combination therapy [vigabatrin with tetracosactide depot OR vigabatrin with prednisolone]): n=181	**Interventions** Intervention group Combination therapy (vigabatrin with tetracosactide depot OR vigabatrin with prednisolone): Vigabatrin PO: given 2 divided doses per day; 50 mg/kg per day for the first 2 doses, increasing to 100 mg/day after 24 hours, and if spasms continued after a further 72 hours, it was increased to 150 mg/kg per day Tetracosactide depot IM: 0.5 mg [40 IU] on alternate days for 2 weeks. The dose was increased to 0.75 mg on alternate days if spasms continued on day 7,	**Details** Treatment duration: 14 days (plus additional taper period). Follow-up: 18 months. Outcome measurement: parents or carers filled out a diary to record spasm frequency for the first 42 days. From day 43, infants were reviewed according to clinical need. Infants had 3-monthly reports, including one at 18 months of age, reporting details such as, adverse events, spasms since last assessment, etcetera. Development was assessed by investigators masked to treatment allocation with a phone interview with parents or carers. It was assessed	**Results** *Critical outcomes* Spasms freedom (no witnessed spasms on a 4 week period on and between day 14 and 42 from trial entry, as recorded by parents and carers in a seizure diary) Intervention group: n=133/186 Control group: n=108/191 *Important outcomes* Neurodevelopment outcomes, as assessed by the VABS (Vineland Adaptive Behaviour Scales), mean composite scores (SE) at 18 months follow-up Intervention group: 73.9 (1.3), n=181 (total N analysed in intention to treat)	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, randomisation was done centrally via the trial website 1.2: No information was provided regarding concealment of allocation sequence 1.3: No, there were no differences at baseline (p-values reported) **Domain 2:** Deviations from intended interventions: Some concerns 2.1: Yes, participants were aware of their

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomised controlled trial **Aim of the study** To assess the efficacy, safety and acceptability of oral prednisolone compared with intramuscular tetracosactide combined or not with vigabatrin in children with a clinical diagnosis of infantile spasms **Study dates** March 2007 to May 2014 **Source of funding** The Castang Foundation, Bath Unit for Research in Paediatrics, NIHR	Control group (hormonal therapy [tetracosactide depot OR prednisolone]) :n=181 Characteristics Age, n (%) 60 to 119 days Intervention: 17 (9) Control: 8 (4) 120 to 179 days Intervention: 42 (23) Control: 57 (30) 180 to 239 days Intervention: 70 (38) Control: 63 (33) ≥ 240 days Intervention: 57 (31) Control: 63 (33) Risk of developmental impairment, n (%) Intervention: 103 (55) Control: 104 (54) Males, n (%) Intervention: 99 (53) Control: 111 (58)	or reappeared between day 8 and 14 Prednisolone PO: 40 mg/day for 2 weeks. The dose was increased to 20 mg/ 3 times per day if spasms continued on day 7, or reappeared between day 8 and 14 Control group Hormonal therapy (tetracosactide depot OR prednisolone): same prescription as above	with the Vineland Adaptive Behaviour Scales (VABS). An adverse reaction was judged to be serious if it was life-threatening, caused death or required admission to hospital. Children at risk of developmental impairment were defined as those who had a proven chromosomal abnormality, a proven dysmorphic syndrome diagnosis, a proven diagnosis of cerebral palsy, a previous diagnosis of neonatal encephalopathy with seizures, or a diagnosis of developmental impairment previously done before spasms onset. Data analysed according to intention to treat principle.	Control group: 72.7 (1.4), n=181 (total N analysed in intention to treat) Neurodevelopmental outcomes (VABS) for infants at high risk of developmental impairment at randomisation, mean composite scores (SE) at 18 months follow-up Intervention group: 63.6 (1.2), n=181 Control group: 64.1 (1.4), n=181 Neurodevelopmental outcomes (VABS) for infants at low risk of developmental impairment at randomisation, mean composite scores (SE) at 18 months follow-up Intervention group: 86.5 (1.8), n=181 Control group: 82.7 (2.0), n=181	assigned intervention during the trial 2.2: Yes, parents, carers, and people delivering the intervention were aware of the participant's assigned intervention 2.3: No, there were no deviations from the intended intervention that arose because of the experimental context **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data was available for all participants randomised **Domain 4:** Measurement of the outcome: Some concerns 4.1: No, the method for measuring the outcome was appropriate 4.2: No, measurement of outcomes could not have differed between intervention arms 4.3: Outcome assessors were not aware of treatment allocation, which is relevant

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Clinical diagnosis of infantile spasms Hypsarrhythmia on EEG no more than 7 days before enrolment **Exclusion criteria** <2 months and >14 months >7 days delay since diagnosis Tuberous sclerosis Previous treatment for infantile spasms/ previous use of hormonal treatments or vigabatrin Existence of other condition believed to be lethal before outcome assessment Predictable lack of availability for follow-up at 18 months Difficulty with language used in the assessment				for adverse events and developmental outcomes, however parents and carers were asked to complete a diary with spasm frequency, and they were aware to treatment allocation 4.4: Yes, assessment of the outcomes could have been influenced by knowledge of the intervention received for spasm freedom and EEG resolution 4.5: No, not likely that assessment of the outcomes was influenced by knowledge of the interventions received **Domain 5:** <u>Selection of the reported result:</u> Low risk 5.1: Yes, data was analysed according to a registered protocol 5.2: No, results are not likely to have been selected on the basis of the results from multiple eligible outcome measurements

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					5.3: No, results are not likely to have been selected on the basis of the results from multiple analyses of the data **Domain 6:** Overall judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation O'Callaghan, F. J. K., Edwards, S. W., Alber, F. D., Hancock, E., Johnson, A. L., Kennedy, C. R., Likeman, M., Lux, A. L., Mackay, M., Mallick, A. A., et al.,, Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial, The Lancet	**Sample size** see O'Callaghan 2018 Characteristics see O'Callaghan 2018 Inclusion criteria see O'Callaghan 2018 Exclusion criteria see O'Callaghan 2018	**Interventions** see O'Callaghan 2018	**Details** see O'Callaghan 2018	**Results** *Critical outcomes* EEG resolution by day 42 amongst those for whom both clinical and electrical outcomes were available (n=3 missing values) Intervention group: n=123/185 Control group: n=104/189 % of patients with reported side effects by day 42 Intervention group: n=117/186	**Limitations** see O'Callaghan 2018

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Neurology, 16, 1234, 2017 **Ref Id** 1079409 **Country/ies where the study was carried out** see O'Callaghan 2018 **Study type** see O'Callaghan 2018 **Aim of the study** see O'Callaghan 2018 **Study dates** see O'Callaghan 2018 **Source of funding** see O'Callaghan 2018				Control group: n=111/191 <u>% of patients with reported serious side effects by day 42</u> Intervention group: n=17/186 Control group: n=16/191 *Important outcomes* <u>Spasms relapse by day 42</u> Intervention group: n=33/166 Control group: n=24/132	
Full citation Omar, Fatma Z., Al-Abdulwahab, Nawal O., Ali, Baleegh M., Karashi, Fahd A., Al-Musallam, Sulaiman A., Vigabatrin versus ACTH in the treatment of infantile spasms, Neurosciences (Riyadh,	**Sample size** N=36 enrolled (4 excluded during follow-up due to distance). Intervention group n=16. Control group n=16. **Characteristics** Newly diagnosed paediatric patients with infantile	**Interventions** <u>Intervention group:</u> Adrenocorticotropic hormone – average dose of 20 IU intramuscular daily. <u>Control group:</u> Vigabatrin - average dose of 87mg/ kg /day.	**Details** Treatment duration: Not reported. Follow-up, months, median (range): 6.4 (2 - 12).	**Results** *Critical outcomes* <u>Complete cessation of seizures:</u> Intervention group n=12/16 Control group n=11/16. <u>Side effects (any):</u> Intervention group n=14/16 Control group n=4/16.	**Limitations** <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u> **Domain 1:** <u>Randomisation:</u> High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Saudi Arabia), 7, 18-21, 2002 **Ref Id** 1310594 **Country/ies where the study was carried out** Saudi Arabia. **Study type** Randomised controlled trial. **Aim of the study** To "… compare adrenocorticotropic hormone with vigabatrin as a single mono-therapy for infantile spasms." p 18 **Study dates** Not reported. **Source of funding** Not reported.	spasms (confirmed by clinical diagnosis/presentation). None of the patients had received treatment previously. Age, months, range (mean): 3 – 10 (5.2) Sex: female n=12; male n=20. **Inclusion criteria** Not reported. **Exclusion criteria** Not reported.	NB. No further details on interventions are provided.			1.1: No information. Details on randomisation process are not provided. 1.2: No information. No details regarding allocation concealment are reported. 1.3: No information. Baseline information is not reported by group. **Domain 2:** Deviations from intended interventions: Some concerns 2.1: Yes. It is likely that participants were aware of their assigned interventions due to the nature of these. 2.2: Yes. It is likely that parents/carers and investigators were aware of their assigned interventions due to the nature of these. 2.3: Probably no. It is unlikely that deviations arose due to the trial context.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Domain 3: Missing outcome data: Some concerns 3.1: No. Four participants were excluded during the follow-up due to distance to the treatment centre and it appears as though they were excluded from the analyses. 3.2 No. It is not clear whether results were biased by missing outcome data. 3.3 Probably no. Missingness in outcome data is unlikely to depend on true value. **Domain 4:** Measurement of the outcome: High risk. 4.1: No information. No details provided regarding methods of outcome measurement. 4.2: Probably no. Outcome measurement is unlikely to have differed between groups. 4.3: No information. It is not clear whether

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					outcome assessors were blinded to intervention status. 4.4: No information. 4.5: No information. **Domain 5:** Selection of the reported result: Some concerns 5.1: No information. Analysis plans not provided. 5.2: No information. Analysis plans not provided. 5.3: No information. Analysis plans not provided. **Domain 6:** Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain
Full citation Vigevano, F., Cilio, M. R., Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study, Epilepsia, 38, 1270-4, 1997	**Sample size** Total recruited: N=42 Intervention group (depot ACTH): n=19 Control group (vigabatrin): n=23 **Characteristics** Age at onset, months, mean (range)	**Interventions** Intervention group Depot ACTH 10 IU/day for 20 days (administration route was not reported) Control group	**Details** Treatment duration: 20 days. Follow-up: 20 days. How outcomes were measured and the principle according to which	**Results** *Critical outcomes* Spasms freedom by day 20 Intervention group: n= 14/19 Control group: n= 11/23	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 753514 **Country/ies where the study was carried out** Italy **Study type** Randomised controlled trial **Aim of the study** To assess the safety and effectiveness of vigabatrin as compared to depot ACTH in infants with West Syndrome **Study dates** Not reported (publication date 1997) **Source of funding** Not reported	Intervention: 5.3 (2-9) Control: 5.8 (2.5-9) Males, n (%) Intervention: 7 (36.84) Control: 14 (60.86) **Inclusion criteria** Newly diagnosed and previously untreated infantile spasms 2 to 9 months of age **Exclusion criteria** Not reported	Vigabatrin 100 to 150 mg/kg/day for 20 days (administration route was not reported)	data was analysed to was not reported	EEG resolution by day 20 amongst those who achieved spasm freedom Intervention group: n= 11/14 Control group: n=4/11 Treatment cessation due to adverse events by day 20 Intervention group: n=1/19 Control group: n=1/23	1.1: No information. Randomisation method was not reported 1.2: No information. Concealment of allocation sequence was not reported 1.3: Yes, there were differences in baseline characteristics between intervention groups **Domain 2:** Deviations from intended interventions: Low risk 2.1: Yes, participants were aware of their assigned intervention 2.2: Yes, parents and carers were aware of participant's assigned intervention during the trial 2.3: No, there were no deviations from the intended intervention **Domain 3:** Missing outcome data: Low risk 3.1: No missing data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Domain 4: Measurement of the outcome: Some concerns 4.1: No information was provided regarding the method for measuring the outcome 4.2: Probably no, the measurement of the outcome could not have differed between interventions 4.3: No information was provided to assess whether the outcome assessors were blinded to treatment allocation 4.4: Yes, outcome assessment involved some level of judgement 4.5: No, it is not likely that assessment of the outcome was influenced by knowledge of the outcome received **Domain 5:** Selection of the reported result: Some concerns 5.1: No protocol was reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					5.2: No protocol was reported 5.3: No protocol was reported **Domain 6:** Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain
Full citation Wanigasinghe, J., Arambepola, C., Ranganathan, S. S., Sumanasena, S., Randomized, Single-Blind, Parallel Clinical Trial on Efficacy of Oral Prednisolone Versus Intramuscular Corticotropin: A 12-Month Assessment of Spasm Control in West Syndrome, Pediatric Neurology, 76, 14-19, 2017 **Ref Id** 1079742 **Country/ies where the study was carried out** Sri Lanka	**Sample size** see Wanigasinghe 2015 **Characteristics** see Wanigasinghe 2015 **Inclusion criteria** see Wanigasinghe 2015 **Exclusion criteria** see Wanigasinghe 2015	**Interventions** see Wanigasinghe 2015	**Details** Treatment duration: 2 weeks. Follow-up: 12 months (assessments at 3 months, 6 months, and 12 months (considered as markers of spasm control). The injectable steroids group were given the option of administration of injections as outpatients every other day or inpatient therapy. Those in the oral steroids group were discharged 48 hours after treatment. Parents were monitored thorough phone conversations to ensure treat-	**Results** *Critical outcomes* Spasms freedom at 3 months (absence of any spasms witnessed by the parents over the previous 7 days within 3 months of starting treatment) Intervention group: n=31/48 Control group: n=19/49 Spasm freedom at 6 months (absence of any spasms witnessed by the parents over the previous 7 days within 6 months of starting treatment) Intervention group: n=28/48 Control group: n=22/49	**Limitations** see Wanigasinghe 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type see Wanigasinghe 2015 **Aim of the study** To assess the spasm control for infants who received oral steroids as compared with injectable steroids in the long-term. **Study dates** see Wanigasinghe 2015 **Source of funding** see Wanigasinghe 2015			ment adherence and adverse events monitoring. They were also asked to record any adverse events in a diary. Data analysed according to intention to treat.	Spasm freedom at 12 months (absence of any spasms witnessed by the parents over the previous 7 days within the previous 12 months of starting treatment) Intervention group: n=27/48 Control group: n=20/49 *Important outcomes* Spasms relapse within 12 months Intervention group: n=6/28 Control group: n=8/18	
Full citation Wanigasinghe, J., Arambepola, C., Sri Ranganathan, S., Sumanasena, S., Attanapola, G., Randomized, single-blind, parallel clinical trial on efficacy of oral prednisolone versus intramuscular corticotropin on immediate and continued spasm control in	**Sample size** Total recruited: N= 121 Intervention group (oral steroids, prednisolone): n=48 Control group (injectable steroids, ACTH): n=49 **Characteristics** Age, months, mean (SD) Intervention: 8.31 (6.19) Control: 9.93 (8.67) Number with preceding/ concurrent seizures, n (%) Intervention: 17 (35.4)	**Interventions** Intervention group Oral steroids (prednisolone) 40 to 60 mg divided into 4 doses per day for 14 days Control group Injectable steroids (synthetic ACTH) 40-60 IU (0.5 to 0.75 mg) every other day for 14 days	**Details** Treatment duration: 14 days. Follow-up: 5 weeks (assessments at 14 days and 42 days). The injectable steroids group were given the option of administration of injections as outpatients every other day or inpatient therapy.	**Results** *Critical outcomes* Spasms freedom on day 14 (absence of any spasms [single or cluster] for at least 48 hours on day 14 after randomisation) Intervention group: n=28/48 Control group: n=18/49 Spasms freedom on day 42 (absence of any	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: Yes, randomisation was computer generated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
west syndrome, Pediatric Neurology, 53, 193-199, 2015 **Ref Id** 1079743 **Country/ies where the study was carried out** Sri Lanka **Study type** Randomised, single blind, parallel, clinical trial. **Aim of the study** To assess the efficacy, safety and tolerability of prednisolone and ACTH in children with West syndrome. **Study dates** 2010 to 2014 **Source of funding** Sri Lanka Medical Association.	Control: 15 (30.6) Number of females, n (%) Intervention: 23 (47.9) Control: 18 (36.7) **Inclusion criteria** Infants with newly diagnosed west syndrome between 2 and 30 months of age **Exclusion criteria** Infants with a diagnosis of tuberous sclerosis Previous treatment for West syndrome Contraindications for use of hormonal therapies Infants whose parents did not provide consent to participate in the trial or were not able to monitor treatment response	The response was assessed at 7 days and if there was a single spasm on that day, the oral steroids dose was increase to 15 mg four times a day and the ACTH dose to 60 IU every other day. Crossover of treatment arm or other medication was permitted only at the end of taper, unless a parent requested it or the lead author decided it based on the spasm load.	Those in the oral steroids group were discharged 48 hours after treatment. Parents were monitored thorough phone conversations to ensure treatment adherence and adverse events monitoring. They were also asked to record any adverse events in a diary. Data analysed according to intention to treat.	spasms [single or cluster] for at least 48 hours on day 42 after randomisation) Intervention group: n=32/48 Control group: n=20/49 Time taken for cessation of spasms (number of consecutive days free of spasms preceding and including day 14), mean days (SD) Intervention group: 3.85 (2.4) Control group: 8.65 (3.7) EEG resolution (spasm cessation and resolution of hypsarrhythmia on day 14) Intervention group: n=21/48 Control group: n=9/49 Treatment cessation due to adverse events on day 14 Intervention group: n=1/48 Control group: n=0/49	1.2: Yes, assignment was sequentially allocated and kept in sealed envelopes 1.3: No, no significant differences between groups at baseline **Domain 2:** Deviations from intended interventions: Low risk 2.1: Yes, the study does not provide details about blinding of participants, but it would have been impossible to blind them due to the nature of the intervention (oral versus intramuscular) 2.2: Yes, as above 2.3: Probably no, the study does mention that participants were allowed to cross over to the other intervention after taper, unless parents requested it or if the main author decided it, based on spasm load. This is believed to be due to ethical reasons and not because parents/carers or investigators were seeking

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the opposite intervention. **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data was available for all participants randomised **Domain 4:** Measurement of the outcome: Some concerns 4.1: Probably no, outcomes have been well defined, although there is no information as to how they were assessed or by whom 4.2: Probably no, outcomes included cessation of spasms, EEG resolution, and spasms relapse. These are unlikely to differ between treatment arms 4.3: No for EEG remission yes for spasm cessation and treatment cessation due to adverse events as parents were aware of treatment allocation and were recording spasm and adverse

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					events frequency in a diary 4.4: Probably yes, the outcomes reported involved some judgement 4.5: Probably no, the study was comparing two types of steroids, so there is no reason to believe that the knowledge of the intervention status may have influenced the outcome assessment **Domain 5:** Selection of the reported result: Some concerns 5.1: No information, the study authors do not make reference to any study protocol, and it is unclear whether the outcomes and procedures undertaken were planned 5.2: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					5.3: No information, analysis intentions are not available and there is more than one way in which the outcomes could have been measured **Domain 6:** Overall judgment of bias: Some concerns The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
Full citation Yanagaki, S., Oguni, H., Hayashi, K., Imai, K., Funatuka, M., Tanaka, T., Yanagaki, M., Osawa, M., A comparative study of high-dose and low-dose ACTH therapy for West syndrome, Brain and Development, 21, 461-467, 1999 **Ref Id** 1079794	**Sample size** Total recruited: N= 32; total included N=25 Intervention group (high-dose synthetic ACTH): n=13 Control group (low-dose synthetic ACTH): n=12 **Characteristics** Age at onset, months, mean (SD) Intervention: 4.89 (2.59) Control: 5.80 (3.77) Males, n (%) Intervention: 8 (61.53)	**Interventions** Intervention group High-dose IM synthetic ACTH 0.025 mg/kg/day (= 1 U/kg/day) for 2 weeks Control group Low-dose IM synthetic ACTH 0.005 mg/kg/day (= 0.2 U/kg/day) for 2 weeks	**Details** Treatment duration4 weeks (including taper period). Follow-up: ≥ 1year. Outcome measurement: spasms frequency was documented in diaries by the parents of the children included in the trial. The principle according to which the data was analysed was not reported	**Results** *Critical outcomes* Spasms freedom within 2 weeks Intervention group: n=11/13 Control group: n=9/13 *Important outcomes* Spasms relapse in those who were followed-up for more than 1 year Intervention group: n=3/8 Control group: n=3/9	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Low risk 1.1: No information was provided to assess whether the allocation sequence was random 1.2: No information was provided to as-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Japan **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of high-dose versus low-dose ACTH **Study dates** Not reported (study published in 1999) **Source of funding** Not reported	Control: 7 (58.33) **Inclusion criteria** Infants with West Syndrome **Exclusion criteria** Those who had previously received ACTH, corticosteroids or IV gamma globulin				sess whether the allocation sequence was concealed 1.3: No differences in baseline characteristics were reported **Domain 2:** Deviations from intended interventions: High risk 2.1: Yes, participants were aware of their assigned intervention during the trial 2.2: Yes, parents and carers were aware of treatment allocation during the trial 2.3: Probably no, there were no deviations from the intended interventions **Domain 3:** Missing outcome data: Low risk 3.1: Yes, data available for nearly all participants randomised **Domain 4:** Measurement of the outcome: Some concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					4.1: No, the method for measuring the outcome was appropriate 4.2: Yes, outcomes could have differed between intervention groups 4.3: Some outcome assessors were aware of the intervention received by study participants 4.4: Probably yes. Assessment of the outcome could have been influenced by knowledge of intervention received 4.5: Probably no. There is no reason to believe that assessment of the outcome was influenced by knowledge of the intervention received **Domain 5:** Selection of the reported result: High risk 5.1: No information. Trial protocol was not available 5.2: No information. Trial protocol was not available

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					5.3: No information. Trial protocol was not available **Domain 6:** Overall judgment of bias: High risk The study is judged to be at high risk of bias in at least one domain.
Full citation Yi, Z., Wu, H., Yu, X., Zha, J., Chen, H., Chen, Y., Zhong, J., High-dose prednisone therapy for infantile spasms and late-onset epileptic spasms in China: The addition of topiramate provides no benefit, Seizure, 71, 174-178, 2019. **Ref Id** 1115471. **Country/ies where the study was carried out** China.	**Sample size** N=77. Prednisone only group n=39; prednisone + add-on topiramate group n=38. **Characteristics** Children with infantile spasms or late-onset epileptic spasms (age at onset > 2 years) in clusters or single attacks with hypsarrhythmia or its variants on EEG. Sex, male: Monotherapy n=26 (66.7%), combination therapy n=27 (71.1%), p=0.678 Age at onset, median, months (range): Monotherapy 6 (2-39); combination therapy 5.7 (0.4-46), p=0.443.	**Interventions** High-dose prednisone only vs high-dose prednisone + add-on topiramate. High-dose prednisone only group: Prednisone administered orally as follows: 10 mg, four times a day for 14 days. If spasms continued at day 7, the dose was increased to 15 mg, four times a day for a further 7 days. After 14 days of treatment, whether spasms had completely ceased or not, prednisone was reduced	**Details** Treatment duration: 49 or 56 days. Follow-up: 120 days. Randomisation by random number tables. All children hospitalised in first 14 days of study period. Spasm frequency measured via seizure diaries and EEG. Cessation of spasms defined as no witnessed 'clinical spasms' ≥28 consecutive days. Spasm freedom defined as no reported spasms (for at least 48 h) on day 14 and the rate of cessation of	**Results** Number of children (%) with complete spasm freedom on day 14: monotherapy n=28/39; combination therapy n=29/38. Number of children (%) with complete spasm freedom at the end of hormone therapy (day 49 or 56): monotherapy n=28/39; combination therapy n=25/38. Number of children (%) with complete spasm freedom at day 120 (4 months): monotherapy n=24/39; combination therapy n=19/38.	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1:** Randomisation: Some concerns 1.1: Yes, random number table used. 1.2: No, no information provided regarding concealment of allocation 1.3: No, no differences observed. **Domain 2:** Deviations from intended interventions: High risk.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial. **Aim of the study** To compare the efficacy and safety of high-dose prednisone only to high-dose prednisone and topiramate for the treatment of infantile spasms and to determine whether topiramate provides 'secondary prevention' for infantile spasms. **Study dates** January 2015 - October 2016. **Source of funding** Not reported.	Age at treatment, median, months (range): Monotherapy 9.2 (3.5-40); combination therapy 7.8 (3-52), p=0.465. Time to diagnsosis, median months (range): Monotherapy 1.5 (0.2-31); combination therapy 1.75 (0.1-15), p=0.934. EEG at presentation - Hypsarrhythmia: Monotherapy n=8 (20.5%), combination therapy n=6 (15.8%); hypsarrhythmia variant – monotherapy: n=31 (79.5%), combination therapy n=32 (84.2%), p=0.591. Etiology (%): Hypoxic ischemic encephalopathy - monotherapy n=14 (35.9%); combination therapy n=16 (42.1%), p=0.577. Cortical dysplasia and malformations - monotherapy n=6 (15.4%); combination therapy n= 4 (10.5%), p=0.737. Postinfection brain injury - monotherapy n=2 (5.1%); combination therapy n= 1	weekly to complete a 49 day or 56 day course (for example, 40 mg once daily for 1 week or 30 mg once daily for 1 week, 20 mg once daily for 1 week, 10 mg daily for 1 week, 5 mg daily for 1 week, then 5 mg alternate days for 1 week). After 14 days, non-responders in the prednisone only group received other treatments such as antiseizure medications (including topiramate) and ketogenic diet. High-dose prednisone + topiramate group: Prednisone administered as in the prednisone only group and topiramate was administered as follows: 1 mg/kg/day, two times a day, and	spasms on day 120, respectively.	Resolution of hypsarrhythmia on EEG at 2 weeks in children with spasm freedom - partial resolution – monotherapy n=7/28, combination therapy 9/29; complete resolution - monotherapy n=21/28; combination therapy n=20/29. Treatment cessation due to adverse events – monotherapy n=0; combination therapy n=0. Number of relapsed children in follow-up at 7 or 8 weeks (on day 49 or 56): monotherapy n=1/28; combination therapy n=4/29. Number of relapsed children in follow-up at day 120 (4 months): monotherapy n=4/28: combination therapy n=10/29.	2.1: No information was provided to assess whether participants were aware of their assigned intervention 2.2: No information was provided to assess whether carers were aware of the participant's assigned intervention 2.3: Yes, non-responders received other treatments (for example, ketogenic diets) after 14 days in the monotherapy group and after 56 days in the combination therapy group, however only minimal information is provided in relation to this and it is not possible to determine whether these deviations were balanced between groups. **Domain 3:** Missing outcome data: Some risk.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(2.6%), p=1.000. Neonatal hypoglycemia - monotherapy n=3 (7.7%); combination therapy n= 0(0), p=0.240. Intracranial hemorrhage monotherapy - n=2 (5.1%); combination therapy n= 0(0), p=0.494. Tuberous sclerosis - monotherapy n=1 (2.6%); combination therapy n= 0(0), p=1.000. Head trauma - monotherapy n=0(0); combination therapy n=1 (2.6%), p=1.000. Unknown causes - monotherapy n=14 (35.9%); combination therapy n= 15 (39.5%), p=0.746. Development Quotient test score (%) normal (≥ 70) - monotherapy n=4 (10.3%); combination therapy n=2 (5.3%), p=0.675. mild (<70) - monotherapy n=14 (35.9%); combination therapy n=15 (39.5%), p=0.746. moderate (<50) - monotherapy n=4 (10.3%); combination therapy n=4 (10.5%), p=1.000.	then gradually titrated to 3 mg/kg/day in the 7th day and 5 mg/kg/day in the 14th day. After 14 days, topiramate was administered at 5 mg/kg/day on a bodyweight basis for 35 or 42 days. Non-responders received other treatments after 56 days (for example, Ketogenic diet).		Number of relapsed children at 12 months (data only available for 15/28 patients in monotherapy group and 16/29 patients in combination therapy group): monotherapy n=5/15; combination therapy n=10/16.	3.1: Possibly yes, most data are available for all participants randomised with the exception of a small number of outcomes. **Domain 4:** Measurement of the outcome: Low risk. 4.1: Probably no. 4.2: No, measurement or ascertainment of the outcome is unlikely to have differed between groups. 4.3: No information. It is not clear if outcome assessors were blinded to intervention assignment. 4.4: No, knowledge of assignment is unlikely to have influenced outcome assessments. **Domain 5:** Selection of the reported result: Some concerns. 5.1: No information, protocol/analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	severe (<35) - monotherapy n=9 (23.1%); combination therapy n=10 (26.3%), p=0.742. profound (<20) - monotherapy n=8 (20.4%); combination therapy n=7 (18.4), p=0.817. **Inclusion criteria** Clinical diagnosis of infantile spasms and late-onset epileptic spasms (confirmed using definition proposed by Lux, et al., 2004), including patients newly diagnosed. No previous hormone therapy **Exclusion criteria** Contraindication to hormone treatment (eg. active tuberculosis).				plans not provided. 5.2: No information, only minimal details are provided in relation to how outcomes were measured. 5.3: No information. **Domain 6:** Overall judgment of bias: High risk. The study is judged to be at high risk of bias in at least one domain. **Other information** NA.

ACTH: adrenocorticotropic hormone; AEs: adverse events; AEDs: anti-epileptic drugs; EEG: electroencephalogram; IM: intramuscular; ICISS: International Collaborative Infantile Spasms Study; IQR: interquartile range; IM: intramuscular; IU: international units; IV: intravenous; KD: ketogenic diet; kg: kilogram; m2: body surface; mg: milligram; N: number of participants in study; NR: not reported; PO: per oral; RCT: randomised controlled trial; TINE: Touwen Infant Neurological Examination; TS: tuberous sclerosis; U: units; UK: United Kingdom; UKISS: United Kingdom Infantile Spasms Study; US: United States; VABS: Vineland Adaptive Behavior Scale; WHO: World Health Organization

Appendix E – Forest plots

Forest plots for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here, but the quality assessment for these outcomes is provided in the GRADE profiles in appendix F.

Comparison 2: injectable steroids versus vigabatrin

Figure 2: Spasms freedom

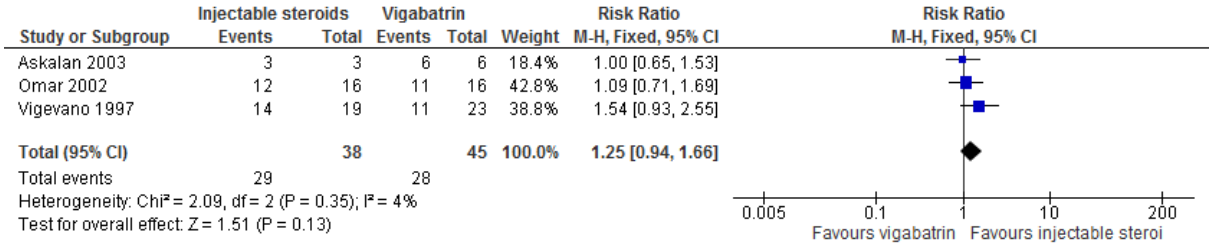
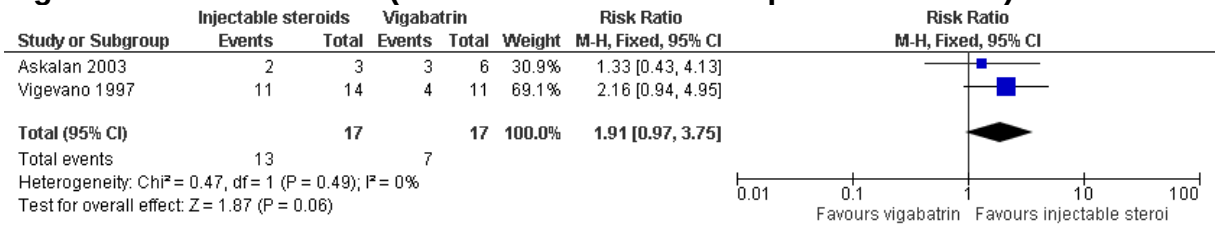


Figure 3: EEG resolution (in those who achieved spasms freedom)



Comparison 3: oral steroids versus injectable steroids

Figure 4: Spasms freedom (short term)

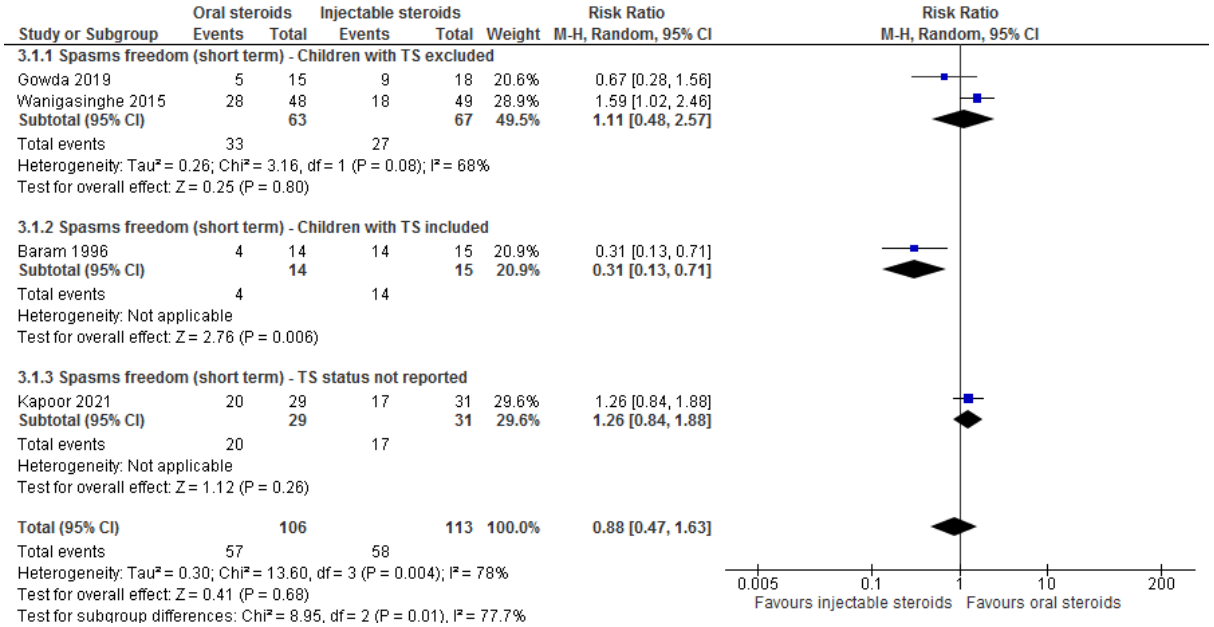


Figure 5: Spasms freedom (medium term)

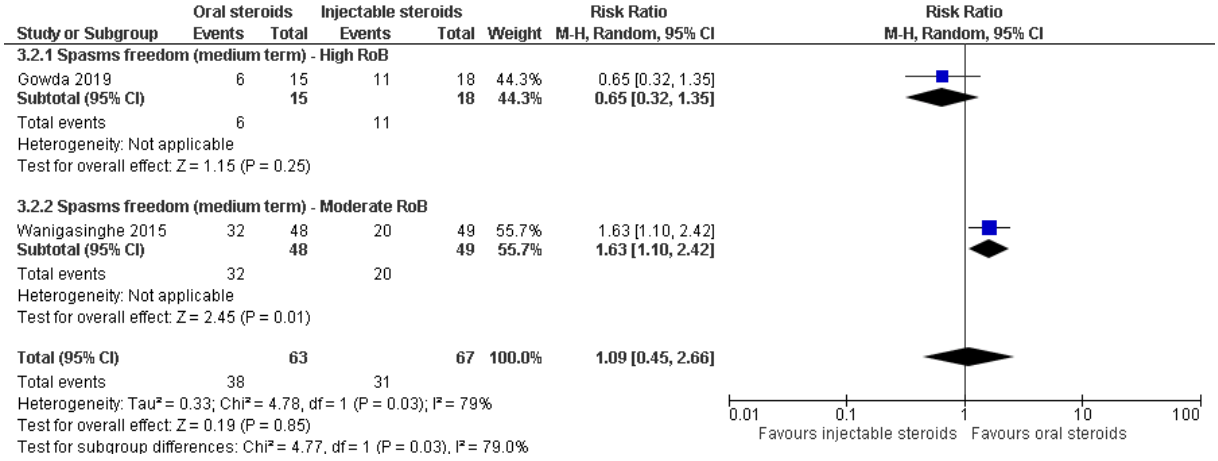


Figure 6: Time taken to spasms freedom (days)

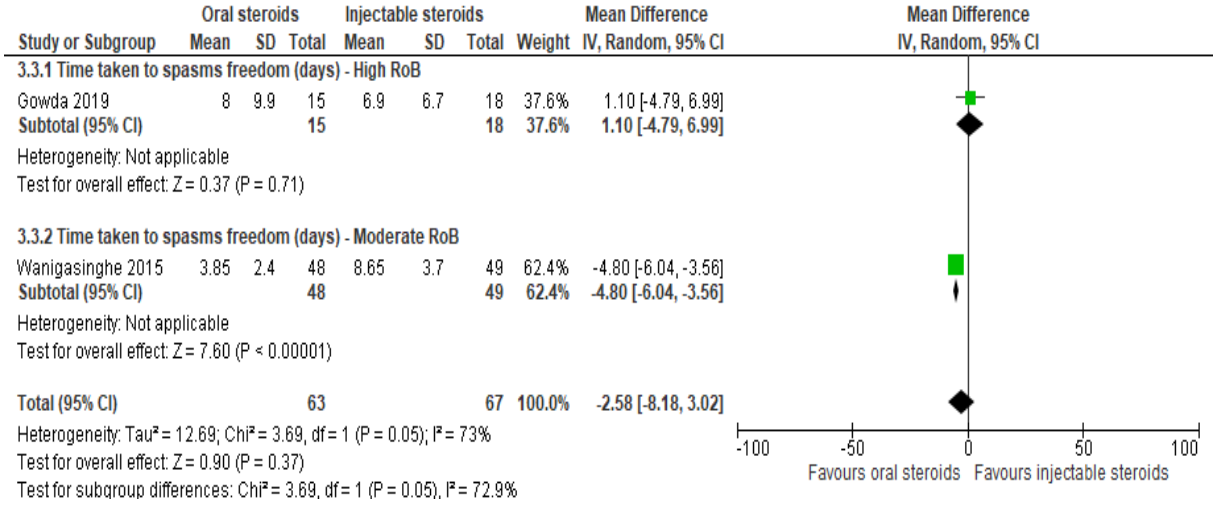


Figure 7: EEG resolution

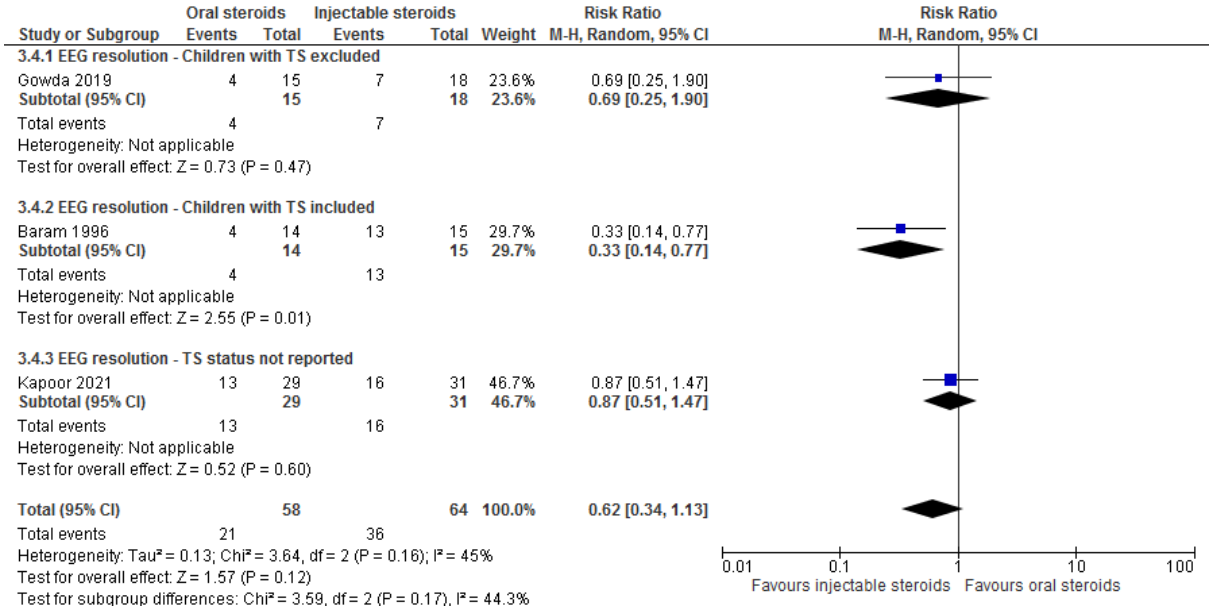
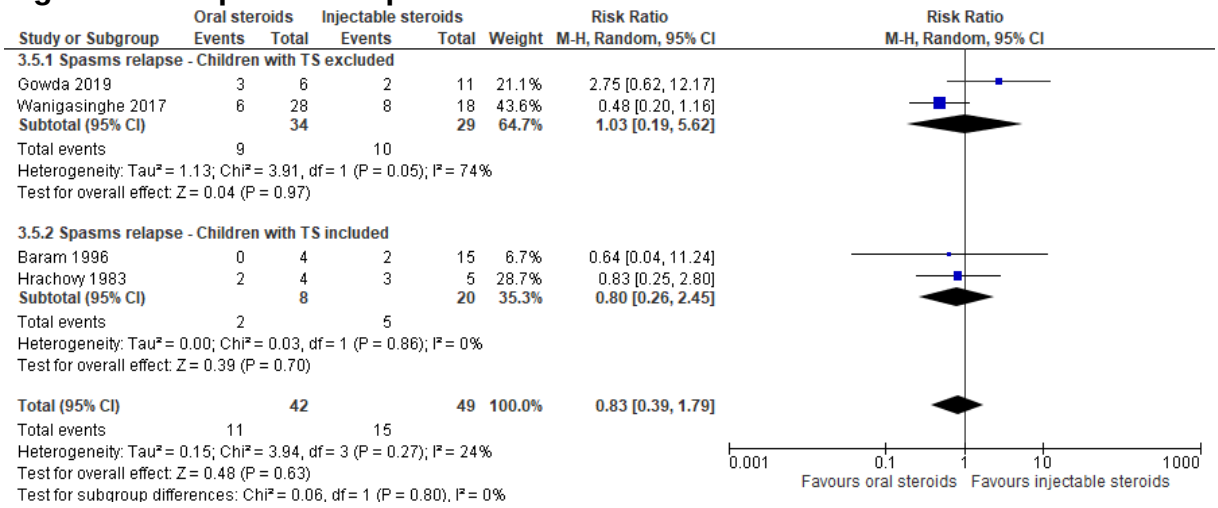


Figure 8: Spasms relapse



Comparison 10: high-dose injectable steroids versus low-dose injectable steroids

Figure 9: Spasms freedom

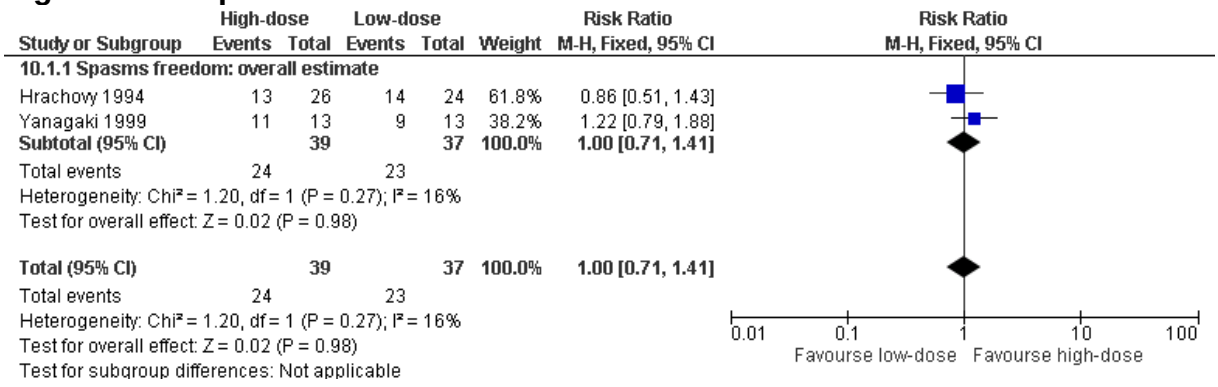
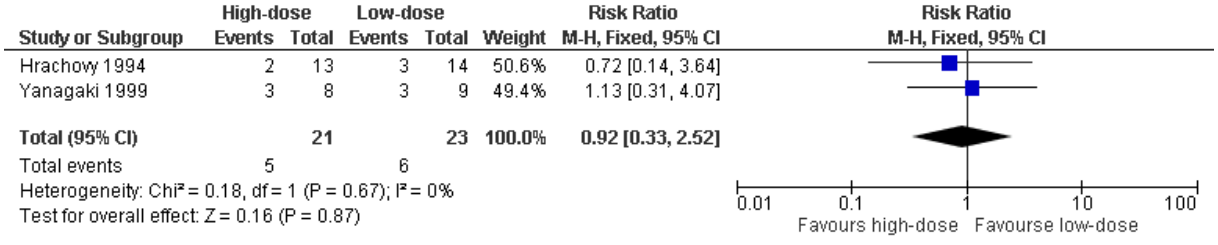


Figure 10: Spasms relapse



Appendix F – GRADE tables

GRADE tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

Table 19: Clinical evidence profile. Comparison 1: vigabatrin versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vigabatrin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (follow-up 5 days)												
1 (Appleton 1999)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/20 (35%)	2/20 (10%)	RR 3.50 (0.83 to 14.83)	250 more per 1000 (from 17 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
EEG resolution (in those who achieved spasms freedom) (follow-up 5 days)												
1 (Appleton 1999)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/7 (71.4%)	1/2 (50%)	RR 1.43 (0.33 to 6.17)	215 more per 1000 (from 335 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
% of patients with reported side effects (follow-up 5 days)												
1 (Appleton 1999)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/20 (60%)	6/20 (30%)	RR 2 (0.94 to 4.27)	300 more per 1000 (from 18 fewer to 981 more)	⊕⊕OO LOW	CRITICAL

1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (1.25)
3 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 20: Clinical evidence profile. Comparison 2: injectable steroids versus vigabatrin

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Injectable steroids	Vigabatrin	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (follow-up mean 17 days)												
3 (Askalan 2003, Omar 2002, Vigevano 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/38 (76.3%)	28/45 (62.2%)	RR 1.25 (0.94 to 1.66)	156 more per 1000 (from 37 fewer to 411 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution (in those who achieved spasm freedom) (follow-up mean 17 days)												
2 (Askalan 2003, Vigevano 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/17 (76.5%)	7/17 (41.2%)	RR 1.91 (0.97 to 3.75)	375 more per 1000 (from 12 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Side effects – any												
1 (Omar 2002)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/16 (87.5%)	4/16 (25%)	RR 3.50 (1.47 to 8.34)	625 more per 1000 (from 118 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse events (follow-up 20 days)												
1 (Vigevano 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/19 (5.3%)	1/23 (4.3%)	RR 1.21 (0.08 to 18.09)	9 more per 1000 (from 40 fewer to 743 more)	⊕OOO VERY LOW	CRITICAL

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (1.25)
3 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 21: Clinical evidence profile. Comparison 3: oral steroids versus injectable steroids

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral steroids	Injectable steroids	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (short term) - Overall estimate (follow-up 2 weeks)												
4 (Baram 1996, Gowda 2019, Kapoor 2021, Wanigasinghe 2015)	RCT	very serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	57/106 (53.8%)	58/113 (51.3%)	RR 0.88 (0.47 to 1.63)	62 fewer per 1000 (from 272 fewer to 323 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (short term) - Children with TS excluded (follow-up 2 weeks)												
2 (Gowda 2019, Wanigasinghe 2015)	RCT	very serious[1]	serious[4]	no serious indirectness	very serious[3]	none	33/63 (52.4%)	27/67 (40.3%)	RR 1.11 (0.48 to 2.57)	44 more per 1000 (from 210 fewer to 633 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (short term) - Children with TS included (follow-up 2 weeks)												
1 (Baram 1996)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/14 (28.6%)	14/15 (93.3%)	RR 0.31 (0.13 to 0.71)	644 fewer per 1000 (from 271 fewer to 812 fewer)	⊕⊕OO LOW	CRITICAL
Spasms freedom (short term) (total cessation of spasms and EEG cessation) (follow-up 2 weeks)												
1 (Hrachovy 1983)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/12 (33.3%)	5/12 (41.7%)	RR 0.80 (0.28 to 2.27)	83 fewer per 1000 (from 300 fewer to 529 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (short term) - Aetiology group - Cryptogenic (follow-up 2 weeks)												
1 (Baram 1996)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/14 (7.1%)	3/15 (20%)	RR 0.36 (0.04 to 3.04)	128 fewer per 1000 (from 192 fewer to 408 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (short term) - Aetiology group - Symptomatic (follow-up 2 weeks)												
1 (Baram 1996)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	3/14 (21.4%)	11/15 (73.3%)	RR 0.29 (0.1 to 0.83)	521 fewer per 1000 (from 125 fewer to 660 fewer)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (medium term) - Overall estimate (follow-up 35 days)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral steroids	Injectable steroids	Relative (95% CI)	Absolute	Quality	Importance
2 (Gowda 2019, Wanigasinghe 2015)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	38/63 (60.3%)	31/67 (46.3%)	RR 1.09 (0.45 to 2.66)	42 more per 1000 (from 254 fewer to 768 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (medium term) - High RoB (follow-up 28 days)												
1 (Gowda 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/15 (40%)	11/18 (61.1%)	RR 0.65 (0.32 to 1.35)	214 fewer per 1000 (from 416 fewer to 214 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (medium term) - Moderate RoB (follow-up 42 days)												
1 (Wanigasinghe 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	32/48 (66.7%)	20/49 (40.8%)	RR 1.63 (1.1 to 2.42)	257 more per 1000 (from 41 more to 580 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (long term) (follow-up 3 months)												
1 (Wanigasinghe 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	31/48 (64.6%)	19/49 (38.8%)	RR 1.67 (1.11 to 2.51)	260 more per 1000 (from 43 more to 586 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (long term) (follow-up 6 months)												
1 (Wanigasinghe 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	28/48 (58.3%)	22/49 (44.9%)	RR 1.30 (0.88 to 1.92)	135 more per 1000 (from 54 fewer to 413 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (long term) (follow-up 12 months)												
1 (Wanigasinghe 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	27/48 (56.3%)	20/49 (40.8%)	RR 1.38 (0.91 to 2.1)	155 more per 1000 (from 37 fewer to 449 more)	⊕OOO VERY LOW	CRITICAL
Time taken to spasms freedom (days) - Overall estimate (follow-up 14 days; Better indicated by lower values)												
2 (Gowda 2019, Wanigasinghe 2015)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	63	67	-	MD 2.58 lower (8.18 lower to 3.02 higher)	⊕OOO VERY LOW	CRITICAL
Time taken to spasms freedom (days) - High RoB (follow-up 14 days; Better indicated by lower values)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral steroids	Injectable steroids	Relative (95% CI)	Absolute	Quality	Importance
1 (Gowda 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	15	18	-	MD 1.1 higher (4.79 lower to 6.99 higher)	⊕OOO VERY LOW	CRITICAL
Time taken to spasms freedom (days) - Moderate RoB (follow-up 14 days; Better indicated by lower values)												
1 (Wani-gasinghe 2015)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	48	49	-	MD 4.8 lower (6.04 to 3.56 lower)	⊕OOO VERY LOW	CRITICAL
EEG resolution - Overall estimate (follow-up 2 weeks)												
3 (Baram 1996, Gowda 2019, Kap-por 2021)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	21/58 (56.3%)	36/64 (36.2%)	RR 0.62 (0.34 to 1.13)	214 fewer per 1000 (from 371 fewer to 73 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution - Children with TS excluded (follow-up 2 weeks)												
1 (Gowda 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/15 (26.7%)	7/18 (38.9%)	RR 0.69 (0.25 to 1.9)	121 fewer per 1000 (from 292 fewer to 350 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution - Children with TS included (follow-up 2 weeks)												
1 (Baram 1996)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/14 (28.6%)	13/15 (86.7%)	RR 0.33 (0.14 to 0.77)	581 fewer per 1000 (from 199 fewer to 745 fewer)	⊕⊕OO LOW	CRITICAL
EEG resolution (spasms cessation and resolution of hypsarrhythmia) (follow-up 2 weeks)												
1 (Wani-gasinghe 2015)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	21/48 (43.8%)	9/49 (18.4%)	RR 2.38 (1.22 to 4.66)	253 more per 1000 (from 40 more to 672 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution - Aetiology group - Cryptogenic (follow-up 2 weeks)												
1 (Baram 1996)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1/14 (7.1%)	2/15 (13.3%)	RR 0.54 (0.05 to 5.28)	61 fewer per 1000 (from 127 fewer to 571 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution (follow-up 6 weeks)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral steroids	Injectable steroids	Relative (95% CI)	Absolute	Quality	Importance
1 (Kapoor 2021)	RCT	serious[9]	no serious inconsistency	no serious indirectness	serious[6]	none	22/29 (75.9%)	14/31 (45.2%)	RR 1.68 (1.08 to 2.61)	307 more (from 37 more to 727 more)	⊕⊕OO LOW	CRITICAL
EEG resolution - Aetiology group - Symptomatic (follow-up 2 weeks)												
1 (Baram 1996)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	3/14 (21.4%)	11/15 (73.3%)	RR 0.29 (0.1 to 0.83)	521 fewer per 1000 (from 125 fewer to 660 fewer)	⊕OOO VERY LOW	CRITICAL
% of patients with reported side effects (follow-up 2 weeks)												
1 (Gowda 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/15 (20%)	3/18 (16.7%)	RR 1.2 (0.28 to 5.1)	33 more per 1000 (from 120 fewer to 683 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse events (follow-up 2 weeks)												
1 (Wani-gasinghe 2015)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/48 (2.1%)	0/49 (0%)	RR 3.06 (0.13 to 73.34)	20 more per 1000 (from 30 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of spasms - (follow-up 6 weeks)												
1 (Kapoor 2021)	RCT	serious[9]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/20 (0%)	6/17 (19.4%)	RR 0.07 (0.00 to 1.09)	328 fewer per 1000 (from 353 fewer to 32 more)	⊕⊕OO LOW	IMPORTANT
Spasms relapse - Overall estimate (follow-up mean 13 months)												
4 (Baram 1996, Gowda 2019, Hra-chovy 1983, Wani-gasinghe 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/42 (26.2%)	15/49 (30.6%)	RR 0.83 (0.39 to 1.79)	52 fewer per 1000 (from 187 fewer to 242 more)	⊕OOO VERY LOW	IMPORTANT
Spasms relapse - Children with TS excluded (follow-up mean 9 months)												
2 (Gowda 2019, Wani-gasinghe 2017)	RCT	very serious[1]	serious[4]	no serious indirectness	very serious[3]	none	9/34 (26.5%)	10/29 (34.5%)	RR 1.03 (0.19 to 5.62)	10 more per 1000 (from 279 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Spasms relapse - Children with TS included (follow-up mean 13 months)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral steroids	Injectable steroids	Relative (95% CI)	Absolute		
2 (Baram 1996, Hrachovy 1983)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/8 (25%)	5/20 (25%)	RR 0.8 (0.26 to 2.45)	50 fewer per 1000 (from 185 fewer to 363 more)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 Very serious heterogeneity unexplained by subgroup analysis
3 95% CI crosses 2 MIDs (0.8 and 1.25)
4 Serious heterogeneity unexplained by subgroup analysis
5 95% CI crosses 1 MID (0.8)
6 95% CI crosses 1 MID (1.25)
7 95% CI crosses 1 MID (+/-0.5x control group SD, for time taken to spasms freedom - overall estimate = +/-3.88, for time taken to spasms freedom - Moderate RoB =+-4.32)
8 95% CI crosses 2 MIDs (+/-0.5 x control group SD, for time taken to spasms freedom - high RoB = +/-3.45)
9 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 22: Clinical evidence profile. Comparison 4: high-dose oral steroids versus low-dose oral steroids

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose oral steroids	Low-dose oral steroids	Relative (95% CI)	Absolute		
Spasms freedom (follow-up 2 weeks)												
1 (Chellamu-thu 2014)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/31 (51.6%)	8/32 (25%)	RR 2.06 (1.04 to 4.12)	265 more per 1000 (from 10 more to 780 more)	⊕⊕OO LOW	CRITICAL
EEG resolution (in those who achieved seizure freedom) (follow-up 2 weeks)												
1 (Chellamu-thu 2014)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/16 (56.3%)	4/8 (50%)	RR 1.13 (0.5 to 2.55)	65 more per 1000 (from 250 fewer to 775 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse events (follow-up 2 weeks)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose oral steroids	Low-dose oral steroids	Relative (95% CI)	Absolute	Quality	Importance
1 (Chellamuthu 2014)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/31 (0%)	0/32 (0%)	RD 0.00 (-0.06 to 0.06)	0 per 1000 (from 60 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up 6 months)												
1 (Chellamuthu 2014)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/16 (31.3%)	4/8 (50%)	RR 0.62 (0.23 to 1.71)	190 fewer per 1000 (from 385 fewer to 355 more)	⊕OOO VERY LOW	IMPORTANT
Ongoing seizures (follow-up 6 months)												
1 (Chellamuthu 2014)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/31 (3.2%)	0/32 (0%)	RR 3.09 (0.13 to 73.17)	30 more per 1000 (from 50 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT

1 *1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 *2 95% CI crosses 1 MID (1.25)*
3 *3 95% CI crosses 2 MIDs (0.8 and 1.25)*
4 *4 Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)*

5 **Table 23: Clinical evidence profile. Comparison 5: vigabatrin versus oral steroids**

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vigabatrin	Oral steroids	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (follow-up 1 months)												
1 (Chiron 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/11 (100%)	5/11 (45.5%)	RR 2.09 (1.12 to 3.91)	495 more per 1000 (from 55 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vigabatrin	Oral steroids	Relative (95% CI)	Absolute		
% of patients with reported side effects (follow-up 1 month)												
1 (Chiron 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/11 (27.3%)	8/11 (72.7%)	RR 0.38 (0.13 to 1.05)	451 fewer per 1000 (from 633 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up 2 months)												
1 (Chiron 1997)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/11 (9.1%)	0/5 (0%)	RR 1.5 (0.07 to 31.57)	90 more per 1000 (from 200 fewer to 380 more)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (1.25)
3 95% CI crosses 1 MID (0.8)
4 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 24: Clinical evidence profile. Comparison 6: nitrazepam versus injectable steroids

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrazepam	Injectable steroids	Relative (95% CI)	Absolute		
Spasms freedom (patients who were 75% to 100% spasms free) (follow-up 1 months)												
1 (Dreifuss 1986)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/27 (51.9%)	12/21 (57.1%)	RR 0.91 (0.54 to 1.52)	51 fewer per 1000 (from 263 fewer to 297 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse events (follow-up 2 weeks)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrazepam	Injectable steroids	Relative (95% CI)	Absolute		
1 (Dreifuss 1986)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/27 (0%)	6/25 (24%)	RR 0.07 (0 to 1.21)	223 fewer per 1000 (from 240 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 2 MIDs (0.8 and 1.25)
3 95% CI crosses 1 MID (0.8)

Table 25: Clinical evidence profile. Comparison 7: ketogenic diet versus injectable steroids

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Ketogenic diet	Injectable steroids	Relative (95% CI)	Absolute		
Spasms freedom (follow-up median 12 months)												
1 (Dressler 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/16 (37.5%)	7/16 (43.8%)	RR 0.86 (0.37 to 3.27)	61 fewer per 1000 (from 276 fewer to 993 more)	⊕OOO VERY LOW	CRITICAL
% of patients with reported side effects (follow-up median 12 months)												
1 (Dressler 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	14/16 (87.5%)	16/16 (100%)	RR 0.88 (0.71 to 1.09)	120 fewer per 1000 (from 290 fewer to 90 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up median 12 months)												
1 (Dressler 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/10 (40%)	4/11 (36.4%)	RR 1.1 (0.37 to 3.27)	36 more per 1000 (from 229 fewer to 825 more)	⊕OOO VERY LOW	IMPORTANT
% of patients with an age-appropriate psychomotor development (follow-up median 12 months)												
1 (Dressler 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/16 (25%)	5/16 (31.3%)	RR 0.80 (0.26 to 2.45)	62 fewer per 1000 (from 231	⊕OOO VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	Ketogenic diet	Injectable steroids	Relative (95% CI)	Absolute		
										fewer to 453 more)		
% of patients with an age-appropriate adaptive level (follow-up median 12 months)												
1 (Dressler 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/10 (30%)	6/11 (54.5%)	RR 0.55 (0.18 to 1.64)	245 fewer per 1000 (from 447 fewer to 349 more)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 2 MIDs (0.8 and 1.25)
3 95% CI crosses 1 MID (0.8)

Table 26: Clinical evidence profile. Comparison 8: high-dose vigabatrin versus low-dose vigabatrin

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	High-dose vigabatrin	Low-dose vigabatrin	Relative (95% CI)	Absolute		
Spasms freedom (follow-up median 1.2 years)												
1 (Elterman 2010)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73/107 (68.2%)	59/114 (51.8%)	RR 1.32 (1.06 to 1.64)	166 more per 1000 (from 31 more to 331 more)	⊕OOO VERY LOW	CRITICAL
% of patients with reported side effects (follow-up median 1.2 years)												
1 (Elterman 2010)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52/107 (48.6%)	58/114 (50.9%)	RR 0.96 (0.73 to 1.25)	20 fewer per 1000 (from 137 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up median 1.2 years)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider-ations	High-dose vigabatrin	Low-dose vigabatrin	Relative (95% CI)	Absolute	Quality	Importance
1 (Elterman 2010)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/17 (11.8%)	2/8 (25%)	RR 0.47 (0.08 to 2.76)	132 fewer per 1000 (from 230 fewer to 440 more)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (1.25)
3 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 27: Clinical evidence profile. Comparison 9: nitrazepam versus topiramate

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrazepam	Topiramate	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (follow-up 6 months)												
1 (Fallah 2014)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/25 (16%)	12/25 (48%)	RR 0.33 (0.12 to 0.89)	322 fewer per 1000 (from 53 fewer to 422 fewer)	⊕OOO VERY LOW	CRITICAL
% of patients with reported side effects (follow-up 6 months)												
1 (Fallah 2014)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/25 (36%)	8/25 (32%)	RR 1.12 (0.52 to 2.44)	38 more per 1000 (from 154 fewer to 461 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse events (follow-up 6 months)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrazepam	Topiramate	Relative (95% CI)	Absolute	Quality	Importance
1 (Fallah 2014)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/25 (0%)	0/25 (0%)	RD 0.00 (-0.07 to 0.07)	0 per 1000 (from 70 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (0.8)
3 95% CI crosses 2 MIDs (0.8 and 1.25)
4 Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)

Table 28: Clinical evidence profile. Comparison 10: high-dose injectable steroids versus low-dose injectable steroids

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose injectable steroids	Low-dose injectable steroids	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom - overall estimate (follow-up 8 weeks)												
2 (Hrachovy 1994, Yanagaki 1999)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24/39 (61.5%)	23/37 (62.2%)	RR 1 (0.71 to 1.41)	0 fewer per 1000 (from 180 fewer to 255 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom - aetiology group - Spasms freedom: cryptogenic (follow-up 8 weeks)												
1 (Hrachovy 1994)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/26 (11.5%)	4/24 (16.7%)	RR 0.69 (0.17 to 2.78)	52 fewer per 1000 (from 138 fewer to 297 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom - aetiology group - Spasms freedom: symptomatic (follow-up 8 weeks)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose injectable steroids	Low-dose injectable steroids	Relative (95% CI)	Absolute		
1 (Hrachovy 1994)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/26 (38.5%)	10/24 (41.7%)	RR 0.92 (0.47 to 1.82)	33 fewer per 1000 (from 221 fewer to 342 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution (in those who achieved spasms freedom) (follow-up 8 weeks)												
1 (Hrachovy 1994)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/13 (23.1%)	3/14 (21.4%)	RR 1.08 (0.26 to 4.42)	17 more per 1000 (from 159 fewer to 733 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up 8 weeks)												
2 (Hrachovy 1994, Yanagaki 1999)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/21 (23.8%)	6/23 (26.1%)	RR 0.92 (0.33 to 2.52)	21 fewer per 1000 (from 175 fewer to 397 more)	⊕OOO VERY LOW	IMPORTANT

1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 29: Clinical evidence profile. Comparison 12: short-term ketogenic diet versus long-term ketogenic diet

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term ketogenic diet	Long-term ketogenic diet	Relative (95% CI)	Absolute		
Time to spasms freedom (follow-up median 2 years; Better indicated by lower values)												
1 (Kang 2011)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13	11	-	MD 6 lower (24.08 lower to	⊕OOO VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term ketogenic diet	Long-term ketogenic diet	Relative (95% CI)	Absolute	Quality	Importance
										12.08 higher)		
EEG resolution (follow-up median 2 years)												
1 (Kang 2011)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/13 (100%)	16/16 (100%)	RR 1 (0.88 to 1.14)	0 fewer per 1000 (from 120 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse events (follow-up median 2 years)												
1 (Kang 2011)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/13 (0%)	5/16 (31.3%)	RR 0.11 (0.01 to 1.83)	278 fewer per 1000 (from 309 fewer to 259 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up median 2 years)												
1 (Kang 2011)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/16 (18.8%)	3/19 (15.8%)	RR 1.19 (0.28 to 5.09)	30 more per 1000 (from 114 fewer to 646 more)	⊕OOO VERY LOW	IMPORTANT
Mean Bayley Developmental Test scores (follow-up median 2 years; Better indicated by higher values)												
1 (Kang 2011)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	19	-	MD 0.39 higher (11.45 lower to 12.23 higher)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 2 MIDs (+/-0.5x control group SD, for time to spasms freedom= +/-10.46, for mean Bayley Developmental Test Scores=+/-8.93)
3 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 30: Clinical evidence profile. Comparison 12: pyridoxine in combination with prednisolone versus oral steroids

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pyridoxine + prednisolone	Oral steroids	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (follow-up 2 weeks)												
1 (Kunnanayaka 2018)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/30 (36.7%)	12/32 (37.5%)	RR 0.98 (0.51 to 1.87)	7 fewer per 1000 (from 184 fewer to 326 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution (in those who achieved spasms freedom) (follow-up 2 weeks)												
1 (Kunnanayaka 2018)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/11 (54.5%)	9/12 (75%)	RR 0.73 (0.39 to 1.37)	202 fewer per 1000 (from 458 fewer to 278 more)1000 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up 1 months)												
1 (Kunnanayaka 2018)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/11 (9.1%)	4/12 (33.3%)	RR 0.27 (0.04 to 2.08)	243 fewer per 1000 (from 320 fewer to 360 more)	⊕OOO VERY LOW	IMPORTANT

1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 31: Clinical evidence profile. Comparison 13: prednisolone in combination with tetracosactide versus vigabatrin

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisolone + tetracosactide	Vigabatrin	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (short term) (follow-up 2 weeks)												
1 (Lux 2004)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/55 (72.7%)	28/52 (53.8%)	RR 1.35 (1 to 1.82)	188 more per 1000 (from 0 more to 442 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (long term) - known aetiology (follow-up 10 months)												
1 (Lux 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/29 (69%)	21/29 (72.4%)	RR 0.95 (0.68 to 1.33)	36 fewer per 1000 (from 232 fewer to 239 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (long term) - unkown aetiology (follow-up 10 months)												
1 (Lux 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/26 (80.8%)	18/22 (81.8%)	RR 0.99 (0.75 to 1.3)	8 fewer per 1000 (from 205 fewer to 245 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution (for those who were hypsarrhythmic at baseline and had an EEG done) (follow-up 2 weeks)												
1 (Lux 2004)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/32 (81.3%)	20/36 (55.6%)	RR 1.46 (1.04 to 2.05)	256 more per 1000 (from 22 more to 583 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse events (follow-up 2 weeks)												
1 (Lux 2004)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/55 (3.6%)	0/52 (0%)	RR 4.73 (0.23 to 96.3)	40 more per 1000 (from 20 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up 3 months)												
1 (Lux 2004)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/40 (45%)	9/28 (32.1%)	RR 1.4 (0.74 to 2.65)	129 more per 1000 (from 84	⊕OOO VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisolone + tetracosactide	Vigabatrin	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 530 more)		
Mean VABS scores - overall estimate (follow-up 10 months; Better indicated by higher values)												
1 (Lux 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	51	-	MD 1.1 higher (4.54 lower to 6.74 higher)	⊕⊕OO LOW	IMPORTANT
Mean VABS scores- aetiology group - Mean VABS score - known aetiology (follow-up 10 months; Better indicated by higher values)												
1 (Lux 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	29	-	MD 5.1 lower (10.87 lower to 0.67 higher)	⊕⊕OO LOW	IMPORTANT
Mean VABS scores- aetiology group - Mean VABS score - unkown aetiology (follow-up 10 months; Better indicated by higher values)												
1 (Lux 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	26	-	MD 9.3 higher (0.67 to 17.93 higher)	⊕⊕OO LOW	IMPORTANT

1 *1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 *2 95% CI crosses 1 MID (1.25)*
3 *3 95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 32: Clinical evidence profile. Comparison 14: vigabatrin in combination with oral steroids versus oral steroids

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vigabatrin + oral steroids	Oral steroids	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (follow-up 14 to 42 days)												
1 (O'Callaghan 2018)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	133/186 (71.5%)	108/191 (56.5%)	RR 1.26 (1.08 to 1.47)	147 more per 1000 (from 45 more to 266 more)	⊕OOO VERY LOW	CRITICAL
EEG resolution (amongst those for whom both clinical and electrical outcomes were available) (follow-up 42 days)												
1 (O'Callaghan 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	123/185 (66.5%)	104/189 (55%)	RR 1.21 (1.02 to 1.42)	116 more per 1000 (from 11 more to 231 more)	⊕OOO VERY LOW	CRITICAL
% of patients with reported side effects (follow-up 42 days)												
1 (O'Callaghan 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	117/186 (62.9%)	111/191 (58.1%)	RR 1.08 (0.92 to 1.27)	46 more per 1000 (from 46 fewer to 157 more)	⊕OOO VERY LOW	CRITICAL
% of patients with reported serious side effects (follow-up 42 days)												
1 (O'Callaghan 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/186 (9.1%)	16/191 (8.4%)	RR 1.09 (0.57 to 2.09)	8 more per 1000 (from 36 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Spasms relapse (follow-up 42 days)												
1 (O'Callaghan 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	33/166 (19.9%)	24/132 (18.2%)	RR 1.09 (0.68 to 1.76)	16 more per 1000 (from 58 fewer to 138 more)	⊕OOO VERY LOW	IMPORTANT
Mean VABS scores - overall estimate (follow-up 18 months; Better indicated by higher values)												
1 (O'Callaghan 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	181	181	-	MD 1.2 higher (2.54 lower	⊕⊕OO LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vigabatrin + oral steroids	Oral steroids	Relative (95% CI)	Absolute	Quality	Importance
										to 4.94 higher)		
Mean VABS scores - risk of developmental impairment at randomisation - Mean VABS scores - babies at high risk of developmental impairment at randomisation (follow-up 18 months; Better indicated by higher values)												
1 (O'Callaghan 2018)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	181	181	-	MD 0.5 lower (4.11 lower to 3.11 higher)	⊕⊕OO LOW	IMPORTANT
Mean VABS scores - risk of developmental impairment at randomisation - Mean VABS scores - babies at low risk of developmental impairment at randomisation (follow-up 18 months; Better indicated by higher values)												
1 (O'Callaghan 2018)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	181	181	-	MD 3.8 higher (1.47 lower to 9.07 higher)	⊕⊕OO LOW	IMPORTANT

1 *1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
2 *2 95% CI crosses 1 MID (1.25)*
3 *3 95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 33: Clinical evidence profile. Comparison 15: high-dose prednisone only versus high-dose prednisone in combination with topiramate

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose Prednisone only	High-dose Prednisone + add-on topiramate	Relative (95% CI)	Absolute	Quality	Importance
Spasms freedom (follow-up 14 days)												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/39 (71.8%)	29/38 (76.3%)	RR 0.94 (0.72 to 1.23)	46 fewer per 1000 (from 214 fewer to 176 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (at end of treatment period - 49 or 56 days)												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	28/39 (71.8%)	25/38 (65.8%)	RR 1.09 (0.81 to 1.48)	59 more per 1000 (from 214 fewer to 176 more)	⊕OOO VERY LOW	CRITICAL
Spasms freedom (follow-up 120 days)												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	24/39 (61.5%)	19/38 (50.0%)	RR 1.23 (0.82 to 1.84)	115 more per 1000 (from 90 fewer to 420 more)	⊕OOO VERY LOW	CRITICAL
Resolution of hypsarrhythmia on EEG at 2 weeks in children with spasm freedom - partial												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/28	9/29	RR 0.81 (0.35 to 1.87)	59 fewer per 1000 (from 202 fewer to 270 more)	⊕OOO VERY LOW	IMPORTANT
Resolution of hypsarrhythmia on EEG at 2 weeks in children with spasm freedom - complete												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	21/28 (75.0%)	20/29 (69.0%)	RR 1.09 (0.79 to 1.50)	62 more per 1000 (from 145 fewer to 345 more)	⊕OOO VERY LOW	CRITICAL
Treatement cessation due to adverse events												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose Prednisone only	High-dose Prednisone + add-on topiramate	Relative (95% CI)	Absolute	Quality	Importance
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/28	0/29	RD 0.00 (-0.07 to 0.07)	0 per 1000 (from 70 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Spasms relaspse at end of treatment period (49 or 56 days)												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/28 (3.6%)	4/29 (13.8%)	RR 0.26 (0.03 to 2.18)	102 fewer per 1000 (from 134 fewer to 163 more)	⊕OOO VERY LOW	IMPORTANT
Spasms relaspse at 120 days												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/28 (14.3%)	10/29 (34.5%)	RR 0.41 (0.15 to 1.16)	345 fewer per 1000 (from 293 fewer to 59 more)	⊕OOO VERY LOW	IMPORTANT
Spasms relapse at 12 months - data only available for 15/28 patients in monotherapy group and 16/29 patients in combination therapy group												
1 (Yi 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/15	10/16	RR 0.53 (0.24 to 1.20)	294 fewer per 1000 (from 475 fewer to 125 more)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (0.8)
3 95% CI crosses 1 MID (1.25)
4 95% CI crosses 2 MIDs (0.8 and 1.25)
5 Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix H – Economic evidence tables

Economic evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

No evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

Clinical studies

Table 34: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Efficacy and safety of vigabatrin in Japanese patients with infantile spasms: primary short-term study and extension study, Epilepsy & Behavior, 78, 2018	Observational study
Non-pharmacological medical treatment in pediatric epilepsies, Revue neurologique. 172 (3) (pp 182-185), 2016. Date of publication: 01 MAR 2016., 2016	Narrative review
Abdelmoity, A., Kayyali, H. R., Ketogenic diet efficacy in the treatment of intractable infantile spasms, Epilepsy Currents. Conference: 64th Annual Meeting of the American Epilepsy Society, AES and 3rd Biennial North American Regional Epilepsy Congress. San Antonio, TX United States. Conference Publication:, 11, 2011	Observational study
Aicardi, J., Treatment of infantile spasms, Journal of Pediatrics, 103, 171-2, 1983	Letter
Al Ajlouni, S., Shorman, A., Daoud, A. S., The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: a multi-center clinical trial, Seizure, 14, 459-63, 2005	Observational study
Al-Baradie, R. S., Elseed, M. A., West syndrome, can topiramate be on top?, Neurosciences, 16, 53-6, 2011	Observational study
Albsoul-Younes, A. M., Salem, H. A., Ajlouni, S. F., Al-Safi, S. A., Topiramate slow dose titration: improved efficacy and tolerability, Pediatric Neurology, 31, 349-52, 2004	Observational study
Almaabdi, K. H., Alshehri, R. O., Althubiti, A. A., Alsharef, Z. H., Mulla, S. N., Alshaer, D. S., Alfaidi, N. S., Jan, M. M., Intravenous methylprednisolone for intractable childhood epilepsy, Pediatric Neurology, 50, 334-6, 2014	Observational study
Al-Mendalawi, M. D., West syndrome, can topiramate be on top?, Neurosciences, 16, 290; author reply 290-1, 2011	Letter to the editor
Alvarez, N., Besag, F., Iivanainen, M., Use of antiepileptic drugs in the treatment of epilepsy in people with intellectual disability, Journal of Intellectual Disability Research, 42 Suppl 1, 1-15, 1998	Not available. Last checked 26/03/21
Amano, R., Mizukawa, M., Ohtsuka, Y., Ohtahara, S., High-dose sodium valproate therapy for childhood refractory epilepsy, Japanese Journal of Psychiatry & Neurology, 44, 343-4, 1990	Observational study

Study	Reason for Exclusion
Anderson, M., Choonara, I., A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period, Archives of Disease in Childhood, 95, 731-738, 2010	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Angappan, D., Sahu, J. K., Malhi, P., Singhi, P., Safety, tolerability, and effectiveness of oral zonisamide therapy in comparison with intramuscular adrenocorticotropic hormone therapy in infants with West syndrome, European Journal of Paediatric Neurology, 2018	Intervention not relevant (zonisamide)
Arya, R., Shinnar, S., Glauser, T. A., Corticosteroids for the treatment of infantile spasms: A systematic review, Journal of Child Neurology, 27, 1284-1288, 2012	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Biswas, A., Yossofzai, O., Vincent, A., Go, C., Widjaja, E., Vigabatrin-related adverse events for the treatment of epileptic spasms: systematic review and meta-analysis, Expert review of neurotherapeutics., 20, 2020	No relevant outcomes reported
Bitton, J. Y., Sauerwein, H. C., Weiss, S. K., Donner, E. J., Whiting, S., Dooley, J. M., Snead, C., Farrell, K., Wirrell, E. C., Mohamed, I. S., et al.,, A randomized controlled trial of flunarizine as add-on therapy and effect on cognitive outcome in children with infantile spasms, Epilepsia, 53, 1570-1576, 2012	Intervention not relevant (flunarizine)
Bustamante-Chavez, H., Pacheco-Barrios, N., Alva-Diaz, C., Pacheco-Barrios, K., Efficacy of prednisolone in the treatment of infantile spasms: Systematic review and meta-analysis, Annals of Neurology, 86 (Supplement 24), S74, 2019	Conference abstract
Chang, Y. H., Chen, C., Chen, S. H., Shen, Y. C., Kuo, Y. T., Effectiveness of corticosteroids versus adrenocorticotropic hormone for infantile spasms: a systematic review and meta-analysis, Annals of Clinical and Translational Neurology, 6, 2270-2281, 2019	All studies included in this paper have already been reported in this review
Chhun, S., Troude, P., Villeneuve, N., Soufflet, C., Napuri, S., Motte, J., Pouplard, F., Alberti, C., Helfen, S., Pons, G., Dulac, O., Chiron, C., A prospective open-labeled trial with levetiracetam in pediatric epilepsy syndromes: Continuous spikes and waves during sleep is definitely a target, Seizure, 20, 320-325, 2011	Observational study
Chi, Ctr Iir, Ketogenic diet therapy for rare epilepsy syndromes, multicenter randomly controlled clinical trial, Http://www.who.int/trialsearch/trial2.aspx?Trialid=chictr-iir-16008342, 2016	Study protocol
Chi, Ctr Ipn, Ketogenic Diets as an Add-on Therapy in Infantile spasms: a Prospective, Multicenter Pilot Study, Http://www.who.int/trialsearch/trial2.aspx?Trialid=chictr-ipn-17014209, 2017	Study protocol
Connock, M., Frew, E., Evans, B. W., Bryan, S., Cummins, C., Fry-Smith, A., Li Wan Po, A.,	Study protocol

Study	Reason for Exclusion
Sandercock, J., The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review, Health Technology Assessment, 10, iii-118, 2006	
Ctri,, Effect of methylprednisolone when compared to oral prednisolone in treatment of children with West syndrome, Http://www.who.int/trialsearch/trial2.aspx? Trialid=ctri/2017/12/010877, 2017	Study protocol
Ctri,, Use of "Zonisamide" oral medicine in children with epilepsy "West Syndrome", Http://www.who.int/trialsearch/trial2.aspx? Trialid=ctri/2013/07/003843, 2013	Study protocol
Darke, K., Edwards, S. W., Hancock, E., Johnson, A. L., Kennedy, C. R., Lux, A. L., Newton, R. W., O'Callaghan, F. J., Verity, C. M., Osborne, J. P., Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multicentre randomised trial, Archives of Disease in Childhood, 95, 382â€• 386, 2010	No relevant outcomes reported
Debus, O. M., Kurlemann, G., Sulthiame in the Primary Therapy of West Syndrome: A Randomized Double-blind Placebo-controlled Add-on Trial on Baseline Pyridoxine Medication, Epilepsia, 45, 103-108, 2004	Intervention not relevant (sulthiame)
Dressler, A., Benninger, F., Trimmel-Schwahofer, P., Gröppel, G., Porsche, B., Abraham, K., Mühlebner, A., Samueli, S., Male, C., Feucht, M., Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: a single-center parallel-cohort randomized controlled trial, Epilepsia, 60, 441-451, 2019	Duplicate of Dressler 2019, which has already been included in this review
Dressler, A., Trimmel-Schwahofer, P., Reithofer, E., Groppel, G., Muhlebner, A., Samueli, S., Abraham, K., Benninger, F., Feucht, M., The ketogenic diet versus ACTH in the treatment of infantile spasms: A prospective randomised study, Zeitschrift fur Epileptologie, 28 (1 Supplement 1), 12-13, 2015	Conference abstract
Duchowny, M. S., Chopra, I., Niewoehner, J., Wan, G. J., Devine, B. A systematic literature review and indirect treatment comparison of efficacy of repository corticotropin injection versus synthetic adrenocorticotropic hormone for infantile spasms. Journal of Health Economics and Outcomes Research 2021	Systematic review, all studies included in this paper have already been included in this review
Dumitrascu, V., Matusz, A. A., Vlad, D. C., Barac, B., Cheveresan, A., Safety and efficacy of Topiramate, in pediatric epileptic Patients, Basic and Clinical Pharmacology and Toxicology, 1), 129, 2009	Conference abstract
Dyken, P. R., DuRant, R. H., Minden, D. B., King, D. W., Short term effects of valproate on infantile spasms, Pediatric Neurology, 1, 34-37, 1985	Does not report outcomes specified in protocol

Study	Reason for Exclusion
Elia, M., Klepper, J., Leiendecker, B., Hartmann, H., Ketogenic diets in the treatment of epilepsy, Current Pharmaceutical Design, 23, 5691-5701, 2017	Narrative review
Elterman, R. D., Collins, S. D., Shields, D., Mansfield, K. A., Nakagawa, J., Efficacy of vigabatrin in subjects with infantile spasms, Epilepsia, 46 Suppl 8, 167, 2005	Conference abstract
Elterman, R. D., Shields, W. D., Collins, S., Vigabatrin effective in multiple etiologies of infantile spasms, Epilepsia, 47 Suppl 4, 179, 2006	Conference abstract
Elterman, R. D., Shields, W. D., Mansfield, K. A., Nakagawa, J., Randomized trial of vigabatrin in patients with infantile spasms, Neurology, 57, 1416-1421, 2001	Initial results of Elterman 2010, final report has already been included in this review
Eltman, R. D., Vigabatrin valuable in infantile spasms of multiple etiology, P and T, 32, 109-110, 2007	Study abstract
Fayyazi, A., Eslamian, R., Khajeh, A., Dehghani, M., Comparison of the effect of high and low doses of adrenocortico-tropic hormone (Acth) in the management of infan-tile spasms, Irani-an Journal of Child Neurology, 14, 17-25, 2020	Does not report outcomes specified in protocol
Gupta, A., Combined treatment of 'vigabatrin and corticoids' for infantile spasms: A superiority complex or truly superior to corticoids monotherapy?, Epilepsy Currents, 17, 355-357, 2017	Editorial comment
Hancock, E. C., Osborne, J. P., Edwards, S. W., Treatment of infantile spasms, Cochrane Database of Systematic Reviews, 2013	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Hancock, E., Osborne, J., Treatment of infantile spasms with high-dose oral prednisolone, Developmental Medicine & Child Neurology, 40, 500, 1998	Letter to the editor
Hancock, E., Osborne, J. P., Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review, Journal of Child Neurology, 14, 71-4, 1999	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Harvey, A. S., Topiramate: Potential trade-offs between efficacy and tolerability in the treatment of epilepsy, Journal of Paediatrics and Child Health, 39, 414-415, 2003	Commentary paper
Hrachovy, R. A., Frost Jr, J. D., Glaze, D. G., Single-blind study of high-dose versus low-dose ACTH therapy in infantile spasms, Epilepsia, 33 Suppl 3, 113, 1992	Conference abstract
Hrachovy, R. A., Frost, J. D., Glaze, D. G., Low-dose ACTH versus prednisone therapy in infantile spasms: further observations, Epilepsia, 30, 654-655, 1989	Conference abstract
Hrachovy, R. A., Frost, J. D., Jr., Glaze, D. G., Rose, D., Treatment of infantile spasms with methysergide and alpha-methylparatyrosine, Epilepsia, 30, 607-10, 1989	Intervention not relevant (methysergide and alpha-methylparatyrosine)

Study	Reason for Exclusion
Hrachovy, R. A., Frost, J. D., Jr., Kellaway, P., Zion, T., A controlled study of prednisone therapy in infantile spasms, Epilepsia, 20, 403-7, 1979	Observational study
Hsieh, M. Y., Lin, K. L., Wang, H. S., Chou, M. L., Hung, P. C., Chang, M. Y., Low-dose topiramate is effective in the treatment of infantile spasms, Chang Gung Medical Journal, 29, 291-6, 2006	Observational study
Ibrahim, S., Gulab, S., Ishaque, S., Saleem, T., Clinical profile and treatment of infantile spasms using vigabatrin and ACTH - a developing country perspective, BMC Pediatrics, 10 (no pagination), 2010	Observational study
Irct138808052639N,, Comparison of efficacy of Topiramate and Nitrazepam in infantile spasms treatment, Http://www.who.int/trialsearch/trial2.aspx?Trialid=irct138808052639n1, 2009	Study protocol
Irct20091027002639N,, Effect of levetiracetam and topiramate in infantile spasms, Http://www.who.int/trialsearch/trial2.aspx?Trialid=irct20091027002639n21, 2018	Study protocol
Irct2015060110634N,, A Comparative of high dose and low dose adrenocorticotropic hormone (ACTH) therapy for infantile spasm, Http://www.who.int/trialsearch/trial2.aspx? Trialid=irct2015060110634n2, 2016	Study protocol
Isrctn,, A randomised double blind trial of add-on flunarizine to prevent the cognitive deterioration associated with infantile spasms, Http://www.who.int/trialsearch/trial2.aspx?Trialid=isrctn36757519, 2005	Study protocol
Jaseja, H., Drug-choice in management of West syndrome (infantile spasms): Early ACTH treatment may offer a better prognostic outcome, Medical Hypotheses, 70, 197-8, 2008	Letter to the editor
Jaseja, H., Jaseja, B., Adrenocorticotrophic hormone (ACTH) therapy in infantile spasms (IS): current evidence for its superior therapeutic efficacy, Clinical Neurology & Neurosurgery, 115, 1919-20, 2013	Letter to the editor
Jaseja, H., Jaseja, B., Badaya, S., Tonpay, P., Superior therapeutic efficacy of adrenocorticotrophic hormone (ACTH) in infantile spasms: emerging evidence, Epilepsy & Behavior, 25, 250, 2012	Letter to the editor
Kang, H. C., Lee, Y., Lee, J., Lee, E., Eom, S., You, S., Kim, H., Evaluation of prognosis after a short-term and long-term trial of the ketogenic diet in infantile spasms: A randomized, controlled comparison, Epilepsia, 11), 128-129, 2009	Conference abstract
Knupp, K. G., Hormonal therapy with vigabatrin is superior to hormonal therapy alone in infantile spasms, Journal of Pediatrics, 184, 235-238, 2017	Conference abstract
Kondo, Y., Okumura, A., Watanabe, K., Negoro, T., Kato, T., Kubota, T., Hiroko, K., Comparison of two low dose ACTH therapies for West syndrome: their	Observational study

Study	Reason for Exclusion
efficacy and side effect, Brain & Development, 27, 326-30, 2005	
Lambrechts, D. A., de Kinderen, R. J., Vles, J. S., de Louw, A. J., Aldenkamp, A. P., Majoie, H. J., A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy, Acta Neurologica Scandinavica, 135, 231â€• 239, 2017	Included patients with a range of epileptic syndromes and and subgroup analyses for patients with infantile spasms are not reported
Li, S., Zhong, X., Hong, S., Li, T., Jiang, L., Prednisolone/prednisone as adrenocorticotropic hormone alternative for infantile spasms: a meta-analysis of randomized controlled trials, Developmental Medicine and Child Neurology, 62, 575-580, 2020	All studies included in this paper have been included and reported in this review
Lux, A. L., Edwards, S. W., Hancock, E., Johnson, A. L., Kennedy, C. R., Newton, R. W., O'Callaghan, F. J., Verity, C. M., Osborne, J. P., The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide in a randomised trial: developmental outcome at 14 months, Epilepsia, 45 Suppl 7, 273-274, 2004	Conference abstract
Lux, A. L., Edwards, S. W., Osborne, J. P., Hancock, E., Johnson, A. L., Verity, C. M., Kennedy, C. R., O'Callaghan, F. J. K., Newton, R. W., Randomized trial of vigabatrin in patients with infantile spasms [1], Neurology, 59, 648, 2002	Letter to the editor
Mahmoud, A., Ineffectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids, Neurology. Conference: 65th American Academy of Neurology Annual Meeting. San Diego, CA United States. Conference Publication:, 80, 2013	Conference abstract
Mahmoud, A. A., Ineffectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids, Journal of the Neurological Sciences, 1), e583-e584, 2013	Conference abstract
Mahmoud, A. A. H., Effectiveness of topiramate and levetiracetam in infantile spasms nonresponsive to steroids, European Journal of Neurology, 19 (SUPPL.1), 207, 2012	Conference abstract
Mahmoud, A. A. H., Effectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids, Developmental Medicine and Child Neurology, 54 (SUPPL.1), 76-77, 2012	Conference abstract
Mahmoud, A. A., Rizk, T. M., Mansy, A. A., Ali, J. A., Al-Tannir, M. A., Ineffectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids. Open labeled randomized prospective study, Neurosciences (riyadh, saudi arabia), 18, 143â€• 146, 2013	No relevant outcomes reported
Mahmoud, A. A., Rizk, T. M., Mansy, A. A., Ali, J. A., Al-Tannir, M. A., Ineffectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids: Open labeled randomized prospective study, Neurosciences, 18, 143-146, 2013	No relevant outcomes reported

Study	Reason for Exclusion
Mahmoud, A., Rizk, T., Mansy, A., Ali, J., Riaz, M., Al Tannir, M., Effectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids, Developmental Medicine and Child Neurology, 4), 164-165, 2012	Conference abstract
Moavero, R., Santarone, M. E., Galasso, C., Curatolo, P., Cognitive and behavioral effects of new antiepileptic drugs in pediatric epilepsy, Brain and Development, 39, 464-469, 2017	Narrative review
Mytinger, J. R., Camfield, P. R., Synthetic ACTH is not superior to prednisolone for infantile spasms: Randomized clinical trials and tribulations, Pediatric Neurology, 53, 181-182, 2015	Narrative review
Nct,, Intravenous Methylprednisolone Versus Oral Prednisolone for Infantile Spasms, Https://clinicaltrials.gov/show/nct03876444, 2019	Study protocol
Nct,, Evaluation of the Modified Atkins Diet in Children With Epileptic Spasms, Https://clinicaltrials.gov/show/nct03807141, 2019	Study protocol
Nct,, A Randomized, Controlled Trial of Ganaxolone in Patients With Infantile Spasms, Https://clinicaltrials.gov/show/nct00441896, 2007	Study protocol
Nct,, Addition of Pyridoxine to Prednisolone in Infantile Spasms, Https://clinicaltrials.gov/show/nct01828437, 2013	Study protocol
Negoro, T., Watanabe, K., Treatment of epilepsy in infancy with special emphasis on ACTH therapy, Japanese Journal of Psychiatry & Neurology, 40, 315-21, 1986	Observational study
O'Callaghan, F. J. K., Edwards, S., Dietrich Alber, F., Hancock, E., Johnson, A., Kennedy, C. R., Lux, A., Mackay, M. T., Mallick, A., Newton, R., et al.,, The International Collaborative Infantile Spasm Study (ICISS): the clinical, electro-clinical and developmental outcomes, Developmental Medicine and Child Neurology, 58, 2â€• 3, 2016	Conference abstract
O'Callaghan, F. J. K., Edwards, S., Hancock, E., Johnson, A., Kennedy, C., Lux, A., Mackay, M., Newton, R., Nolan, M., Rating, D., et al.,, The International Collaborative Infantile Spasms Study (ICISS) comparing hormonal therapies (prednisolone or tetracosactide depot) and vigabatrin versus hormonal therapies alone in the treatment of infantile spasms: early clinical outcome, European Journal of Paediatric Neurology., 19, S16â€• S17, 2015	Conference abstract
O'Callaghan, F. J. K., Lux, A. L., Edwards, S. W., Hancock, E., Johnson, A. L., Kennedy, C. R., Newton, R. W., Verity, C. M., Osborne, J. P., The relationship between lead-time to treatment and subsequent development in infantile spasms, European Journal of Paediatric Neurology, 1), S11-S12, 2009	Conference abstract
O'Callaghan, F. J., Edwards, S., Dietrich Alber, F., Hancock, E., Johnson, A. L., Kennedy, C. R., Lux, A. L., Likeman, M., Mackay, M., Mallick, A., et al.,,	Conference abstract

Study	Reason for Exclusion
The International Collaborative Infantile Spasms Study (ICISS) comparing hormonal therapies and vigabatrin versus hormonal therapies alone in the treatment of infantile spasms: developmental and epilepsy outcome at 18 months, European Journal of Paediatric Neurology, 21, e87â€• , 2017	
O'Callaghan, F. J., Lux, A. L., Darke, K., Edwards, S. W., Hancock, E., Johnson, A. L., Kennedy, C. R., Newton, R. W., Verity, C. M., Osborne, J. P., The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study, Epilepsia, 52, 1359â€• 1364, 2011	No relevant outcomes reported
O'Callaghan, F., Edwards, S., Hancock, E., Johnson, A., Kennedy, C., Lux, A., Mackay, M., Newton, R., Nolan, M., Rating, D., et al.,, The international collaborative infantile spasms study (ICISS) comparing hormonal therapies (prednisolone or tetracosactide depot) and vigabatrin versus hormonal therapies alone in the treatment of infantile spasms: early clinical outcome, Archives of disease in childhood., 100, A24â€• A25, 2015	Conference abstract
O'Callaghan, F., Edwards, S., Hancock, E., Johnson, A., Kennedy, C., Lux, A., Mackay, M., Newton, R., Nolan, M., Rating, D., Schmitt, B., Verity, C., Osborne, J., The international collaborative infantile spasms study (ICISS) comparing hormonal therapies (prednisolone or tetracosactide depot) and Vigabatrin versus hormonal therapies alone in the treatment of infantile spasms: Early clinical outcome, Zeitschrift fur Epileptologie, 28 (1 Supplement 1), 51-52, 2015	Conference abstract
Peters, A. C. B., Appleton, R. E., Roi, L., Thornton, J. L., Vigabatrin as first-line monotherapy in newly diagnosed infantile spasms: a placebo-controlled double-blind study, Epilepsia, 37 Suppl 4, 118, 1996	Conference abstract
Prabaharan, C., Aneja, S., Sharma, S., Seth, A., High dose (4 mg/kg/day) versus usual dose (2 mg/kg/day oral prednisolone in the treatment of infantile spasms: A randomized open trial, European Journal of Paediatric Neurology, 17, 2013	Conference abstract
Prezioso, G., Carlone, G., Zaccara, G., Verrotti, A., Efficacy of ketogenic diet for infantile spasms: A systematic review, Acta Neurologica Scandinavica, 137, 4-11, 2018	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Rajpurohit, M., Gupta, A., Madaan, P., Sahu, J. K., Singhi, P., Safety, Feasibility and Effectiveness of Pulse Methylprednisolone Therapy in Comparison with Intramuscular Adrenocorticotropic Hormone in Children with West Syndrome, Indian Journal of Pediatrics., 2020	Not randomised
Sauerwein, H. C., Bitton, J. Y., Impact of infantile spasms on cognition: A multicenter randomized	Conference abstract

Study	Reason for Exclusion
controlled trial of flunarizine as add-on therapy, Epilepsia, 6), 219-220, 2011	
Seo,J.H., Lee,Y.M., Lee,J.S., Kang,H.C., Kim,H.D., Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios--comparison of 3:1 with 4:1 diet, Epilepsia, 48, 801-805, 2007	Included patients with a range of epileptic syndromes and and subgroup analyses for patients with infantile spasms are not reported
Shields, D., Collins, S. D., Elterman, R. D., Nakagawa, J., Mansfield, K. A., AEs and safety of vigabatrin in subjects with infantile spasms, Epilepsia, 46 Suppl 8, 161, 2005	Conference abstract
Shu, X. M., Li, J., Zhang, G. P., Mao, Q., A comparative study of conventional dose and low dose adrenocorticotrophic hormone therapy for West syndrome, Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics], 11, 445-448, 2009	Publication not in English
Slctr,, Randomized Clinical Trial on Prednisolone Vs ACTH for the treatment of Infantile Spasms, Http://www.who.int/trialsearch/trial2.aspx?Trialid=slctr/2010/010, 2010	Study protocol
Song, J. M., Hahn, J., Kim, S. H., Chang, M. J., Efficacy of treatments for infantile spasms: A systematic review, Clinical Neuropharmacology, 40, 63-84, 2017	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Vigevano, F., Cilio, M. R., Claps, D., Faberi, A., Gisondi, A., Vigabatrin versus ACTH as first line therapy in West syndrome, Bollettino - Lega Italiana contro l'Epilessia, 113-114, 1994	Conference abstract
Wanigasinghe, J., Arambepola, C., Jayasundara, K. A., Jayasinghe, Y., Muhandirum, E., Epilepsy outcome in west syndrome at 4 years of life following treatment with ACTH or prednisolone as first line therapy: Preliminary findings from a randomized clinical trial, Epilepsia, 1), 214, 2015	Conference abstract
Wanigasinghe, J., Arambepola, C., Sri Ranganathan, S., Sumanasena, S., Muhandiram, E. C., The efficacy of moderate-to-high dose oral prednisolone versus low-to-moderate dose intramuscular corticotropin for improvement of hypsarrhythmia in west syndrome: A randomized, single-blind, parallel clinical trial, Pediatric Neurology, 51, 24-30, 2014	No relevant outcomes reported
Wanigasinghe, J., Arambepola, C., Sri Ranganathan, S., Sumanasena, S., Muhandirum, E., Spasm control at 3, 6 and 12 months in west syndrome: Randomised, single blind clinical trial on intramuscular long acting ACTH versus oral prednisolone, Epilepsia, 1), 6, 2015	Conference abstract
Wanigasinghe, J., Attanapola, G. M., Arambepola, C., Liyanage, C. B., Kankanamge, P. K. S. J., Sumanasena, S., Sri Ranganathan, S., Randomised clinical trial comparing prednisolone and acth in reversal of hypsarrhythmia in untreated epileptic spasms, Epilepsia, 3), 5-6, 2013	Conference abstract

Study	Reason for Exclusion
Wanigasinghe, J., Murugupillai, R., Arambepola, C., Kapurubandara, R., Effect of the initial treatment on the quality of life of children aged 6 years, with history of west syndrome: Randomized clinical trial, Epilepsia, 60 (Supplement 2), 198, 2019	Conference Abstract
Widjaja, E., Go, C., McCoy, B., Snead, O. C., Neurodevelopmental outcome of infantile spasms: A systematic review and meta-analysis, Epilepsy Research, 109, 155-162, 2015	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Zeng, L., Luo, R., Zhang, L., Efficacy of high-dose ACTH versus low-dose ACTH in infantile spasms: A meta-analysis with direct and indirect comparison of randomized trials, Journal of Pediatric Neurology, 9, 141-149, 2011	Systematic review, no relevant data could be extracted for inclusion. References checked for inclusion
Zou, L. P., Wang, X., Dong, C. H., Chen, C. H., Zhao, W., Zhao, R. Y., Three-week combination treatment with ACTH + magnesium sulfate versus ACTH monotherapy for infantile spasms: A 24-week, randomized, open-label, follow-up study in China, Clinical Therapeutics, 32, 692-700, 2010	Intervention not relevant (magnesium sulphate)

Economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information

Appendix L – Research recommendations

Research recommendations for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of infantile spasms?

Research question:

What antiseizure therapies (alternative or add-on) are effective in the treatment of complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome]) when first-line therapy is unsuccessful or not tolerated?

Why this is important

There is paucity of evidence from RCTs to support evidence-based treatment decisions in complex epilepsy syndromes when first-line therapy is not successful or not tolerated. These complex epilepsy syndromes are considerered developmental and epileptic encephalopathies due to the negative effects on cognition and behaviour. Seizures are frequently drug-resistant and, in some cases, these syndromes can have long-lasting effects on cognition. Research is needed to identify the safety and effectiveness of second-line antiseizure therapies in Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy (Doose syndrome)

Table 35: Research recommendation rationale

Research question	**What antiseizure therapies (alternative or add-on) are effective in the treatment of complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome]) when first-line therapy is unsuccessful or not tolerated?**
Why is this needed	
Importance to 'patients' or the population	To generate evidence to inform which treatments or combinations of treatments are most likely to result in the significant reduction of seizures and/or achieve the best balance between reducing the frequency of seizures and better outcomes for patients when first-line therapy is unsuccessful or not tolerated
Relevance to NICE guidance	This recommendation is to enable better guidance for the treatment of complex epilepsy syndrome
Relevance to the NHS	Evidence in this area would lead to optimisation of medicines usage in the holistic approach to treating people with complex epilepsy syndromes
National priorities	Complex epilepsy syndromes are a difficult to control form of epilepsy. Ongoing seizures result in risk of mortality and morbidity and injury
Current evidence base	The current evidence supports the use of first-line antiseizure medications, but current evidence base does not enable to support evidence-based treatment decisions when first-line therapy is not successful or not tolerated
Equality	N/A
Feasibility	N/A
Other comments	Dravet syndrome and Lennox-Gastaut syndrome can present in adults and children. Doose syndrome and infantile

Research question	What antiseizure therapies (alternative or add-on) are effective in the treatment of complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome]) when first-line therapy is unsuccessful or not tolerated?
	spasms can extend into adulthood, so studies should not only be limited to children

N/A: not applicable

Table 36: Research recommendation modified PICO table

Criterion	Explanation
Population	People with complex epilepsy syndromes (that is, Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and myoclonic atonic epilepsy [Doose syndrome])
Intervention	Antiseizure medications Dietary treatments Novel treatments Surgical therapies
Comparator	Placebo No treatment Combinations of above

Outcomes	Important outcomes:
	• Reduction in seizure frequency >50%
	• Ongoing seizures
	
	Tolerability:
	• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures, intolerable side effects, behavioural changes)
	• Adverse events, as assessed by:
	  ○ % of patients with reported side effects (as defined by trialists)
	  ○ Treatment cessation due to adverse medication effects
	
	Other outcomes:
	• Social functioning changes (behaviour reported by parents/caregivers/school or validated tools)
	• Overall quality of life (reported by caregiver/the individual with epilepsy and as measured with a validated scale)

Study design	Multicentre/UK wide RCT
Timeframe	12 months
Additional information	Consider a concomitant qualitative research methodology that explores people with complex epilepsy syndromes and carers' views and experiences of the treatment approaches.

RCT: randomised controlled trial