Clinical evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of tonic or atonic seizures/drop attacks?

Table 10: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Arzimanoglou, A., Ferreira, J., Satlin, A., Olhaye, O., Kumar, D., Dhadda, S., Bibbiani, F., Evaluation of long-term safety, tolerability, and behavioral outcomes with adjunctive rufinamide in pediatric patients (>=1 to <4 years old) with Lennox-Gastaut syndrome: Final results from randomized study 303, European Journal of Paediatric Neurology, 23, 126-135, 2019 **Ref Id** 1113441 **Country/ies where the study was carried out** Canada, France, Greece, Italy, Poland, USA **Study type** Randomised controlled trial	**Sample size** N=37 (N=25 in the rufinamide group and n= 12 in the 'any other antiseizure medication' group) **Characteristics** Age, months, mean (SD) Intervention: 28.3 (10) Control: 29.8 (9.9) Males, n (%) Intervention: 14 (56) Control: 10 (83.3) Time since diagnosis, mean months (SD) Intervention:19.9 (9.9) Control: 23 (9.5) **Inclusion criteria** • 1 to 4 years of age • Clinical diagnosis of Lennox-Gastaut syndrome	**Interventions** Oral suspension rufinamide (45 mg/kg/day) versus any other investigator-chosen antiseizure medication	**Details** Treatment duration: 106-weeks, including an initial 2-week titration phase and a 104-week maintenance phase After a baseline period where participants were monitored to assess whether they displayed Lennox-Gastaut syndrome, participants were randomised to rufinamide or to an ASM chosen by the investigator as adjunctive of the participant's existing 1 to 3 antiseizure medications. Follow-up: 110 weeks. Final follow-up visits occurred 4 weeks after the last dose of rufinamide or other add-on	**Results** *Primary outcomes* Time to withdrawal of treatment due to adverse events or lack of seizure efficacy; median (weeks) Intervention group: 142 weeks Control group: 28 weeks (no IQR or p-value were reported) % of patients with reported serious side effects Intervention group: 10/25 Control group: 5/12 Treatment cessa-	**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 to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: High risk** 2.1: Yes, study was open label 2.2: Yes, study was open label

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the effectiveness of rufinamide in the treatment of Lennox-Gastaut Syndrome **Study dates** June 2011 and November 2015 **Source of funding** Eisai Inc.	**Exclusion criteria** • Those with epilepsy syndromes not suggesting the electroclinical profile of patients within the LGS (i.e h benign myoclonic epilepsy of infancy, atypical benign partial epilepsy) • Those with an inadequate response to treatment after a fixed dose of 1 to 3 concomitant ASMs for a minimum of 4 weeks prior randomisation • Those with familial short QT syndrome • Those who had previously received rufinamide		AED at the end of the maintenance phase or after withdrawal from the study Randomisation method was not reported. Study was open label	tion due to adverse drug effects Intervention group: 2/25 Control group: 1/12 *Secondary outcomes* Social functioning changes: difference in total problems scores, mean difference between groups (95% CI) 1.197 (-7.6 to 5.3), p =0.7083	2.3: No information whether there were deviations from the intended intervention **Domain 3: Missing outcome data: High risk** 3.1: No information 3.2: No evidence 3.3: No information 3.4: No information **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no **Domain 6: Overall judgment of bias: High risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					The study is judged to be at high risk of bias in at least one domain for this result
Full citation Conry, J. A., Ng, Y. T., Paolicchi, J. M., Kernitsky, L., Mitchell, W. G., Ritter, F. J., Collins, S. D., Tracy, K., Kormany, W. N., Abdulnabi, R., et al.,, Clobazam in the treatment of Lennox-Gastaut syndrome, Epilepsia, 50, 1158-1166, 2009 **Ref Id** 1176847 **Country/ies where the study was carried out** USA **Study type** Phase II RCT **Aim of the study** To assess the effectiveness of clobazam in the treatment of people with LGS **Study dates** Not reported, study published in 2009	**Sample size** N=68 (n=32 in the low-dose clobazam group and n=36 in the high-dose clobazam group) **Characteristics** Age, years, median (range): 7.4 (2 to 26) Male:female: 42:26 Patients randomised to each treatment group were comparable. No p-values were reported **Inclusion criteria** • EEG with slow spike and wave and multifocal spikes • ≥ 1 type of generalised seizure for at least 6 months • <11 years old at the onset of LGS • >12.5 kgs • Up to 3 antiseizure medications • At least 2 drop seizures per week	**Interventions** Low-dose clobazam (target dose of 25 mg/kg/day to a maximum of 10mg/day) or high-dose clobazam (target dose 1.0mg/kg/day to a maximum of 40mg/day)	**Details** Treatment duration: 3 week titration period followed by a 4-week maintenance period, and either an open-label extension study or, for patients not continuing into the open-label extension, a taper of up to 3 weeks. Follow-up: 11 weeks. Final visit occurred 1 week after final dose. Method of randomisation was not reported. Patients and assessors were blinded to treatment allocation. Seizures were parental or carer reported. Analyses were "intention to treat"	**Results** *Primary outcomes* Reduction in seizure frequency >50% Low-dose group: 12/32 High-dose group: 30/36 Reduction in drop attacks, mean (SD) Low-dose group at baseline: 141 (188) Low-dose group during maintenance: 91 (122) High-dose group at baseline: 207 (229) High-dose group during maintenance: 32 (57) % of patients with reported severe side effects Low-dose group: 1/32 High-dose group: 2/36 Treatment cessation due to adverse	**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 to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Nearly all, n=7 did

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Ovation Pharmaceuticals.	**Exclusion criteria** • Those with an episode of status epilepticus within 12 weeks of baseline • Those in whom the aetiology of the seizures was a progressive neurologic disease (except tuberous sclerosis) • Those who had taken corticotropins in the 6 months before screening			drug effects Low-dose group: 3/32 High-dose group: 6/36 *Secondary outcomes* Social functioning changes: % of patients considered to be "improved" or "very much improved" at 3 weeks (patient/ carer global evaluations) Low-dose group: 16/29 High-dose group: 30/32 Social functioning changes: % of patients considered to be "improved" or "very much improved" at 3 weeks (investigator evaluations) Low-dose group: 13/29 High-dose group: 30/32	not have at least one measurement during the maintenance period **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **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 for this result
Full citation Dodson, W. E., Fel-	**Sample size** See Felbamate Study	**Interventions** See Felbamate Study	**Details** See Felbamate Study	**Results** *Secondary out-*	**Limitations** See Felbamate Study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
bamate in the treatment of Lennox-Gastaut syndrome: Results of a 12-month open-label study following a randomized clinical trial, Epilepsia, 34, S18-S24, 1993 **Ref Id** 1162839 **Country/ies where the study was carried out** See Felbamate Study Group 1993 **Study type** See Felbamate Study Group 1993 **Aim of the study** See Felbamate Study Group 1993 **Study dates** See Felbamate Study Group 1993 **Source of funding** See Felbamate Study Group 1993	Group 1993 **Characteristics** See Felbamate Study Group 1993 **Inclusion criteria** See Felbamate Study Group 1993 **Exclusion criteria** See Felbamate Study Group 1993	Group 1993	Group 1993	*comes* Global outcome variable (proxy outcome for quality of life) during the maintenance period, mean (SD) Intervention group: 0.823 (0.756), n=37 Control group: 0.256 (0.685), n=36	Group 1993
Full citation Felbamate study group in Lennox-Gastaut Syndrome.Efficacy of felbamate in childhood epi-	**Sample size** N=73 (n=37 randomised to the felbamate group and n=36 randomised to the placebo group)	**Interventions** Felbamate (15mg/kg/day) versus placebo. Felbamate was in-	**Details** Treatment duration: 14 day titration period and a 56 day maintenance period.	**Results** *Primary outcomes* Complete cessation of all seizures during the	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
leptic encephalopathy (Lennox-Gastaut syndrome), New England Journal of Medicine, 328, 29-33, 1993 **Ref Id** 1176788 Country/ies where the study was carried out USA **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of felbamate in people with LGS **Study dates** Not reported, study published in 1993 **Source of funding** Not reported	**Characteristics** Age, months, mean (range) Intervention:12 (4 to 24) Control:14 (4 to 36) Males, n (%) Intervention: 27 (72.9) Control: 24 (66.66) Total number of antiseizure medications taken previously, mean (range) Intervention: 8 (3 to 16) Control: 8 (4 to 12) Total seizure frequency during baseline phase Intervention group: 1617 (no SD/ range reported) Control group: 716 (no SD/ range reported) No p-values were reported **Inclusion criteria** • Those with a history of multiple seizure types and a minimum of 90 atonic seizures or atypical absence seizures/ month during an 8 weeks prior to baseline • Those between 4 and	creased to 30 mg/kg/day after 7 days and the maximal dose after 14 days. The maximum dose could be either 45 mg/kg/day or 3600 mg/day, whichever was lower. During the maintenance period, participants continued to receive the maximal tolerated dose.	Follow-up: 98 days. Participants were randomised in blocks of 2 to receive either felbamate or placebo. Randomisation was done by a separate computer-generated randomisation schedule at each participating centre. Felbamate or placebo were added to the standard antiseizure medication regimen. Detailed estimate for quality of life outcome reported in Dodson 1993.	maintenance period Intervention group: 4/37 Control group: 1/36 Complete cessation of atonic seizures during the maintenance period Intervention group: 5/28 Control group: 0/22 Complete cessation of tonic-clonic seizures during the maintenance period Intervention group: 7/16 Control group: 1/13 Mean change (range) % in frequency of all seizures (atonic, tonic, generalised tonic-clonic, atypical absence, and complex partial) Intervention group: -26 (-100 to 521), SD= -58, n=37 Control group: 5 (-100 to 321), SD=11, n=36	(Version 2.0) **Domain 1: Randomisation: High risk** 1.1: Yes, computer generated random numbers 1.2: No information was provided regarding randomisation concealment 1.3: Yes, the total seizure frequency in the felbamate group is higher than in the placebo group (1617 versus 716, respectively) **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	25 years **Exclusion criteria** • Those taking more than 2 antiseizure medications • Those with evidence of progressive central nervous system lesions on magnetic resonance imaging or computed tomography • Those pregnant or not taking adequate contraception • Those with a history of identifiable progressive neurologic disorders, anoxic episodes within the previous year, or other major medical illness • Those with previous suicide attempts • Those with poor compliance with past antiseizure therapy • Those with a history of drug or alcohol abuse • Those who had recently received corticotropin, were following ketogenic diets • Those with inade-			p<0.001 <u>Mean change (range) % in frequency of atonic seizures</u> Intervention group: -44 (-100 to 145), SD=94, n=28 Control group: -7 (-88 to 57), SD=13, n=22 p=0.02 <u>Mean change (range) % in frequency of generalised tonic-clonic seizures</u> Intervention group: -40 (-100 to 206), SD=59, n=16 Control group: 12 (-100 to 293), SD=15, n=13 p=0.017 <u>Treatment cessation due to adverse drug effects during the maintenance period</u> Intervention group: 1/37	4.2: Probably no 4.3: No, double blind study **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no **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** Raw data was not provided for the change from baseline among the neuropsychological tests performed, therefore it has not been reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	quate supervision from parents/ guardians			Control group: 1/36 Mortality during the maintenance period Intervention group: 0/37 Control group: 0/36	
Full citation Glauser, T., Kluger, G., Sachdeo, R., Krauss, G., Perdomo, C., Arroyo, S., Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome, Neurology, 70, 1950-1958, 2008 **Ref Id** 1080418 **Country/ies where the study was carried out** Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, and USA **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of rufinamide in people with LGS **Study dates** March 1998	**Sample size** N=138 (n=74 allocated to rufinamide and n=64 allocated to placebo) **Characteristics** Age, years, median (range) Intervention: 13 (4 to 35) Control: 10.5 (4 to 37) Males, n (%) Intervention: 46 (62.2) Control: 40 (62.5) Duration of LGS, median years (range) Intervention: 7.9 (0.1 to 32.7) Control: 7.5 (0.1 to 34.1) **Inclusion criteria** • Those aged between 4 and 30 years • Those with a history of multiple seizure types, including atypical absence seizures and	**Interventions** Rufinamide versus placebo	**Details** Treatment duration: The study consisted of a 28 day baseline period followed by a 84 day double blind phase. For the ITT analyses, all 84 days were included (14 day titration period + 70 day maintenance period). Follow-up: 84 days. Randomisation was produced at the country/center level and were assigned with sequential numbers during the first visit. Patients and assessors were blinded to treatment allocation.	**Results** *Primary outcomes* Reduction in total seizure frequency >50% after 28 days Intervention group: 23/74 Control group: 7/64 Improvement in seizure severity at the end of the double-blind phase Intervention group: 39/73 Control group: 19/62 Reduction in drop-attacks Median (range) reduction in the intervention group -42.5 (-100.0 to 1190.8), n=73 Median (range) re-	**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, computer generated random numbers 1.2: No information was provided regarding randomisation concealment 1.3: No baseline differences between intervention groups suggesting a randomisation problem **Domain 2: Deviations from intended** interventions: Low risk 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and November 2000 **Source of funding** Eisai Pharmaceutical, conducted by Novartis Pharmaceutical	drop attacks • Those with a minimum of 90 seizures in the month prior to trial entry • EEG showing a pattern of slow spike and wave complexes • > 18kgs • 1 to 3 ASMs in a fixed dose **Exclusion criteria** • Not reported			duction in the control group 1.4 (-100 to -709.6), n=60 p<0.0001 <u>% of patients with reported serious side effects</u> Intervention group: 2/74 Control group: 2/64 <u>Treatment cessation due to adverse drug effects</u> Intervention group: 6/74 Control group: 1/64	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 4.2: Probably no 4.3: No, double blind study **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no **Domain 6: Overall judgment of bias: Low** risk of bias The study is judged to be at low risk of bias for all domains **Other information** Social functioning could not be reported because

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					SD of the mean was not reported
Full citation Motte, J., Trevathan, E., Arvidsson, J. F. V., Barrera, M. N., Mullens, E. L., Manasco, P., Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome, New England Journal of Medicine, 337, 1807-1812, 1997 **Ref Id** 1080908 **Country/ies where the study was carried out** France, USA, UK, Spain **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of lamotrigine in people with Lennox-Gastaut syndrome **Study dates** February 1994 - November 1995 **Source of funding** Glaxo Wellcome	**Sample size** N= 169 (n= 79 in the lamotrigine group and n=90 in the placebo group) **Characteristics** Age, years, mean (SD) Intervention: 9.6 (5.2) Control:10.9 (5.9) Males, n (%), p= 0.02 Intervention: 54 (68) Control: 45 (50) Moderate or severe learning disability, n (%) Intervention: 73 (92) Control: 82 (91) **Inclusion criteria** • Those between 3 and 25 years old • >1 type of predominantly generalised seizure during the last year • Those <11 years old at the time of onset • Seizures every other day with a similar average frequency • Those with intellectual	**Interventions** Lamotrigine versus placebo in addition to patients' standard antiseizure-medication regimens	**Details** Treatment duration: A 4-week base-line period in which all participants received placebo was followed by a 4 weeks single blind baseline period. Participants were then assigned to one of four dosing regimens according to concomitant valproate use and body weight. Follow-up: 20 weeks. Method of randomisation was not reported. Participants and assessots were blinded to treatment allocation.	**Results** *Primary outcomes* Reduction in seizure frequency >50% Intervention group: 26/79 Control group: 14/90 Reduction in drop attacks, median % (IQR was not reported) Intervention group: -34%, n= 75 Control group: -16%, n=90 p=0.01 Treatment cessation due to adverse drug effects Intervention group: 3/79 Control group: 7/90	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: High risk** 1.1: No information was provided to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: The intervention group had more males than the control group (p=0.02) **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Nearly all, n=10 were not enrolled because of lack of compliance

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	impairment or a clinical impression of intellectual deterioration **Exclusion criteria** • Those with progressive neurodegenerative disorder • Those who were receiving more than three antiseizure medications • Those who weighed less than 15 kg and were taking valproate				**Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was produced in accordance with a pre-specified analysis plan 5.2: Probably no 5.3: Probably no **Domain 6: Overall judgement of bias: Some concerns** The study is judged to have some concerns in at least one domain
Full citation Ng, Y. T., Conry, J. A., Drummond, R., Stolle, J., Weinberg, M. A., Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome, Neurology, 77, 1473-1481, 2011 **Ref Id** 818717	**Sample size** N=238 (n=59 randomised to placebo, n=58 randomised to clobazam 0.25 mg/kg/day [low dose], n=62 randomised to clobazam 0.5 mg/kg/day [medium dose], and n=59 randomised to clobazam 1 mg/kg/day [high dose])	**Interventions** Clobazam (low, medium and high dose) versus placebo	**Details** Treatment duration: The study consisted of a 4-week baseline period, 3-week titration period, and a 12-week maintenance period. Follow-up: Not reported. Approximately 50% of	**Results** *Primary outcomes* Reduction in seizure frequency >50% Placebo group: 18/57 Low dose group: 23/53 Medium dose group: 34/58	**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, an interactive voice system was used 1.2: No information was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA, Europe, India and Australia **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of clobazam in people with Lennox-Gastaut syndrome **Study dates** August 2007 to December 2009 **Source of funding** Lundbeck Inc.	**Characteristics** Age, mean years (SD) Placebo group: 13 (9.2) Low dose group: 10.9 (7.2) Medium dose group: 14.1 (10.4) High dose group: 11.7 (8.5) Male, n (%) Placebo group: 38 (64.4) Low dose group: 36 (62.1) Medium dose group: 36 (58.1) High dose group: 34 (57.6) Baseline weekly seizure rate, mean (SD) Placebo group: 95.6 (168.2) Low dose group: 98.3 (198.5) Medium dose group: 58.8 (119.6) High dose group: 94.6 (152.2) **Inclusion criteria** • Those aged 2 to 60 years old • Weighing ≥12.5 kg		all patients were receiving concomitant valproic acid, valproate semisodium, or valproate sodium. Patients were assigned through central randomisation via an interactive voice response system to one of the 4 groups. Study was double-blind.	High dose group: 38/49 100% reduction in drop attacks Placebo group: 2/57 Low dose group: 4/53 Medium dose group: 7/58 High dose group: 12/49 % of patients with a change in medication dose Placebo group: 1/57 Low dose group: 4/53 Medium dose group: 9/58 High dose group: 15/49 % of patients with reported serious side effects Placebo group: 2/57 Low dose group: 3/53 Medium dose group: 6/58 High dose group: 5/49	provided to assess whether the allocation sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: No, roughly 25% of those randomised did not have data available 3.2: Yes, analyses were intention to treat **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Onset of LGS before 11 years old **Exclusion criteria** • Not reported			Mortality Placebo group: 0/57 Low dose group: 0/53 Medium dose group: 0/58 High dose group: 0/49 Treatment cessation due to adverse drug effects Placebo group: 0/38 Low dose group: 1/36 Medium dose group: 4/36 High dose group: 5/34	5.1: Yes, data was analysed according to a protocol 5.2: No, eligible reported results for the outcome domain correspond to all intended outcome measurements 5.3: No, all eligible reported results for the outcome measurement correspond to all intended analyses **Domain 6: Overall judgment of bias: Low risk** The study is judged to be at low risk of bias
Full citation Ohtsuka, Y., Yoshinaga, H., Shirasaka, Y., Takayama, R., Takano, H., Iyoda, K., Rufinamide as an adjunctive therapy for Lennox-Gastaut syndrome: A randomized double-blind placebo-controlled trial in Japan, Epilepsy Research, 108, 1627-1636, 2014 **Ref Id** 1080978	**Sample size** N=59 (n=29 randomised to rufinamide and n=30 randomised to placebo) **Characteristics** Age, years, mean (SD) Intervention: 16.0 (7.1) Control: 13.9 (6.1) Males, n (%) Intervention: 17 (60.7) Control: 19 (63.3) Time since diagnosis, mean years (SD)	**Interventions** Concomitant rufinamide versus placebo	**Details** Treatment duration: The study consisted of a 4-week baseline, a 2-week titration, and a 10-week maintenance period. Follow-up: 84 days. Eligible patients were randomised in a 1:1 ratio according to body weight. Most patients were concomitantly	**Results** *Primary outcomes* Reduction in seizure frequency >50% Intervention group: 7/28 Control group: 2/30 Reduction in tonic seizures Median reduction in intervention group= -24.2%	**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 to assess whether the allocation sequence was random 1.2: No information was provided to assess whether the allocation

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 efficacy of rufinamide as an adjunctive therapy in people with Lennox-Gastaut syndrome. **Study dates** Not reported. **Source of funding** Eisai Co. and a grant from the Japanese government.	Intervention: 10.5 (7.1) Control: 9.3 (5.8) **Inclusion criteria** • People with Lennox-Gastaut syndrome taking between 1 and 3 antiseizure medications • Those aged between 4 and 30 years old weighing > 15 kilos **Exclusion criteria** • Those who experienced <90 seizures during the 28 days prior entering the study • Those experiencing status epilepticus during the 28 days prior entering the study		receiving 2 or 3 antiseizure medications.	Median reduction in the control group=-3.6%, p=0.031 <u>Reduction in atonic seizures</u> Median reduction in the intervention group= -63.1% Median reduction in the control group= -6.1%, p=0.221 <u>Reduction in tonic-clonic seizures</u> Median reduction in intervention group= -57.4% Median in control group= 2.4%, p=0.107 <u>Reduction in tonic-clonic seizures</u> The median percent change in the frequency of tonic-atonic seizures was −57.4% (n=2) in the rufinamide group and 2.4% (n=10) in the placebo group, p=0.107	sequence was concealed 1.3: Groups were comparable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: No, roughly 13% of those randomised did not have data available 3.2: Probably yes **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was analysed according to a protocol

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				% of patients with a dose reduction due to safety concerns Intervention group: 7/28 Control group: 1/30 Treatment cessation due to adverse drug effects Intervention group: 4/28 Control group: 1/30 % of patients with reported side effects Intervention group: 17/28 Control group: 5/30	5.2: No, eligible reported results for the outcome domain correspond to all intended outcome measurements 5.3: No, all eligible reported results for the outcome measurement correspond to all intended analyses **Domain 6: Overall judgment of bias: Low risk** The study is judged to be at low risk of bias
Full citation Sachdeo, R. C., Glauser, T. A., Ritter, F., Reife, R., Lim, P., Pledger, G., A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome, Neurology, 52, 1882-1887, 1999 **Ref Id** 1081125 **Country/ies where the study was carried out**	**Sample size** N=98 (n=48 allocated to topiramate and n=50 allocated to placebo) **Characteristics** Age, years, mean (SD) Intervention: 11.2 (6.2) Control: 11.2 (7.7) Males, n (%) Intervention: 25 (25) Control: 28 (58.3) **Inclusion criteria**	**Interventions** Topiramate versus placebo	**Details** Treatment duration: The trial consisted of a baseline phase followed by 4 weeks and a 11 week treatment phase. Follow-up: 11 weeks. Randomisation was computer generated, and participants and investigators were concealed to treatment	**Results** *Primary outcomes* Reduction in major seizure frequency (drop attacks and tonic-clonic seizures) >50% Intervention group: 15/46 Control group: 4/50 Complete cessation of drop attacks Intervention group: 5/46	**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, computer generated 1.2: No information was provided to assess whether the allocation sequence was concealed 1.3: Groups were compa-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** Randomised controlled trial **Aim of the study** To assess the efficacy and safety of topiramate as an adjunctive treatment for Lennox-Gastaut syndrome **Study dates** Not reported **Source of funding** Not reported	• Those aged 1 to 30 years • Those with EEG showing a slow pike and wave pattern • Those with seizure types such as drop attacks and atypical absence seizures • Those with at least 60 seizures in the month prior joining the study **Exclusion criteria** Not reported		allocation.	Control group: 0/50 <u>Treatment cessation due to adverse drug effects</u> Intervention group: 0/46 Control group: 0/50 <u>% of patients with reported severe adverse side effects</u> Intervention group: 11/46 Control group: 5/50 <u>% of patients with dose reduction or temporary discontinuation of treatment</u> Intervention group: 9/46 Control group: 3/50	rable at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Yes, nearlly all participants (no data was available for n=1) **Domain 4: Measurement of the outcome: Low risk** 4.1: No, the method for measuring the outcome was appropriate 4.2: No, comparable methods of outcome measurement were used **Domain 5: Selection of the reported result: Low risk** 5.1: Yes, data was analysed according to a protocol 5.2: No, eligible reported results for the outcome domain correspond to all

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					intended outcome measurements 5.3: No, all eligible reported results for the outcome measurement correspond to all intended analyses **Domain 6: Overall judgment of bias: Low risk** The study is judged to be at low risk of bias

ASM(s): antiseizure medication(s); EEG: electrocardiogram; IQR: interquartile range; Kg: kilogram; LGS: Lennox-Gastaut syndrome; mg: milligram; RCT: randomised controlled trial; SD: standard deviation