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

Table 11: Clinical evidence profile. Comparison 1: add-on rufinamide versus any other add-on antiseizure medication in paediatric patients

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Any other add-on antiseizure medication	Relative (95% CI)	Absolute	Quality	Importance
Time to withdrawal of treatment due to adverse events or lack of seizure efficacy (paediatric patients) (median)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25	12	Median time in the intervention group= 142 weeks	Median time in the control group=28 weeks	⊕OOO VERY LOW	CRITICAL
% of patients with reported serious side effects (paediatric patients)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/25 (40%)	5/12 (41.7%)	RR 0.96 (0.42 to 2.19)	17 fewer per 1000 (from 242 fewer to 496 more)	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse drug effects (paediatric patients)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/25 (8%)	1/12 (8.3%)	RR 0.96 (0.1 to 9.57)	3 fewer per 1000 (from 75 fewer to 714 more)	⊕OOO VERY LOW	CRITICAL
Social functioning changes: difference in total problems scores (measured with: CBCL; Better indicated by lower values) (paediatric patients)												
1 (Arzimanoglou 2019)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	25	12	-	-	MD 1.2 higher (7.6 lower to 9.99 higher)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 Evidence was downgraded by 2 as IQRs have not been reported and therefore the medians provided are subjectively very imprecise
3 95% CI crosses 2 MIDs (0.8 and 1.25)
4 95% crosses 2 MIDs (+/- 0.5 x control group SD for social functioning changes=+/-6.55)

Table 12: Clinical evidence profile. Comparison 2: Add-on low-dose clobazam versus add-on high-dose clobazam

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Add-on high-dose clobazam	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
2 (Conry 2009, Ng 2011)	RCT	serious[1]	no serious in-consistency	no serious indirectness	no serious imprecision	none	35/85 (41.2%)	68/85 (80%)	RR 0.51 (0.39 to 0.68)	392 fewer per 1000 (from 256 fewer to 488 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mean reduction in drop attacks (Better indicated by lower values)												
1 (Conry 2009)	RCT	serious[1]	no serious in-consistency	no serious indirectness	serious[2]	none	32	36	-	MD 125 higher (55.3 to 194.7 higher)	⊕⊕OO LOW	CRITICAL
Complete reduction in drop attacks												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[3]	none	4/53 (7.5%)	12/49 (24.5%)	RR 0.31 (0.11 to 0.89)	169 fewer per 1000 (from 27 fewer to 218 fewer)	⊕⊕⊕O MODERATE	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	no serious imprecision	none	4/53 (7.5%)	15/49 (30.6%)	RR 0.25 (0.09 to 0.69)	230 fewer per 1000 (from 95 fewer to 279 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
% of patients with reported severe side effects												
2 (Conry 2009, Ng 2011)	RCT	serious[1]	no serious in-consistency	no serious indirectness	very seri-ous[4]	none	4/85 (4.7%)	7/85 (8.2%)	RR 0.56 (0.17 to 1.83)	36 fewer per 1000 (from 68 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious	no serious in-	no serious	very seri-	none	0/53	0/49	RD 0.00	0 per 1000	⊕⊕OO	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Add-on high-dose clobazam	Relative (95% CI)	Absolute		
		risk of bias	consistency	indirectness	ous[5]		(0%)	(0%)	(-0.04 to 0.04)	(from 40 fewer to 40 more)	LOW	
Treatment cessation due to adverse drug effects												
2 (Conry 2009, Ng 2011)	RCT	serious[1]	no serious in-consistency	no serious indirectness	serious[3]	none	4/68 (5.9%)	11/70 (15.7%)	RR 0.38 (0.13 to 1.13)	97 fewer per 1000 (from 137 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Social functioning changes: % of patients cosidered to be "improved" or "much improved" (patient/ carer global evaluation)												
1 (Conry 2009)	RCT	serious[1]	no serious in-consistency	no serious indirectness	serious[3]	none	16/29 (55.2%)	30/32 (93.8%)	RR 0.59 (0.42 to 0.83)	384 fewer per 1000 (from 159 fewer to 544 fewer)	⊕⊕OO LOW	IMPORTANT
Social functioning changes: % of patients cosidered to be "improved" or "much improved" (investigator evaluation)												
1 (Conry 2009)	RCT	serious[1]	no serious in-consistency	no serious indirectness	no serious imprecision	none	13/29 (44.8%)	30/32 (93.8%)	RR 0.48 (0.32 to 0.72)	488 fewer per 1000 (from 262 fewer to 637 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (+/-0.5 x control group SD for mean reduction in drop attacks= +/- 114.5)
3 95% CI crosses 1 MID (0.8)
4 95% CI crosses 2 MIDs (0.8 and 1.25)
5 Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)

Table 13: Clinical evidence profile. Comparison 3: add-on felbamate versus placebo

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on felbamate	Placebo	Relative (95% CI)	Absolute		
Complete cessation of all seizures¥												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/37 (10.8%)	1/36 (2.8%)	RR 3.89 (0.46 to 33.17)	80 more per 1000 (from 15 fewer to 894 more)	⊕OOO VERY LOW	CRITICAL
Complete cessation of atonic seizures												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/28 (17.9%)	0/22 (0%)	RR 8.72 (0.51 to 149.75)	180 more per 1000 (from 20 more to 330 more)	⊕OOO VERY LOW	CRITICAL
Complete cessation of generalised tonic-clonic seizures												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	7/16 (43.8%)	1/13 (7.7%)	RR 5.69 (0.8 to 40.51)	361 more per 1000 (from 15 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Mean change in frequency of all seizures¥ (Better indicated by lower values)												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37	36	-	MD 31 lower (50 to to 11 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean change in frequency of atonic seizures (Better indicated by lower values)												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	28	22	-	MD 37 lower (72.24 to 1.76 lower)	⊕⊕OO LOW	CRITICAL
Mean change in frequency of generalised tonic-clonic seizures (Better indicated by lower values)												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	13	-	MD 52 lower (82.04 to 21.96 lower)	⊕⊕⊕O MODERATE	CRITICAL
Treatment cessation due to adverse drug effects												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/37 (2.7%)	1/36 (2.8%)	RR 0.97 (0.06 to 14.97)	1 fewer per 1000 (from 26 fewer to 388 more)	⊕OOO VERY LOW	CRITICAL
Mortality												
1 (Felbamate study group 1993)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/37 (0%)	0/36 (0%)	RD 0.00 (-0.05 to 0.05)	0 per 1000 (from 50 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Global outcome variable (proxy outcome for quality of life) (Better indicated by higher values)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on felbamate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1 (Felbamate study group 1993)	RCT	serious[1]	no serious in-consistency	no serious indirectness	serious[5]	none	37	36	-	MD 0.57 higher (0.24 to 0.9 high-er)	⊕⊕OO LOW	IMPORTANT

¥All seizures: atonic, tonic, generalised tonic-clonic, atypical absence, and complex partial
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)
3 95% CI crosses 1 MID (1.25)
4 Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)
5 95% CI crosses 1 MID (+/- 0.5 x SD in the control group for mean change in frequency of atonic seizures= +/- 6.5, for global outcome variable= +/-0.3425)

Table 14: Clinical evidence profile. Comparison 4: add-on rufinamide versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
2 (Glauser 2008, Ohtsuka 2014)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	no serious imprecision	none	30/102 (29.4%)	9/94 (9.6%)	RR 3.03 (1.52 to 6.02)	194 more per 1000 (from 50 more to 481 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Improvement in seizure severity												
1 (Glauser 2008)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	no serious imprecision	none	39/73 (53.4%)	19/62 (30.6%)	RR 1.74 (1.13 to 2.68)	227 more per 1000 (from 40 more to 515 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in drop-attacks (median)												
1 (Glauser 2008)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	73	60	Median (range) reduction in the intervention group -42.5 (-100.0 to 1190.8)	Median (range) reduction in the control group 1.4 (-100 to -709.6), p<0.0001	⊕⊕OO LOW	CRITICAL
Reduction in tonic seizures (median)												
1 (Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	28	28	Median reduction in intervention group= -24.2%	Median reduction in the control group= -3.6%, p=0.031	⊕⊕OO LOW	CRITICAL
Reduction in atonic seizures (median)												
1 (Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10	12	Median reduction in the intervention group= -63.1%	Median reduction in the control group= -6.1%, p=0.221	⊕⊕OO LOW	CRITICAL
Reduction in tonic-clonic seizures (median)												
1 (Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2	10	Median reduction in intervention group= -57.4%	Median in control group= 2.4%, p=0.107	⊕⊕OO LOW	CRITICAL
% of patients with a dose reduction due to safety concerns												
1 (Ohtsuka	RCT	no serious	no serious in-	no serious	serious[3]	none	7/28	1/30	RR 7.5 (0.98 to	217 more per 1000	⊕⊕⊕O	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on rufinamide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
2014)		risk of bias	consistency	indirectness			(25%)	(3.3%)	57.16)	(from 1 fewer to 1000 more)	MODERATE	
Treatment cessation due to adverse drug effects												
2 (Glauser 2008, Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10/102 (9.8%)	2/94 (2.1%)	RR 4.76 (1.07 to 21.23)	80 more per 1000 (from 1 more to 430 more)	⊕⊕⊕O MODERATE	CRITICAL
% of patients with reported serious side effects												
2 (Glauser 2008, Ohtsuka 2014)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/102 (18.6%)	7/94 (7.4%)	RR 2.79 (1.31 to 5.92)	133 more per 1000 (from 23 more to 366 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] *Evidence downgraded by 2 as ranges are subjectively very wide*
[2] *Evidence was downgraded by 2 as IQRs have not been reported and therefore the medians provided are subjectively very imprecise*
[3] *The evidence was downgraded by 1 as the 95% CI crosses 1 MID (1.25)*

Table 15: Clinical evidence profile. Comparison 5: add-on lamotrigine versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on lamotrigine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
1 (Motte 1997)	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/79 (32.9%)	14/90 (15.6%)	RR 2.12 (1.19 to	174 more per 1000 (from 30	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on lamotrigine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
									3.76)	more to 429 more)		
Reduction in drop attacks												
1 (Motte 1997)	RCT	serious[1]	no serious in-consistency	no serious indirectness	very serious[2]	none	75	90	Median reduction in intervention group= -34%	Median reduction in control group= -16% p=0.01	⊕OOO VERY LOW	CRITICAL
Treatment cessation due to adverse drug effects												
1 (Motte 1997)	RCT	serious[1]	no serious in-consistency	no serious indirectness	very serious[3]	none	3/79 (3.8%)	7/90 (7.8%)	RR 0.49 (0.13 to 1.82)	40 fewer per 1000 (from 68 fewer to 64 more)	⊕OOO VERY LOW	CRITICAL

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Evidence was downgraded by 2 as IQRs have not been reported and therefore the medians provided are subjectively very imprecise*
[3] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 16: Clinical evidence profile. Comparison 6: add-on low-dose clobazam versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[1]	none	23/53 (43.4%)	18/57 (31.6%)	RR 1.37 (0.84 to	117 more per 1000	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on low-dose clobazam	Placebo	Relative (95% CI)	Absolute		
									2.24)	(from 51 fewer to 392 more)		
Complete reduction in drop attacks												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	4/53 (7.5%)	2/57 (3.5%)	RR 2.15 (0.41 to 11.26)	40 more per 1000 (from 21 fewer to 360 more)	⊕⊕OO LOW	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	4/53 (7.5%)	1/57 (1.8%)	RR 4.3 (0.5 to 37.27)	58 more per 1000 (from 9 fewer to 636 more)	⊕⊕OO LOW	CRITICAL
% of patients with reported serious side effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	3/53 (5.7%)	2/57 (3.5%)	RR 1.61 (0.28 to 9.28)	21 more per 1000 (from 25 fewer to 291 more)	⊕⊕OO LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[3]	none	0/53 (0%)	0/57 (0%)	RD 0.00 (-0.03 to 0.03)	0 per 1000 (from 30 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse drug effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	1/36 (2.8%)	0/38 (0%)	RR 3.16 (0.13 to 75.2)	30 more per 1000 (from 40 fewer to 100 more)	⊕⊕OO LOW	CRITICAL

1 95% CI crosses 1 MID (1.25)
2 95% CI crosses 2 MIDs (0.8 and 1.25)
3 Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)

Table 17: Clinical evidence profile. Comparison 7: add-on medium-dose clobazam versus placebo

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on medium-dose clobazam	Placebo	Relative (95% CI)	Absolute		
Reduction in seizure frequency >50%												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[1]	none	34/58 (58.6%)	18/57 (31.6%)	RR 1.86 (1.2 to 2.88)	272 more per 1000 (from 63 more to 594 more)	⊕⊕⊕O MODERATE	CRITICAL
Complete reduction in drop attacks												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	7/58 (12.1%)	2/57 (3.5%)	RR 3.44 (0.75 to 15.86)	86 more per 1000 (from 9 fewer to 521 more)	⊕⊕OO LOW	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[1]	none	9/58 (15.5%)	1/57 (1.8%)	RR 8.84 (1.16 to 67.57)	138 more per 1000 (from 3 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
% of patients with reported serious side effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	6/58 (10.3%)	2/57 (3.5%)	RR 2.95 (0.62 to 14)	68 more per 1000 (from 13 fewer to 456 more)	⊕⊕OO LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[3]	none	0/58 (0%)	0/57 (0%)	RD 0.00 (-0.03 to 0.03)	0 per 1000 (from 30 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse drug effects												
1 (Ng 2011)1	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	very serious[2]	none	4/36 (11.1%)	0/38 (0%)	RR 9.49 (0.53 to 170.17)	110 more per 1000 (from 0 to 220 more)	⊕⊕OO LOW	CRITICAL

[1] *95% CI crosses 1 MID (1.25)*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[3] *Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)*

Table 18: Clinical evidence profile. Comparison 8: add-on high-dose clobazam versus placebo

Quality assessment							No of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on high-dose clobazam	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Reduction in seizure frequency >50%												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/49 (77.6%)	18/57 (31.6%)	RR 2.46 (1.63 to 3.7)	461 more per 1000 (from 199 more to 853 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete reduction in drop attacks												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/49 (24.5%)	2/57 (3.5%)	RR 6.98 (1.64 to 29.68)	210 more per 1000 (from 22 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
% of patients with a change in medication dose												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/49 (30.6%)	1/57 (1.8%)	RR 17.45 (2.39 to 127.38)	289 more per 1000 (from 24 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
% of patients with reported serious side effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/49 (10.2%)	2/57 (3.5%)	RR 2.91 (0.59 to 14.33)	67 more per 1000 (from 14 fewer to 468 more)	⊕⊕OO LOW	CRITICAL
Mortality												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/49 (0%)	0/57 (0%)	RD 0.00 (-0.04 to 0.04)	0 per 1000 (from 40 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse drug effects												
1 (Ng 2011)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/34 (14.7%)	0/38 (0%)	RR 12.26 (0.7 to 213.79)	150 more per 1000 (from 20	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on high-dose clobazam	Placebo	Relative (95% CI)	Absolute		
										more to 270 more)		

1 95% CI crosses 2 MIDs (0.8 and 1.25)
2 Absolute effect range crosses 2 absolute MIDs (10 more and 10 fewer per 1000)

Table 19: Clinical evidence profile. Comparison 9: add-on topiramate versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on topiramate	Placebo	Relative (95% CI)	Absolute		
Reduction in major seizure frequency (drop attacks and tonic-clonic seizures) >50%												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/46 (32.6%)	4/50 (8%)	RR 4.08 (1.46 to 11.39)	246 more per 1000 (from 37 more to 831 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete cessation of drop attacks												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/46 (10.9%)	0/50 (0%)	RR 11.94 (0.68 to 210.06)	110 more per 1000 (from 10 more to 200 more)	⊕⊕OO LOW	CRITICAL
% of patients with reported severe side effects												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/46 (23.9%)	5/50 (10%)	RR 2.39 (0.90 to 6.36)	139 more per 1000 (from 10 fewer to 290 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment cessation due to adverse drug effects												
1 (Sachdeo	RCT	no serious	no serious in-	no serious	very seri-	none	0/46	0/50	RD 0.00	0 per 1000	⊕⊕OO	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Add-on topiramate	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1999)		risk of bias	consistency	indirectness	ous[3]		(0%)	(0%)	(-0.04 to 0.04)	(from 40 fewer to 40 more)	LOW	
% of patients with dose reduction or temporary discontinuation of treatment												
1 (Sachdeo 1999)	RCT	no serious risk of bias	no serious in-consistency	no serious indirectness	serious[2]	none	9/46 (19.6%)	3/50 (6%)	RR 3.26 (0.94 to 11.31)	136 more per 1000 (from 4 fewer to 619 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[2] *The evidence was downgraded by 1 as the 95% CI crosses 1 MID (1.25)*
[3] *Absolute effect range crosses 2 absolute MIDs (10 more per 1000 and 10 fewer per 1000)*