[New 2015]

EPI 5: Anti-epileptic medicines for medication resistant convulsive epilepsy. [New 2015]

SCOPING QUESTION: **For adults and children with medication-resistant convulsive epilepsy, which anti-epileptic medications produce benefits and/or harm in the specified outcomes when compared to a placebo or a comparator?**

Back to Table of Contents

BACKGROUND

Epilepsy is associated with premature mortality, particularly when convulsive seizures are present. For example, the mortality rate in a cohort of persons with active convulsive epilepsy (ACE) was 33.3/1000 person-years compared to 6.1/1000 person-years for those without ACE in a recent Kenyan study (Ngugi et al. 2014). This is concerning if one considers the large treatment gap in low- and middle-income countries (LAMICs), which can be over 75% (Dua et al., 2011). There is universal agreement that the benefits of treating epilepsy with anti-epileptic medications outweigh the risks. Fortunately, 70% of patients respond to medical management, with around 30% of those with epilepsy who are medication-resistant (Zhang et al., 2014).

For some, epilepsy surgery may be an option. However, for many, anti-epileptic medications are still the mainstay of treatment. The essential medicines (carbamazepine, phenobarbital, phenytoin and valproic acid [sodium valproate])) were introduced before randomized controlled trials (RCTs) played an important role in evidence-based medicine. However, most of the newer anti-epileptic medications (such as lamotrigine, levetiracetam and topiramate) have been subjected to RCTs examining their efficacy as add-on therapy in those with medication-resistant epilepsy. The aim of this scoping question is to review the existing evidence regarding which of the most commonly used standard and newer anti-epileptic medications produce benefits/harm for adults and children with medication-resistant convulsive epilepsy.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults and children with medication-resistant focal and generalized convulsive epilepsy
- **Interventions:** Standard (specifically, carbamazepine, phenobarbital, phenytoin and valproic acid) and newer anti-epileptic medications (specifically, lamotrigine, levetiracetam and topiramate)
- **Comparison:** Placebo or a comparator

- **Outcomes:**
    - **Critical –** Seizure recurrence, mortality, adverse events
    - **Important –** Treatment acceptability (dropout)

Definitions

Medication-resistant: For the purpose of this review, medication-resistant epilepsy was defined as inadequate response to more than one appropriate anti-epileptic medication for the epilepsy syndrome, as this was the definition used by the majority of currently available systematic reviews. According to the new definition endorsed by the International League Against Epilepsy (ILAE), medication-resistant epilepsy is the failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic medication schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom (12 months or three times the longest duration of seizure freedom) (Kwan et al., 2010), however using this new definitionwould have resulted in the exclusion of most included papers. Thus, this review focuses on the use of anti-epileptic medications as add-on therapy in adults and children with active convulsive epilepsy..

Convulsive epilepsy: Any epilepsy that is associated with convulsive seizures (i.e., myoclonic, tonic, clonic, tonic-clonic and focal seizures evolving to bilateral convulsive activity).

Adverse events: For the purpose of this evidence profile, withdrawal (dropouts) was used as a surrogate measure of adverse events since overall adverse event data were not available. In many studies, withdrawal was most commonly due to adverse events (and only rarely due to inadequate seizure control).

Generalized and focal epilepsy: For the purpose of this review, we present the evidence for generalized vs. focal epilepsy separately where possible, as the management of generalized vs. focal epilepsies at times differs. For example, broad-spectrum anti-epileptic medications may be helpful for both types of epilepsies, while non-broad spectrum anti-epileptic medications could worsen the convulsive epilepsies in some situations. However, at times the evidence identified did not differentiate between these two types of epilepsies; therefore, the outcomes are presented for both types of epilepsies combined.

Search Strategy

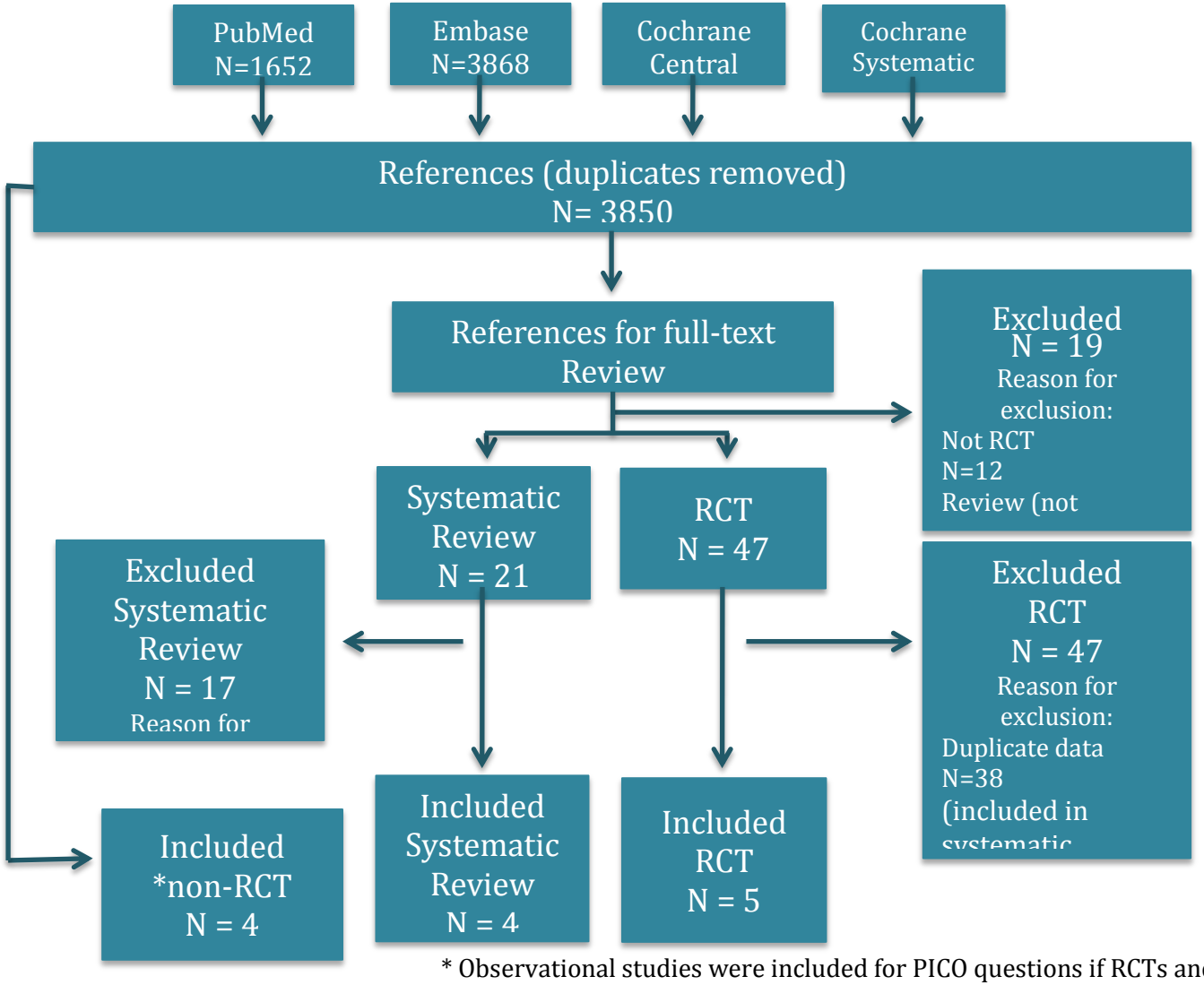
Epilepsy (explode)
AND

Drug resistan* OR Drug-resistan* OR Refractor* OR Pharmacoresistan* OR Medication resistan* OR Intract*
AND
Carbamazepine OR Phenobarbital OR Phenytoin OR Lamotrigine OR Levetiracetam OR Topiramate OR Valproic acid OR Valpro*

The above search strategy was run on 4 September 2014 in Embase, MEDLINE, Cochrane Central and Cochran Library. Included articles were searched by hand, as was a grey literature search (including, but not limited to, National Guidelines Clearinghouse). There were no terms that limited the search by language, date or study design. Studies were included if there were systematic reviews or randomized controlled trials of the anti-epileptic medication of interest vs. each other or placebo. The results of the search process are outlined in Figure 1 below.

[New 2015]

Figure 1. Results of search process



* Observational studies were included for PICO questions if RCTs and systematic reviews were not available.

[New 2015]

Evidence included in evidence profile

Systematic reviews (included in GRADE tables)

- Mbizvo GK, Dixon P, Hutton J, Marson A (2012). Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database of Systematic Reviews.9:CD001901.

- Pulman J, Jette N, Dykeman J, Hemming K, Hutton JL, Marson AG (2008). Topiramate add-on for drug-resistant partial epilepsy.[Update of Cochrane Database Syst Rev.3:CD001417; (2014) Cochrane Database of Systematic Reviews.2:CD001417.

- Ramaratnam S, Marson AG, Baker GA (2010). Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews. 3:CD001909. doi:10.1002/14651858.CD001909.

- Tjia-Leong E, Leong K, Marson AG (2010). Lamotrigine adjunctive therapy for refractory generalized tonic-clonic seizures. Cochrane Database of Systematic Reviews.12:CD007783. doi:10.1002/14651858.CD007783.pub2.

Individual randomized control trials (included as footnotes to GRADE tables)

- Aldenkamp AP, Baker G, Mulder OG, Chadwick D, Cooper P, Doelman J, Duncan R, Gassmann-Mayer C, de Haan GJ, Hughson C et al. (2000). A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. Epilepsia.41(9):1167-1178.

- Baulac M, Leon T, O'Brien TJ, Whalen E, Barrett J (2010). A comparison of pregabalin, lamotrigine and placebo as adjunctive therapy in patients with refractory partial-onset seizures. Epilepsy Research.91(1):10-9. doi:10.1016/j.eplepsyres.2010.05.008.

- Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S (2002). Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. Epilepsy Research.48(1-2):77-89.

- Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CB, Gauer LJ, Lu Z et al (2006). Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology.66(11):1654-60.

- Trevathan E, Kerls SP, Hammer AE, Vuong A, Messenheimer JA (2006). Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. Pediatrics.118(2):e371-e378.

Observational studies (no GRADE)

- Ashok PP and Maheshwari MC (1984). Role of combination of valproic acid with diphenylhydantoin and carbamazepine in the management of intractable seizures. Journal of the Association of Physicians of India.32(7):565-7.

- Bootsma HPR, Ricker L, Diepman L, Gehring J, Hulsman J, Lambrechts D, Leenen L, Majoie M, Schellekens A, de Krom M, Aldenkamp AP et al (2008). Long-term effects of levetiracetam and topiramate in clinical practice: A head-to-head comparison. Seizure.17(1):19-26.

- Fels A, Habetswallner F, Pagliuca M, Simonelli V, Coppola S (2003). Gabapentin, Lamotrigine, Topiramate, Vigabatrin, Oxcarbazepine and Levetiracetam in add-on therapy: Our clinical experience. [Italian] Gabapentin, Lamotrigina, Topiramato, Vigabatrin, Oxcarbazepina e Levetiracetam in add-on therapy: Valutazione clinica comparativa della nostra casistica. Bollettino - Lega Italiana contro l'Epilessia. 121-122:227-229.

- Lesser RP, Pippenger CE, Luders H, Dinner DS (1984). High-dose monotherapy in treatment of intractable seizures. Neurology.34(6):707-11.

Excluded from GRADE Tables and Footnotes

Beyenburg S, Stavem K, Schmidt D (2010). Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: Systematic review and meta-analysis. Epilepsia.51(1):7-26. doi:10.1111/j.1528-1167.2009.02299.x.
REASON FOR EXCLUSION: There is duplicate data and other studies are more up-to-date, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam et al. (2010).

Bodalia PN, Grosso AM, Sofat R, Macallister RJ, Smeeth L, Dhillon S, Casas JP, Wonderling D, Hingorani AD (2013). Comparative efficacy and tolerability of anti-epileptic drugs for refractory focal epilepsy: systematic review and network meta-analysis reveals the need for long term comparator trials. British Journal of Clinical Pharmacology.76(5):649-667. doi:10.1111/bcp.12083.
REASON FOR EXCLUSION: There is duplicate data and other studies are more comprehensive, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam et al. (2010).

Chaisewikul R, Privitera MD, Hutton JL, Marson AG (2001). Levetiracetam add-on for drug-resistant localization related (partial) epilepsy. Cochrane Database of Systematic Reviews.1:CD001901.
REASON FOR EXCLUSION: This review is an older version of Mbizvo et al. (2012).

Costa J, Fareleira F, Ascenaao R, Borges M, Sampaio C, Vaz-Carneiro A (2011). Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: A systematic review and meta-analysis. Epilepsia. 52(7):1280-1291. doi:10.1111/j.1528-1167.2011.03047.x.

REASON FOR EXCLUSION: There is duplicate data and other studies are more comprehensive, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam (2010).

Cramer JA, Ben Menachem E, French J (2001). Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. Epilepsy Research.47(1-2):17-25.
REASON FOR EXCLUSION: There is duplicate data and other studies are more up-to-date, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam (2010).

French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Wheodore WH, Brazil C, SStern J, Schaachter SC, Bergen D et al. (2004). Efficacy and Tolerability of the New Antiepileptic Drugs, II: Treatment of Refractory Epilepsy: Report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia.45(5):410-423.
REASON FOR EXCLUSION: There is duplicate data and other studies are more up-to-date, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam (2010).

French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Wheodore WH, Brazil C, SStern J, Schaachter SC, Bergen D et al. (2004). Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 62(8):1261-73.
REASON FOR EXCLUSION: There is duplicate data and other studies are more up-to-date, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam (2010).

French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Wheodore WH, Brazil C, SStern J, Schaachter SC, Bergen D et al. (2004). Appendix D: Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. CONTINUUM Lifelong Learning in Neurology.13(4 EPILEPSY):212-224
REASON FOR EXCLUSION: There is duplicate data and other studies are more up-to-date, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam (2010).

Hancock EC and Cross HJ (2013). Treatment of Lennox-Gastaut syndrome. Cochrane Database of Systematic Reviews. 2: doi:10.1002/14651858.CD003277.pub2.
REASON FOR EXCLUSION: This review does not provide data for the outcomes of interest.

Hemery C, Ryvlin P, Rheims S (2014). Prevention of generalized tonic-clonic seizures in refractory focal epilepsy: A meta-analysis. Epilepsia.55(11):1789-1799. doi:10.1111/epi.12765.

REASON FOR EXCLUSION: This systematic review was published just as the data for this guideline was being analyzed. It did not add any additional studies that were not included in the other systematic reviews included in the GRADE tables.

Jette NJ, Marson AG, Hutton JL (2002). Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews.3:CD001417.
REASON FOR EXCLUSION: This review is an older version of Pulman et al. (2014)

Lo B, Kyu H, Jichici D, Upton A, Akl E, Meade M (2011). Meta-analysis of randomized trials on first line and adjunctive levetiracetam. Canadian Journal of Neurological Sciences.38(3):475-486.
REASON FOR EXCLUSION: Mbizvo et al. (2012) covered the same PICO question and is more up-to-date.

Maguire M, Marson AG, Ramaratnam S (2011). Epilepsy (partial). BMJ Clinical Evidence.pii: 1214.
REASON FOR EXCLUSION: No data was provided that could be used in the GRADE table.

Maguire M, Marson AG, Ramaratnam S (2012). Epilepsy (generalised). BMJ Clinical Evidence.pii:1201.
REASON FOR EXCLUSION: No data was provided that could be used in the GRADE table.

Marson AG, Maguire M, Ramaratnam S (2009). Epilepsy. BMJ Clinical Evidence.pii: 1201.
REASON FOR EXCLUSION: No data was provided that could be used in the GRADE table.

Zaccara G, Sisodiya SM, Giovannelli F, Walker MC, Heaney DC, Angus-Leppan H, Wehner T, Eriksson SH, Liu R, Rugg-Gunn F et al. (2013). Network meta-analysis and the comparison of efficacy and tolerability of anti-epileptic medications for treatment of refractory focal epilepsy. British Journal of Clinical Pharmacology.76(5):827-828. doi:10.1111/bcp.12175.
REASON FOR EXCLUSION: There is duplicate data and other studies are more up-to-date, including: Mbizvo et al. (2012); Pulman et al. (2014); Tjia-Leong et al. (2012); and Ramaratnam (2010).

PICO Table

Population: People with medication-resistant convulsive epilepsy					
Intervention	**Comparison**	**Outcomes[1]**	**Relevant evidence for developing the evidence profile**	**Justification for systematic review used**	**Relevant table**
Standard anti-epileptic medication[2]					
Carbamazepine	Phenytoin	Seizure reduction treatment acceptability	*Systematic reviews and RCTs:* No systematic review or RCTs available	N/A	N/A

		(dropouts)	*Observational studies:* Focal epilepsy – Ashok et al. (1984) Focal and generalized epilepsy – Lesser et al. (1984)		Table 1 Table 2
Newer anti-epileptic medication[3]					
Lamotrigine	Placebo	Seizure reduction, treatment acceptability (dropouts)	*Systematic reviews and RCTs:* Focal and generalized epilepsy – Tjia-Leong et al. (2011) Cochrane Review; Trevethan et al. (2006) Focal epilepsy – Ramaratnam et al. (2010) Cochrane Review	Tjia-Leong et al., 2011 and Ramaratnam et al., 2010 were the most recent systematic review available for PICO. Tjia-Leong et al, 2011 included because it included generalized epilepsies which Ramaratnam et al, 2010 did not include. Ramaratnam et al, 2010 included because it included focal epilepsies which Tjia-Leong et al, 2011 did not include.	Table 3 and 4 Table 5
			Observational studies: No additional observational studies included.		
Lamotrigine	Levetiracetam	Seizure reduction	*Systematic reviews and RCTs:* No systematic review or RCTs available	N/A	
			Observational studies: Focal and generalized epilepsy – Fels et al. (2003)		Table 6
Lamotrigine	Topiramate	Seizure reduction	*Systematic reviews and RCTs:* No systematic review or RCTs	N/A	

			available		
			Observational studies: Focal and generalized epilepsy – Fels et al. (2003)		Table 7
Levetiracetam	Placebo	Seizure reduction, treatment acceptability (dropouts)	*Systematic reviews and RCTs:* Focal epilepsy – Mbizvo et al. (2012); Baulac et al. (2010) ; Boon et al. (2001) Glausser et al. (2006)	Mbizvo et al. (2012) is the most recent and comprehensive systematic review available for PICO.	Table 8-11
			Observational studies: No additional observational studies included.		
Topiramate	Placebo	Seizure reduction, seizure freedom, treatment acceptability (dropouts)	*Systematic reviews and RCTs:* Pulman et al. (2014)	Pulman et al. (2014) was the most recent systematic review available for PICO.	Table 12
			Observational studies: No additional observational studies included		
Topiramate	Levetiracetam	Seizure reduction, seizure freedom, treatment acceptability (dropouts)	*Systematic reviews and RCTs:* No systematic review or randomized control trials available	N/A	
			Observational studies: Focal and generalized epilepsy – Bootsma et al. (2008)		Table 13

Topiramate	Valproic acid	Seizure reduction, treatment acceptability (dropouts)	*Systematic reviews and RCTs:* No systematic review available Focal epilepsy – Aldenkamp et al. (2000)	N/A	Table 14
			Observational studies: No additional observational studies included		

Footnotes:
1. Mortality was one of the outcomes of interest; however, there were no studies found that reported mortality as an outcome.
2. No systematic reviews were identified that evaluated the efficacy or safety of carbamazepine, phenobarbital, phenytoin or valproic acid as add-on therapy or as monotherapy for patients with medication-resistant epilepsy.
3. No systematic reviews were identified that evaluated the head-to-head efficacy or safety of carbamazepine, phenobarbital, phenytoin, lamotrigine, levetiracetam, topiramate or valproic acid.

Summary of evidence for each anti-epileptic medication and corresponding comparator

	COMPARATOR							
INTERVENTION	Carbamazepine	Phenobarbital	Phenytoin	Valproic acid	Lamotrigine	Levetiracetam	Topiramate	Placebo
Carbamazepine			Observational Study					
Phenobarbital								
Phenytoin	Observational Study							
Valproic acid							Single RCT	
Lamotrigine						Observational Study	Observational Study	Two systematic reviews, single RCT
Levetiracetam					Observational Study		Observational Study	Systematic Review, two RCTs
Topiramate				Single RCT	Observational Study	Observational Study		Systematic Review

Narrative description of the studies that went into the analysis

Tjia-Leong et al. (2011) included studies that were randomized, single, double or unblended, parallel or crossover designs. Participants were of any age with medication-resistant generalized tonic-clonic seizures. The treatment had to include lamotrigine as add-on therapy vs. placebo or an active control. The included trials were deemed to have high risk of bias and included 169 participants from 2 trials. The outcomes of interest were: 50% seizure reduction, seizure freedom, treatment withdrawal, adverse events and quality of life measures. The two included trials were not similar enough to perform a meta-analysis. Based on these two trials, it was found that lamotrigine was effective at managing primary generalized tonic-clonic seizures, but these findings are based on low quality evidence in a small number of studies.
Ramaratnam et al. (2010) included studies that were randomized, single, double or unblended, parallel or crossover designs. Participants were of any age with medication-resistant focal epilepsy. The treatment had to include lamotrigine as add-on therapy vs. placebo. The included trials were deemed to have low risk of bias and included 1524 participants from 13 trials. The outcomes of interest were: 50% reduction of seizures, seizure freedom, treatment withdrawal, adverse events and quality of life measures. Eleven trials were included in the meta-analysis, which found that lamotrigine was superior to placebo (OR^{i} = 2.51 [95% CI 1.86-3.4]) with regards to 50% seizure reduction. There were 13 studies included in the meta-analysis of treatment withdrawal, which found comparable withdrawal rates between lamotrigine and placebo (OR = 1.13 [95% 0.83-1.54]).

Mbizvo et al. (2012) included studies that were randomized, single or double blinded, parallel or crossover designs, with a treatment period of at least 8 weeks. Included studies involved participants of all ages, genders and ethnicities that had medication-resistant focal epilepsies, which was not defined by a given number of failed anti-epileptic medication trials, but rather by search terms. The treatment had to include levetiracetam as add-on therapy vs. placebo. The included trials were deemed to have low risk of bias and included 1861 participants from 11 trials. The outcomes of interest were: 50% reduction of seizures, seizure freedom, treatment withdrawal, adverse events and quality of life measures. The estimates of effect for 10 studies were pooled to evaluate the efficacy of levetiracetam vs. placebo. This meta-analysis found levetiracetam to be superior to placebo (RR = 2.43 [95% CI 2.04-2.9]) with regards to 50% seizure reduction. Of the 10 trials reporting 50% seizure reduction, two (both investigating 2000 mg dose) were included in the meta-analysis to examine the 50% seizure reduction and found levetiracetam to be superior to placebo in adults (RR = 4.9 [95% CI 2.75-8.77). Two studies examining the efficacy of levetiracetam in children were pooled in a meta-analysis and found that in children, levetiracetam is superior to placebo with regards to 50% seizure reduction (RR = 1.19 [95% CI 1.38-2.63). Those participants in the levetiracetam group and placebo group had similar treatment withdrawal rates (adults RR = 0.98 [95% CI 0.73-1.3]; child RR = 0.80 [95% 0.43-1.46]).

Pulman et al. (2014) included studies that were randomized, single or double blinded, parallel or crossover designs, with a treatment period of at least 8 weeks. Participants were of all ages with medication-resistant focal epilepsy. The treatment had to include topiramate as add-on therapy vs. placebo, another dose of topiramate or another anti-epileptic medication as a control. The included trials were deemed to have low risk of bias and included 1401 participants from 11 trials. The outcomes of interest were: 50% reduction of seizures, seizure freedom, treatment withdrawal and adverse events. There were 11 trials included in the meta-analysis for the 50% reduction of seizures intention-to-treat (ITT) analysis. The authors found that topiramate was superior to placebo (RR = 2.97 [95% CI 2.38-3.72]) for the 50% seizure reduction outcome. Five of the 11 trials were pooled to examine seizure freedom between those taking topiramate and those in the placebo group and found that topiramate was superior to placebo (RR = 3.41 [95% CI 1.37-8.51]). There were 10 studies included in the ITT analysis of treatment withdrawal, which revealed that treatment withdrawal in the topiramate group was greater than those in the placebo group (RR = 2.44 [95%CI 1.64-3.62]).

Note: Systematic reviews of medication-resistant focal epilepsy had to include some patients with focal seizures evolving into bilateral convulsive activity as participants. If the systematic review only included patients without focal seizures evolving to bilateral convulsive activity, it would have been excluded. Thus, the outcomes are often reported as overall estimates for patients with and without convulsive seizures.

GRADE Tables and other evidence (not GRADED)

Table 1. Carbamazepine vs. phenytoin for treatment of medication-resistant convulsive focal epilepsy in adults

Question: Should carbamazepine vs. phenytoin be used as therapy in adults with medication-resistant convulsive focal epilepsy?
Bibliography (observational study): Ashok PP and Maheshwari MC (1984). Role of combination of valproic acid with diphenylhydantoin and carbamazepine in the management of intractable seizures. Journal of the Association of Physicians of India.32(7):565-7.

Study Design/Methods	Prospective cohort	
Participants	25 participants with medication-resistant epilepsy on valproic acid monotherapy Median age of 28 years old (range=13-51 years old) 15 males (60%) Generalized or focal-onset epilepsy Cohort attended an outpatient neurology clinic	
Interventions	Carbamazepine group: n=15 as add-ons therapy to valproic acid Phenytoin group: n=10 as add-ons therapy to valproic acid	
Outcomes	*Seizure reduction (50% or greater)* Carbamazepine group: 47% (n=7) Phenytoin group: 10% (n=1) *Seizure freedom* Carbamazepine group: 20% (n=3) Phenytoin group: 70% (n=7) *Treatment acceptability (dropouts)* One participant in the carbamazepine group withdrew due to adverse events	
Notes	The results of this study suggest that the combination of valproic acid and phenytoin was superior in this population to the combination of valproic acid and carbamazepine.	
Study Quality (using GRADE criteria for observational studies)		
	Risk of bias	**Justification for judgment**
Eligibility criteria	Serious risk	Minimal eligibility criteria. Unclear if the participant characteristics were similar

		between groups (cannot assess degree of matching). All participants were from the same population.
Measurement	Low risk	Measurements were appropriate and similar between groups.
Confounding	Serious risk	Unclear if the participant characteristics were similar between groups and therefore if any confounding variables were unaccounted for. No attempt at controlling for confounding variables.
Follow-up	Low risk	The cohort was followed for eight months, at which time their seizure frequency was evaluated.
Overall quality	VERY LOW	

Table 2. Carbamazepine vs. phenytoin for treatment of medication-resistant convulsive focal and generalized epilepsy in adults

Question: Should carbamazepine vs. phenytoin be used as therapy in adults with medication-resistant convulsive focal and generalized epilepsy?
Bibliography (observational study): Lesser RP, Pippenger CE, Luders H, Dinner DS (1984). High-dose monotherapy in treatment of intractable seizures. Neurology.34(6):707-11.

Study Design/Methods	Prospective cohort
Participants	28 participants with medication-resistant epilepsy Age range = 19-46 years
Interventions	High dose carbamazepine (dose ranging from 700 to 1700 mg) group: n=18 High dose phenytoin (dose ranging from 300-600 mg) group: n=11
Outcomes	*Seizure reduction* Carbamazepine group: 27.8% (n=5) participants had a seizure reduction of 66% or more Phenytoin group: 18.2% (n=2) participants had a seizure reduction of 66% or more *Seizure freedom* Carbamazepine group: 16.7% (n=3) participants became seizure free Phenytoin group: 45.5% (n=5) participants were seizure free *Treatment acceptability (dropouts)* Not reported
Notes	The authors concluded that high doses of either carbamazepine or phenytoin monotherapy were superior to polytherapy, but there were no significant differences between carbamazepine and phenytoin in terms of efficacy at controlling seizures or adverse events.
Study Quality (using GRADE criteria for observational studies)	

	Risk of bias	Justification for judgment
Eligibility criteria	Serious risk	Minimal eligibility criteria. Unclear if the participant characteristics were similar between groups (cannot assess degree of matching). All participants were from the same population.
Measurement	Low risk	Measurements were appropriate and similar between groups.
Confounding	Serious risk	Unclear if the participant characteristics were similar between groups and therefore if any confounding variables were unaccounted for. No attempt at controlling for confounding variables.
Follow-up	Serious risk	Follow-up time was not reported.
Overall quality	VERY LOW	

Note: There were no systematic reviews or RCTs examining the effectiveness and safety of carbamazepine vs. phenytoin. However, there were two observational studies that were taken into consideration. Meta-analysis could not be performed on these two observational studies (the estimates could not be pooled).

Table 3. Lamotrigine vs. placebo as add-on therapy for medication-resistant convulsive generalized epilepsy in people of all ages

Question: Should lamotrigine vs. placebo be used as an add-on therapy for medication-resistant convulsive generalized epilepsy in people of all ages?
Bibliography (systematic reviews): TjiaLeong E, Leong K, Marson AG (2010). Lamotrigine adjunctive therapy for refractory generalized tonic-clonic seizures. Cochrane Database of Systematic Reviews.12:CD007783. doi:10.1002/14651858.CD007783.pub2.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamotrigine**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Efficacy (50% seizure reduction)												
Efficacy (seizure freedom)												
Treatment acceptability (dropouts)												
2	Randomized trials	Serious [1]	Serious [2]	Serious [3]	Not serious	Publication bias strongly suspected	20/84 (23.8%)	16/85 (18.8%)	**RR 1.27** (0.71 to 2.26)	51 more per 1000 (from 55 fewer to 237 more)	VERY LOW	IMPORTANT

1. Studies were randomized, dropout rates were similar between groups and below 30%, but the blinding of outcome assessment was unclear.
2. No statistical test of heterogeneity, but visually the estimates are fairly different (RR=1.16 vs. 2.0).
3. One of the included studies was a single centre study.

NOTE: There were insufficent data in the Tija-Leong et al. (2001) systematic review to do a meta-analysis of seizure outcome. No data was provided on seizure outcome for the included Beran et al. (1998) study. The Biton et al. (2005) study found that a greater proportion of those treated with add-on lamotrigine than placebo achieved total seizure cessation in the maintenance phase, as well as in the escalation and maintenance phases combined (38% vs. 24%; 21% vs. 17%, respectively) (p=0.50). A subgroup analysis in children found that 33% were seizure free on lamotrigine vs. 21% on placebo in the escalation phase, while the estimates were 48% vs. 17% respectively during the maintenance phase only (p+0.051).

Trevethan et al. (2006) was not included in the GRADEd Tija-Leong et al. (2001) systematic review. Study details are as follows:

Table 4. Lamotrigine vs. placebo as add-on therapy for medication-resistant convulsive generalized epilepsy in people of all ages

Question: Should lamotrigine vs. placebo be used as an add-on therapy for medication-resistant convulsive generalized epilepsy in people of all ages?
Bibliography (systematic reviews): Trevathan E, Kerls SP, Hammer AE, Vuong A, Messenheimer JA (2006). Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. Pediatrics.118(2):e371-e378.

Study Design/Methods	Multicenter, randomized, double-blind, placebo controlled study
Participants	45 participants with medication-resistant epilepsy Mean age = 11 years old (range = 2-19 years) Generalized tonic-clonic seizures
Interventions	Lamotrigine group = 21 Placebo group = 24

Outcomes	*Seizure reduction* Lamotrigine group: 77% reduction Placebo group: 40% reduction Favours lamotrigine (p=0.044) *Seizure freedom* Lamotrigine group: 48% Placebo group: 17% Favours lamotrigine (p=0.051) *Treatment acceptability (dropouts)* Lamotrigine group: 1 withdrew due to adverse events Placebo group: 1 withdrew due to adverse events	
Notes	The authors of the study concluded that lamotrigine is an effective and safe adjunctive anti-epileptic medication for the treatment of people with medication-resistant generalized epilepsy.	
Study Quality (using GRADE criteria for randomized trials)		
	Risk of bias	**Justification for judgment**
Allocation concealment	Low risk	Randomization was done using a central computer-generator.
Magnitude of effect	Moderate risk	It is presumed that the magnitude of effect is moderate. A standard deviation is not reported but the mean difference in seizure reduction is only 37%.
Blinding	Moderate risk	The authors say that double blinding was used but this is not described.
Follow-up	Low risk	Follow-up was 12 weeks after maximum dose was reached, which was adequate. Few participants were lost to follow-up.
Reporting of outcomes	Low risk	Reporting of outcomes was similar between groups.
Overall quality	MODERATE	

[New 2015]

Table 5. Lamotrigine vs. placebo for treatment of medication-resistant convulsive focal epilepsy in people of all ages

- **Question: Should lamotrigine vs. placebo be used for treatment of medication-resistant convulsive focal epilepsy in people of all ages?**
  Bibliography (systematic reviews): Ramaratnam S, Marson AG, Baker GA (2010). Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews. 3:CD001909. doi:10.1002/14651858.CD001909.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamotrigine**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Efficacy (50% seizure reduction)												
11	Randomized trials	Serious [1]	Not serious	Not serious	Serious [2]	Publication bias strongly suspected strong association	158/549 (28.8%)	69/491 (14.1%)	**OR 2.51** (1.86 to 3.4)	150 more per 1000 (from 93 more to 217 more)	⊕⊕OO LOW	CRITICAL
Efficacy (seizure freedom)												
Treatment acceptability (dropouts)												
13	Randomized trials	Serious [1]	Not serious	Not serious	Very serious [3]	Publication bias strongly suspected	140/902 (15.5%)	86/622 (13.8%)	**OR 1.13** (0.83 to 1.54)	15 more per 1000 (from 21 fewer to 60 more)	⊕OOO VERY LOW	IMPORTANT

1. Masking of outcome assessment was not adequately described.
2. The 95% confidence interval included no effect and an appreciable benefit.
3. The effect size was small and the 95% confidence interval included no effect and an appreciable harm.

[New 2015]

Table 6. Lamotrigine vs. levetiracetam as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy?

Question: Should lamotrigine vs. levetiracetam be used as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy?
Bibliography (observational study): Fels A, Habetswallner F, Pagliuca M, Simonelli V, Coppola S (2003). Gabapentin, Lamotrigine, Topiramate, Vigabatrin, Oxcarbazepine and Levetiracetam in add-on therapy: Our clinical experience. [Italian] Gabapentin, Lamotrigina, Topiramato, Vigabatrin, Oxcarbazepina e Levetiracetam in add-on therapy: Valutazione clinica comparativa della nostra casistica. Bollettino - Lega Italiana contro l'Epilessia. 121-122:227-229.

NOTE: There were no systematic reviews or randomized control trials examining the effectiveness and safety of lamotrigine vs. levetiracetam. However, there was an observational study that was taken into consideration.

Study Design/Methods	Cohort study	
Participants	441 patients with medication-resistant epilepsy Median age = 32 years old (range=2-82 years old) 236 males and 205 females. Generalized or focal onset epilepsy (majority with focal onset epilepsy). Cohort was attending an outpatient neurology clinic	
Interventions	Lamotrigine group: n = 107 Levetiracetam group: n = 46	
Outcomes	*Seizure reduction (50% or greater)* Lamotrigine group: 16.8% (n=18) Levetiracetam group: 32.6% (n=15) *Seizure freedom* Lamotrigine group: 21.5% (n=23) Levetiracetam group: 17.4% (n=8) *Treatment acceptability (dropouts)* Lamotrigine group: 21.5% (n=23) Levetiracetam group: 19.6% (n=9)	
Notes:	The authors concluded that levetiracetam and lamotrigine show good efficacy but that there was a considerable number of adverse events with both.	
Study Quality (using GRADE criteria for observational studies)		
	Risk of bias	**Justification for judgment**

Eligibility criteria	Low risk	Cases were exposed to different AED[ii] but were selected from the same population. The six groups are reported to be similar at baseline, with respect to socio-demographic and clinical characteristics.
Measurement	Low risk	Similar definition and measurement of exposure in the six groups. There were similar outcome assessments in the six groups of exposed patients.
Confounding	Serious risk	There is no adjustment for any known or unknown confounding variable.
Follow-up	Low risk	Follow up time was between 6 and 46 months (median was 14 months), which was adequate. The dropout rate was similar between groups.
Overall quality	LOW	

Table 7. Lamotrigine vs. topiramate as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy.

Question: Should lamotrigine vs. topiramate be used as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy?
Bibliography (systematic reviews): Fels A, Habetswallner F, Pagliuca M, Simonelli V, Coppola S (2003). Gabapentin, Lamotrigine, Topiramate, Vigabatrin, Oxcarbazepine and Levetiracetam in add-on therapy: Our clinical experience. [Italian] Gabapentin, Lamotrigina, Topiramato, Vigabatrin, Oxcarbazepina e Levetiracetam in add-on therapy: Valutazione clinica comparativa della nostra casistica. Bollettino - Lega Italiana contro l'Epilessia. 121-122:227-229.

Study Design/Methods	Cohort study
Participants	441 patients with medication-resistant epilepsy Median age = 32 years old (range=2-82 years old) 236 males and 205 females Generalized or focal onset epilepsy (majority with focal onset epilepsy) Cohort was attending an outpatient neurology clinic
Interventions	Lamotrigine group: n = 107 Topiramate group: n = 93
Outcomes	*Seizure reduction (50% reduction)* Lamotrigine group: 16.8% (n=18) Topiramate group: 12.9% (n=12) *Seizure freedom* Lamotrigine group: 21.5% (n=23) Topiramate group: 14.0% (n=13)

	Treatment acceptability (dropouts) Lamotrigine group: 21.5% (n=23) Topiramate group: 14.0% (n=13)	
Notes:	The authors concluded that levetiracetam and lamotrigine show good efficacy, but that there were a considerable number of adverse events associated with both.	
Study Quality (using GRADE criteria for observational studies)		
	Risk of bias	**Justification for judgment**
Eligibility criteria	Low risk	Cases were exposed to different AED but were selected from the same population. The six groups are reported to be similar at baseline, with respect to socio-demographic and clinical characteristics.
Measurement	Low risk	Similar definition and measurement of exposure in the six groups. There were similar outcome assessments in the six groups of exposed patients.
Confounding	Serious risk	There is no adjustment for any known or unknown confounding variable.
Follow-up	Low risk	Follow up time was between 6 and 46 months (median 14 months). The dropout rate was similar lower in the topiramate group compared to the lamotrigine.
Overall quality	LOW	

NOTE: There were no systematic reviews or RCTs examining the effectiveness and safety of lamotrigine vs. topiramate. However, there was an observational study that was taken into consideration.

[New 2015]

Table 8. Levetiracetam vs. placebo for treatment of medication-resistant convulsive focal epilepsy

Question: Should levetiracetam vs. placebo be used for treatment of medication-resistant convulsive focal epilepsy?
Bibliography (systematic reviews): Mbizvo GK, Dixon P, Hutton J, Marson A (2012). Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. Cochrane Database of Systematic Reviews.9:CD001901.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Levetiracetam**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Efficacy (50% seizure reduction)												
10	Randomized trials	Serious [1]	Serious [2]	Not serious	Not serious	Publication bias strongly suspected strong association	423/1028 (41.1%)	129/714 (18.1%)	**RR 2.43** (2.04 to 2.9)	258 more per 1000 (from 188 more to 343 more)	⊕⊕OO LOW	CRITICAL
Efficacy (seizure freedom)												
Treatment acceptability (dropouts)												
11	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	143/1108 (12.9%)	86/753 (11.4%)	**RR 1.03** (0.8 to 1.33)	3 more per 1000 (from 23 fewer to 38 more)	⊕⊕⊕O MODERATE	IMPORTANT

1. Unclear blinding of outcome in 30% of included studies.
2. Herterogeneity is 62%.

Baulac et al. (2010) was not included in the GRADEd Mbizvo et al. (2012) systematic review, as it was published after the search was conducted for the above systematic review. Study details are as follows:

[New 2015]

Table 9. Levetiracetam vs. placebo for treatment of medication-resistant convulsive focal epilepsy

Question: Should levetiracetam vs. placebo be used for treatment of medication-resistant convulsive focal epilepsy?
Bibliography: Baulac M, Leon T, O'Brien TJ, Whalen E, Barrett J (2010). A comparison of pregabalin, lamotrigine and placebo as adjunctive therapy in patients with refractory partial-onset seizures. Epilepsy Research.91(1):10-9. doi:10.1016/j.eplepsyres.2010.05.008.

Study Design/Methods	Multicenter, randomized, double-blind, placebo controlled study	
Participants	433 participants with medication-resistant epilepsy Mean age = 11 years old (range = 2-19 years) Focal seizures	
Interventions	Lamotrigine group = 141 Placebo group: 141	
Outcomes	*Seizure reduction (>50%)* Lamotrigine group: 24.1% reduction Placebo group: 21.4% reduction No differences *Seizure freedom* Lamotrigine group: 11% Placebo group: 11% No differences *Treatment acceptability (dropouts)* Lamotrigine group: 28% (n=40) Placebo group: 24.8% (n=35) No differences	
Notes	The authors concluded that lamotrigine was superior to placebo.	
Study Quality (using GRADE criteria for observational studies)		
	Risk of bias	**Justification for judgment**
Allocation concealment	Moderate risk	Unclear how randomization was done.
Magnitude of effect	Severe risk	The magnitude of effect was small.
Blinding	Low risk	Double blinding was accomplished by giving the same number of tablets to each participant.
Follow-up	Severe risk	The maintenance phase ranged from 12 to 17 weeks depending on the allocation however follow-up was only 2 weeks after maximum dose was reached, which was inadequate. Quite a few participants were lost to follow-up however the numbers

		were similar between groups.
Reporting of outcomes	Low risk	Reporting of outcomes was adequate and similar between groups.
Overall quality	LOW	

Boon et al. (2001) was also not included in the GRADEd Mbizvo et al. (2012) systematic review. Study details are as follows:

Table 10. Levetiracetam vs. placebo for treatment of medication-resistant convulsive focal epilepsy

Question: Should levetiracetam vs. placebo be used for treatment of medication-resistant convulsive focal epilepsy?
Bibliography: Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S (2002). Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. Epilepsy Research.48(1-2):77-89.

Study Design/Methods	Multicenter, randomized, double-blind, placebo controlled, cross-over study	
Participants	324 participants with medication-resistant epilepsy Mean age = 37 years old (range = 14-69 years) Focal seizures	
Interventions	Placebo-levetiracetam 1000 mg/day: n=58 Placebo-levetiracetam 2000 mg/day: n=54 Levetiracetam 1000 mg/day-placebo: n=53 Levetiracetam 1000 mg/day-levetiracetam 2000 mg/day: n=53 Levetiracetam 2000 mg/day-placebo: n=54 Levetiracetam 2000 mg/day-levetiracetam 1000 mg/day: n=52	
Outcomes	*Seizure reduction* Levetiracetam 1000 mg/day group: mean difference over placebo of 16.9% reduction Levetiracetam 2000 mg/day group: mean difference over placebo of 18.5% reduction Favours Levetiracetam 2000 mg/day ($p<0.001$) *Seizure freedom* Levetiracetam 1000 mg/day group: 5.5% (n=10) Levetiracetam 2000 mg/day group: 5.7% (n=10) Placebo group: 1.2% (n=2) *Treatment acceptability (dropouts)* Levetiracetam 1000 mg/day group: 7% (n=14) Levetiracetam 2000 mg/day group: 12.9% (n=26) Placebo group: 8% (n=16)	
Notes	The authors of this study conclude that levetiracetam significantly reduces seizure frequency in a dose dependent manner when used as add-on therapy for people with medication-resistant focal epilepsy.	
Study Quality (using GRADE criteria for randomized trials)		
	Risk of bias	**Justification for judgment**

Allocation concealment	Low risk	Randomization was done using a central computer-generator. Randomization was stratified by country.
Magnitude of effect	Moderate risk	Magnitude of effect was moderate.
Blinding	Moderate risk	The authors say that double blinding was used but this is not described.
Follow-up	Moderate risk	Follow-up was a maximum of 4 weeks after maximum dose was reached, which was inadequate. Few participants were lost to follow-up.
Reporting of outcomes	Low risk	Reporting of outcomes was similar between groups and appropriate.
Overall quality	MODERATE	

Glauser et al. (2006) was also not included in the GRADEd Mbizvo et al. (2012) systematic review. Study details are as follows:

Table 11. Levetiracetam vs. placebo for treatment of medication-resistant convulsive focal epilepsy

Question: Should levetiracetam vs. placebo be used for treatment of medication-resistant convulsive focal epilepsy?
Bibliography: Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CB, Gauer LJ, Lu Z et al (2006). Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology.66(11):1654-60.

Study Design/Methods	Multicenter, randomized, double-blind, placebo controlled study
Participants	198 participants with medication-resistant epilepsy Mean age was 10 years old (range = 4-16 years). Focal seizures (including secondary generalized)
Interventions	101 participants were on levetiracetam 97 participants were on placebo
Outcomes	*Seizure reduction (50% reduction)* Levetiracetam group: 44.6% of participants Placebo group: 19.6% of participants Odd Ratio=3.3 (95% CI 1.75-6.24; p=0.0002) *Seizure freedom* Levetiracetam group: 6.9% (n=7) Placebo group: 1% (n=1) *Treatment acceptability (dropouts due to adverse events)* Levetiracetam group: 5% (n=5) withdrew due to adverse events Placebo group: 9.3% (n=9) withdrew due to adverse events

Notes	The authors concluded that levetiracetam was superior to placebo in efficacy and was well tolerated.	
Study Quality (using GRADE criteria for randomized trials)		
	Risk of bias	**Justification for judgment**
Allocation concealment	Low risk	Randomization was done using a central computer-generator by centre.
Magnitude of effect	Low risk	There is a strong association (OR >3.1).
Blinding	Low risk	Double blinding was well done (that is, investigators and participants were blinded to allocation and precautions were taken to prevent unblinding).
Follow-up	Moderate risk	Follow-up was 10 weeks after maximum dose was reached, which was only adequate. The number of participants lost to follow-up was not excessive but there were considerable difference between groups.
Reporting of outcomes	Low risk	Reporting of outcomes was similar between groups and well done.
Overall quality	MODERATE	

Table 12. Topiramate vs. placebo for treatment of medication-resistant convulsive focal epilepsy

Question: Should topiramate vs. placebo be used for treatment of medication-resistant convulsive focal epilepsy?
Bibliography (systematic reviews): Pulman J, Jette N, Dykeman J, Hemming K, Hutton JL, Marson AG (2008). Topiramate add-on for drug-resistant partial epilepsy.[Update of Cochrane Database Syst Rev.3:CD001417; (2014) Cochrane Database of Systematic Reviews.2:CD001417.

Quality assessment							No. of patients		Effect		Quality	Importance
No.of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topiramate**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Efficacy (50% seizure reduction)												
11	Randomized trials	Serious [1]	Not serious	Not serious	Not serious	Publication bias strongly suspected strong association dose response gradient	403/899 (44.8%)	73/502 (14.5%)	**RR 2.97** (2.38 to 3.72)	286 more per 1000 (from 201 more to 396 moremore)	⊕⊕⊕O MODERATE	CRITICAL
Efficacy (seizure freedom)												

Quality assessment							No. of patients		Effect		Quality	Importance
No.of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95% CI)	Absolute (95% CI)		
5	Randomized trials	Serious [1]	Not serious	Not serious	Serious [2]	Publication bias strongly suspected strong association dose response gradient	23/356 (6.5%)	5/277 (1.8%)	**RR 3.41** (1.37 to 8.51)	44 more per 1000 (from 7 more to 136 more)	⊕⊕OO LOW	CRITICAL
Treatment acceptability (dropouts)												
10	Randomized trials	Serious [1]	Not serious	Not serious	Serious [2]	Publication bias strongly suspected strong association dose response gradient	136/853 (15.9%)	29/462 (6.3%)	**RR 2.44** (1.64 to 3.62)	90 more per 1000 (from 40 more to 164 more)	⊕⊕OO LOW	IMPORTANT

1. Details of outcome assessment blinding not adequately provided, dropout rate less than 30% but not similarly distributed between groups.
2. The 95% confidence intervals included no effect and an appreciable harm.

Table 13. Topiramate vs. levetiracetam as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy

Question: Should topiramate vs. levetiracetam be used as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy?
Bibliography (observational study): Bootsma HPR, Ricker L, Diepman L, Gehring J, Hulsman J, Lambrechts D, Leenen L, Majoie M, Schellekens A, de Krom M, Aldenkamp AP et al (2008). Long-term effects of levetiracetam and topiramate in clinical practice: A head-to-head comparison. Seizure.17(1):19-26.

Study Design/Methods	Retrospective cohort
Participants	730 participants with medication-resistant epilepsy Mean age = 34 years old (range = 1-75 years) Focal seizures = 74% vs. Generalized seizures = 6% Tertiary care setting
Interventions	Levetiracetam group = 301 Topiramate group = 429

Outcomes	*Seizure reduction* Not reported *Seizure freedom* Levetiracetam group: 20.0% Topiramate group: 14.3% *Treatment acceptability (dropouts)* Levetiracetam group: 6% Topiramate group: 22%
Notes	These results suggest that while the efficacy (seizure freedom) of topiramate and levetiracetam are comparable, the retention rate of levetiracetam is superior to topiramate, which is likely due to a more favorable safety profile of levetiracetam.

Study Quality (using GRADE criteria for observational studies)

	Risk of bias	**Justification for judgment**
Eligibility criteria	Low risk	Minimal eligibility criteria. Participant characteristics were similar between groups and therefore matching was adequate. All participants were from the same population.
Measurement	Low risk	Measurements were appropriate and similar between groups.
Confounding	Moderate risk	Participant characteristics were similar between groups. However, no attempt was made to control for confounding variables.
Follow-up	Serious risk	Follow-up time was 24 months, which was adequate. There was a significantly lower retention rate (52%) for the topiramate group compared to that of the levetiracetam group (66%).
Overall quality	LOW	

[New 2015]

Table 14. Topiramate vs levetiracetam as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy

Question: Should topiramate vs levetiracetam be used as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy?
Bibliography (observational study): Fels A, Habetswallner F, Pagliuca M, Simonelli V, Coppola S (2003). Gabapentin, Lamotrigine, Topiramate, Vigabatrin, Oxcarbazepine and Levetiracetam in add-on therapy: Our clinical experience. [Italian] Gabapentin, Lamotrigina, Topiramato, Vigabatrin, Oxcarbazepina e Levetiracetam in add-on therapy: Valutazione clinica comparativa della nostra casistica. Bollettino - Lega Italiana contro l'Epilessia. 121-122:227-229.

Study Design/Methods	Cohort study	
Participants	441 patients with medication-resistant epilepsy Median age = 32 years old (range=2-82 years old) 236 males and 205 females Generalized or focal onset epilepsy (majority with focal onset epilepsy) Cohort was attending an outpatient neurology clinic	
Interventions	Topiramate group: n = 93 Levetiracetam group: n = 46	
Outcomes	*Seizure reduction (50% reduction)* Topiramate group: 12.9% (n=12) Levetiracetam group: 32.6% (n=15) *Seizure freedom* Topiramate group: 14.0% (n=13) Levetiracetam group: 17.4% (n=8) *Treatment acceptability (dropouts)* Topiramate group: 14.0% (n=13) Levetiracetam group: 19.6% (n=9)	
Notes	The authors conclude that levetiracetam and lamotrigine show good efficacy, but that there were considerable number of complaints of adverse events with both.	
Study Quality (using GRADE criteria for observational studies)		
	Risk of bias	**Justification for judgment**
Eligibility criteria	Low risk	Cases were exposed to different AED but were selected from the same population. The six groups are reported to be similar at baseline, with respect to socio-demo-

		graphic and clinical characteristics.
Measurement	Low risk	Similar definition and measurement of exposure in the six groups. There were similar outcome assessments in the six groups of exposed patients.
Confounding	Serious risk	There is no adjustment for any known or unknown confounding variable.
Follow-up	Low risk	Follow up time was between 6 and 46 months (median 14 months),which was adequate. The dropout rate was similar lower in the topiramate group compared to the levetiracetam group.
Overall quality	LOW	

NOTE: There were no systematic reviews or RCTs examining the effectiveness and safety of levetiracetam vs. topiramate. However, there were two observational studies that was taken into consideration. Meta-analysis could not be performed on these two observational studies (because the estimates could not be pooled)

[New 2015]

Table 15. Topiramate vs. valproic acid as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy

Question: Should topiramate vs. valproic acid be used as add-on therapy in patients of all ages with medication-resistant convulsive epilepsy?
Bibliography (RCT): Aldenkamp AP, Baker G, Mulder OG, Chadwick D, Cooper P, Doelman J, Duncan R, Gassmann-Mayer C, de Haan GJ, Hughson C et al. (2000). A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. Epilepsia.41(9):1167-1178.

Study Design/Methods	Multi-centre randomized controlled trial	
Participants	53 participants with medication-resistant epilepsy on carbamazepine monotherapy Mean age = 26.5 years old (range = 18-60 years) Focal (with or without secondary generalization)	
Interventions	Topiramate group: n = 24 Valproic acid: n = 29	
Outcomes	*Seizure reduction* Topiramate group: 30% seizure reduction Valproic acid group: 22% seizure reduction *Seizure freedom* Not reported *Treatment acceptability (dropouts)* Topiramate group: 33% (8) Valproic acid group: 14% (4)	
Notes	The authors of this study concluded that there was a similar efficacy profile between topiramate and valproic acid in terms of seizure control, but that the safety profile of topiramate was less desirable then that of valproic acid.	
Study Quality (using GRADE criteria for randomized trials)		
	Risk of bias	**Justification for judgment**
Allocation concealment	Low risk	Randomization was done using a central computer-generator and was stratified by centre.
Magnitude of effect	Serious risk	It is presumed that the magnitude of effect is small. A standard deviation is not reported but the mean difference in seizure reduction is only 7.5%.
Blinding	Moderate risk	The observer was blinded to participant's treatment assignment but the treating physician and participants were not blinded to the treatment.
Follow-up	Serious risk	Follow-up was 8 weeks after maximum dose was obtained, which was inadequate. There was a small proportion of participants lost to follow-up.
Reporting of outcomes	Moderate risk	Reporting of outcomes was similar between groups. However, how the outcomes

		were collected is unclear.
Overall quality	LOW	

NOTE: There were no systematic reviews examining the effectiveness and safety of topiramate vs. valproic acid. However, there was a single RCT that was taken into consideration.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

	COMPARISONS							
OUTCOME	**Carbamazepine vs. phenytoin**	**Lamotrigine vs. placebo**	**Lamotrigine vs. levetiracetam**	**Lamotrigine vs. topiramate**	**Levetiracetam vs. placebo**	**Topiramate vs. placebo**	**Topiramate vs. levetiracetam**	**Topiramate vs. valproic acid**
Seizure reduction	2 observational studies Ashok et al. (1984): OR=7.9 (0.8-78.7), no differences Lesser et al. (1984): OR=1.7(0.3-11.0) No difference	1 systematic review with 11 RCTs Ramaratnam et al. (2010): OR=2.51 (1.86-3.4), favours lamotrigine Trevethan et al. (2006): Single RCT lamotrigine=77 % vs. placebo=40% (p=0.04), favours lamotrigine	1 observational study Fels et al. (2003): OR=2.4 (1.1-5.3), favours levetiracetam	1 observational study Fels et al. (2003): OR=1.4 (0.6-3.0), no difference	1 systematic review with 10 RCTs Mbizvo et al. (2012): RR=2.43 (2.04-2.9), favours levetiracetam *Single RCTs* Baulac et al. (2010): levetiracetam=24.1% reduction vs. placebo=21.4% reduction, no differences Boon et al. (2001): not reported	1 systematic review with 11 RCTs Pulman et al. (2014): RR=2.97 (2.38-3.72), favours topiramate	2 observational studies Bootsma et al. (2008): not reported Fels et al. (2003): OR=1.4 (0.6-0.3), no differences	1 RCT Aldenkamp et al. (2000), OR=1.6 (0.5-5.6), no difference

					Glauser et al. (2006): OR=3.3 (1.75-6.24), favours levetiracetam			
Quality of evidence summary	VERY LOW	LOW	LOW	LOW	LOW	MODERATE	LOW	LOW
Seizure freedom	2 observational studies Ashok et al. (1984): OR=0.1(0.02-0.7), favours phenytoin Lesser et al. (1984): OR=0.2(0.04-1.4), no difference	Not reported in 2 systematic reviews Single RCT Trevethan et al. (2006): lamotrigine=48 % vs. placebo=17%, favours lamotrigine	1 observational study Fels et al. (2003): OR=1.3 (0.5-3.2), no difference	1 observational study Fels et al. (2003): OR=1.7 (0.8-3.6), no difference	1 systematic review with 10 randomized trials Mbizvo et al. (2012): not reported Single RCTs Baulac et al. (2010): lamotrigine=11% vs. placebo=11% no differences Boon et al. (2001): levetiracetam 1000 mg/day=5.5% vs. levetiractem 2000 mg/day=5.7% vs. placebo= 1.2%, favours levetiracetam	1 systematic review with 5 randomized trials Pulman et al. (2014): RR = 3.41 (1.37-8.51), favours topirmate	2 observational studies Bootsma et al. (2008): OR=1.5(1.0-2.2), favours levetiracetam Fels et al. (2003): OR=0.8(0.3-2.0), no differences	1 RCT Aldenkamp et al. (2000): not reported

					Glauser et al. (2006): OR=7(0.9-58.0) no difference			
Quality of evidence summary	VERY LOW	MODERATE	LOW	LOW	MODERATE	LOW	LOW	LOW
Treatment acceptability (dropouts)	2 observational studies Ashok et al. (1984): no differences Lesser et al. (1984): not reported	2 systematic reviews Tjia-Leong et al. (2011): 2 randomized trials, RR 1.27 (0.71-2.26), no difference Ramaratnam et al. (2010): 13 randomized trials, OR = 1.13 (0.83-1.54), no difference	1 observational study Fels et al. (2003): OR=1.1(0.5-2.7), no difference	1 observational study Fels et al. (2003): OR=1.7 (0.8-3.6) no difference	1 systematic review with 11 randomized trials Mbizvo et al. (2012): RR=1.0 (0.8-1.33) no differences *Single RCTs* Baulac et al. (2010): OR=1.2 (0.7-2.0), no differences Boon et al. (2001): levetiracetam 1000 mg/day=7% vs. levetiracetam 2000 mg/day=12.9% vs. placebo=8%, no differences Glauser et al. (2006): OR=0.5(0.2-1.6), no differences	1 systematic review with 10 randomized trials Pulman et al. (2014): Relative risk=2.44 (1.64-3.62), favours topiramate	2 observational studies Bootsma et al. (2008): OR=0.2 (0.1-0.4), favours levetiracetam Fels et al. (2003): OR=0.7(0.3-1,7), no differences	1 RCT Aldenkamp et al. (2000): OR=3.1(0.8-12.1), favours valproic acid
Quality of evidence	VERY LOW	VERY LOW	VERY LOW	LOW	MODERATE	LOW	LOW	LOW

summary								
Mortality	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Evidence to recommendation table

Benefits	Lamotrigine, levetiracetam and topiramate are more effective than placebo as add-on therapy in controlling seizures in patients of all ages with medication-resistant convulsive epilepsy. No systematic reviews of RCTs were found examining the efficacy of carbamazepine, phenobarbital, phenytoin or valproic acid as add-on therapy in controlling seizures in patients of all ages with medication-resistant convulsive epilepsy. No systematic reviews of RCTs were found examining the head-to-head efficacy of any of the anti-epileptic medications of interest for patients with medication-resistant convulsive epilepsy. Anti-epileptic medications have been found to decrease morbidity and premature mortality; therefore, it is considered unethical to compare the efficacy of anti-epileptic medications against placebo alone in patients with established epilepsy, whether medication-resistant or not. This may limit the availability of evidence on the efficacy of anti-epileptic medication.
Harms	All anti-epileptic medications are associated with adverse effects. However, lamotrigine (in two RCTs) and levetiracetam (in one RCT) had comparable withdrawal rates to placebo in patients of all ages with medication-resistant convulsive epilepsy. Topiramate had higher withdrawal rates than placebo in patients of all ages with medication-resistant convulsive epilepsy, based on one systematic review. One RCT found a higher dropout rate due to adverse events compared to valproic acid.
Summary of the quality of evidence	The balance of benefit vs. harms is in favour of treatment of children and adults with medication-resistant convulsive epilepsy. However, the quality of the evidence is low to high for critical outcomes. For important outcomes, the quality of the evidence ranged from very low to moderate.

Value and preferences	
In favour	Treatment is preferred over placebo to reduce seizure frequency, as well as morbidity and mortality associated with ongoing seizures.
Against	All anti-epileptic medications are associated with a risk of medication withdrawal (usually due to adverse events) and other secondary effects, although the benefits outweigh the risks in most studies.
Uncertainty or variability?	There is no major uncertainty or variability. Despite the fact that anti-epileptic medications are associated with some adverse events, most people with medication-resistant convulsive epilepsy would choose to be on these medications to decrease the risk of morbidity and mortality.

Feasibility (including resource use considerations)	Carbamazepine, phenytoin, phenobarbital and valproic acid are included in the WHO Essential Medicines List. However, there is a paucity of research examining the effect of these medications as add-on therapy in patients with medication-resistant convulsive epilepsy. Although the newer anti-epileptic medications (such as levetiracetam, lamotrigine and topiramate) are not on the WHO Essential Medicines List and are significantly more costly than the older anti-epileptic medications, there is evidence to support their use as add-on therapy in patients with medication-resistant convulsive epilepsy.
Uncertainty or variability?	There is some variability in terms of the feasibility of these interventions in some countries, due to the fact that these medications are not on the WHO Essential Medicines List and so cost may prove a barrier to use in low-resource settings.

Recommendation and remarks

Recommendation

Certain newer anti-epileptic medications (lamotrigine, levetiracetam and topiramate) should be offered as add-on therapy in patients with medication resistant convulsive epilepsy.

The essential anti-epileptic medications (carbamazepine, phenobarbital, phenytoin, and valproic acid) may be of benefit as add-on therapy in patients with medication resistant convulsive epilepsy.

Rationale: The balance of benefit versus harms is in favour of treatment with newer antiepileptic medications in medication-resistant convulsive epilepsy. The evidence for essential antiepileptic medications as an add-on therapy was based on observational studies. There were no head-to-head studies comparing the efficacy of the essential anti-epileptic medications and the newer anti-epileptic medications of interest against each other for adults and children with medication resistant convulsive epilepsy. Despite the fact that anti-epileptic medications are associated with some adverse events, most people with medication-resistant convulsive epilepsy would choose to be on these medications to decrease the risk of morbidity and mortality. The newer antiepileptic medications are not on the WHO Essential Medicines List and so cost may prove a barrier to use in low-resource settings.

Remarks

Medication selection should also be appropriate based on the type of epilepsy as some anti-epileptic medications can worsen generalized convulsive seizures (e.g., carbamazepine, phenytoin and phenobarbital should be avoided in patients with myoclonic epilepsy). Patients' comorbidities and childbearing potential also have to be considered when recommending a newer antiepileptic medication in those with medication resistant convulsive epilepsy as some antiepileptic medications are associated with a higher risk of teratogenicity and worst neurodevelopmental outcomes than others (e.g., valproic acid), or could worsen comorbid conditions (e.g., depression, obesity, etc.).
epilepsy as some AEDs are associated with a higher risk of teratogenicity and worst neurodevelopmental outcomes than others (e.g., valproic acid), or could worsen comorbid conditions (e.g., depression, obesity, etc.).

[New 2015]

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High **X Moderate** □ Low □ Very low
Balance of benefits versus harms	**X Benefits clearly outweigh harms** □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	**X No major variability** □ Major variability
Resource use	□ Less resource-intensive **X More resource-intensive**
Strength	**CONDITIONAL**

OTHER REFERENCES

Dua T, Barbui C, Clark N, Fleischmann A, Poznyak V, van Ommeren M, Yasamy T, Ayuso-Mateos JL, Birbeck GL, Drummond C, Freeman M, Giannakopolos P et al (2011). Evidence-Based Guidelines for Mental, Neurological, and Substance Use Disorders in Low- and Middle-Income Countries: Summary of WHO Recommendations. PLoS Medicine.8(11):e1001122. doi:10.1371/journal.pmed.1001122.

Ngugi AK, Bottomley C, Fegan G, Chengo E, Odhiambo R, Bauni E, Neville B, Kleinschmidt I, Sander JW, Newton C (2014). Premature mortality in active convulsive epilepsy in rural Kenya: Causes and associated factors. Neurology. 82(7):582-589. doi:10.1212/WNL.0000000000000123.

Zhang J, Liu W, Chen H, Zia H, Zhou Z, Mei S, Liu Q, Li Y (2014). Multimodal neuroimaging in presurgical evaluation of medication-resistant epilepsy. Neuroimage: Clinical.4:35-44. doi:10.1016/j.nicl.2013.10.017.

[i] Odds ratio (OR)
[ii] Antiepileptic medication (AED)