SYSTEMATIC LITERATURE REVIEW ON THE EFFICACY AND SAFETY OF ANTIEPILEPTIC DRUGS IN PEDIATRIC PATIENTS WITH FOCAL SEIZURES – ARE CURRENTLY APPROVED THERAPIES SUFFICIENT FOR THE MANAGEMENT OF PAEDIATRIC PATIENTS?

PND3

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BACKGROUND

- The prevalence of epilepsy in children ranges approximately from 3.2-5.5 per 1,000 in developed countries to 3.6-44 per 1,000 in developing countries, with a reported global incidence of 41-187 per 100,000 person-years[1]
- Focal seizures originate within networks limited to one hemisphere of the brain and are the most common type of epileptic seizures, constituting up to 60% of all seizures[2,3,4] and majority of childhood epilepsy burden[5]
- Treatment decisions for paediatric epilepsy are highly dependent on patient-specific factors including seizure frequency, epilepsy syndrome type and neurological findings. Various guidelines highlight the need to individualise anti-epileptic drug (AED) therapy, as per paediatric needs[6,7]

OBJECTIVE

- To review the clinical efficacy and safety of AEDs in paediatric patients with focal seizures in order to understand the existing unmet need in the management of these patients and the possible implications of AED choice in clinical practice

METHODS

- A systematic literature review (SLR) was conducted based on a pre-specified protocol as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines
- Searches were conducted for relevant articles indexed in Embase, MEDLINE, MEDLINE In-Process and the Cochrane Library databases using Ovid interface through August 2016, using a combination of Medical Subject Headings (MeSH) and free-text terms following the Patient, Intervention & Comparator, Outcomes, Study design (PICOS) statement approach (Table 1)

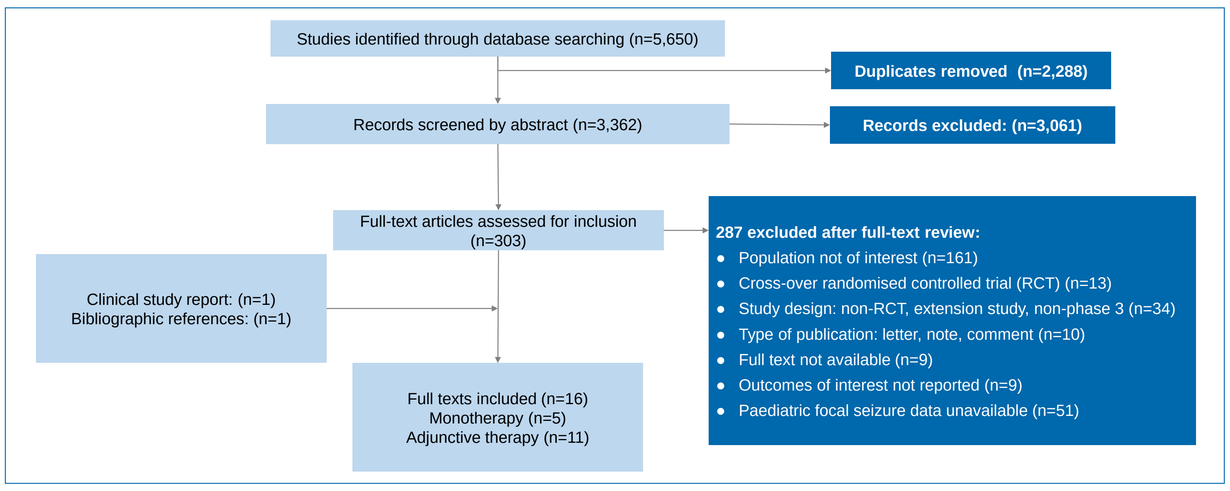
Table 1: Inclusion criteria for studies used in the SLR

Population
• Paediatric patients with focal seizures
Intervention and Comparator
• AEDs administered as monotherapy or adjunctive treatment in defined patient population: brivaracetam, carbamazepine, carisbamate, eslicarbazepine acetate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, retigabine/ezogabine, tiagabine, topiramate, valproic acid, vigabatrin, zonisamide or placebo
Outcomes
• Efficacy outcomes: seizure frequency, seizure freedom
• Safety outcomes: adverse events and treatment withdrawals
Study Design
• Phase III or II/III randomised controlled trials

RESULTS

- Of the 5,650 records retrieved from Ovid, sixteen RCTs were included in the final analysis (Figure 1)

Figure 1: PRISMA diagram for study selection



- Out of 16 included RCTs, 11 evaluated AEDs as adjunctive therapy while five investigated AED monotherapies (Table 1)
- None of the RCTs on adjunctive therapy presented head-to-head comparisons between different AEDs and three of the monotherapy trials were active-controlled RCTs
- The mean age of patients included ranged from 0.8 years to 11.6 years across studies. The mean duration of epilepsy was below 1 year across all monotherapy studies and ranged between 0.4 and 8.9 years in adjunctive therapy studies (Table 2)

Table 2: Baseline patient characteristics for included studies

Study	Treatment (N)	Age Mean (SD; range) years	Male (%)	Duration of Epilepsy; Mean (SD; range) years	Baseline Seizure Frequency Median (range)
Monotherapy studies					
Eun 2011	Low dose zonisamide (65)	8.3 (3.0)	31.0%	0.7 (1.6)[b]	NR
	High dose zonisamide (60)	7.8 (3.0)	34.0%	0.7 (1.0)[b]	NR
Glauser 2007*[£]	Topiramate 50 mg/day (74)	12[a]	46.0%	0.1	NR
	Topiramate 400 mg/day (77)		57.0%		NR
Guerreiro 1997*[£]	Oxcarbazepine (97)	10.2 (5-17)	47.4%	0.6 (0.0-5.2)	0.3[¥]
	Phenytoin (96)	10.9 (6-17)	52.1%	0.7 (0.2-14.0)	0.3[¥]
Sobaniec 2005	Vigabatrin (26)	9.9 (2.30; 5-18)	50.0%	NR	NR
	Carbamazepine (28)	9.0 (3.2; 2-17)	60.7%	NR	NR
Zamponi 1999*	Vigabatrin (38)	7.3 (1-10)	55.3%	NR	NR
	Carbamazepine (32)	9.4 (3-13)	53.1%	NR	NR
Adjunctive therapy studies					
Appleton 1999*	Gabapentin (119)	8.5 (2.4)	49.6%	5.7 (3.0; <1-11.3)	24.1 (2.7-2,9)[€]
	Placebo (128)	8.4 (2.7)	58.6%	5.4 (3.1; <1-11.9)	28 (1.3-698)[€]
Duchowny 1999*	Lamotrigine (98)	NR	48.0%	NR	NR
	Placebo (101)	NR	55.4%	NR	NR
Elterman 1999*	Topiramate (41)	8.8 (3.6; 2-16)	56.1%	NR	22 (2-232)[€]
	Placebo (45)	9.0 (3.4; 2-16)	55.6%	NR	19 (2-1.1)[€]
Glauser 2000*	Oxcarbazepine (138)	11.0 (3-17)	51.0%	NR	12 (3.0-1.5)[€]
	Placebo (129)	11.0 (3-17)	55.0%	NR	13 (2-554)[€]
Glauser 2006*	Levetiracetam (101)	10.2	53.5%	7.4	4.7 (0-696)[¥]
	Placebo (97)	9.8	47.4%	6.8	5.3 (0-467)[¥]
Guerrini 2013*	Zonisamide (107)	11.6 (3.3)	49.5%	5.6 (3.9; 0.4-15.6)	10.5 (4-261)[€]
	Placebo (100)	11.2 (3.2)	55.0%	5.4 (3.7; 0.2-17.1)	10 (4-882)[€]
Novotny 2010[@]	Topiramate 5 mg/kg/day (38)	1.1 (0.6)	58.0%	0.5 (0.0-1.9)[a]	(0-175)[Δ]
	Topiramate 15 mg/kg/day (37)	1.0 (0.5)	51.0%	0.4 (0.0-1.7)[a]	5 (0-78.5)[Δ]
	Topiramate 25 mg/kg/day (37)	0.8 (0.4)	62.0%	0.5 (0.0-1.7)[a]	8 (0-100)[Δ]
	Placebo (37)	1.0 (0.5)	38.0%	0.5 (0.1-1.7)[a]	6 (0-240)[Δ]
Pina-Garza 2005[#]	Low dose oxcarbazepine (64)	NR	55.0%	NR	7.0[¥]
	High dose oxcarbazepine (64)	NR	59.0%	NR	3.8[¥]
Piña-Garza 2008*	Lamotrigine (19)	1.1 (1-2)[a]	63.0%	0.8 (0.3-1.8)[a]	NR
	Placebo (19)	1.2 (0.2-2)[a]	47.0%	0.7 (0.1-1.9)[a]	
Pina-Garza 2009[#]	Levetiracetam (58)	2.0 (1.1)	50.0%	NR	15.2 (4.5-39.0)[¥]
	Placebo (51)	2.0 (1.0)	48.2%	NR	6.8 (2.0-16.2)[¥a]
SCO/BIA-2093-305*	Eslicarbazepine acetate (134)	9.9 (4.2)	47.8%	2-6 years: 3.1 (1.4) 7-11 years: 6.6 (3.0) 12-18 years: 8.9 (4.2)	11.5 (3.7-605.8)[€]
	Placebo (129)	9.5 (3.9)	48.1%	2-6 years: 3.6 (1.4) 7-11 years: 6.3 (2.7) 12-18 years: 8.8 (4.1)	7.0 (3.9-1,972.5)[€]

*Tablet; [#]Oral suspension; [@]Sprinkle capsules or oral liquid formulation; [£]Reported for focal seizures and generalised tonic-clonic seizures; [a]Median value; [Δ]Seizure frequency per day; [¥]Seizure frequency per 7 days; [€]Seizure frequency per 28 days; NR: not reported

RESULTS (CONTINUED)

- Oxcarbazepine, phenytoin and different doses of topiramate and zonisamide were successful in preventing all seizures in over 60% of patients when administered as monotherapy although no statistically significant differences vs comparator were reported
- A significantly higher proportion of seizure-free patients were observed with adjunctive zonisamide versus placebo (14% vs. 3% at 12 weeks; p=0.0049) (Table 3)

Table 3: Seizure freedom data reported in the included studies

Study	Treatment	Proportion with no seizures	Seizure-free duration
Monotherapy studies			
Eun 2011	Low dose zonisamide	60.3%	24 weeks
	High dose zonisamide	66.0%	
Glauser 2007[#]	Topiramate 50 mg/day	78.0%	24 weeks
	Topiramate 400 mg/day	86.0%	
	Topiramate 50 mg/day	60.0%	48 weeks
	Topiramate 400 mg/day	81.0%	
Guerreiro 1997[#]	Oxcarbazepine	61.0%[&]	48 weeks
	Phenytoin	60.0%[&]	
Adjunctive therapy studies			
Elterman 1999[#]	Topiramate	5.0%	8 weeks
	Placebo	0.0%	
	Topiramate	10.0%	16 weeks
	Placebo	5.0%	
Glauser 2000[#]	Oxcarbazepine	3.7%	14 weeks
	Placebo	0.8%	
Glauser 2006[#]	Levetiracetam	6.9%	14 weeks
	Placebo	1.1%	
Guerrini 2013[#]	Zonisamide	14.0%[!]	12 weeks
	Placebo	3.0%[!]	
Pina-Garza 2005*[@]	Low dose oxcarbazepine	NR[$]	48 weeks
	High dose oxcarbazepine	NR[$]	
SCO/BIA-2093-305[#]	Eslicarbazepine acetate	3.9%	12 weeks
	Placebo	2.4%	

[#]Tablet; *Oral suspension; [@]Age group ≤14 years; [&]Oxcarbazepine vs. Phenytoin: 1.04 [95% CI: 0.52 to 2.08]; [$]Low dose vs. High dose: 2.23 [95% CI: 0.93 to 5.35]; [!]p=0.0049

- Among adjunctive therapy RCTs, only levetiracetam, lamotrigine, and zonisamide showed significantly higher 50% responder rates compared to placebo (p<0.005) (Table 4)

Table 4: 50% responder rate data reported in the included studies

Study	Treatment	50% Responder Rate
Adjunctive therapy studies		
Appleton 1999*	Gabapentin	21%
	Placebo	18%
Duchowny 1999*[1]	Lamotrigine	42%[a], 45%[b]
	Placebo	16%[a], 15%[b]
Glauser 2000*	Oxcarbazepine	41%
	Placebo	22%
Glauser 2006*[1]	Levetiracetam	44.6%
	Placebo	19.6%
Guerrini 2013*	Zonisamide	50%
	Placebo	31%
Novotny 2010[@]	Topiramate 5 mg/kg/d	27%
	Topiramate 15 mg/kg/d	38%
	Topiramate 25 mg/kg/d	44%
	Placebo	36%
Pina-Garza 2009[#1]	Levetiracetam	43.1%[A], 54.5%[€], 47.4%[$], 35.7%[&]
	Placebo	19.6%[A], 20.0%[€], 25.0%[$], 16.0%[&]
SCO/BIA-2093-305*	Eslicarbazepine acetate	30.6%
	Placebo	31.0%

*Tablet; [#]Oral suspension; [@]Sprinkle capsules or oral liquid formulation; [1]statistically significant; [A]1 month to <4 years; [€]1 month to <1 year; [$]1 month to <2 year; [&]2 years to <4 years; responders rate defined as ≥50% reduction in seizure frequency from baseline; [a]From Week 1 to Week 18; [b]From Week 7 to Week 18

- Phenytoin was associated with significantly higher rate of withdrawals due to adverse events (AEs) compared to oxcarbazepine (18% vs 3%; p=0.002) (Table 5)
- Among adjunctive therapy RCTs, the proportion of patients withdrawing due to any cause ranged from 0% to 21.9%, while the rate of withdrawals due to AE ranged between 0% to 10% for all AEDs. Withdrawals due to death were below 1% patients for all AEDs
- Safety data on the use of monotherapy was limited and adjunctive AED therapies were commonly associated with risk of somnolence, dizziness, nausea, vomiting, and diarrhoea.

Table 5: Frequency of any general AEs and study withdrawals reported in the included studies

Study	Treatment	Evaluated Population, N	Any AE	Any Drug-Related AE	Withdrawals due to any cause	Withdrawals due to AE	Withdrawals due to Deaths
Monotherapy studies							
Eun 2011	Low dose zonisamide	65	NR	NR	NR	3.1%	0.0%
Guerreiro 1997	Oxcarbazepine	81	NR	NR	NR	2.5%*	NR
	Phenytoin	77	NR	NR	NR	18.2%*	NR
Sobaniec 2005	Vigabatrin	26	NR	NR	14.0%	NR	NR
Adjunctive therapy studies							
Appleton 1999	Gabapentin	119	NR	34.0%	17.6%	2.3%	0%
	Placebo	128	NR	20.0%	21.9%	5.0%	0%
Duchowny 1999	Lamotrigine	98	NR	NR	10.2%	5.1%	NR
	Placebo	101	NR	NR	15.8%	5.9%	NR
Elterman 1999	Topiramate	41	NR	NR	0.0%	0.0%	0.0%
	Placebo	45	NR	NR	4.4%	2.2%	0.0%
Glauser 2000	Oxcarbazepine	138	91.0%	NR	NR	10.0%	0.7%
	Placebo	129	82.0%	NR	NR	3.0%	0.0%
Glauser 2006	Levetiracetam	101	88.1%	55.4%	6.9%	5.0%	NR
	Placebo	97	91.8%	40.2%	14.4%	9.3%	NR
Guerrini 2013	Zonisamide	107	55.1%	33.6%	13.1%	0.9%	0.9%
	Placebo	100	50.0%	24.0%	10.0%	3.0%	0.0%
Novotny 2010	Topiramate 5 mg/kg/day	38	81.0%	NR	NR	4.0%	0.0%
	Topiramate 15 mg/kg/day	37		NR	NR	0.0%	0.0%
	Topiramate 25 mg/kg/day	37		NR	NR	0.0%	0.0%
	Placebo	37	51.0%	NR	NR	5.0%	0.0%
Pina-Garza 2005	Low dose oxcarbazepine	64	40.6%	4.7%	10.0%	3.9%	NR
	High dose oxcarbazepine	64	71.8%	31.3%			NR
Pina-Garza 2008	Lamotrigine	19	NR	NR	10%	0%	NR
	Placebo	19	NR	NR	0%	0%	NR
SCO/BIA-2093-305	Eslicarbazepine acetate	134	83.6%	41.8%	10.2%	5.2%	0.7%
	Placebo	129	72.9%	24.8%	8.7%	2.3%	0.8%

*p=0.002; AE: adverse event; NR: not reported

CONCLUSIONS

- **High quality evidence on the efficacy and safety of AEDs for focal seizures in paediatric patients is limited, especially in monotherapy**
- **The subtle differences observed in the efficacy and safety profiles of AEDs highlight the need for more available therapy options. This will ensure that treatment choices are tailored to the patient, allowing the combination of efficacy and safety profiles for AEDs to best fit the needs of individual patients**

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