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Pharmacotherapy of Focal Epilepsy in Children: A Systematic Review of Approved Agents

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Abstract

Background—Partial-onset seizures contribute the bulk of seizure burden in childhood epilepsy. The therapeutic decision making involves consideration of factors specific to drug, patient and socioeconomic situation.

Objectives—This paper systematically reviews the available efficacy/effectiveness evidence for various anti-epileptic drugs (AED) as monotherapy and adjunctive therapy for partial-onset seizures in children.

Data sources—Relevant randomized clinical trials (RCTs) were identified by a structured PubMed search, supplemented by an additional hand search of reference lists and authors' files.

Study appraisal and synthesis methods—Eligible studies were reviewed and data extracted into tables. Included RCTs were classified based on accepted published criteria.

Outcomes—Only efficacy and effectiveness outcome measures were evaluated since there is little scientifically rigorous comprehensive AED adverse effects data.

Results—Oxcarbazepine is the only AED with Class I evidence for efficacy/effectiveness as initial monotherapy for partial-onset seizures in children. Carbamazepine, clobazam, lamotrigine, phenobarbital, phenytoin, topiramate, valproate, vigabatrin and zonisamide have, at best, Class III efficacy/effectiveness evidence for monotherapy of partial-onset seizures in children. For adjunctive therapy, gabapentin, lamotrigine, levetiracetam, oxcarbazepine and topiramate have Class I efficacy/effectiveness evidence for treatment of pediatric partial-onset seizures.

Conclusions and implications of key findings—This efficacy/effectiveness analysis must not be used in isolation when selecting therapy. AED selection for a specific child needs to integrate a drug's efficacy/effectiveness data with its safety and tolerability profile, pharmacokinetic properties, available formulations, and patient specific characteristics. It is critical that physicians and patients incorporate all these relevant variables when choosing AED therapy.

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1 Introduction

Partial-onset seizures constitute up to 60 % of all seizure types in population-based studies [1]. Based on pediatric studies using the International Classification of Epileptic Seizures [2], partial-onset seizures contribute the bulk of seizure burden in childhood epilepsy. Both for initial monotherapy in children with new-onset or untreated partial seizures, or, for adjunctive therapy in children who have failed one or more adequately chosen anti-epileptic drugs (AEDs), the actual drug choice depends on several factors. Decision making incorporates patient-related variables like age, gender, comorbidities; drug-specific factors like adverse effects, pharmacokinetics, and interactions; and, socioeconomic factors like availability and cost. Having chosen an appropriate AED, the goal of therapy is to achieve complete seizure remission, minimal or no drug-related adverse effects and the best quality of life for the child. In some children with medically refractory epilepsy, the goals include substantial seizure reduction rather than complete control.

Ideally, the following review would include a comprehensive systematic analysis of all factors involved with drug decision making. Unfortunately, the methodology of epilepsy clinical studies prevents an evidence-based analysis of AED dose-dependent adverse effects, idiosyncratic reactions, chronic toxicities, teratogenicity or differential pharmacokinetics. As a result, this paper examines only the available efficacy/effectiveness evidence for various AEDs for initial monotherapy and adjunctive therapy of partial seizures in children. For Class I studies, the most common adverse effects whose frequency was 5 % higher than the comparator arm are summarized.

2 Methods

2.1 Search Strategy and Classification of Studies

A PubMed search was conducted (July 2012) with the term 'Epilepsies, Partial' [Mesh], using the study type and age filters to identify randomized clinical trials (RCTs), systematic reviews and meta-analyses for the pediatric population. The reference lists of identified studies were hand searched to obtain additional relevant trials. The following types of studies were excluded: those reporting only quality-of-life outcomes, those focused only on cognitive or behavioral AED effects as outcome(s), those only partially including adolescents (e.g. patients >16 years of age) or partially including children (e.g. patients aged >12 years, but not reporting separate data for children), studies comparing two different types of formulations for the same compound, or studies reporting only serum levels or neurophysiologic data as outcomes. Eligible studies were reviewed by both authors and data extracted into tables for analysis (Fig. 1). This review's criteria for evaluation and classification of each study's level of evidence were derived from the International League Against Epilepsy (ILAE) guideline for initial monotherapy in seizures and epilepsy syndromes and its recent update [3, 4] and the joint report of American Academy of Neurology and American Epilepsy Society on treatment of refractory epilepsy [5]. The justifications for these criteria have been previously published and are not discussed here (Table 1). The only modification to the published criteria was the addition of a minimum duration (12 weeks) for the double-blind phase of an adjunctive therapy study to be considered to have Class 1 evidence. This represents a balance between the desire for longer

treatment observation periods (as in monotherapy trials) and the safety concern of not exposing a study subject with refractory epilepsy to an ineffective medication longer than necessary.

2.2 Definitions

Certain terms used in this review are clarified below. Partial-onset seizures, now referred to as focal seizures [6], are those seizures in which the first clinical or electroencephalographic change(s) indicate initial activation of a system of neurons limited to part of one cerebral hemisphere. In this review, the terms partial-onset and focal are used interchangeably. Efficacy is the ability of an AED to produce seizure freedom, whereas, tolerability represents incidence, severity and impact of AED-related adverse effects. Effectiveness is an aggregate of efficacy and tolerability, reflected in patients' retention on treatment [3]. It is sometimes measured negatively by discontinuation of treatment.

2.3 Outcome Measures

For monotherapy of new-onset or untreated seizures, the efficacy outcome was complete seizure freedom during the observed unit time. The efficacy outcomes conventionally used in clinical trials for medically refractory epilepsy include the 50 % responder rate and median percentage reduction in seizure frequency. We believe the former to be more clinically relevant and our choice for this review. The responder rate represents the proportion of patients experiencing a reduction of 50 % in seizure frequency during the treatment phase compared with the baseline phase. The effectiveness outcomes are similar to the efficacy outcomes for both situations and are based on retention of patients on study medication. This measure is an aggregate capturing both efficacy and tolerability, as discontinuation of study treatment is either due to lack of efficacy or unacceptable adverse effects or both. Pertinent outcome data were extracted from the identified studies and are summarized under each AED.

3 Results

AEDs are discussed in alphabetical order, with monotherapy evidence followed by adjunctive therapy data.

3.1 Carbamazepine

3.1.1 Monotherapy—In a Class III double-blind RCT comparing topiramate (TPM) (100 or 200 mg/day) with either carbamazepine (CBZ 600 mg/day) or valproate (VPA 1250 mg/day), the time to first seizure, time to exit based on clinical response and the proportion of seizure-free patients during last 6 months of treatment in the pediatric partial-onset seizure subset were statistically similar across trial arms [7]. The subgroup with partial-onset seizures consisted of 67 patients aged 6–16 years, 17 of whom received CBZ. Another Class III study comparing CBZ or phenytoin (PHT) with clobazam (CLB) is discussed in Sect. 3.2. One meta-analysis examined CBZ versus oxcarbazepine (OXC) as initial monotherapy. However, the only clinical trial with adequate outcome measures excluded children. Hence, no conclusions concerning efficacy could be made comparing CBZ with OXC in children [8].

3.1.2 Adjunctive Therapy—For adjunctive therapy, one study ($n = 51$) evaluated PHT and CBZ in patients with partial-onset seizures unresponsive to barbiturates. However, this study had a before-after comparison design [9], and found about two-thirds of the patients to be seizure free during the 6-month study period, with better efficacy in secondarily generalized seizures. The trial did not report differential efficacy or PHT versus CBZ as an outcome, and hence remains uninformative [9].

3.2 Clobazam

A Class III double-blind RCT showed retention on CLB for the first 12 months of therapy to be equivalent to standard therapy (either CBZ or PHT). This outcome was reported for the entire study cohort that included both untreated and previously treated children with either partial-onset or primary generalized seizures. In the untreated subgroup ($n = 115$), no difference was found between CLB ($n = 63$) and CBZ ($n = 52$) for the retention on therapy for the first 12 months, though the data for partial-onset seizures were not presented separately [10]. There is no systematic evidence for use of CLB as adjunctive therapy in a pediatric age group.

3.3 Clonazepam

In the only Class III double-blind study comparing CBZ with clonazepam (CLN) the sample size of each group was insufficient (CBZ = 6, CLN = 8) to draw any efficacy or effectiveness conclusions [3]. There is no systematic evidence for use of CLN as adjunctive therapy in a pediatric age group.

3.4 Gabapentin

3.4.1 Monotherapy—One clinical trial investigated use of gabapentin (GBP) as monotherapy in children with benign epilepsy with centro-temporal spikes. This Class III double-blind, placebo-controlled, forced-exit trial compared GBP ($n = 113$) to placebo ($n = 112$) in 225 children with benign epilepsy with centro-temporal spikes. The study's two statistical analyses showed slightly different results: in one GBP had superior effectiveness compared with placebo (Wilcoxon test, $p = 0.0395$) while the other showed a trend (log rank test, $p = 0.06$) [11]. This study has only appeared in abstract form.

3.4.2 Adjunctive Therapy—A single Class I study evaluated the efficacy of GBP as adjunctive therapy in 247 children aged 3–12 years with refractory partial seizures in a 12-week double-blind placebo-controlled trial where the dose was up-titrated to 23–35 mg/kg/day [12]. The primary efficacy measure was the response ratio, which is calculated by comparing seizure frequency during baseline (B) with seizure frequency during treatment (T): response ratio = $(T - B)/(T + B)$. For comparison purposes, it was evaluated using analysis of variance, including for effects for treatment and center. Children randomized to the GBP arm ($n = 119$) had a median decrease in the frequency of complex partial seizures of 35 % (versus 12 % in the placebo arm, $n = 128$) and of 28 % for secondarily generalized seizures as compared with 13 % increase in the placebo arm (p -value for response ratio = 0.0407). The discontinuation rate was 5 % for children on GBP versus 2 % for those on placebo. Common adverse effects reported were viral infection (10.9 %), fever (10.1 %), nausea/vomiting (8.4 %), somnolence (8.4 %), and hostile behavior (7.6 %) [12].

3.5 Lamotrigine

3.5.1 Monotherapy—For monotherapy of new-onset or untreated partial seizures, lamotrigine (LTG) had similar efficacy/effectiveness to CBZ in a Class III open-label trial [13]. Additionally, two meta-analyses have examined LTG versus CBZ monotherapy for epilepsy; however, the total number of children studied was too small to draw any definitive conclusions [14, 15].

3.5.2 Adjunctive Therapy—One Class I study evaluated efficacy of adjunctive LTG versus placebo in 199 children aged 2–16 years with partial seizures [16]. The target dose of LTG varied depending on the baseline medication(s) at the time of randomization: 1–3 mg/kg/day in case of VPA only, 1–5 mg/kg/day in case of an enzyme-inducing AED (PHT, CBZ, phenobarbital [PHB]) along with VPA, and 5–15 mg/kg/day in case of the child only on an enzyme-inducing AED. A decrease of 44 % in weekly seizure frequency was observed in children on LTG ($n = 98$) as compared with 12.8 % in those on placebo ($n = 101$, $p = 0.012$). The proportion of patients having a reduction of >50 % in weekly seizure burden was 45 % and 25 % for LTG and placebo arms, respectively ($p = 0.004$). The discontinuation rate due to adverse events was not statistically different for LTG (5 %) and placebo (6 %) arms. The most commonly reported adverse effects included somnolence (24.5 %), vomiting (22.4 %), dizziness (21.4 %), headache (18.4 %), rash (16.3 %), fever (14.3 %), diarrhea (13.3 %), abdominal pain (13.3 %), tremor (12.2 %), nausea (11.2 %), asthenia (11.2 %), and ataxia (10.2 %) [16].

A Class III efficacy and tolerability study on adjunctive LTG for partial-onset seizures in children aged 1–24 months used a responder-enriched design. All patients received adjunctive LTG during an open-label phase (maximum maintenance dose 5.1 mg/kg/day for children on non-enzyme-inducing AED or VPA, and 15.6 mg/kg/day for those on a non-enzyme-inducing AED). Patients meeting response criteria (all ‘optimized’ patients i.e., those with maximum seizure control and minimum adverse events, with at least 40 % reduction in partial-onset seizures from the historic baseline) were randomly assigned to double-blind treatment for 8 weeks with continued LTG ($n = 19$) or withdrawal to placebo ($n = 19$) while maintaining other AEDs [17]. The proportion of patients who met exit criteria or withdrew before completing the double-blind phase was lower with LTG (58 %) as compared with placebo (84 %) but the difference was not significant. A secondary outcome of median time to exit was longer with LTG (42 days) than with placebo (22 days) [18].

3.6 Levetiracetam

3.6.1 Monotherapy—No Class I monotherapy RCTs have been conducted using levetiracetam (LEV) in children with new-onset or untreated partial-onset seizures.

3.6.2 Adjunctive Therapy—A Class I multicenter RCT evaluated the efficacy and tolerability of LEV as adjunctive therapy in children aged 4–16 years in medically refractory partial-onset seizures with an 8-week baseline and 14-week double-blind treatment period [19]. During the double-blind phase ($n = 198$) patients received either adjunctive LEV (up-titrated to 60 mg/kg/day) or placebo. The reduction in weekly seizure frequency for adjunctive LEV over placebo therapy was significant (26.8 %; $p = 0.0002$; 95 % CI 14.0 %

to 37.6 %). A >50 % reduction in weekly seizure frequency was attained in 44.6 % of the LEV group (45/101) compared with 19.6 % (19/97) receiving placebo ($p = 0.0002$). The most common treatment-emergent adverse events were somnolence (23 %), vomiting (15 %), anorexia (13 %), behavioral hostility (12 %), cough (11 %), nervousness (10 %), asthenia (9 %), diarrhea (8 %), dizziness (7 %), and emotional lability (6 %). A similar number of patients in each group required a dose reduction or withdrew from the study as a result of an adverse event.

Another multicenter, double-blind, randomized, placebo-controlled Class II study evaluated the efficacy and tolerability of adjunctive LEV in infants and younger children (aged 1 month to <4 years) with partial-onset seizures inadequately controlled with <2 AEDs [20]. This study consisted of a 48-h inpatient baseline video-EEG and a 5-day inpatient treatment period (1-day up-titration; 48-h evaluation video-EEG in the last 2 days). Children who experienced at least two partial-onset seizures during the 48-h baseline video-EEG were randomized to either LEV [40 mg/kg/day (age 1 to <6 months); 50 mg/kg/day (age 6 months to <4 years)] or placebo. The duration of the double-blind period was 20 days. Of 175 patients screened, 116 patients were randomized (60 LEV, 56 placebo), and 111 completed the study. The 50 % responder rate for mean daily partial-onset seizures frequency assessed by video-EEG monitoring was 43.1 % for LEV (modified intention-to-treat population, $n = 58$) versus 19.6 % for placebo ($n = 51$; $p = 0.013$), with odds ratio for response 3.11 (95 % CI 1.22–8.26). The median percent reduction from baseline in average daily partial-onset seizure frequency was 43.6 % for LEV and 7.1 % for placebo. The most frequently reported treatment-emergent adverse events were somnolence (13.3 %) and irritability (11.7 %).

3.7 Oxcarbazepine

3.7.1 Monotherapy—A single Class I study has demonstrated differential effectiveness between OXC and PHT [21]. This multicenter study randomized children aged 5–18 years with partial or generalized seizures to receive either PHT or OXC in 1:1 parallel-group design. The subgroup with partial-onset seizures consisted of 151 children, 73 being on OXC. The double-blind treatment phase consisted of an 8-week flexible titration period (starting dose 150 mg/day OXC or 50 mg PHT, increased gradually based on clinical response) followed by a 48-week maintenance period (OXC 450–2400 mg/day, PHT 150–800 mg/day, both in three divided doses). The primary efficacy outcome was proportion of seizure free patients with at least 1 assessment during maintenance period. The primary tolerability outcome was the proportion of patients who prematurely discontinued the study medication due to adverse experiences. Clinical utility was assessed by comparing treatment retention (rate of premature discontinuation either due to adverse events or unsatisfactory therapeutic response). In the primary efficacy analysis, no significant difference was seen between the groups ($p = 0.91$). During the maintenance period, 60 % of patients with partial seizures were seizure free in the OXC group versus 62 % in the PHT group. However, in the primary tolerability analysis there was a statistically significant difference between groups favoring OXC, with only two OXC recipients withdrawing due to adverse effects (rash in both cases), as compared with 14 PHT recipients ($p = 0.002$ based on log-rank test for time to discontinue due to adverse effects).

Two meta-analyses have examined the efficacy of OXC as monotherapy in children with partial-onset seizures. The first meta-analysis included individual patient data from eight double-blind RCTs, five of which were called adequate and well controlled. For these five adequate and well controlled studies, the two groups were labeled treated (OXC 600–2400 mg/day, $n = 24$) and control (OXC 300 mg/day or placebo, $n = 23$), respectively. The other three studies contributed an additional 113 patients who were classified as treated. The outcomes included time-to-reach protocol-specific endpoint (adequate and well controlled studies only) and a change in seizure frequency (all studies). The first outcome showed a trend towards superior efficacy of OXC in the treated group but did not reach statistical significance. However, the reduction in seizure frequency was significantly in favor of OXC for both adequate studies and in an analysis combining all studies [22]. Another meta-analysis included both adults and children, and examined the Class I study already described in this section [21]. The overall conclusion was that “For patients with partial onset seizures OXC is significantly less likely to be withdrawn, but current data do not allow a statement as to whether OXC is equivalent, superior or inferior to phenytoin in terms of seizure control” [23].

3.7.2 Adjunctive Therapy—One double-blind placebo-controlled study has generated Class I evidence for efficacy of OXC as adjunctive therapy in children aged 3–17 years ($n = 267$, OXC = 138, placebo = 129) with a target dose of 30–46 mg/kg/day [24]. The 50 % responder proportion was 41 % in children receiving OXC versus 22 % in those taking placebo ($p = 0.0005$). A 35 % median reduction in seizure frequency was observed among children on OXC as compared with 8.9 % for those on placebo ($p = 0.0001$). The discontinuation rate related to adverse effects was 10 % in the OXC group versus 3 % in the placebo group. Occurrence of rash was noted in 4 % of children on OXC and 5 % children on placebo. Other common adverse effects reported were somnolence (35 %), headache (32 %), dizziness (29 %), ataxia (14 %), nystagmus (10 %), vomiting (36 %), nausea (22 %), abdominal pain (9 %), fatigue (13 %), and diplopia (17 %).

Another Class III dose comparison trial tested efficacy, safety and pharmacokinetics of high-dose (60 mg/kg/day) versus low-dose (10 mg/kg/day) OXC in children aged 1 month to <4 years ($n = 128$) with inadequately controlled partial-onset seizures taking up to two concomitant AEDs [25]. The primary efficacy outcome was change in 24-h frequency or electrographic partial-onset seizures with a behavioral correlate assessed in the previous 72 h of continuous video-EEG monitoring in the treatment phase, compared with baseline seizure frequency. The median absolute change in seizure frequency per 24 h was greater in the high-dose group (−2.00) than the low-dose group (−1.37, $p = 0.043$). The median percentage reduction was also higher in the high-dose group (83.3 %) versus 46.2 % in the low-dose group ($p = 0.047$). Somnolence and pyrexia occurred in >10 % of children as adverse events. Importantly, the duration of treatment phase after randomization, was different for the two arms of this trial. The high-dose arm had an additional 26-day titration period before a 9-day maintenance period, which was common to both arms.

3.8 Phenobarbital

The efficacy/effectiveness of PHB monotherapy in children with partial-onset seizures was similar to CBZ, PHT and VPA in Class III open-label trials [26–28]. Since none of these other AEDs have Class 1 efficacy/effectiveness data as initial monotherapy, the status of PHB as monotherapy remains undefined. There is no systematic evidence for the efficacy, effectiveness or tolerability of PHB as adjunctive therapy in children with refractory partial-onset seizures.

3.9 Phenytoin

The study by Guerreiro et al. [21] described in Sect. 3.7.1 provided efficacy (62 % patients with seizure freedom during maintenance period) and tolerability (14 adverse effect-related withdrawals) data for PHT in children with partial-onset seizures. In this study, the main causes of withdrawal were reported to be hypertrichosis and/or gingival hyperplasia ($n = 10$), and rash ($n = 4$, one also having acute cerebellar syndrome). Overall, the efficacy results were not statistically different between compounds but the tolerability and effectiveness of PHT were inferior as compared with OXC. There is no systematic evidence for the efficacy, effectiveness or tolerability of PHT as adjunctive therapy in children with refractory focal seizures.

3.10 Stiripentol

No Class I monotherapy RCTs have been conducted using stiripentol (STP) in children with new-onset or untreated partial-onset seizures. As adjunctive therapy, STP is approved in Europe for treatment of severe myoclonic epilepsy of infancy (Dravet's syndrome), with “orphan designation” for other indications. A Class III open-label trial examined the efficacy of adjunctive STP in children with refractory partial-onset seizures already receiving CBZ [29]. In an enrichment-withdrawal design, among the 67 children who entered a 4-month open-label adjunctive STP period following a 1-month single-blind baseline, 32 responders (50 % decrease in seizure frequency compared with baseline during the third month of the open period) were randomized for 2 months either to continue STP ($n = 17$) or to withdraw to placebo ($n = 15$). The primary efficacy endpoint of forced exit by a 50 % increase in seizures compared with baseline was achieved in six patients on STP and eight on placebo (not significant). However, a decrease in seizure frequency compared with baseline was greater on STP (–75 %) than on placebo (–22 %, $p < 0.025$).

3.11 Topiramate

3.11.1 Monotherapy—In the Class III study comparing TPM/CBZ/VPA described in Sect. 3.1.1 [7], the proportion of children with no seizures during the last 6 months of double-blind treatment was 63 %, 59 %, 53 % and 39 % for patients receiving TPM 100 mg/day, TPM 200 mg/day, VPA and CBZ, respectively. The incidence of adverse events of sufficient severity to cause discontinuation of study treatment was 11 %, 18 %, 32 % and 4 %, respectively for these same four groups. These outcomes were not reported separately for children with partial seizures, which constituted 56.3 % (67/119) of the total study population [7]. No efficacy or effectiveness outcome data were reported for the pediatric partial-onset seizure subset of two high- versus low-dose forced-exit TPM RCTs [30, 31].

However, no statistical difference was found in seizure freedom rates at 12 months between 400 mg/day (81 %) and 50 mg/day (60 %) of TPM in the latter study [31].

3.11.2 Adjunctive Therapy—A Class I study has generated evidence for the efficacy of TPM as adjunctive therapy versus placebo in children aged 2–16 years ($n = 86$, TPM = 41, placebo = 45) with partial-onset seizures [32]. In this 16-week trial, the TPM dose was titrated from 25 mg/day up to 125–400 mg/day. The 50 % responder rate was 39 % for children taking TPM as compared with 20 % for those on placebo ($p = 0.080$). The median reduction in seizure frequency was 33 % versus 10.5 % for TPM and placebo groups, respectively ($p = 0.034$). No child taking TPM discontinued it because of intolerable adverse effects, whereas two children did so in the placebo group. Common adverse effects reported included purpura or other bleeding problems (15 %), somnolence (12 %), anorexia (12 %), emotional lability (12 %), rash (12 %), mood problems (10 %), aggression (10 %), nervousness (10 %), and diarrhea (10 %).

In another Class II double-blind, placebo-controlled, international dose comparison study [33], infants (mean age = 12 months, $n = 149$) with partial-onset seizures were randomized to receive adjunctive 5, 15, 25 mg/kg/day of TPM and placebo, respectively for 20 days. Median percentage reduction from baseline in daily seizure frequency assessed with 48-h video-EEG was not significantly different between any daily dose of TPM (20.4 % for 25 mg/kg/day) versus placebo (13.1 %) in an intention-to-treat population ($p = 0.97$). Treatment-emergent adverse events experienced by 5 % of patients in any of the TPM groups included skin problems, bronchospasm, somnolence, nervousness, anorexia, weight loss, vomiting, excessive salivation, dry mouth, diarrhea and ataxia.

3.12 Valproate

In the Class III study by Wheless et al. [7] described in Sect. 3.1.1, VPA had similar efficacy/effectiveness as TPM. Additional multiple Class III open-label trials have compared VPA with CBZ [34, 35], PHT [36, 37], both CBZ and PHT [38], and, with CBZ, PHT and PHB [39]. There was no statistical difference among reported estimates for efficacy/effectiveness in these studies. There are no relevant trials for use of VPA as adjunctive therapy in children with partial-onset seizures.

3.13 Vigabatrin

Three Class III studies have reported similar efficacy and effectiveness between vigabatrin (VGB) and CBZ as monotherapy [40–42]. In a predominantly adult study that included an unknown number of adolescents aged 12–18 years old [42], 459 patients from 44 European centers were randomized to either VGB (2 g day, $n = 229$) or CBZ (600 mg/day, $n = 230$). On intention-to-treat analysis, time to withdrawal for lack of efficacy or adverse effects did not differ between groups. No significant difference was found between VGB and CBZ for time to achieve the 6-month seizure remission period. However, time to first seizure after 6 weeks from randomization was significantly longer in the CBZ group as compared with the VGB group ($p = 0.0001$). There are no relevant trials for use of VGB as adjunctive therapy in children with focal seizures.

3.14 Zonisamide

A Class III open-label RCT compared low (3–4 mg/kg/day, $n = 65$) and high (6–8 mg/kg/day, $n = 59$) doses of zonisamide (ZNS) in children with newly diagnosed epilepsy, 81 % of whom were classified as having localization-related epilepsy. The proportion of patients achieving the primary outcome measure (seizure-free rate for 6 months) was comparable in both groups (63.1 % vs. 57.6 % respectively, $p = 0.66$) on intention-to-treat analysis [43]. There are no relevant trials for use of ZNS as adjunctive therapy in children with partial-onset seizures.

3.15 Other Drugs

There are a few AEDs approved for use in the pediatric age group, despite lack of published Class I or II level of evidence studies. Tiagabine (TGB) is approved by the US Food and Drug Administration (FDA) for adjunctive use in children over 12 years of age with partial-onset seizures. However, there are no dedicated published trials for TGB in the pediatric age group. The available evidence is from predominantly adult studies for TGB as adjunctive therapy in refractory partial-onset seizures, which included a proportion of adolescents above 12 years of age [44–46].

Similarly, there is no controlled evidence for the efficacy of primidone in pediatric trials, though it is approved for use in children [47].

Although felbamate (FBM) is approved by the FDA for treatment of seizures in the context of Lennox–Gastaut syndrome, its status for partial-onset seizures occurring outside this context is uncertain. FBM has been tested as monotherapy and adjunctive therapy in adults with partial-onset seizures [48–51]; however, it has only open-label uncontrolled efficacy data (Class IV) in children for adjunctive treatment in refractory partial-onset seizures [52], which are not reviewed further.

4 Additional Issues

4.1 Methodology Limits Applicability to Clinical Practice

There is a paucity of good quality evidence particularly for monotherapy of new-onset or untreated partial-onset seizures in children (Table 2). In this regard, since placebo control design is considered unethical (except for studies of benign epilepsy with centrottemporal spikes, where the need for treatment is not clear), alternative active control designs like pseudo-placebo (comparison with lowest dose of standard treatment) or adjunctive-taper-to-monotherapy design are used. Further, the duration of trial is very short e.g. in pre-surgical withdrawal design. These design issues result in clinical trial data that may be satisfactory for regulatory purposes but are difficult to translate into clinical practice. This gap is perhaps best reflected by dosing considerations. The information that is required in clinical practice i.e. initial dose, titration schedule and target dose, is seldom immediately generalizable from regulatory clinical trial data [53]. The resulting labeled recommendations for starting dose are often too high for routine clinical application. This is an unavoidable consequence of constraints experienced in regulatory focused clinical trial design.

4.2 Not All Patients Have New-Onset/Untreated or Medically Refractory Seizures

Many patients fall between the diagnosis of new-onset/untreated and medically refractory seizures. These are patients whose first appropriate AED fails and are presented with the dilemma of alternate monotherapy versus adjunctive therapy. Unfortunately, this common situation is under-represented in clinical trials. In the only open-label study addressing this question, patients with partial epilepsy not controlled after more than one AED were randomized to alternate monotherapy versus adjunctive therapy [54]. The actual AED to be added or substituted and dose adjustments were determined by the treating physician's best judgment. Of a total of 157 patients (94 previously exposed to only one AED), 76 were randomized to alternate monotherapy and 81 to adjunctive therapy, with the two groups being comparable at baseline. Patients <15 years of age constituted 13 % of those randomized to the alternate monotherapy arm and 15 % of those to the adjunctive therapy arm; however, results were not analyzed separately. The 12-month cumulative probability of remaining on the assigned treatment was 55 % in patients on alternative monotherapy and 65 % in those receiving adjunctive therapy ($p = 0.74$). The 12-month probability of remaining seizure free was 14 and 16 %, respectively [54]. Adverse effects were similar in the two groups.

4.3 Challenges Pertinent to Infants and Young Children

Infants and young children (usually 2 years of age) represent a unique population not sufficiently represented in AED clinical trials. This situation results, to some extent, from challenges in classification of seizures by clinical semiology in this age group. In a small study ($n = 20$) of children aged 26 months, a significant disagreement and poor correlation was found between two epilepsy experts for clinical classification into generalized versus focal seizures [55]. It was demonstrated that there is considerable overlap between generalized and focal seizures in terms of individual semiology characteristics. The authors concluded that ILAE criteria for semiology classification are unreliable in this age group [55]. It has been suggested that there is an ontogeny of ictal clinical and EEG manifestations and individual semiology features are a function of age in children with partial-onset seizures [56]. As a result, trials in this age range require continuous EEG monitoring to detect and classify seizures, which significantly negatively impacts trial design, duration, feasibility and cost.

Another issue is that the lower age limit for inclusion in AED clinical trials for partial-onset seizures, which translates into labeling recommendations, is often arbitrary and varies with each drug and trial. As such, AEDs are often approved without any pediatric information to guide clinicians. There is little biological basis for exclusion of children above age 4 years in adolescent or adult focal seizure trials since the causes, clinical features and AED pharmacokinetics do not significantly differ across these ages. This age barrier may be related to formulation or blinding issues, or in some cases may be due to caution on the part of pharmaceutical companies and regulatory agencies about protecting children. It is hoped that preapproval drug development will include infants and children for future AEDs [53, 57].

5 Conclusions

Based on our review of the evidence for initial monotherapy in children with newly diagnosed or untreated partial-onset seizures, OXC is the only medication with established efficacy and effectiveness (Class I evidence). Nine other AEDs (CBZ, CLB, LTG, PHB, PHT, TPM, VPA, VGB and ZNS) have Class III evidence for efficacy/effectiveness as initial monotherapy meaning they may be effective but the clinical trial data are weak. The situation is much better for adjunctive therapy of intractable partialonset seizures, where there is Class I efficacy/effectiveness evidence for GBP, LTG, LEV, OXC and TPM in children.

Currently, the selection of a medication for children with focal seizures remains a complex clinical decision influenced by the efficacy/effectiveness analysis presented in this paper, coupled with patient- and drug-specific factors not addressed in this review. This approach could be substantially improved if more objective measures of drug-specific adverse effects were developed and integrated with existing efficacy/effectiveness data to produce patient-specific clinical decision support models. Such models are not available for routine clinical practice at present. Until evidence-based prediction models are integrated into electronic health record systems, clinicians will need to combine the evidence described in this article with patient- and drug-related factors to choose optimal medications for their pediatric patients with epilepsy.

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Fig. 1. PRISMA flow diagram for the systematic review. *AED* antiepileptic drug

Table 1

Criteria for classification of studies: the monotherapy and add-on therapy criteria are modified respectively from updated International League Against Epilepsy (ILAE) guidelines and American Academy of Neurology/American Epilepsy Society (AAN/AES) report [4, 5]

	Monotherapy	Add-on therapy
Class I	Class I A randomized controlled clinical trial (RCT) or meta-analysis of RCTs, in a representative population that meets all 6 criteria: <ol style="list-style-type: none"> 1 Primary outcome variable: efficacy or effectiveness 2 Treatment duration: 48 weeks 3 Study design: double blind 4 For superiority trials: superiority demonstrated; for non-inferiority trials or failed superiority trials: the study treatment's efficacy/effectiveness lower limit (95 % confidence interval) is above a 20 % lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per protocol study population (for age/seizure type subgroups) 5 Study exit: not forced by a predetermined number of treatment emergent seizures 6 Appropriate statistical analysis 	A RCT with masked outcome assessment, in a representative population fulfilling the following criteria: <ol style="list-style-type: none"> 1 Clearly defined primary outcome measure 2 Clearly stated inclusion and exclusion criteria to define study population 3 Adequate accounting for losses, protocol violations and crossovers with sufficiently low numbers to minimize bias 4 Comparison of relevant baseline characteristics of treatment groups presented and equivalence shown or appropriate statistical adjustment made for differences 5 The double-blind phase having duration of at least 12 weeks
Class II	A RCT or meta-analysis meeting all the Class I criteria except: <ol style="list-style-type: none"> 1 Treatment duration: 24 weeks but <48 weeks; OR 2 For non-inferiority trials or failed superiority trials: the study treatment's efficacy/effectiveness lower limit (95 % confidence interval) is between the 21 % and 30 % lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per protocol study population (for age/seizure type subgroups) 	Either a prospective matched-group cohort study in a representative population with masked outcome assessment that otherwise meets all of the 4 criteria for Class I study, or, a RCT in a representative population that lacks any 1 criterion for classification as a Class I study
Class III	A RCT or meta-analysis not meeting criteria for Class I or II	Other controlled studies (including well-defined natural history controls, or before-after design) in a representative population with outcome assessment independent of treatment allocation
Class IV	Non-randomized, prospective, controlled or uncontrolled studies, case series, or expert reports	Uncontrolled studies, case series or case reports

Table 2

Summary of best evidence and the US Food and Drug Administration (FDA)-approved labeling, doses and contra-indications for listed anti-epileptic drugs

Medication	Best evidence as monotherapy (study class)	Best evidence as adjunctive therapy (study class)	FDA-labeled epilepsy indication	FDA-labeled age	Starting dose (mg/kg/day)	Usual maintenance dose (mg/kg/day)	Contraindications
Carbamazepine	III	XXXX	Epilepsy: partial, generalized and mixed types	All pediatric	5–10	30–40	History of previous bone marrow depression Concomitant use of an MAO inhibitor, or use within 14 days of discontinuing a MAO inhibitor Hypersensitivity to carbamazepine or tricyclic compounds
Clobazam	III	XXXX	Lennox–Gastaut syndrome (adjunct)	2 years and older	0.1–0.2	0.4–0.8	Specific contraindications have not been determined
Clonazepam	XXXX	XXXX	Seizure	Up to 10 years of age or 30 kg weight	0.01–0.02	0.1–0.2	Hypersensitivity to benzodiazepines
Gabapentin	XXXX	I	Partial seizure (adjunct)	3–12 years	10–15	25–40	Significant liver disease Acute narrow angle glaucoma Hypersensitivity to gabapentin or any component of the product
Lamotrigine	III	I	Partial seizure (adjunct or monotherapy)	2 years and older (immediate release); 13 years and older (extended release)	Monotherapy (0.3) With enzyme inducers (0.6)	Monotherapy (2–8) With enzyme inducers (5–15)	Hypersensitivity to lamotrigine or any component of the product
			Primary generalized tonic clonic seizure (adjunct)	2 years and older (Immediate release); 13 years and older (extended release only)	With valproate (0.15)	With valproate (1–5)	
Levetiracetam	XXXX	I	Lennox–Gastaut syndrome (adjunct) Partial seizure (adjunct)	2 years and older 1 month and older (oral solution and immediate release tablets); 16 years and older (extended release)	20	30–40	Specific contraindications have not been determined

Medication	Best evidence as monotherapy (study class)	Best evidence as adjunctive therapy (study class)	FDA-labeled epilepsy indication	FDA-labeled age	Starting dose (mg/kg/day)	Usual maintenance dose (mg/kg/day)	Contraindications
Oxcarbazepine	I	I	Primary generalized tonic-clonic seizure (adjunct)	tablets and intravenous) 6 years and older (oral)	10	30–45	Hypersensitivity to oxcarbazepine or to any component of the product
			Myoclonic seizure (adjunct)	12 years and older			
	III	XXXX	Partial seizure (monotherapy)	4 years and older	2 months–1 year (4–11)	4–11	Acute intermittent porphyria, personal or family history
			Partial seizure (adjunct)	2 years and older			
Phenytoin	III	XXXX	Epilepsy	All pediatric	1–6 years (3–7) 7 years (2–5)	3–7	Hypersensitivity to barbiturates
			Generalized tonic-clonic and complex partial (psychomotor and temporal lobe) seizures	All pediatric (chewable tablets, extended-release capsules and oral suspension)			
	III	XXXX	Seizure (during and following neurosurgery, treatment and prophylaxis)	All pediatric (chewable tablets, extended-release capsules)	5	5–10	History of sedative or hypnotic addiction
			Partial seizure (initial monotherapy)	2 years and older			
Stiripentol	III	XXXX	Partial seizure (adjunct)	2–16 years	50	4 g/day (total dose)	Hypersensitivity
			Primary generalized tonic-clonic seizure (initial monotherapy)	2 years and older			
Topiramate	III	XXXX	Partial seizure (adjunct)	2–16 years	With enzyme inducers: (1–2)	Monotherapy (3–5)	Specific contraindications have not been determined
			Primary generalized tonic-clonic seizure (adjunct)	2–16 years			
Valproate	III	XXXX	Lennox–Gastaut syndrome (adjunct)	2 years and older	15	20–40	Hepatic disease or significant hepatic dysfunction
			Complex partial seizure	10 years and older			

Medication	Best evidence as monotherapy (study class)	Best evidence as adjunctive therapy (study class)	FDA-labeled epilepsy indication	FDA-labeled age	Starting dose (mg/kg/day)	Usual maintenance dose (mg/kg/day)	Contraindications
			Absence seizure	10 years and older			
			Multiple seizure types (adjunct)	10 years and older			Hypersensitivity to valproate sodium, valproic acid, or divalproex sodium
Vigabatrin	III	XXXX	Refractory complex partial seizure (adjunct)	Only adults	40	2000–3000 mg/day (total dose)	Known urea cycle disorder or history of hyperammonemic encephalopathy
			West syndrome	1 month–2 years of age	50	150	Specific contraindications have not been determined
Zonisamide	III	XXXX	Partial seizure (adjunct)	16 years and older	Monotherapy (1–2)	Monotherapy: 8	Hypersensitivity to zonisamide or sulfonamides
					With enzyme inducers (1–2)	With enzyme inducers: 12	

XXXX insufficient evidence for classification, MAO monoamine oxidase

Sources of information: Clinical trials listed in this paper, US FDA web-based resources (Available from: <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/default.htm>), Micromedex® 2.0 and related DRUGDEX® tool (Available from: <http://www.micromedexsolutions.com/micromedex2/librarian/>) (requires institutional/personal access)