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SYSTEMATIC REVIEW

A Revisited Strategy for Antiepileptic Drug Development in Children

Designing an Initial Exploratory Step

Catherine Chiron · Behrouz Kassai · Olivier Dulac · Gerard Pons · Rima Nabbout

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Abstract
Background Randomized controlled trials (RCTs) in refractory paediatric epilepsy usually involve the two main types of epilepsy shared by children and adults, focal epilepsy and Lennox-Gastaut syndrome (LGS). Most other epilepsy syndromes, specifically paediatric, are excluded from drug development. In order to identify among them the candidate(s) for dedicated RCTs with a new drug, the European Medicine Agency (EMA) recently recommended proceeding in two steps: (1) an exploratory (prospective-observational) trial (POT) including a large variety of paediatric epilepsy syndromes and (2) a subsequent RCT in each of those that disclose a signal for possible efficacy.
Objective Our objective was to address the three following issues that have not been addressed by the EMA: (1) to determine a minimal threshold for this signal; (2) to establish a list of epilepsies to evaluate; and (3) to estimate the number of patients to include in such POTs.
Methods We extensively reviewed the POTs (including various syndromes) and RCTs reported in paediatric patients with uncontrolled epilepsy using MEDLINE (from 1990 to 2011) and the Cochrane library. We determined the threshold as the lowest percentage of responders observed in a POT with a positive corresponding RCT. The syndromes that reached this threshold in a POT were those to evaluate in an RCT. The minimal number of patients to include for each syndrome for a POT with a new antiepileptic drug was estimated in order to reach at least this threshold of responders with a 95 % confidence interval.
Results We found the minimal responder threshold to be 25 %. We identified eight epilepsy types/syndromes reaching this threshold and estimated for each of them the minimal sample needed: refractory focal epilepsy ($n = 40$), Lennox-Gastaut syndrome ($n = 32$), infantile spasms ($n = 50$), Dravet syndrome ($n = 32$), childhood absence epilepsy ($n = 12$), other symptomatic generalized epilepsy ($n = 38$), epileptic encephalopathy with continuous spikes and waves during sleep ($n = 7$) and epilepsy with myoclonic-astatic seizures ($n = 4$) [the two last samples may be underestimated due to the lack of RCTs in these conditions].
Conclusion Among the eight epilepsy types/syndromes that we recommend to systematically include in exploratory trials using the POT procedure, we assume that, for the minimal sample given above, a responder threshold of 25 % will provide a reliable efficacy signal, to be confirmed by a dedicated RCT. This strategy should avoid missing new therapeutic possibilities for children with epilepsy and reduce the off-label use of drugs in paediatric neurology.

C. Chiron (✉) · O. Dulac · G. Pons · R. Nabbout
Inserm, U663, Service de Neurologie et Metabolisme,
Hopital Necker, 149 rue de Sevres, 75015 Paris, France
e-mail: catherine.chiron@nck.aphp.fr

C. Chiron · O. Dulac · G. Pons · R. Nabbout
University Paris Descartes, Paris, France

C. Chiron · O. Dulac · R. Nabbout
APHP, Department of Pediatric Neurology and Metabolism,
Hospital Necker – Enfants Malades, Paris, France

B. Kassai
Department of Clinical Pharmacology, Epicime-CIC
201/Inserm-Hospices Civils de Lyon, RIPPS, UMR 5558 CNRS,
University Hospital of Lyon, Lyon, France

G. Pons
APHP, Department of Pediatric Clinical Pharmacology, RIPPS,
Hospital Cochin – Saint Vincent de Paul, Paris, France

1 Introduction

Drugs need to be specifically developed for paediatric epilepsy because diseases, pharmacokinetics, safety and treatment effects may be different between children and adults [1]. Randomized controlled trials (RCTs) in children raise specific technical (biological sampling, assessment of drug effect), logistical (recruitment), financial (cost considered to be high for a small market) and legal (informed consent obtained by proxy) difficulties. Over the past decade some financial incentives encouraged pharmaceutical companies to perform trials in children [2], and in 2006 the European Pediatric Regulation required a paediatric investigation plan for any new drug. Since then, children tend to be targeted earlier in the development of new antiepileptic drugs (AEDs), but controlled paediatric trials are still mostly restricted to the two types of epilepsy shared by children and adults, i.e. focal epilepsy (so-called epilepsy with partial-onset seizures) and Lennox-Gastaut syndrome. Consequently, about half the children with drug-resistant seizures are excluded [3], i.e. those suffering from infantile spasms (West syndrome), severe myoclonic epilepsy in infancy (Dravet syndrome), childhood absence epilepsy, epilepsy with myoclonic-astatic seizures (Doose syndrome), and continuous spikes and waves during sleep (CSWS). These rare but devastating epilepsies most often evolve to epileptic encephalopathy because of motor or cognitive deterioration as a consequence of the epilepsy itself, making the need for new drugs crucial for these children. However, only two compounds have been developed for them through a controlled procedure, vigabatrin for infantile spasms [4–6] and stiripentol for Dravet syndrome [7].

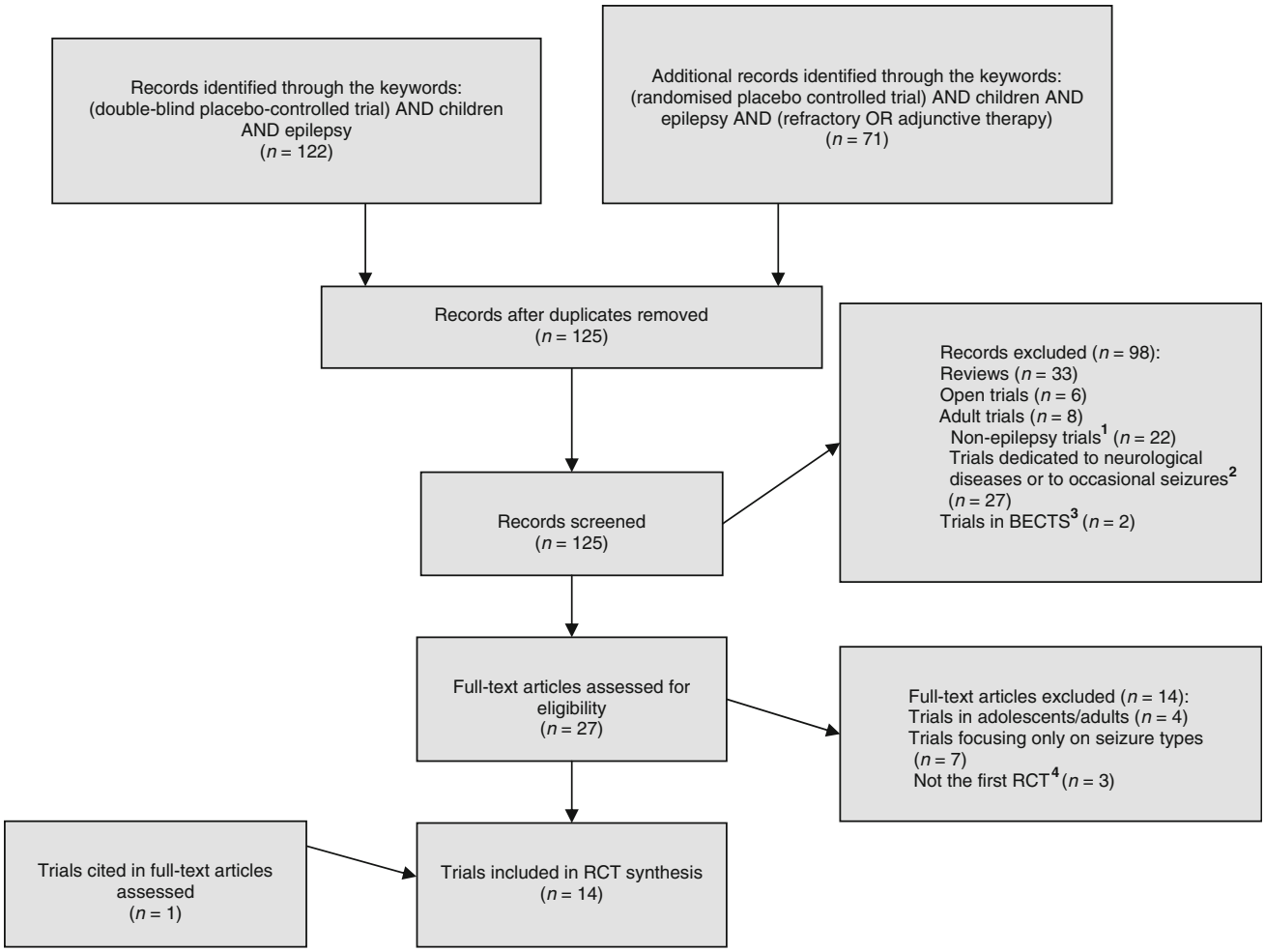
Exploratory observational trials were essential to identify both conditions as potential targets for controlled trials. The drug was studied as adjunctive therapy and using dose ranging up to a maximum tolerated dose, in a single prospective open-labelled study including a large variety of paediatric epilepsy syndromes. Then, a confirmatory trial was designed at the optimal dose targeting the 'responder' syndromes [8, 9]. This proved to be remarkably successful and ethically beneficial as a small homogeneous sample was enough to demonstrate efficacy of the investigated drug (important size of treatment effect) in infantile spasms and Dravet syndrome [4, 7, 44]. Without such exploratory studies, children with these epilepsies would have missed these effective treatments.

Although this exploratory/confirmatory sequence was repeatedly performed in the 1990s [4, 7–18], it has been neglected in the past 10 years. The last AEDs developed in children were directly studied in RCTs, and solely in focal epilepsy (e.g. levetiracetam, zonisamide and eslicarbazepine) and Lennox-Gastaut syndrome (e.g. rufinamide) [19–22]. Specific indications have been suspected in academic investigations, for levetiracetam in CSWS and topiramate in Dravet syndrome, but were never validated by an RCT [23, 24]. Considering that "it is desirable to explore efficacy in other epilepsy syndromes than focal epilepsy" and that "identifying those that may be candidates for a given drug is a key point", the recently revised European Guidelines on the treatment of epileptic disorders (Committee for Medicinal Products for Human Use [CHMP]/Efficacy Working Party [EWP]/566/98, 22 July 2010) recommend "to enter these patients in exploratory add-on studies, including all types of pediatric epilepsy syndromes" as a first step, followed by controlled studies as a confirmatory step.

Taking into account ethical constraints and the diversity of paediatric epilepsy, these guidelines allow exploratory trials to be observational, open-label, add-on studies, provided they are prospective. However, guidelines to conduct such studies do not exist. In particular, [1] the responder rate threshold to define an efficacy signal, [2] the list of the epilepsy syndromes to be evaluated and [3] the minimum number of patients that need to be included for each given syndrome at the exploratory step, have not yet been established. The objective of the present study was to address these three issues, based on a comprehensive review of paediatric trials performed in refractory epilepsies since new AEDs have emerged. Altogether, the aim is to avoid missing a potential target for a new compound as opposed to the usual aim of RCTs that is to avoid overestimating efficacy.

2 Methods

We searched MEDLINE (from January 1990 to June 2011) and the Cochrane Library (the Cochrane Epilepsy Group's Specialised Register and the Cochrane Central Register of Controlled Trials) [December 2010]. All 12 new AEDs developed in paediatrics were included as follows: eslicarbazepine, felbamate, gabapentin, levetiracetam, lamotrigine, oxcarbazepine, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide (there are no paediatric data currently available for lacosamide and pregabalin). For each new AED, we reviewed the following two types of studies reported in children: [1] the first trial comprising a randomized comparison period performed in a given epilepsy type/syndrome (defined as the RCT), based on the following keywords: 'randomised', 'double-blind', 'placebo-controlled', 'trial', 'epilepsy' and 'children' (Fig. 1) and [2] the published, prospective observational studies performed in patients refractory to previous AEDs and treated with adjunctive therapy, provided they were interventional, and results were analysed according to various epilepsy syndromes (defined as the prospective



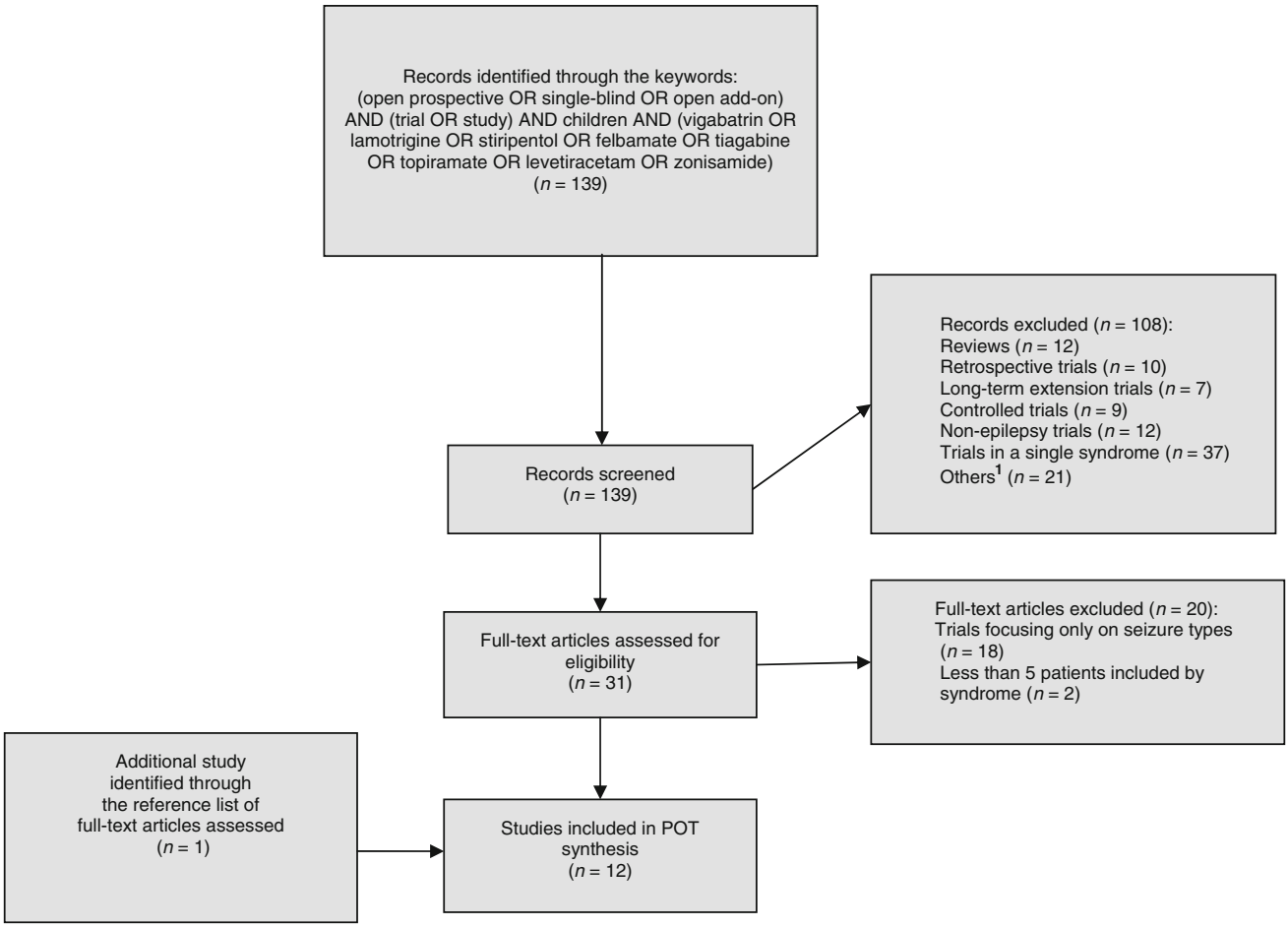
1 Trials performed in psychiatric or behavioural disorders associated with paediatric epilepsy (autistic behaviour, attention disorders and sleep disorders)
2 Trials dedicated to diseases such as Rett or Leigh syndrome, or to occasional seizures such as febrile seizures or due to cystercosis
3 Trials in BECTS (Benign Epilepsy with Centro-Temporal Spikes), supposed to be non-refractory
4 Not the first RCT reported in a given epilepsy type/syndrome and for a given drug

Fig. 1 Flow diagram for randomized controlled trial (RCT) search

observational trials [POTs]); i.e. studies where the included patients were not blinded in order to search for some apparent effect in specific epilepsy syndromes; the search was based on the following keywords: 'open prospective', 'single-blind', 'trial', 'children' and 'vigabatrin/lamotrigine/stiripentol/felbamate/tiagabine/topiramate/levetiracetam/zonisamide' (Fig. 2). The following types of studies were excluded: retrospective studies, prospective non-interventional studies, those focusing only on seizure types and not on epilepsy types/syndromes, and those dedicated to a single epilepsy type/syndrome.

Data were analysed as follows:

1. Based on the data reported, we verified that the syndromes involved fulfilled the diagnostic criteria of the International League Against Epilepsy [25, 26]. We labelled 'other symptomatic generalized epilepsy' the remaining conditions with generalized seizures (tonic-clonic, clonic, tonic, myoclonic or absence seizures) but that lacked the features of specific epilepsy syndromes (West/Dravet/Lennox-Gastaut/Doose syndromes, childhood absence epilepsy or CSWS).
2. We reviewed the temporal sequence of POTs and corresponding RCT(s) for each AED and each epilepsy type/syndrome involved. We separated the POTs performed before the RCT (Table 1) from the POTs paradoxically performed after the RCT (Table 2).
3. We determined the panel of epilepsy types/syndromes we would ultimately recommend to be systematically



1 Trials dedicated to pharmacokinetics, safety, behaviour disorders and quality of life

Fig. 2 Flow diagram for prospective observational trial (POT) search

evaluated in a POT using the three following steps: (1) we selected all the positive RCTs reported for each AED and each epilepsy type/syndrome studied, and we extracted the percentage of responders (called 'observed responder rate') from each corresponding POT (Tables 1 and 2). Responders were defined as usual, by an over 50 % decrease in seizure frequency compared with baseline; others were non-responders, a minority of whom could have experienced seizure exacerbation; (2) among these observed responder rates in a POT, we assumed that the lowest one should be the threshold to be considered for an efficacy signal in a POT, in order to minimize the risk of missing a candidate syndrome that could further prove to benefit from the drug in an RCT (the lowest observed responder rate in our review was 25 % [namely the POT with topiramate in Lennox-Gastaut syndrome, see Table 2] [23]; and (3) we identified for the panel all the epilepsy types/syndromes with at least a 25 % observed responder rate in a POT, including those without a corresponding RCT.

4. We estimated the minimum number of patients to be included in a POT for a given syndrome of the panel, based on the POTs performed before the RCT in this syndrome with any new AED (Table 3), and on the following two steps: (1) we calculated a mean observed responder rate for POT, i.e. the mean observed responder rates of all the reported POTs having enrolled at least five patients and (2) we estimated the minimal number of patients to be included in order to detect this mean responder rate, using the exact test for single proportion (nQuery advisor® software version 7.0; Statistical Solutions Ltd, Cork, Ireland); we chose 25 % of responders as the inferior limit of the range, i.e. as the expected proportion of responders under the null hypothesis, at an α risk of 0.15. We accepted a more lenient α risk because the results of observational studies would be

Table 1 Prospective observational trials (POTs) compared with randomized controlled trials (RCTs) in paediatric epilepsy types/syndromes: POTs performed before RCTs

AED and syndromes[a]	Prospective observational trials			Randomized controlled trials	
	Reference	Number of patients	Responder rate, % (% SF)	Reference	Efficacy result[b]
Vigabatrin					
Global population	[12][c]	61	46 (18)		
FE		31	52 (20)	[43][e]	$p < 0.01$
LGS		6	33	[j]	[j]
SGE		15	47	[j]	[j]
IS	[8][c]	70	80 (43)	[5][f,g]	$p < 0.02$
				[6][g,h]	$p < 0.001$
IS due to TS		14	(86)	[4][g,h]	$p < 0.01$
Lamotrigine					
Global population	[15][d]	120	28 (9)		
LGS		10	60 (30)	[14][f]	$p < 0.01$
SGE		33	48 (16)	[j]	[j]
FE		26	27 (4)	[11][f]	$p < 0.001$
CAE		9	75 (33)	[13][e,g]	$p < 0.03$
IS		13	31 (15)	[j]	[j]
Global population	[10][b]	175	34		
CAE		30	53	[13][e,g]	$p < 0.03$
FE		95	31	[11][f]	$p < 0.001$
Global population (Gen E)	[18][b]	56	43 (11)	[17][i]	$p < 0.00001$
LGS		15	73 (20)		
Other GE		41	32 (7)		
Stiripentol					
Global population	[9][c]	188	58 (14)		
DS		20	50 (15)	[7][f]	$p < 0.0001$
				[44][f]	$p = 0.009$
FE		58	64 (16)	[43][e]	$p < 0.02$
SGE		30	53 (5)	[j]	[j]
IS		12	25 (0)	[j]	[j]
MAE		6	100 (40)		[j]

AEDs antiepileptic drugs, *CAE* childhood absence epilepsy, *CSWS* continuous spikes and waves during sleep, *FE* focal epilepsy ('epilepsy with partial-onset seizures'), *Gen E* generalized epilepsies, *IGE* idiopathic generalized epilepsy, *IS* infantile spasms, *LGS* Lennox-Gastaut syndrome, *MAE* epilepsy with myoclonic-astatic seizures (Doose syndrome), *SF* seizure free, *SGE* symptomatic generalized epilepsy (other than IS and LGS)

[a] We considered here only the syndromes with at least 5 patients included

[b] Responder rate or seizure reduction

[c] Open-labelled prospective trial

[d] Single blind versus placebo trial

[e] Responder enrichment and placebo-controlled withdrawal trial

[f] Randomized placebo-controlled trial in parallel groups

[g] Monotherapy

[h] Randomized comparative trial

[i] Double-blind, placebo-controlled, crossover trial

[j] No confirmatory trial has been performed so far in the corresponding epilepsy syndrome

Table 2 Prospective observational trials (POTs) compared with randomized controlled trials (RCTs) in paediatric epilepsy syndromes: POTs paradoxically performed after RCTs

AED and syndromes[a]	Prospective observational trials			Randomized controlled trials	
	Reference	Number of patients	Responder rate, % (% SF)	Reference	Efficacy result[f]
Felbamate					
Global population	[37][b]	196			
FE		166	27 (5)	[g]	[g]
LGS		54	52 (4)	[32][c]	$p < 0.002$
SGE		21	67 (14)	[g]	A + C[g]
Tiagabine					
Global population	[39][b]	48			
FE		17	35	[30]	$p < 0.001$
SGE		5	60	A + C > 12 years[g]	[g]
Topiramate					
Global population	[24][b]	207	48 (9)		
FE		128	50 (12)	[28][c]	$p < 0.03$
IS		14	36 (0)	[g]	[g]
LGS		16	25	[33][c]	$p < 0.002$
SGE		11	64	[g]	[g]
DS		5	60	[g]	[g]
Levetiracetam					
Global population	[38][b]	110	39 (9)		
FE		53	58 (11)	[19][c]	$p < 0.0002$
DS		6	33 (0)	[g]	[g]
MAE		6	83 (17)	[g]	[g]
SGE		11	36 (9)	[g]	[g]
LGS		8	25 (0)	[g]	[g]
IS		5	20 (0)	[g]	[g]
Global population	[23][b]	102	36 (6)		
FE		36	39 (12)	[19][c]	$p < 0.0002$
DS		9	11 (0)	[g]	[g]
CAE		12	42	[g]	[g]
MAE		6	33 (17)	[g]	[g]
SGE		14	36	[g]	[g]
CSWS		6	66 (50)	[g]	[g]
IS		16	31 (0)	[g]	[g]
Zonisamide					
Global population	[40][b]	1,008[d] (A + C)	54		
FE		673	54	[22][c, e]	
GE		41	66	[g]	[g]
LGS		132	32	[g]	[g]
SGE		100	47	[g]	[g]
IS		9	22 (?)	[g]	[g]

A + C adults and children combined, *CAE* childhood absence epilepsy, *CSWS* continuous spikes and waves during sleep, *FFFE* focal epilepsy ('epilepsy with partial-onset seizures'), *Gen E* generalized epilepsies, *IGE* idiopathic generalized epilepsy, *IS* infantile spasms, *LGS* Lennox-Gastaut syndrome, *MAE* epilepsy with myoclonic-astatic seizures (Doose syndrome), *SF* seizure free, *SGE* symptomatic generalized epilepsy (other than IS and LGS)

[a] We considered here only the syndromes with at least 5 patients included

[b] Open-labelled prospective trial

[c] Randomized placebo-controlled trial in parallel groups

[d] 5 % of the population on monotherapy

[e] Cited in Yagi et al., [40] 2004 (data not accessible)

[f] Responder rate or seizure reduction

[g] No confirmatory trial has been performed so far in the corresponding epilepsy syndrome

Table 3 Estimation of the minimum number of patients to be included in a prospective observational trial

Epilepsy syndrome	Observed responder rates in POTs performed before RCTs and observed number of patients (%)					Estimated number of patients needed
	Vigabatrin [8, 12][a]	Lamotrigine [10, 15, 18][a]	Stiripentol [9][a]	Mean[b]	Range	
Focal epilepsy	52 ($n = 31$)	29 *27* ($n = 26$) *31* ($n = 95$)	64 ($n = 58$)	48	25–48	40
Lennox-Gastaut syndrome	33 ($n = 6$)	66.5 *60* ($n = 10$) *73* ($n = 15$)	($n < 5$)	50	25–50	32
Infantile spasms	80 ($n = 70$)	31 ($n = 13$)	25 ($n = 12$)	45	25–45	50
Dravet syndrome			50 ($n = 20$)	50	25–50	32
Childhood absence epilepsy		65.5 *78* ($n = 9$) *53* ($n = 30$)		65.5	25–65.5	12
Other symptomatic generalized epilepsy	47 ($n = 15$)	40 *48* ($n = 33$) *32* ($n = 41$)	53 ($n = 30$)	47	25–47	38

POT prospective observational trial, *RCT* randomized controlled trial

[a] Number of the corresponding trial(s) in the reference list

[b] Arithmetic mean of the responder rates in the POTs performed before RCTs for a given syndrome

confirmed by an RCT anyway. Then, we compared these estimated numbers of patients with those observed in the reported POTs.

3 Results

3.1 Temporal Sequence of Prospective Observational Trials (POTs) and Randomized Controlled Trials (RCTs)

Three (vigabatrin, lamotrigine and stiripentol) of the 12 new AEDs were developed using first a POT [8–10, 12, 15, 18] before an RCT was dedicated to the candidate syndromes identified (Table 1). They were the only new AEDs in which a paediatric age-specific epilepsy syndrome could further benefit from a syndrome-dedicated randomized trial, namely infantile spasms for vigabatrin, childhood absence epilepsy for lamotrigine and Dravet syndrome for stiripentol [4–7, 13].

For the nine other AEDs, the paediatric development was directly initiated by an RCT comparing the active compound with placebo as adjunctive therapy in two parallel arms. This type of trial was exclusively dedicated to the two epilepsy conditions that are common to adults and children: refractory focal epilepsy (eslicarbazepine, gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide) [19, 21, 22, 27–31] and/or Lennox-Gastaut syndrome (felbamate, rufinamide and topiramate) [20, 32, 33]. The rationale for undertaking these trials comprised previous positive placebo-controlled trials in adults [34] and preliminary observational paediatric data [35, 36]. It is noteworthy that some of these trials (for eslicarbazepine and zonisamide) are still ongoing for children in Europe and the USA. In five out of these nine AEDs, a POT was paradoxically performed subsequently in a larger variety of syndromes (felbamate, levetiracetam, tiagabine, topiramate and zonisamide) [23, 24, 37–40], sometimes after the drug had been approved for paediatric focal epilepsy (topiramate and levetiracetam) or Lennox-Gastaut syndrome (topiramate) [Table 2]. The remaining four AEDs never underwent any POT for the various paediatric syndromes (eslicarbazepine, gabapentin, oxcarbazepine and rufinamide).

3.2 List of Epilepsy Types/Syndromes to be Evaluated in a POT

According to our inclusion criteria (add-on therapy in refractory epilepsy), we found eight epilepsy conditions demonstrating at least 25 % of responders in POTs: refractory focal epilepsy, infantile spasms, Dravet syndrome, childhood absence epilepsy, Lennox-Gastaut syndrome, other symptomatic generalized epilepsy, myoclonic-astatic epilepsy and CSWS. Of interest is that all the published corresponding RCTs (dedicated to the

Table 4 Additional estimation for two syndromes without any randomized controlled trial available

Epilepsy syndromes	Observed responder rates in POTs and observed number of patients (%)				Estimated number of patients needed
	Stiripentol [9][a]	Levetiracetam [23, 38][a]	Mean[b]	Range	
Epilepsy with myoclonic astatic seizures	100 ($n = 6$)	58	79	25–79	4
		83 ($n = 6$)			
		33 ($n = 6$)			
Continuous spikes and waves during sleep		66 ($n = 6$)	66	25–66	7

POTs prospective observational trials

[a] Number of the corresponding trial(s) in the reference list

[b] Arithmetic mean of the responder rates in the POTs

identified syndrome with the given AED) were positive. It is noteworthy that for three of these syndromes, no RCT has ever been reported (other symptomatic generalized epilepsy, epilepsy with myoclonic-astatic seizures and CSWS).

3.3 Estimated Number of Patients to be Included in a POT

Based on our procedure, the number of patients to be included was estimated as between 30 and 50 for most syndromes ($n = 32$ for Lennox-Gastaut syndrome and Dravet syndrome, $n = 38$–40 for focal epilepsy and other symptomatic generalized epilepsy and $n = 50$ for infantile spasms), it was lower ($n = 12$) for childhood absence epilepsy (Table 3). Additional analysis permitted an estimate of preliminary numbers under ten for the two syndromes with no RCT available, epilepsy with myoclonic-astatic seizures and CSWS (Table 4).

For each given syndrome we compared the numbers of patients included in the performed POTs with the estimated number. Numbers were found to be similar (± 20 %) in only 18 % of trials. In 29 % of trials, estimated numbers were lower than observed ones, thus suggesting too many patients had been exposed to the drug in order to detect an efficacy signal in the POT: this was mainly the case for focal epilepsy. On the contrary, estimated numbers were higher than observed ones in the remaining 59 % of trials, thus suggesting that too few patients had been included to detect an efficacy signal in the POT, and an effect could have been missed: this was mainly the case for Lennox-Gastaut syndrome and infantile spasms (except with vigabatrin).

4 Discussion

The present review demonstrates that half of the severe paediatric epilepsies are still excluded from therapeutic trials. Only one-fourth of the new AEDs presently administered to children have benefited from an exploratory (prospective observational) study to detect which syndrome should be a target before the confirmatory (randomized controlled) trial. Such an exploratory step proved to be the only opportunity to detect unexpected target syndromes/epilepsies specific for the paediatric age. All efficacy signals based on a percentage of at least 25 % of responders were confirmed in a subsequent confirmatory step. However, some paediatric syndromes have never been submitted to confirmatory trials, despite efficacy signals repeatedly being demonstrated in exploratory trials. In order to improve the strategy for the development of new AEDs in paediatric epilepsy and to give a larger proportion of children a chance for therapy we are providing the list of the eight epilepsy conditions that should be systematically considered in the future for a prospective observational trial as the first exploratory step, and the minimum number of patients required for each one. As far as safety is acceptable, we suggest that a dedicated RCT should subsequently be designed in any syndrome showing at least 25 % of responders.

4.1 Why an Exploratory Trial is Needed for a Large Panel of Paediatric Refractory Epilepsies

In the 1990s several pharmaceutical companies developing a new antiepileptic compound in children chose to perform one preliminary observational and prospective study on a large variety of refractory epilepsies, particularly epilepsy syndromes not encountered in adults. This strategy permitted discovering targets such as Lennox-Gastaut syndrome for lamotrigine, infantile spasms for vigabatrin and Dravet syndrome for stiripentol that would have been missed otherwise. These drugs have become first line in these indications. Since the turn of the millennium, this exploratory approach was abandoned and paediatric development restricted to epilepsies shared by children and adults (namely refractory focal epilepsy and Lennox-Gastaut syndrome). Reasons given are mainly economical.

Such exploratory trials were perceived as increasing the cost of development and potentially delaying marketing in case they would disclose satisfactory evidence of efficacy in various types of paediatric epilepsy. As a result no drug has been developed for these syndromes since then. To overcome this unacceptable situation, two avenues were recently opened within European guidelines for new AEDs in children: on the one hand, the need is reaffirmed to return to a first exploratory step on a large panel of paediatric syndromes (and in one single study to save time) and, on the other hand, the possibility is given to extrapolate efficacy results from adults to children in refractory focal epilepsy and therefore to reduce the cost of the developing process.

4.2 A POT as a First Exploratory Step for a Randomized Controlled Trial

At the exploratory stage, a large RCT including various epilepsy conditions would not satisfy ethical and technical requirements because of the risk of exposing many children to a drug ineffective or even harmful for specific epilepsy syndromes and the impossibility of using similar trial duration and endpoints for the whole panel of syndromes [3]. Replacing the current off-label drug utilization, the prospective observational and interventional procedure to detect candidate syndromes for RCTs appears to be an acceptable alternative for exploratory trials in children [41]. The efficacy signals must then be confirmed by high-quality RCTs [42]. Based on our review, the RCT always confirmed the effect disclosed by the observational study when a minimal threshold of 25 % of responders was considered. Furthermore, no discrepancy appeared for drugs developed following the reverse sequence (the POT paradoxically subsequent to the RCT): the percentage of responders was over 25 % for all POTs with focal epilepsy or Lennox-Gastaut syndrome that later underwent an RCT.

4.3 A Large Panel of Epilepsy Syndromes Needs to be Included at the Exploratory Stage

Based on the present review, eight epilepsy conditions provided an efficacy signal in a POT for at least one given drug: refractory focal epilepsy, infantile spasms, Dravet syndrome, childhood absence epilepsy, Lennox-Gastaut syndrome, other symptomatic generalized epilepsy, epilepsy with myoclonic-astatic seizures and CSWS. Although RCTs did not cover the whole spectrum, those that were performed showed that this signal had an excellent predictive value.

Refractory focal epilepsy deserves special attention. The EMA recently recommended "extrapolating to children over 4 years of age the results of efficacy trials performed in adults with refractory focal epilepsy" without any additional trial performed in children (CHMP/EWP/566/98, 22 July 2010). One could therefore exclude paediatric patients with this type of epilepsy from the exploratory/confirmatory process when data from such studies are available in adults [3].

Many other epilepsy conditions have been identified in addition to the eight mentioned above, but particular characteristics still prevent them from being considered for exploratory trials. Neonates exhibit specific pharmacokinetic characteristics and endpoint issues. Idiopathic generalized epilepsy with generalized tonic-seizures also carries debated endpoint concerns (rare but severe convulsive seizures, frequent but difficult to quantify myoclonia or absences). Some rare syndromes have recently emerged and require further studies (malignant epilepsy with migrating focal seizures and FIRES [Febrile Infection-Related Epilepsy Syndrome]).

4.4 A Minimum Number of Patients for a Given Syndrome at the Exploratory Stage

Assuming that the minimum acceptable limit for the percentage of responders is 25 %, our review shows that detecting such a signal would need a reasonable number of inclusions for most epilepsy syndromes. Studies that include a minimum of 40 children with refractory focal epilepsy, 12 with childhood absence epilepsy or 38 with other symptomatic generalized epilepsy are not difficult considering the relatively high prevalence of these disorders. Recruiting at least 50 children with infantile spasms, 32 with Lennox-Gastaut syndrome or 32 with Dravet syndrome may be more problematic but this could be solved by multicentric recruitment. As a result, it would be possible in such preliminary prospective trials to close the recruitment for a given syndrome as soon as the required number of subjects is reached, while continuing recruitment for the others.

Moreover, this approach would avoid unnecessary exposure of many children to exploratory trials (about 30 % of the previous observational trials exceeded our presently estimated numbers). By contrast, our samples appear to be overestimated in a few conditions, suggesting a particular efficacy of the given drug in the given syndrome, such as lamotrigine in Lennox-Gastaut syndrome [15, 18] and stiripentol in Dravet syndrome [9]. It should be noted that these numbers do not represent requirements: a smaller sample may be enough to detect 25 % of responders, the signal indicating a subsequent RCT, whereas a lower percentage of responders when reaching these numbers indicate that a positive RCT is very unlikely.

Our methodology raises many issues. We never considered any retrospective data in order to avoid the risk of overestimating the responder rate in a POT. We also excluded prospective observational data dedicated to a single syndrome because they do not serve any exploratory approach of paediatric epilepsies in one single step. Due to the fact that the POTs paradoxically performed after the RCT may introduce a bias in our sample estimations, we based our conclusions only on the POTs performed before the RCT (except in the two conditions with no RCT available). Because such POTs are few, the samples currently based on a single POT may have been underestimated. Infantile spasms also deserve special attention: the dramatic efficacy of vigabatrin [4] would need a specific estimation of the number of patients. Only positive RCTs are usually reported [43], a non-frequent but unacceptable condition (for instance, the two negative trials with gabapentin and rufinamide in focal epilepsy were not published), therefore our threshold of 25 % of responders in a POT might be overestimated, with the theoretical risk of missing some less responsive syndromes as candidates for an RCT. However, from the data we have explored we do not detect large differences between percentage of responders within different syndromes and drugs. No definite threshold exists to estimate the number of subjects needed in an observational study. We used an efficacy threshold and an α risk more lenient than usual because identifying a false-positive signal in a POT was not really a concern for our approach: the results will be confirmed by an RCT. Our priority was rather not to miss any candidate syndrome for a given compound.

5 Conclusion

Extensive review of the literature on AED trials in children shows that RCTs always confirmed the treatment benefit on the target syndromes identified in POTs. For the eight epilepsy conditions that need to be studied during this exploratory step, we assume that a responder rate of at least 25 % for a given syndrome might be a reliable efficacy signal, provided a minimum number of patients have been included. Data obtained in these uncontrolled exploratory trials need to be confirmed by RCTs on the target syndromes. Such a systematic procedure in the strategy of paediatric development of new AEDs would reduce the risk of missing new therapeutic possibilities for children with severe drug-resistant epileptic encephalopathies and would reduce the off-label use of AEDs.

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References

1. Rheims S, Cucherat M, Arzimanoglou A, et al. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med. 2008;5(8):e166.
2. Bosch X. Pediatric medicine: Europe follows U.S. in testing drugs for children [letter]. Science. 2005;309(5742):1799.
3. Chiron C, Dulac O, Pons G. Antiepileptic drug development in children: considerations for a revisited strategy. Drugs. 2008;68(1):17–25.
4. Chiron C, Dumas C, Jambaque I, et al. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Res. 1997;26(2):389–95.
5. Appleton RE, Peters AC, Mumford JP, et al. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia. 1999;40(11):1627–33.
6. Elterman RD, Shields WD, Mansfield KA, et al. Randomized trial of vigabatrin in patients with infantile spasms. Neurology. 2001;57(8):1416–21.
7. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet. 2000;356(9242):1638–42.
8. Chiron C, Dulac O, Beaumont D, et al. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991;Suppl. 2:S52–S59.
9. Perez J, Chiron C, Musial C, et al. Stiripentol: efficacy and tolerability in children with epilepsy. Epilepsia. 1999;40(11):1618–26.
10. Besag FM, Wallace SJ, Dulac O, et al. Lamotrigine for the treatment of epilepsy in childhood. J Pediatr. 1995;127(6):991–7.
11. Duchowny M, Pellock JM, Graf WD, et al. A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children: Lamictal Pediatric Partial Seizure Study Group. Neurology. 1999;53(8):1724–31.
12. Dulac O, Chiron C, Luna D, et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991;Suppl. 2:S30–S37.
13. Frank LM, Enlow T, Holmes GL, et al. Lamictal (lamotrigine) monotherapy for typical absence seizures in children. Epilepsia. 1999;40(7):973–9.
14. Motte J, Trevathan E, Arvidsson JF, et al. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome: Lamictal Lennox-Gastaut Study Group. N Engl J Med. 1997;337(25):1807–12.
15. Schlumberger E, Chavez F, Palacios L, et al. Lamotrigine in treatment of 120 children with epilepsy. Epilepsia. 1994;35(2):359–67.
16. Chiron C, Dulac O, Gram L. Vigabatrin withdrawal randomized study in children. Epilepsy Res. 1996;25(3):209–15.

17. Eriksson AS, Nergardh A, Hoppu K. The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: a randomized, double-blind, crossover study. Epilepsia. 1998; 39(5):495–501.
18. Farrell K, Connolly MB, Munn R, et al. Prospective, open-label, add-on study of lamotrigine in 56 children with intractable generalized epilepsy. Pediatr Neurol. 1997;16(3):201–5.
19. Glauser TA, Ayala R, Elterman RD, et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology. 2006;66(11):1654–60.
20. Glauser T, Kluger G, Sachdeo R, et al. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology. 2008;70(21):1950–8.
21. Pina-Garza JE, Nordli DR Jr, Rating D, et al. Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures. Epilepsia. 2009;50(5):1141–9.
22. Oguni H, Hayashi K, Fukuyama Y. Phase III clinical study of the new antiepileptic drug AD-810, zonisamide, in childhood epilepsy. Jpn J Pediatr. 1988;41:439–50.
23. Chhun S, Troude P, Villeneuve N, et al. A prospective open-labeled trial with levetiracetam in pediatric epilepsy syndromes: continuous spikes and waves during sleep is definitely a target. Seizure. 2011;20(4):320–5.
24. Mikaeloff Y, Saint-Martin A, Mancini J, et al. Topiramate: efficacy and tolerability in children according to epilepsy syndromes. Epilepsy Res. 2003;53(3):225–32.
25. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30(4): 389–99.
26. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51(4):676–85.
27. Appleton R, Fichtner K, LaMoreaux L, et al. Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. Gabapentin Paediatric Study Group. Epilepsia. 1999;40(8):1147–54.
28. Elterman RD, Glauser TA, Wyllie E, et al. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children: Topiramate YP Study Group. Neurology. 1999;52(7):1338–44.
29. Glauser TA, Nigro M, Sachdeo R, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures: the Oxcarbazepine Pediatric Study Group. Neurology. 2000;54(12):2237–44.
30. Uthman BM, Rowan AJ, Ahmann PA, et al. Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial. Arch Neurol. 1998;55(1):56–62.
31. Pina-Garza JE, Espinoza R, Nordli DR, et al. Oxcarbazepine adjunctive therapy in infants and young children with partial seizures. Neurology. 2005;65(9):1370–5.
32. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome): the Felbamate Study Group in Lennox-Gastaut Syndrome. N Engl J Med 1993;328(1):29–33.
33. Sachdeo RC, Glauser TA, Ritter F, et al. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome: Topiramate YL Study Group. Neurology. 1999;52(9):1882–7.
34. Richens A, Chadwick DW, Duncan JS, et al. Adjunctive treatment of partial seizures with tiagabine: a placebo-controlled trial. Epilepsy Res. 1995;21(1):37–42.
35. Glauser TA. Preliminary observations on topiramate in pediatric epilepsies. Epilepsia. 1997;38(Suppl. 1):S37–41.
36. Tiagabine Shinnar S. Semin Pediatr Neurol. 1997;4(1):24–33.
37. Avanzini G, Canger R, Dalla BB, et al. Felbamate in therapy-resistant epilepsy: an Italian experience. Felbamate Italian Study Group. Epilepsy Res. 1996;25(3):249–55.
38. Grosso S, Franzoni E, Coppola G, et al. Efficacy and safety of levetiracetam: an add-on trial in children with refractory epilepsy. Seizure. 2005;14(4):248–53.
39. Uldall P, Bulteau C, Pedersen SA, et al. Tiagabine adjunctive therapy in children with refractory epilepsy: a single-blind dose escalating study. Epilepsy Res. 2000;42(2–3):159–68.
40. Yagi K. Overview of Japanese experience-controlled and uncontrolled trials. Seizure. 2004;13(Suppl. 1):S11–5.
41. Craig JC, Webster AC, Mitchell A, et al. Expanding the evidence base in transplantation: more and better randomized trials, and extending the value of observational data. Transplantation. 2008;86(1):32–5.
42. Klassen TP, Hartling L, Craig JC, et al. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS Med. 2008;5(8):e172.
43. Chiron C, Tonnelier S, Rey E, et al. Stiripentol in childhood partial epilepsy: randomized placebo-controlled trial with enrichment and withdrawal design. J Child Neurol. 2006;21: 496–502.
44. Kassaï B, Chiron C, Augier S, et al. Severe myoclonic epilepsy in infancy: a systematic review and a meta-analysis of individual patient data. Epilepsia. 2008;49(2):343–8.