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RESEARCH ARTICLE

Considerations for determining the efficacy of new antiseizure medications in children age 1 month to younger than 2 years

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Abstract

Objectives: Drug treatment for children with epilepsy should, ideally, be governed by evidence from adequate and well-controlled clinical studies. However, these studies are difficult to conduct, and so direct evidence supporting the informed use of specific drugs is often lacking. The Research Roundtable for Epilepsy (RRE) met in 2020 to align on an approach to therapy development for focal seizures in children age 1 month <2 years of age.

Methods: The RRE reviewed the regulatory landscape, epidemiology, seizure semiology, antiseizure medicine pharmacology, and safety issues applicable to this population.

Results: After reviewing evidence, the conclusion was that pediatric efficacy trials would be impracticable to conduct but a waiver of the regulatory requirement to conduct any study would lead to an absence of information to guide dosing in a

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critical population. Review of available data and discussion of RRE attendees led to the conclusion that the requirements for extrapolation of efficacy from older children down to infants from age 1 month to <2 years old appeared to be met. After the RRE, the US Food and Drug Administration (FDA) approved brivaracetam for use in children with focal epilepsy above the age of 1 month in August 2021 and lacosamide in October 2021, both based on the principle of extrapolation from data in older children.

Significance: These recommendations should result in more rapid accessibility of antiseizure medications for infants.

KEYWORDS

antiseizure medications, clinical trials, extrapolation, pediatric epilepsy

1 | INTRODUCTION

The Research Roundtable for Epilepsy (RRE) is an annual meeting initially convened by the Epilepsy Foundation in 2016[1] involving representatives from the scientific community, pharmaceutical and device companies, patient advocacy groups, and regulatory agencies. The intent is to address issues in therapy development for epilepsy and seizures. In 2020, the RRE convened to address the issue of regulatory requirements to study safety and efficacy of antiseizure medications (ASMs) in children younger than 2 years of age.

The appropriateness of extrapolation of efficacy for all drugs used to treat focal seizures has already been determined (down to age 4 years by European Medicines Agency [EMA],[2] and down to age 2 years by the US Food and Drug Administration [FDA][3]). A review of published clinical trials[4] concluded that efficacy findings in adults predict similar results in children ages 2–18. Based on this analysis, in February 2018, the FDA issued guidance allowing extrapolation the efficacy established in adult clinical trials to children age 4 years and older.[5] Extrapolation of the adult indication for focal seizures to pediatrics age 4 years and older was based on finding that the disease pathophysiology and the effect of drugs are similar between adult and pediatric patients. Similarly, the EMA allows extrapolation of efficacy from adults to children age 4 years and above.[2] Subsequently, after discussion by experts at RRE in 2018 and input from the epilepsy community, based on the similarity between children ages 2 to <4 years and children age 4 years and older, the FDA extended that guidance to children age 2 and older.[3] The basis for extrapolation for 2 to <4 years is different from the basis for extrapolation for 4 to 17 years: for the younger group, extrapolation is based on the similarity of seizures in the 2 to <4 year range to seizures in older children, whereas in older children (4–17 years) extrapolation is based on the similarity with adult seizures. In the United States, eslicarbazepine acetate, lacosamide, and brivaracetam have been approved for pediatric use in focal seizures down to 4-years-old, based on extrapolation.

Key points

- Conducting double-blind randomized placebo-controlled studies of antiseizure medications in young children is challenging.
- Focal seizures in children age 1 month to <4 years are similar to those seen in older children and adults.
- Extrapolation of efficacy results from trials in older populations may be used to inform treatment in children age 1 month to <4 years.
- Studies of pharmacokinetics and safety are still required.

The issue of studying infants was not addressed at the time of the 2018 RRE. Trials in this very young population remained a regulatory requirement, but performing trials in the very young age group was becoming close to impracticable. For the purposes of regulatory discussion, and in this article, the group age 1 month to ;<2 years is defined as "infants," in which age refers to postnatal age, so that 1 months "age" corresponds to 44 weeks post-conception for a full-term infant. It is unclear how to apply these criteria for preterm infants, in whom postmenstrual age may be an important consideration.

The 2020 RRE addressed the following questions:

1. Does focal epilepsy exist in infants?
2. Is focal epilepsy in infants similar to focal epilepsy in children 2 years or older?

3. Should trials be done under the age of 2, or is a waiver or extrapolation reasonable?

In August 2021, the FDA granted approval of the first ASM (brivaracetam) for use in children 1 month and older based on extrapolation from older children. This decision followed a discussion of options at the RRE meeting, as described below.

2 | REGULATORY ENVIRONMENT

Companies that sponsor development and marketing of ASMs for treatment of focal seizures in adults are required to address the safety and efficacy of these drugs in children. In the United States, the requirement is specified in the Pediatric Research Equity Act (PREA), enacted in 2003.[6] PREA requires sponsors to conduct a pediatric assessment for a new drug (or new dose form, or new indication for an existing drug). Similarly, the European Medicines Agency (or EMA) requires Paediatric Investigation Plans (PIPs).[7]

The required pediatric assessment must provide pharmacokinetic information sufficient to advise pediatric dosing. If the pediatric disease and its response to pharmacotherapy is determined to be biologically similar to adults, efficacy may be addressed by extrapolation from efficacy already demonstrated in adults or older children. Safety is evaluated in an open-label long-term safety trial, typically with ≥100 subjects for at least 6 months.

3 | ISSUES IN PERFORMING TRIALS IN CHILDREN 1 MONTH TO <2 YEARS OLD

Clinical trials in infants are extremely challenging for a number of reasons. It takes time for infants to reach a point of "treatment intractability" (as demonstrated by failure of two adequate and appropriately selected ASMs). Therefore, the pool of infants with "intractable" seizures is very small. At this very critical age, there are significant ethical issues related to withholding or delaying treatments. Thus, even an add-on placebo-controlled trial can be problematic. For this reason, trials have been done in infants with a high seizure burden, which allows a treatment response to be identified in days rather than weeks or months. Several design features of the previously conducted trials lead to challenges in recruitment and execution. A substantial challenge for recruiting infants into trials is the duration of the trial, which can be comparable to or longer than the patient's epilepsy history. Parents and caregivers may object to the possibility of the infant being randomized to placebo. The end point is typically seizure count established with multi-day inpatient video–electroencephalography (EEG). Hospital admission, and time burden on caregivers, may be an obstacle. Basing the end point on the number of seizures occurring during a short time period of 2 or 3 days imposes a requirement to recruit only infants with very high seizure frequency, and exposes the trial to risk of spurious findings relating to temporal clustering. Finding qualified sites may be a challenge, and video-EEG interpretation in this age range may have low interobserver consistency.

Despite these issues, two double-blind placebo controlled clinical trials of ASMs for focal seizures have been conducted in the age range of 1 month to <4 years. A study of levetiracetam[8] started in 2004 and finished in 2007 and was conducted at 88 centers (NCT00175890). A study of pregabalin[9] started in 2014 and completed in 2018 and was conducted in 72 centers (NCT02072824). However, since that time it has become more difficult to complete such studies. For a recent trial of lacosamide (NCT02477839) in infants 1 month to 4 years of age, the sponsor contacted 955 clinical trial sites in 37 countries, with a high fraction declining to participate. Sites cited the high burden of conducting video-EEG, the low number of patients meeting inclusion/exclusion criteria, and the availability of lacosamide off-label. Of 187 sites selected, 88 were active. The study failed to enroll many younger infants: 52% of subjects were 2 to 4 years of age, whereas only 13% were 6 months to 1 year and 5% were 1 month to 6 months.[10] With the announcement by the FDA in 2019 that extrapolation could be extended to children age 2 years and older, any future PREA studies would likely be required to enroll subjects 1 month to <2 years, further increasing the challenge of fully recruiting such a study in a reasonable period of time.

4 | IS THE BASIS FOR EXTRAPOLATION MET?

To determine whether extrapolation of efficacy was an appropriate approach, several sequential logical steps were required. The first would be to confirm that focal seizures in infants are similar to those in older children. The second would be to assess whether drug response is similar in both and that there is a similar exposure-response relationship.[11]

4.1 | Similarity of infant focal seizures to those in older children

The interictal signature of focal seizure disorders is a focal sharp wave. These are seen similarly in EEG studies from infants and older patients. Focal seizures in infants have electrographic patterns similar to those recorded in adults. When recording ictal EEG, a common feature is

a paroxysmal depolarizing shift at the onset of seizures. This feature is seen in both infant seizures (age 1 month to; <2 years) and in older children. These have been demonstrated in slice preparations in infants[12] and are similar to those seen in adults.

In addition, studies demonstrate that focal seizures in infants share clinical features with focal seizures in older children. For example, a study compared the ictal video-EEG of 48 children age <2 years to 21 children age 2–6 and 54 children age >6.[13] Ictal behavioral manifestations were similar, with some form of automatisms, clonus, unresponsiveness, autonomic alterations, behavioral arrest, clonus, eye deviation, and tonic posturing seen at all ages. Only one feature, dystonic posturing, was not seen in children <2 years (Table 1). Thus the pathophysiology and clinical features are similar across these age groups.

4.2 | Response to treatment

Extrapolation of efficacy also requires demonstration of similar response to treatment. Only two placebo-controlled trials can provide data to confirm this. A study of pregabalin in infants recruited 67 subjects 2 years of age and younger (see Table 2).[9] The study publication and clinicaltrials.gov (NCT02072824) do not separately present efficacy results by age group. However, based on this study, FDA reviewers approved pregabalin for focal seizures in children 1 month of age and greater, implying that the reviewers agreed that the drug showed efficacy across the age range of the trial.

The second trial conducted in infants with focal seizures studied levetiracetam.[8] Of these, 46% were <2 years of age (Table 3) and 98% of the subjects (all ages) had focal seizures. The fraction of subjects with a 50% reduction in seizure frequency from baseline was similar by age group within the study (see Table 4), and also similar to those seen in phase 3 studies of levetiracetam in adults. Thus two separate completed studies of two drugs with

TABLE 2 Demographics of subjects in pregabalin infant study (adapted from Mann 2020[9])

	Pregabalin 7 mg/kg/d	Pregabalin 14 mg/kg/d	Placebo
	n = 71	*n* = 34	*n* = 70
Age <1 year	9 (13%)	2 (6%)	7 (10%)
Age 1–2 year	19 (27%)	10 (29%)	20 (29%)
Age >2 year	43 (61%)	22 (65%)	43 (61%)

TABLE 1 Age trends of characteristics of seizures (adapted from Nordli 2001[13])

Ictal features	0–2 years *N* = 48	2–6 years *N* = 21	>6 years *N* = 54
Increased with age			
Aura	0 (0%)	1 (5%)	9 (17%)
Automatisms			
Limb	0 (0%)	2 (10%)	7 (13%)
Oroalimentary	2 (4%)	1 (5%)	8 (15%)
Any (includes one complex)	2 (4%)	3 (14%)	16 (30%)
Clonus (Single arm)	11 (23%)	5 (24%)	20 (37%)
Dystonic posturing (arm/hand)	0 (0%)	1 (5%)	16 (30%)
Secondary generalization	1 (2%)	1 (5%)	14 (26%)
Unresponsiveness	6 (13%)	9 (43%)	26 (48%)
Decreased with age			
Autonomic alterations	4 (8%)	1 (5%)	1 (2%)
Behavioral arrest	8 (17%)	3 (14%)	5 (9%)
Clonus (generalized)			
Symmetric	1 (2%)	1 (5%)	2 (4%)
Asymmetric	7 (15%)	2 (10%)	1 (2%)
Eye deviation (R and/or L)	12 (25%)	7 (33%)	9 (17%)
Tonic posturing			
Symmetric	19 (40%)	2 (10%)	3 (6%)
Asymmetric	13 (27%)	9 (43%)	7 (13%)
Either	32 (67%)	11 (52%)	10 (19%)

differing mechanisms of action suggest that the response to treatment for focal seizures is similar between infants and older children.

In summary, the requirements for extrapolation for the 1 month to <2 years age range appear to have been met.

5 | ISSUES RELATED TO MIXED EPILEPSY SYNDROMES

Some epilepsy syndromes, particularly those included in the developmental epileptic encephalopathies (DEE) may include focal, generalized, and unknown seizures. Drugs that may be beneficial for focal seizures must be used with caution in mixed syndromes at any age, since generalized seizures may worsen even while control of focal seizures improves.

In the infant age range, infantile spasms are particularly important to consider. Among patients in the 1 month to <2 years age range who have focal seizures, as discussed above, between 7% and 17% eventually develop infantile spasms. Evolution to infantile spasms appears to be more common in very young infants with focal epilepsy—the Olmsted County study reported median age at onset of focal seizures as 2 to 3 months in those who eventually evolved to infantile spasms.[14] Emergence of infantile spasms is an adverse outcome and should be monitored as a safety signal in trials of new ASMs.

Dravet syndrome, often related to mutations in *SCN1A*, includes seizures of multiple types. The seizures associated with Dravet syndrome can be worsened with exposure to some ASMs, particularly some sodium-channel blocking agents. Therefore, in trials of ASMs for focal seizures in applicable age ranges, especially 1 month to <2 years, patients with Dravet syndrome should generally be excluded unless there is sufficient evidence (possibly from animal models) that the drug being studied would not lead to exacerbation.

TABLE 3 Demographics of levetiracetam infant study (Pina-Garza 2009[8])

	Levetiracetam	Placebo
	n = 60	*n* = 56
6 to <12 months	8 (13.3%)	7 (12.5%)
12 to <24 months	20 (33%)	18 (32.1%)
24 to <48 months	28 (46.7%)	27 (48.2%)

6 | SAFETY TRIAL

Tolerability can be assessed in small trials; however, safety assessment requires understanding of the risks of rare or uncommon events and requires larger, long-term studies.[15] Separate safety studies, often conducted as open-label extensions to the double-blind efficacy trial, are typically conducted. Typically, 100 subjects followed for a minimum of 6 months exposure to the ASM is viewed as a sufficient data set to support approval.

In addition to emergence of infantile spasms and possible exacerbation of other seizure types, another specific safety issue for pediatric epilepsy studies is whether a specific ASM impacts the neurodevelopmental trajectory. For example, phenobarbital administered for prophylaxis of febrile seizures adversely effects subsequent intellectual development.[16] In an open-label uncontrolled safety study, it may be difficult to detect an effect of ASM on neurodevelopment.

7 | SUMMARY

Focal seizures exist in infants as young as 1 month, and patients with focal seizures represent a substantial fraction of the infant population with seizures. Although two controlled, double-blind, randomized trials have been completed in infants, the challenges associated with conduct of such trials are increasing, and such trials are increasingly seen as impracticable. Focal seizures in infants are similar to focal seizures in older patients, both in pathophysiology and in response to treatment. The regulatory requirements for extrapolation of efficacy from older patients to infants appear to be met, and this would be an appropriate pathway to approval of ASMs. Even with extrapolation to provide grounds for efficacy

TABLE 4 Responder rates (RRs) for levetiracetam use in focal seizures, by age range[8]

	Placebo		Levetiracetam		
Age	N	RR	N	RR	Odds ratio (95% confidence interval)
1 month to <4 years	51	19.6%	58	43.1%	3.11 (1.22–8.26)
1 month to <1 year	10	20.0%	11	54.5%	4.80 (0.51–62.31)
1 year to <2 years	16	25.0%	19	47.4%	2.70 (0.53–15.43)
2 years to <4 years	25	16.0%	28	35.7%	2.92 (0.68–14.71)

assessment, pharmacokinetic and safety studies are still required.

AUTHOR CONTRIBUTIONS

French, Jacqueline – conference organizer, discussant, paper writing, review. Cleary, Elena – presentation at conference, discussant, paper review. Dlugos, Dennis – presentation at conference, discussant, paper review. Farfel, Gail – participant at conference, discussant, paper review. Farrell, Kathleen – conference organizer, facilitator, paper review. Gidal, Barry – presentation at conference, discussant, paper review. Grzeskowiak, Caitlin – conference organizer, facilitator, paper review. Gurrell, Rachel – presentation at conference, discussant, paper review. Harden, Cynthia – participant at conference, discussant, paper review. Stalvey, TJ – participant at conference, discussant, paper review. Tsai, Julia – participant at conference, discussant, paper review. Wirrell, Elaine – presentation at conference, discussant, paper review. Blum, David – participant at conference, discussant, paper writing, review. Fountain, Nathan – conference organizer, discussant, paper review.

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CONFLICT OF INTEREST

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