

Predicting Efficacy of AEDs in Children:

Extrapolation of Data From Adult Clinical Trials

O'NEILL D'CRUZ, MD, MBA, FAAN

Pediatric Epileptologist and Neurologist
OD Consulting and Neurological Services, PLLC
Chapel Hill, North Carolina

JOHN B. BODENSTEINER, MD

Consultant in Child and Adolescent Neurology and
Professor of Neurology and Pediatrics
Mayo Clinic and Mayo Medical School
Rochester, Minnesota

Clinical trials for new epilepsy drugs are typically conducted in adults and regulatory approval is based on the results of these trials. Pediatric trials are usually initiated after adult data is available. However, after adult studies are completed and a drug receives regulatory approval, it is often prescribed off-label in children when similar seizures are managed in a clinical setting. Children who may otherwise be eligible for placebo-controlled, double-blind efficacy trials will have already been exposed to the drug through off-label use and therefore ineligible to participate in pediatric trials. In addition, parents may not be willing to enroll children in placebo-controlled trials. This is especially likely if the drug is available in a liquid formulation that is suitable for pediatric use. The pediatric population is relatively small compared with adults, and conducting any clinical trial in children involves additional challenges beyond those seen in adult trials, including clinical, ethical, and operational concerns.^{1,2}

In a clinical setting, off-label use in children may also require case-by-case approval from payers who question the need to reimburse for antiepileptic drugs (AEDs) that have not been FDA-approved for pediatric use, or require lack of effectiveness with multiple older AEDs before considering reimbursement for off-label use of newer AEDs. This can result in difficult choices between use of older AEDs or non-reimbursed use of newer AEDs.

From the industry perspective, the lack of sufficient pediatric study subjects limits a study sponsor's ability to comply with the Pediatric Research Equity Act (PREA). Prior to approval of an indication in adults for diseases that are also present in pediatric populations—including

epilepsy—PREA mandates that industry sponsors of adult studies must make regulatory commitments to conduct studies in pediatric populations. The challenge to enroll adequate numbers in pediatric studies in turn makes it more difficult to obtain a pediatric indication from the US Food and Drug Administration (FDA).

A possible solution to balance the need for pediatric data with the challenges outlined above is to consider whether results of adult trials of AED efficacy can be extrapolated to children. If extrapolation of efficacy is acceptable, only pharmacokinetic and safety studies would be needed in children.¹ Extrapolating efficacy from adult data to the pediatric population in certain situations has been shown to streamline pediatric drug development.²

A Global Concern

Extrapolation of adult efficacy data to pediatric indications is an issue that has been under consideration worldwide. The International Conference on Harmonization (ICH) has published a general guideline on investigating medicines in children with a recent draft addendum addressing the use of data from adults.^{3,4} The ICH states that 2 conditions must be met when extrapolating data from adults for the same indication in a pediatric population. One is that the disease process must be similar between the source population (adults) and the target population (children).⁴ The second is that the efficacy and outcomes of the treatment should be likely to be comparable between those populations.⁴ A 2010 European Medicines Agency (EMA) Guideline indicates that the effects of efficacy trials could potentially be extrapolated from adults to children in patients that have "refractory focal epilepsies," in the EMA phraseology.⁵

DISCLOSURES: Dr. D'Cruz reports that he serves as coordinator and industry representative to PEACE. Dr. Bodensteiner reports that he has received compensation for his time as a member of the Data Safety Review Board for Ionis/Biogen for their drug to treat SMA in clinical trials.

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The FDA employs a pediatric study decision tree to decide whether extrapolation from adult studies is acceptable for a particular medication, potentially including new AEDs (Figure).⁶ Like the ICH guidelines, evidence must exist that the disease is similar between adults and children and that the response to intervention between adults and children is comparable. If those 2 criteria are met, the next query in the decision tree is whether it is reasonable to assume that the exposure response in children is comparable to adults. If all of these criteria are met, then the FDA decision tree indicates that extrapolation of efficacy results from adults to children should be considered, as opposed to requiring a separate clinical efficacy trial in children to label a medication for pediatric use.

The PEACE Initiative

The Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE) was formed “to expedite AED approval for pediatric use.” PEACE includes experts from a number of organizations external to the FDA, including academia and the pharmaceutical industry.⁷ Participants provide clinical expertise in describing similarities and differences between adult and pediatric patients in various types of epilepsy and in responses to specific AEDs.⁸

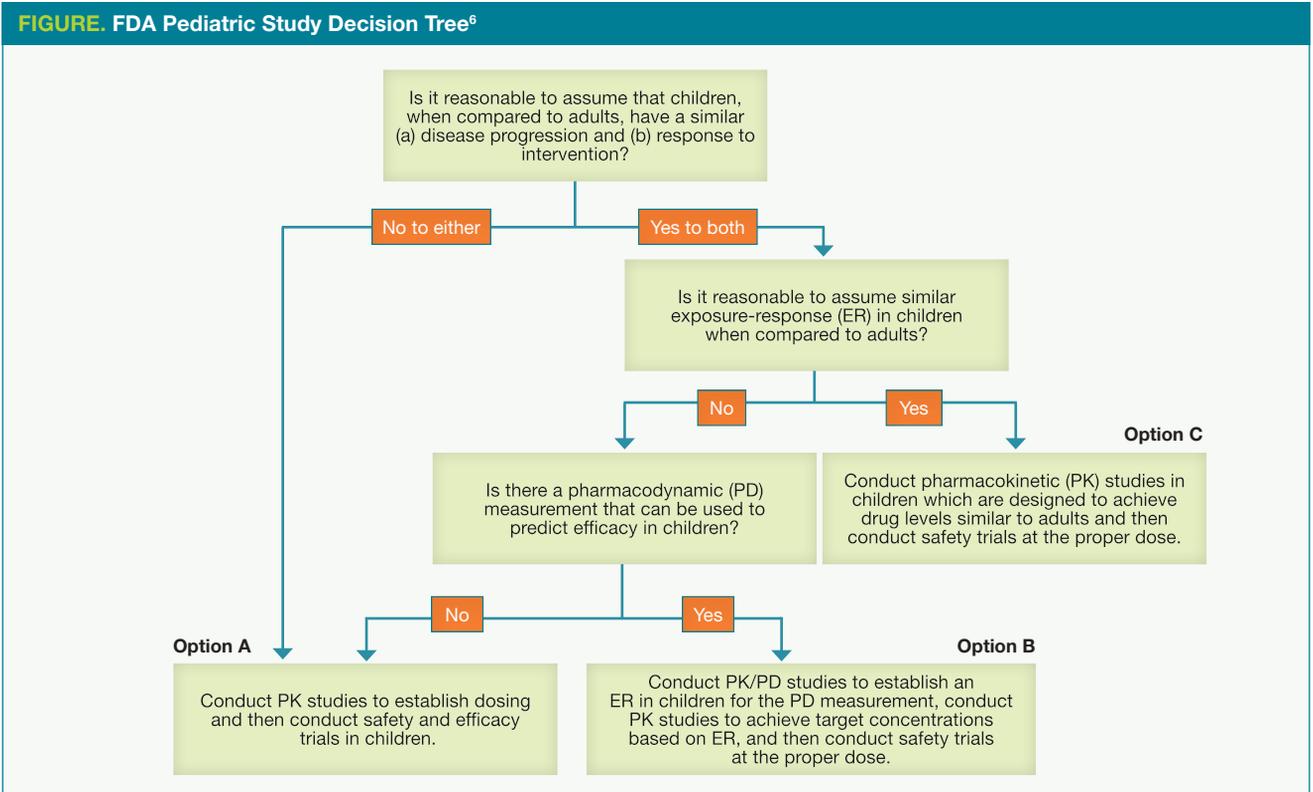
The FDA announced initial results from this research initiative in 2016, noting that it was a joint undertaking of the FDA, PEACE, and the University of Maryland.^{8,9}

Methods

Investigators began by addressing partial-onset seizures (focal seizures), the most common seizure type in children.⁹ Note: while both terms have been used in the literature, the term “focal seizure” is used in this document.

The first goal was to determine whether there is a scientific basis to assume that epilepsy is similar between adults and children.^{9,10} This also included estimating the age at which this begins to be true in young children. PEACE also investigated if clinical trials that had been conducted in adults and children previously had demonstrated similar responses to intervention with specific AEDs. If scientific evidence supported similarity of disease and response to intervention, the next step in this initiative would be to evaluate the concentration response (also known as the exposure response) for AEDs. The final step would be extrapolation of efficacy results from adults to children.

PEACE generated a White Paper describing similarities in disease and interventions in adults and children and determining the age cutoff for comparisons.¹¹ Seizures



Source: US Food and Drug Administration. Pediatric Science and Research Activities.

in very young children are known to differ from those in adults, but as children get older the clinical expression of disease becomes similar to adults.^{12,13} According to the EMA, focal epilepsies in children older than 4 years have a clinical expression similar to that seen in adolescents and adults.⁵

In order to investigate response to intervention between adults and children, Pellock et al conducted a systematic literature review and data analysis in response to a regulatory request from the Pediatric Committee of the EMA.¹ Specific qualifying criteria for published efficacy analyses identified 30 adjunctive therapy trials of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate for focal seizures in children aged older than 2 years and adults.¹

FDA and University of Maryland teams screened all approved AEDs to identify those with efficacy trials for adjunctive use in both adults and children with focal seizures.⁹ Clinical data were obtained from Phase 3 trials of 8 drugs with varying presumed mechanisms of action—levetiracetam, oxcarbazepine, topiramate, lamotrigine, gabapentin, perampanel, tiagabine, and vigabatrin.¹⁰ These covered data from 26 placebo-controlled clinical trials enrolling 6000 patients, including 1400 children.¹⁰

The evaluations to compare efficacy in adult and pediatric subjects included quantitative exposure-response analyses: specifically, steady-state C_{\min} (trough concentrations), AUC (area under the curve) and C_{avg} (average concentrations) as exposure metrics, and percent change from baseline (%CFB) in seizure frequency per 28 days as the response metric.^{9,10} Several comparisons were performed using data from adults and children aged 4 years and older:

- Responses at the approved doses;
- Exposures at the approved doses;
- Exposures and responses in different pediatric age subgroups;
- Exposure-response relationships using graphical and model-based analyses.

Results

Disease Similarity

The PEACE White Paper provided support for disease similarity on preclinical, neurophysiological, and clinical evidence, and proposed an age criterion (≥ 4 years of age) in alignment with EMA guidelines, and similarity of pathophysiology of focal seizures between adults and children ages 4 and older.¹¹

Similarity of Response to Intervention

A systematic literature review concluded that efficacy results in adults may be extrapolated more universally to predict adjunctive treatment response in 2- to 18-year-olds with focal seizures.¹

Similarity of Exposure-Response

For each of the 8 AEDs evaluated, the placebo-corrected responses and exposure measures were consistent between adults and children aged 4 years and older at the approved doses.¹⁰ Slopes of the exposure-response relationships created using graphical and model-based comparisons were also similar between adults and children.¹⁰

Conclusions From the Initial Study

Based on the totality of evidence, including similarities in disease pathophysiology, efficacy for AEDs can be extrapolated from successful adult efficacy trials to pediatric patients with focal seizures aged 4 years and older.^{8,9} Achieving AED concentrations in children that are similar to concentrations in effective doses in adults should result in similar clinical responses.¹⁰ Although pediatric dosing strategies may involve different formulations and strategies, (for example, in terms of milligrams of drug per kilogram body weight rather than fixed doses) if comparable concentrations are achieved then efficacy can still be extrapolated from adults to children. This is an important point when considering young children; those younger than age 6 or 7 years might not safely swallow tablets or capsules, so the availability a liquid formulation suitable for pediatric use is very important.

Ramifications for Future Pediatric AED Approvals by the FDA

A change in FDA regulatory policy was enacted as a result of the findings of the collaboration between FDA, PEACE, and the University of Maryland. The new policy provides a class level PREA waiver and eliminates the previous FDA requirement for independent pediatric efficacy trials for adjunctive therapy of focal seizures in children aged 4 years and older for an AED that has been approved to treat focal seizures in adults, when the drug's pharmacokinetic analysis shows that the dosing regimens provide similar drug exposure in children aged 4 years and older and adults at levels demonstrated to be effective in adults.⁹ Efficacy trials are needed for children younger than age 4 years.⁹

Safety

It is important to note that the PREA waiver for efficacy studies does not mean that safety results for new AEDs can be extrapolated from adults to children aged 4 years and older. Safety issues specific to children include concerns about drug effects on growth, puberty, learning, and motor, speech, language, and cognitive development. Safety studies in adults do not provide adequate information about these concerns. The FDA will still require 1 or more long-term, open-label safety studies in pediatric patients aged 4 years and older.⁹ This can be achieved with open-label studies that collect safety and pharmacokinetics data, rather than placebo-controlled double-blind trials.

Resources for Research

Another impact on clinical research is that allowing extrapolation of efficacy data from adults to children will free up scarce resources. By eliminating the need for pediatric studies of efficacy for AEDs for focal seizures, those resources will hopefully be available for other clinical development work in pediatrics. A recent European proposal draws a similar conclusion.⁷ It suggests that phase I trials of AEDs should continue in adults only, while phase 2 and 3 trials simultaneously recruit adults and pediatric patients older than age 2 years. AEDs could be provisionally licensed for children “subject to a phase 4 collection of neurodevelopmental safety data in this age group.”⁷ The authors of the proposal anticipate that patients would benefit from earlier access to new treatments while the costs for drug approval would drop.⁷

Future PEACE Initiatives

While the scientific evidence in the PEACE White Paper and findings of published clinical trials support extrapolation for children aged 2 years and older, the age cutoff for the original PEACE proposal was based on an effort to obtain harmonization of regulatory policies between EMA (where extrapolation was accepted for 4 years and older) and FDA (where extrapolation was not previously accepted). Future work by PEACE will explore whether the age for extrapolating adult efficacy data from trials of AEDs in focal seizures can be younger than 4 years. Another possible initiative may explore whether and for what ages efficacy might be extrapolated from adult studies of primary generalized tonic-clonic seizures. However, because seizure disorders in neonates and very young children differ from those in older children and adults, it is unlikely that data from clinical trials of AEDs in adults can be used to extrapolate efficacy to very young populations.

Another possibility for a PEACE initiative is reverse extrapolation, where results of trials conducted in children may be extrapolated to adults. Regulatory precedents for reverse extrapolation include neurologic diseases present in adults and children, but more prevalent in the pediatric population (eg, Pompe disease and ADHD). Epileptic encephalopathies are a possible option for reverse extrapolation in epilepsy. ■

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