Assessing quality and quantity of data to establish exposure-response similarity between adults and pediatric patients: PEACE Initiative

Angela Yuxin Men, M.D., Ph.D.
Neurology Team Leader
DCP1/OCP/OTS/CDER
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CERSI Workshop on the Use of Exposure Matching and Exposure Response for Extrapolation of Efficacy in Pediatric Drug Development Disclaimer:

The views presented here do not necessarily reflect those of the US FDA

Outline

- **Critical Path Project**
  - Extrapolation of efficacy from adults to pediatrics (≥ 4yo)
- **Exposure-response similarity between adults and pediatric patients**
  - Data Collection/Analysis/Preliminary results
  - Future Steps

Critical Path Funded Project

Extrapolating Efficacy of AEDs from Adults to Pediatrics

Collaboration among PEACE-UMD-FDA

PEACE (Pediatric Epilepsy Academic Consortium on Extrapolation)

Background

	ADULTS	PEDIATRICS
MONOTHERAPY	Approved based on efficacy/safety trials	Pharmacometric based approval (Trileptal &Topamax)
ADJUNCTIVE THERAPY	Approved based on efficacy/safety trials	**Can we extrapolate efficacy for adjunctive therapy in pediatrics based on adult trials?**

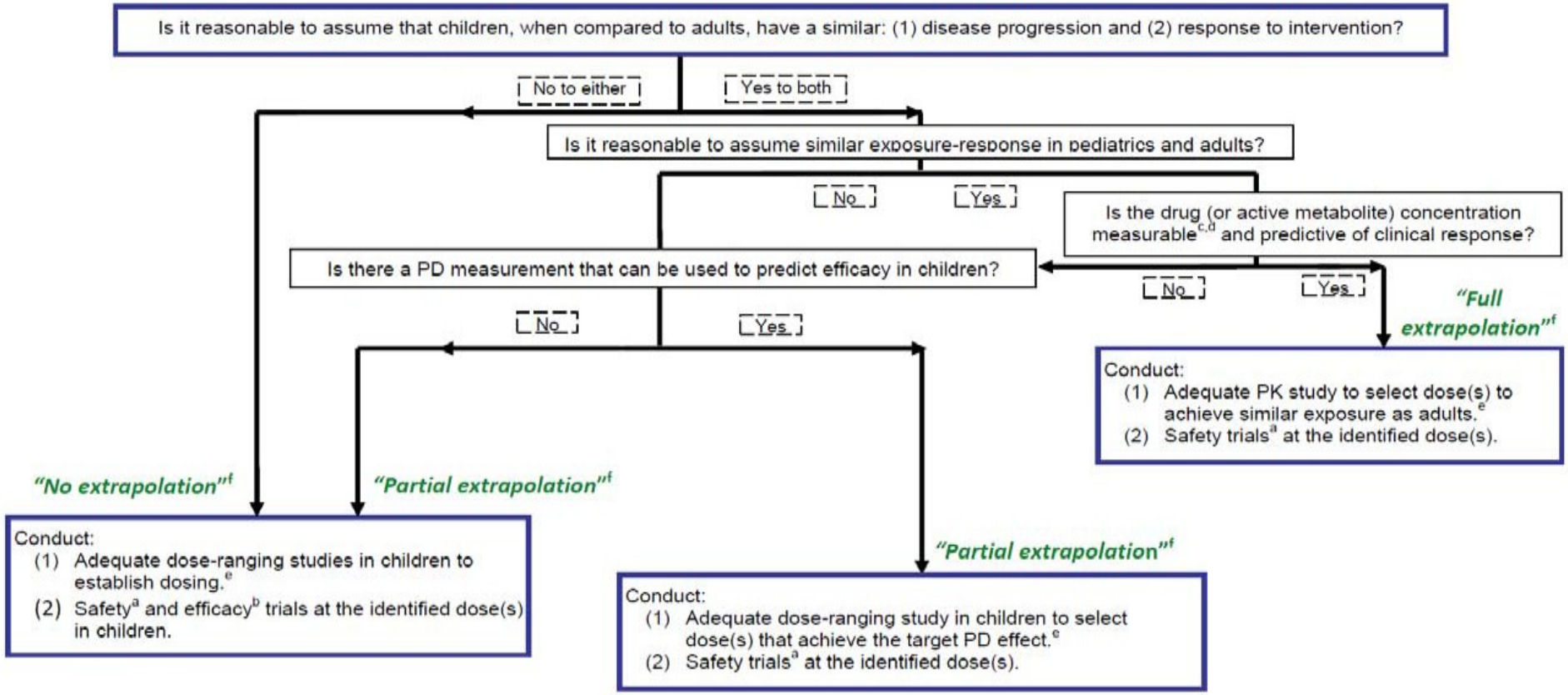
Epilepsy in Pediatrics

- **Epilepsy is a common neurological disorder in childhood.**
- **Childhood is a peak age of onset for seizure onset.**
- **The majority of childhood onset seizures including those in younger children are of <u>partial onset.</u>**

Epilepsy, NICE Clinical Guideline (January 2012)
Epilepsy; NICE CKS, June 2009

As the majority of studies of new AEDs are conducted in adults with partial onset seizures (POS), is it appropriate to extrapolate the efficacy from adults to pediatrics?

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

See the Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Footnote 13).

Two Key Questions

- **Disease similarity?**

- **Exposure-response similarity between adults and pediatric patients?**

Disease Similarity

- PEACE/DNP provides the clinical expertise to describe disease and intervention similarities between adults and pediatrics.

- Biological basis concludes that seizures in children four years of age and older are similar to seizures in adolescents and adults.

- Therefore, AEDs that are shown to be effective in adults with partial seizures, also can be expected to be effective in children ≥ 4 years of age.

Exposure-response similarity between adults & pediatric patients

Data Collection

- **Essential Information Requested Study reports of conducted clinical trials for POS**
  - Standardized seizure frequency data (i.e., seizure frequency per 28 days)
  - Individual level pharmacokinetic concentration data and any pharmacokinetic model used to derive the pharmacokinetic parameters
  - Information on demographics and concomitant medications.

Data Collection

- **Additional Information**
  - Individual level seizure frequency data from diaries
  - Statistical analysis code used to evaluate treatment effects
  - Analysis datasets containing concentration and seizure frequency information in adults and pediatrics.

List Of Approved Drugs To Be Investigated

Drug	Adult	Pediatrics	Indication	Adjunctive
Gabapentin (Neurontin)	> 12y	3y to 12y	Partial Seizures	3y to 12y
	> 16y	1m to 16y	Partial Onset Seizures	
Levetiracetam (Keppra)	> 12y		Myoclonic Seizure in Patients with Juvenile Myoclonic Epilepsy	Y
	> 16y	6y to 16y	Primary Generalized Tonic-clonic Seizures	
Clonazepam (Klonopin)	Y	> 10y or 30kg	Seizure Disorders	
Lamotrigine (Lamictal)	Y	>=2y	Partial Seizures Primary Generalized Tonic-clonic Seizures Generalized Seizures of Lennox-Gastaut Syndrome	Y
Topiramate (Topamax)	Y	2-16y	Primary Generalized Tonic-Clonic Seizures Seizures of Lennox-Gastaut Syndrome Partial Onset Seizures	Y
Oxcarbazepine (Trileptal)	Y	Y	Partial Seizures	Y
Perampanel (Fycompa)	Y	>12y	Partial-onset seizures with or without secondarily generalized seizures	Y
Tiagabine (Gabitril)	Y	>12y	Partial seizures	Y

Approved Dose Ranges

	Adults	Pediatrics (4 years and above)
Oxcarbazepine	**1200 to 2400 mg/day BID**	**20-29 kg - 900 mg/day BID 29.1-39 kg - 1200 mg/day BID >39 kg - 1800 mg/day BID**
Topiramate	**3 to 6 mg/kg/day BID** ~ 70kg Adult 200 - 400 mg/day as BID	**5 to 9 mg/kg/day BID**
Perampanel	**4mg QD to 12mg QD (12 years and above)**	
Levetiracetam	**21 mg/kg BID** ~70kg Adult 1500mg BID	**30 mg/kg BID**
Lamotrigine	**4.3 -7.1 mg/kg/day BID** 300 -500 mg/day	**5 -15 mg/kg/day BID** (max = 400 mg/day)
Gabapentin	**25.7 mg/kg/day as TID** 1800 mg/day as TID	**4 yrs : 40 mg/kg/day as TID; 5-11 yrs : 25-35 mg/kg/day as TID;**

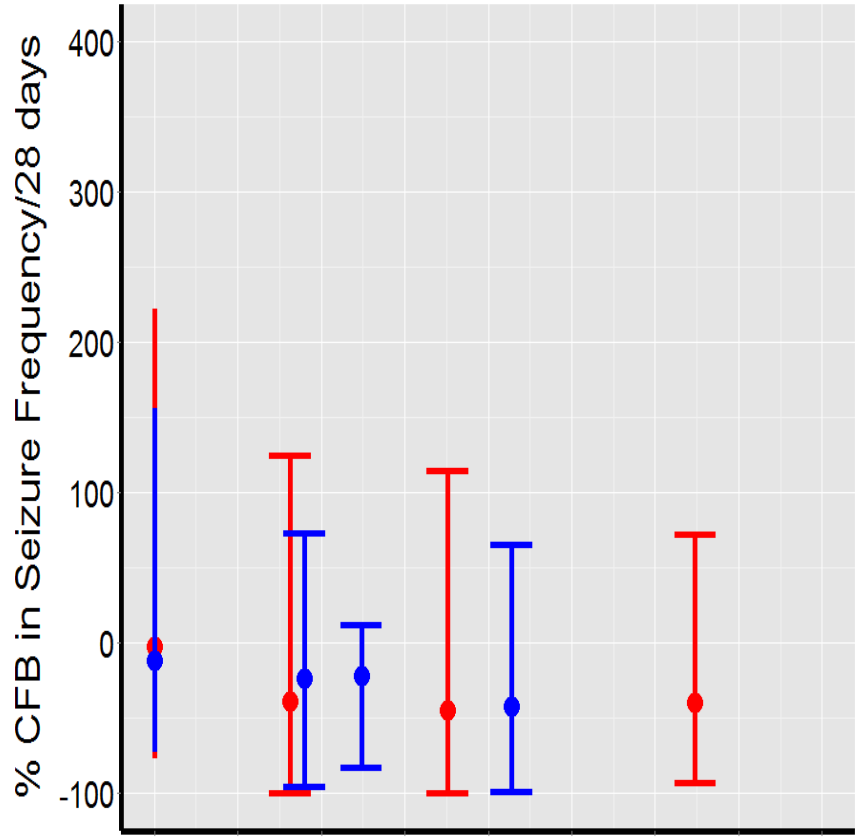
Exposure Response Analysis

- **Graphical display of observed concentration response data**
- **Findings from model based analysis**
- **Compare adults and pediatrics exposure response relationship using equivalence approach**

Exposure Response Analysis

- Graphical display of observed concentration response data
  - Similar E/R between adults and pediatrics for a given drug
- Findings from model based analysis
  - Slopes are compared between adults and pediatrics
- Compare adults and pediatrics exposure response relationship using equivalence approach
  - Approach used during regulatory approval for Trileptal

Observed Exposure Response Relationship



- Metrics evaluated:
  - Conc. comparison
  - N
  - Variability
  - Difference

Exposure Response Analysis

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  - Same metric between adults and pediatrics for a given drug

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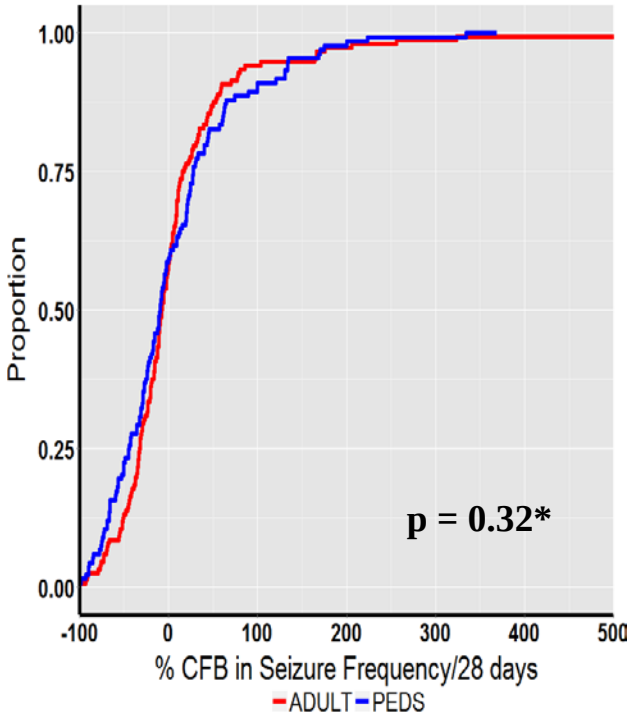
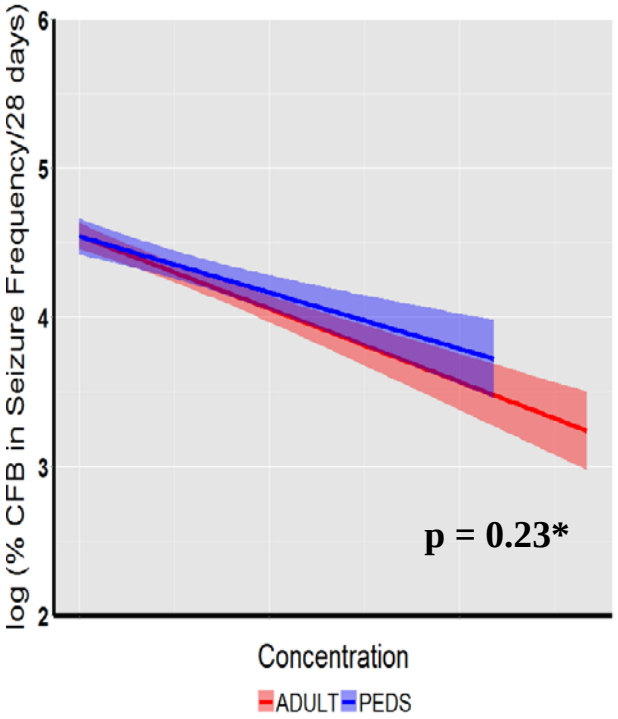
Placebo Response



- *P value > 0.05 indicates the distributions are not statistically different*

E-R Relationship



P value > 0.05 indicates that the difference between slope of exposure-response between adults and pediatrics is not statistically significant

Analysis conducted by Shailly&Tao

Exposure Response Analysis

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Trileptal Equivalence Analysis

Comparison of the model-predicted percent change from baseline in seizure frequency between adult and pediatric patients.

Cmin (umol/L)	Percent change from baseline		Difference: Pediatric patients-Adults	
	Pediatric patients	Adults	Estimated difference (% relative to adults)	95% Confidence interval for difference
0.0	-16.7	-14.1	-2.5 (-17.9%)	(-15.0, 9.9)
17.0	-27.2	-29.5	2.3 (7.8%)	(-6.5, 11.1)
40.8	-40.0	-47.0	7.0 (14.8%)	(-2.5, 16.4)
68.0	-52.2	-62.3	10.1 (16.2%)	(-1.9, 22.1)
73.8	-54.5	-65.1	10.6 (16.2%)	(-1.5, 22.6)

Similar Shape predicts the similar responses to a given concentration achieved over the range of concentrations likely to be experienced.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-014_Trileptal.cfm

Challenges

- Pooling trials across different periods of time and geographic areas
- Six drugs across five different mechanism of actions
- The clinical trials were conducted in different countries at different sites
- How to interpret if the E/R relationship is not similar

Preliminary Results

- Concentration at approved dose are similar
- Exposure response relationship are similar for several drugs evaluated

Future Steps

- **Continuously conduct E-R analysis for AEDs in adults and pediatrics**
- **Discuss with PEACE in early March**
- **Set criteria for extrapolating efficacy from adults to pediatrics in the adjunct therapy setting for POS**

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THANK
YOU!