Quantitative Analysis to Support Full Extrapolation of Efficacy in Children for Partial Onset Seizures in Adjunctive Setting: FDA-PEACE Initiative

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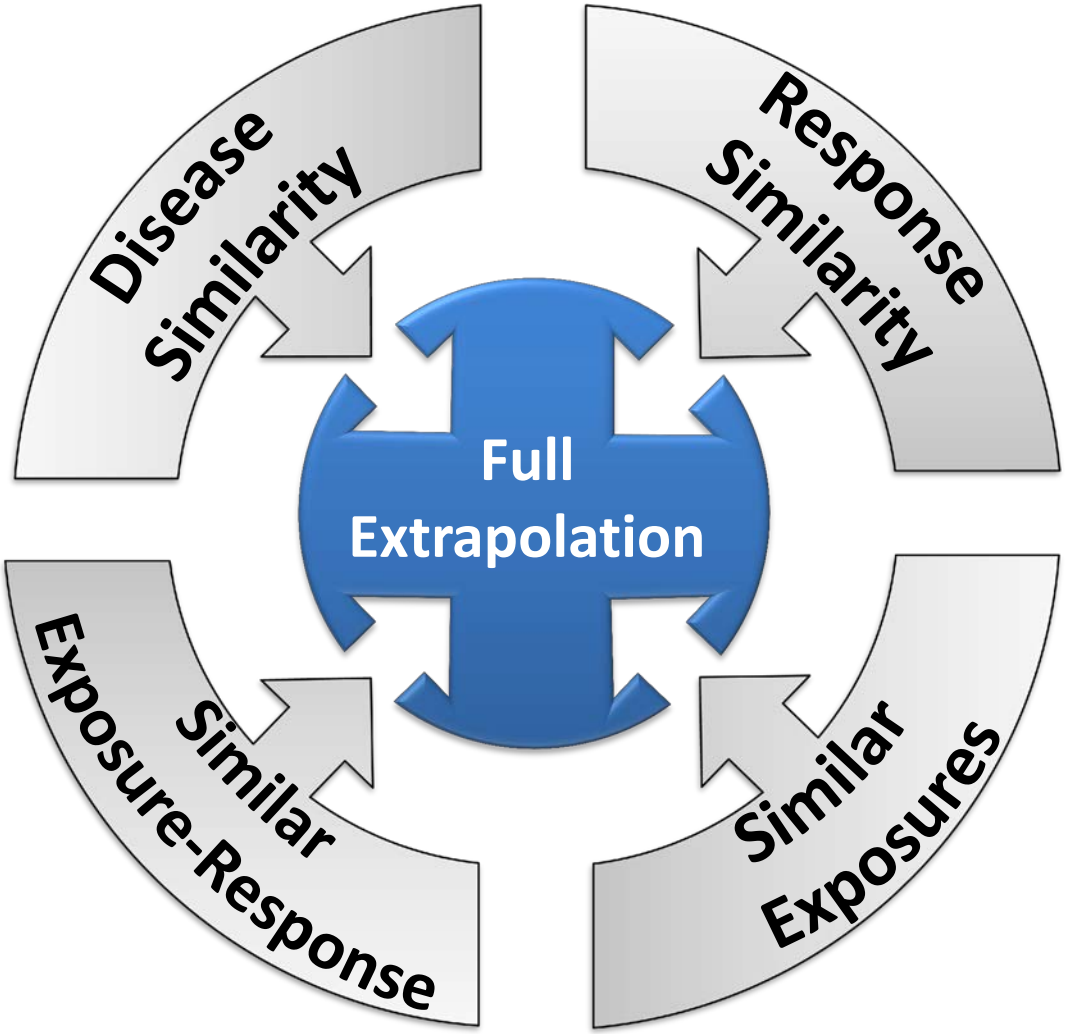
Evidence to Support "Full Extrapolation" of Efficacy



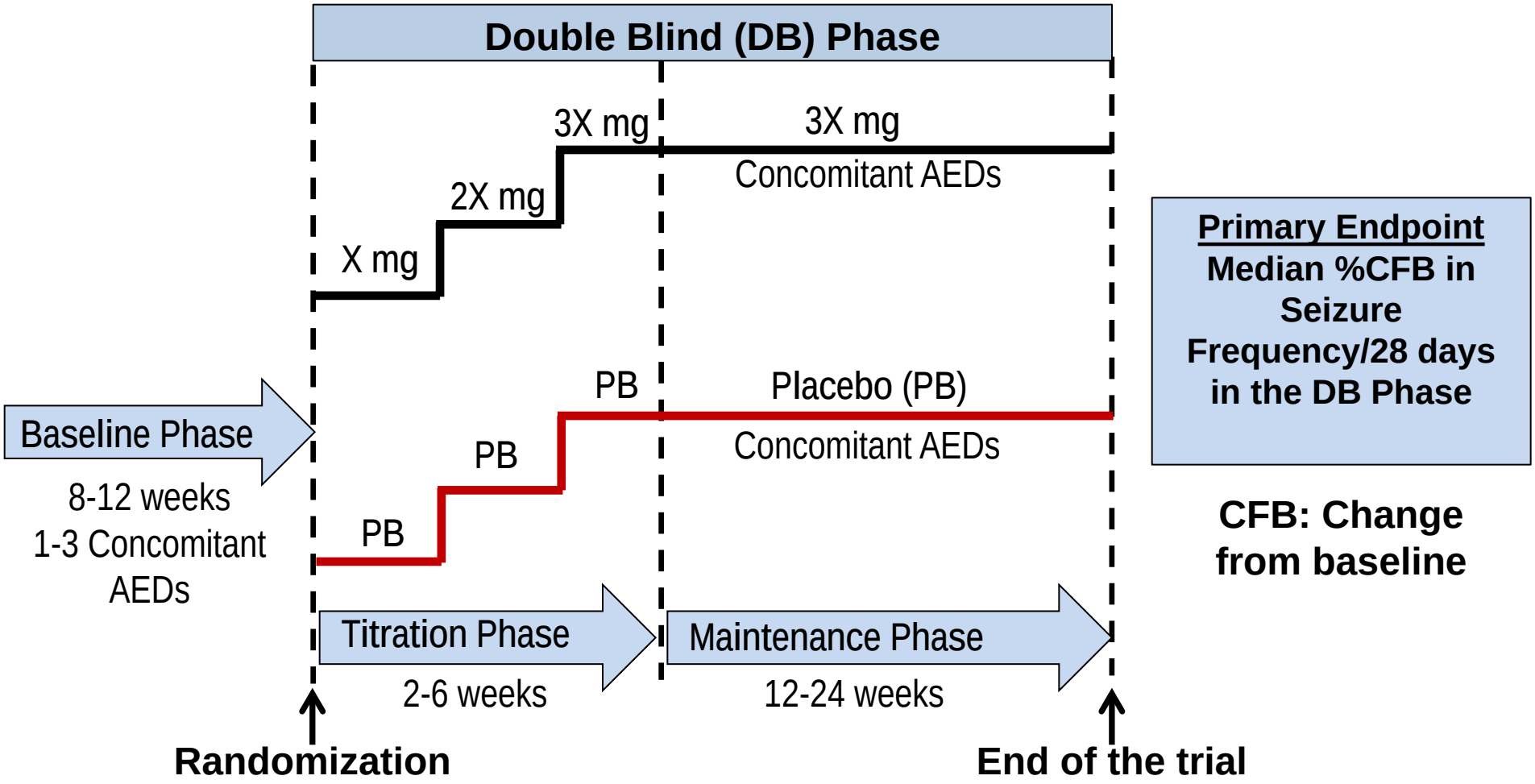
Disease Similarity Between Adults & Children

- PEACE/DNP provided the clinical expertise to describe:
  - the *pathophysiology* of partial onset seizures (POS)
    - After excluding children under age 4 and those with POS associated with epileptic encephalopathies such as Lennox-Gastaut, the pathophysiology of POS is similar in children (≥ 4year old) and adults.

List of Drugs Investigated

Drug	Population	Mechanism of Action
Oxcarbazepine (Trileptal)	≥ 2 year	Blocks voltage dependent Na channels, increase K conductance and modulate high voltage activated Ca channels
Levetiracetam (Keppra)	≥ 1 month	Acts by binding to SV2A protein
Lamotrigine (Lamictal)	≥ 2 year	Inhibits voltage sensitive Na channels, stabilize neuronal membranes and modulates presynaptic release of excitatory neurotransmitter
Topiramate (Topamax)	≥ 2 year	Blocks voltage dependent Na channels, augments GABA activity, antagonize AMPA/Kainate subtype of glutamate receptor, inhibits carbonic anhydrase enzyme
Gabapentin (Neurontin)	≥ 3 years	Not known; binds with α2δ subunit of voltage activated calcium channel but therapeutic effects of binding are unknown
Perampanel (Fycompa)	≥12 year	Noncompetitive antagonist of AMPA glutamate receptor
Tiagabine (Gabitril)	≥12 year	Not known, enhances the activity of GABA an inhibitory neurotransmitter
Vigabatrin (Sabril)	≥10 year	Not known, increase levels of GABA in CNS

Trial Design and Primary Endpoint in Approval of AEDs in Adjunctive Setting



Plasma samples are collected in the maintenance phase

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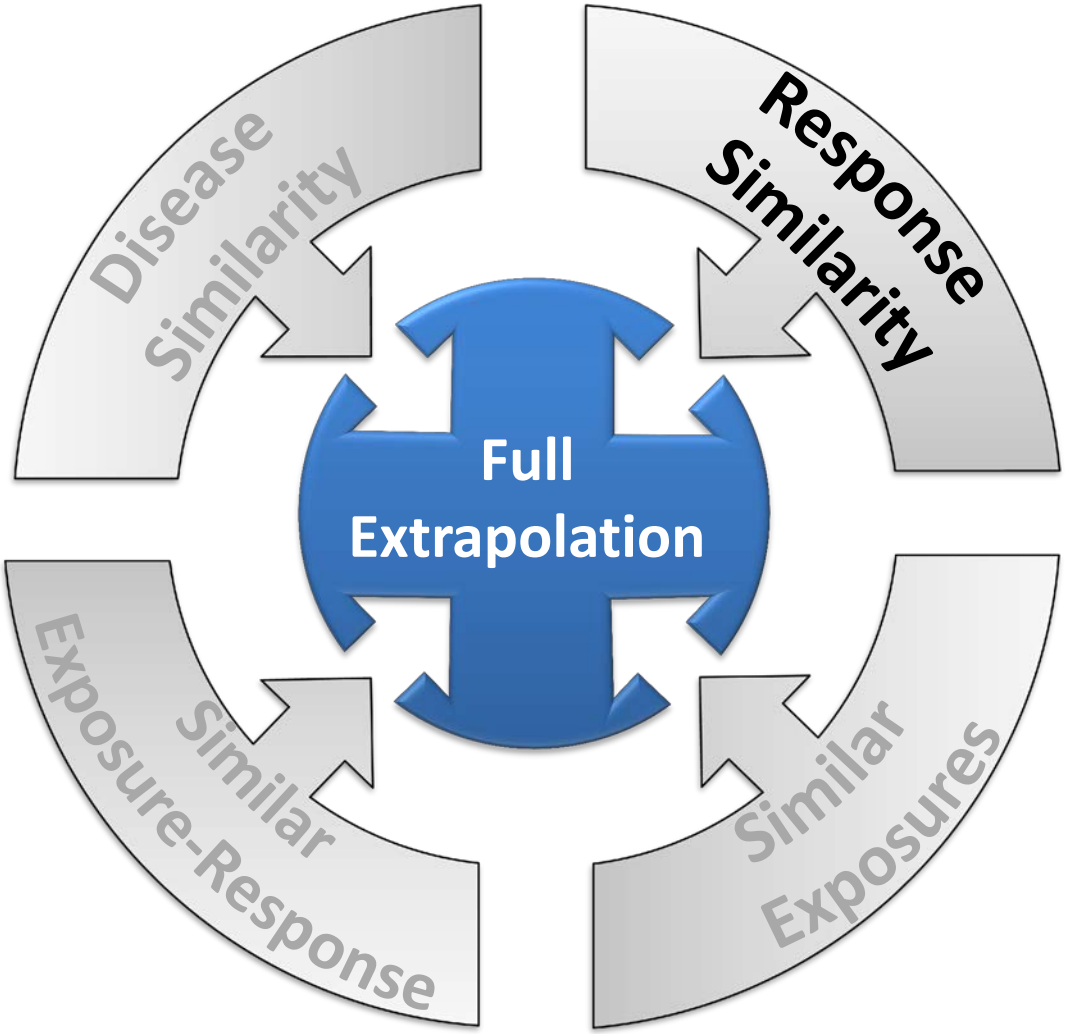
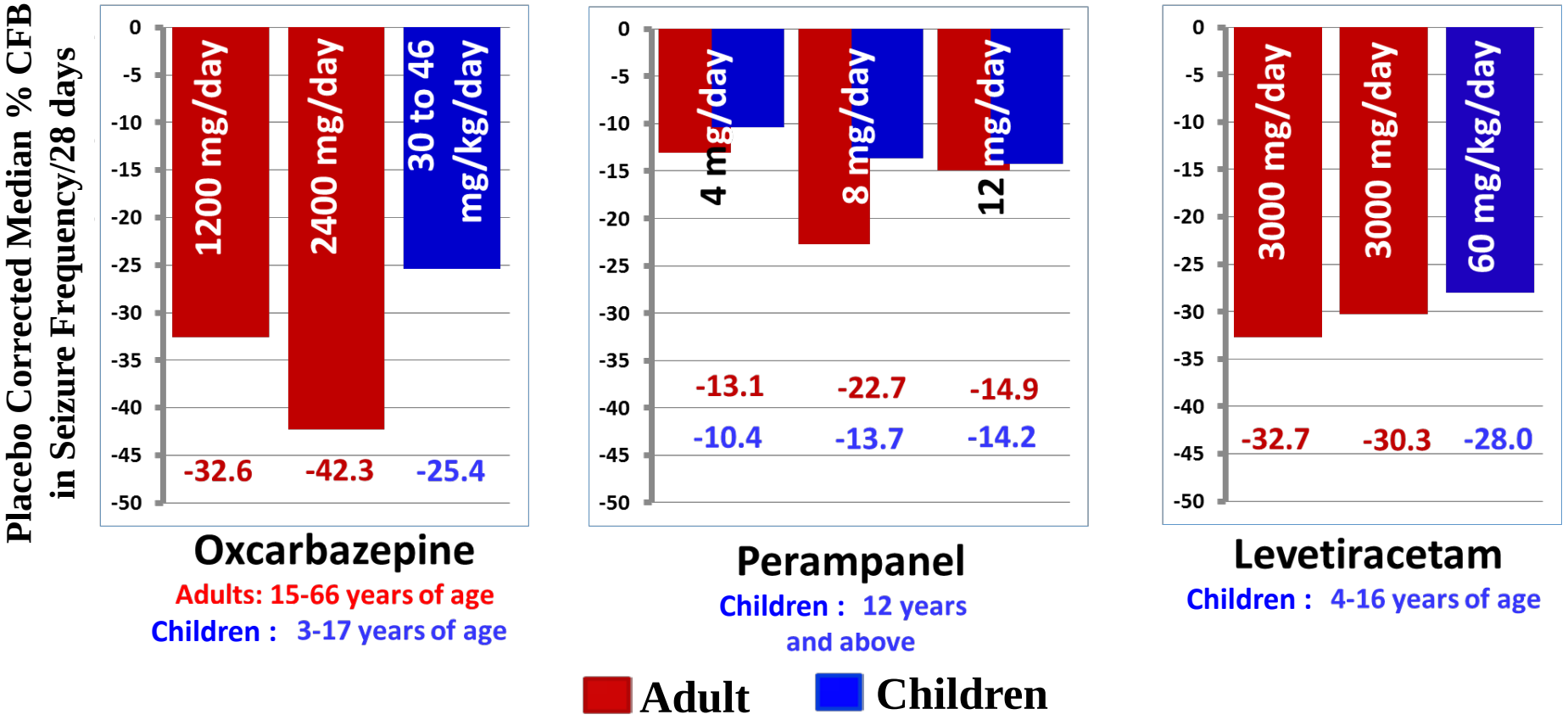
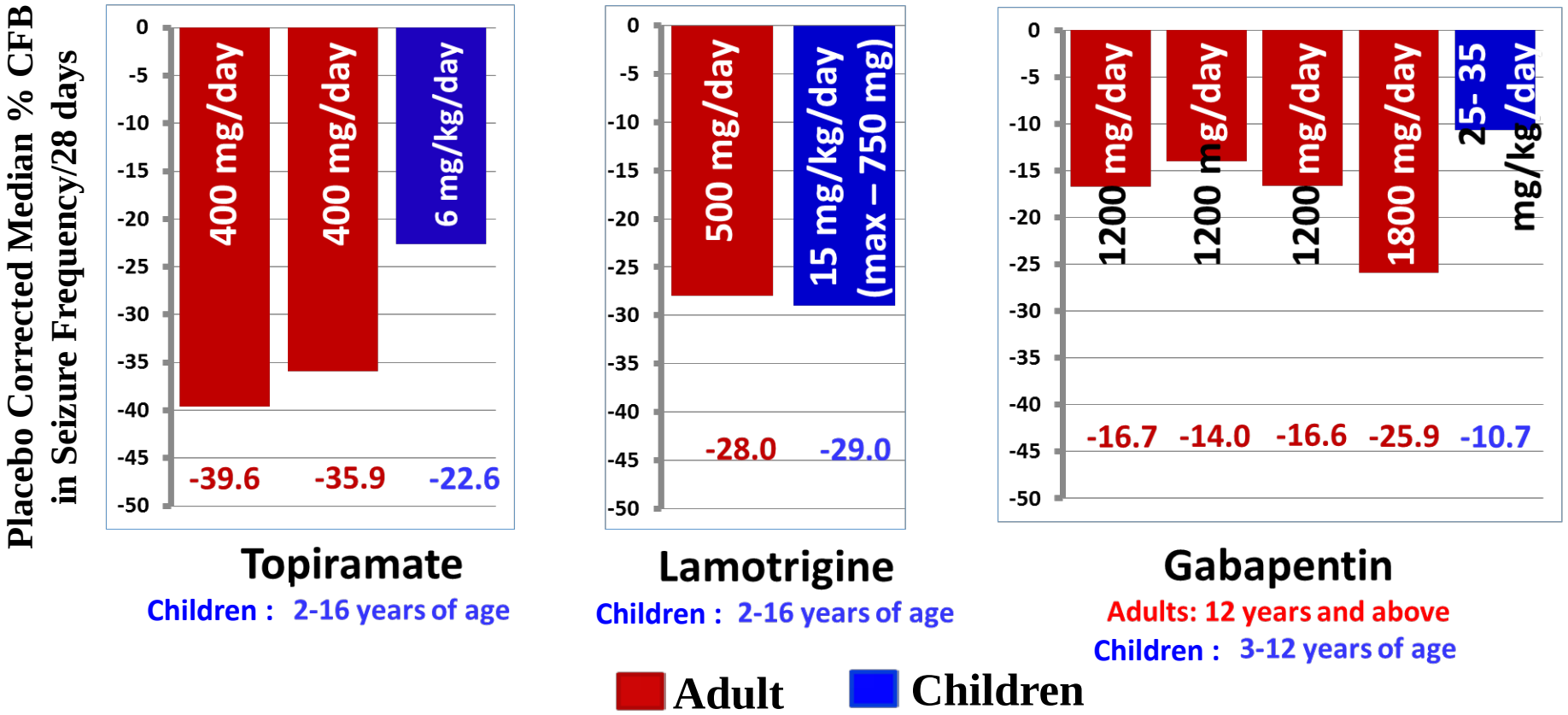


Observed Efficacy of Approved AEDs in Adults & Children from Registration Trials



Source: Labels for oxcarbazepine, perampanel and levetiracetam

Observed Efficacy of Approved AEDs in Adults & Children from Registration Trials



Source: Labels for topiramate, lamotrigine and gabapentin

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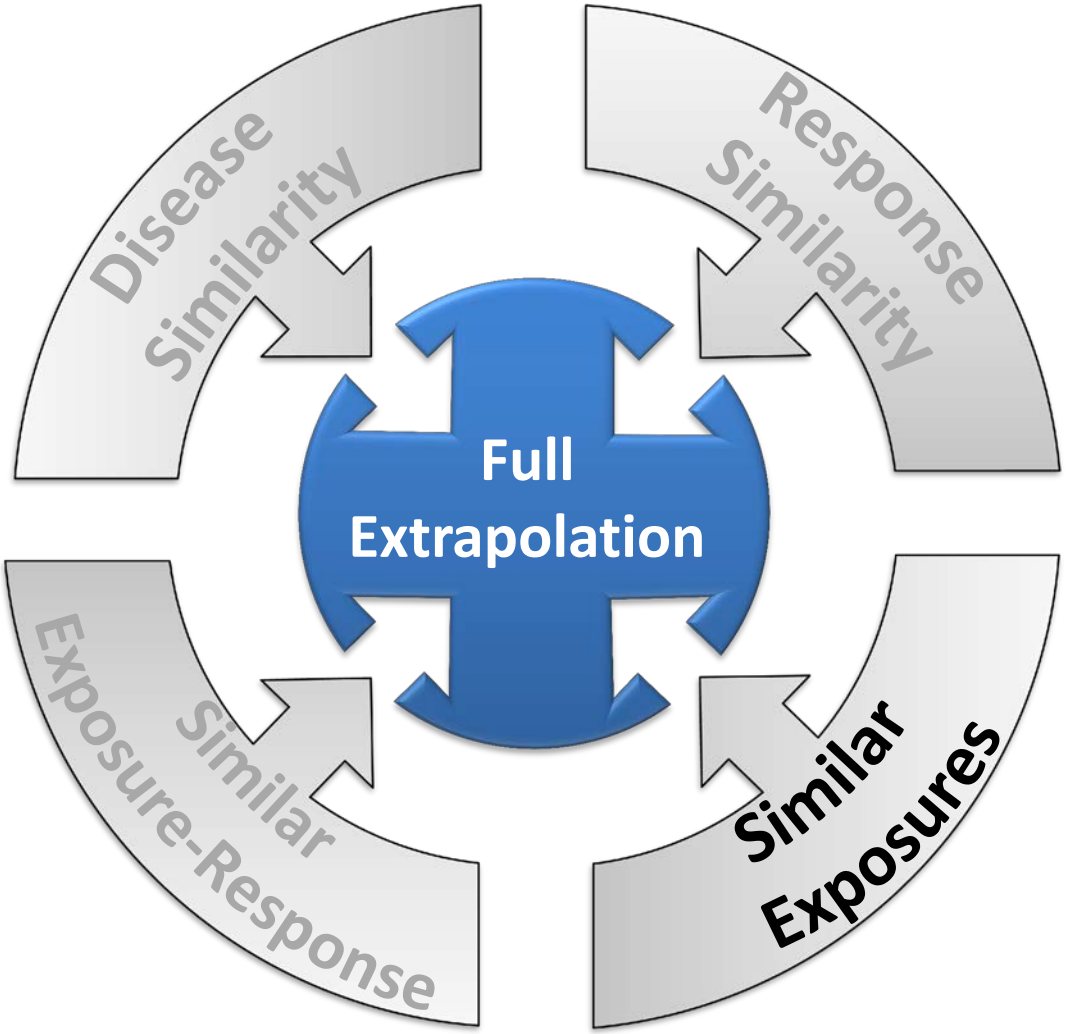
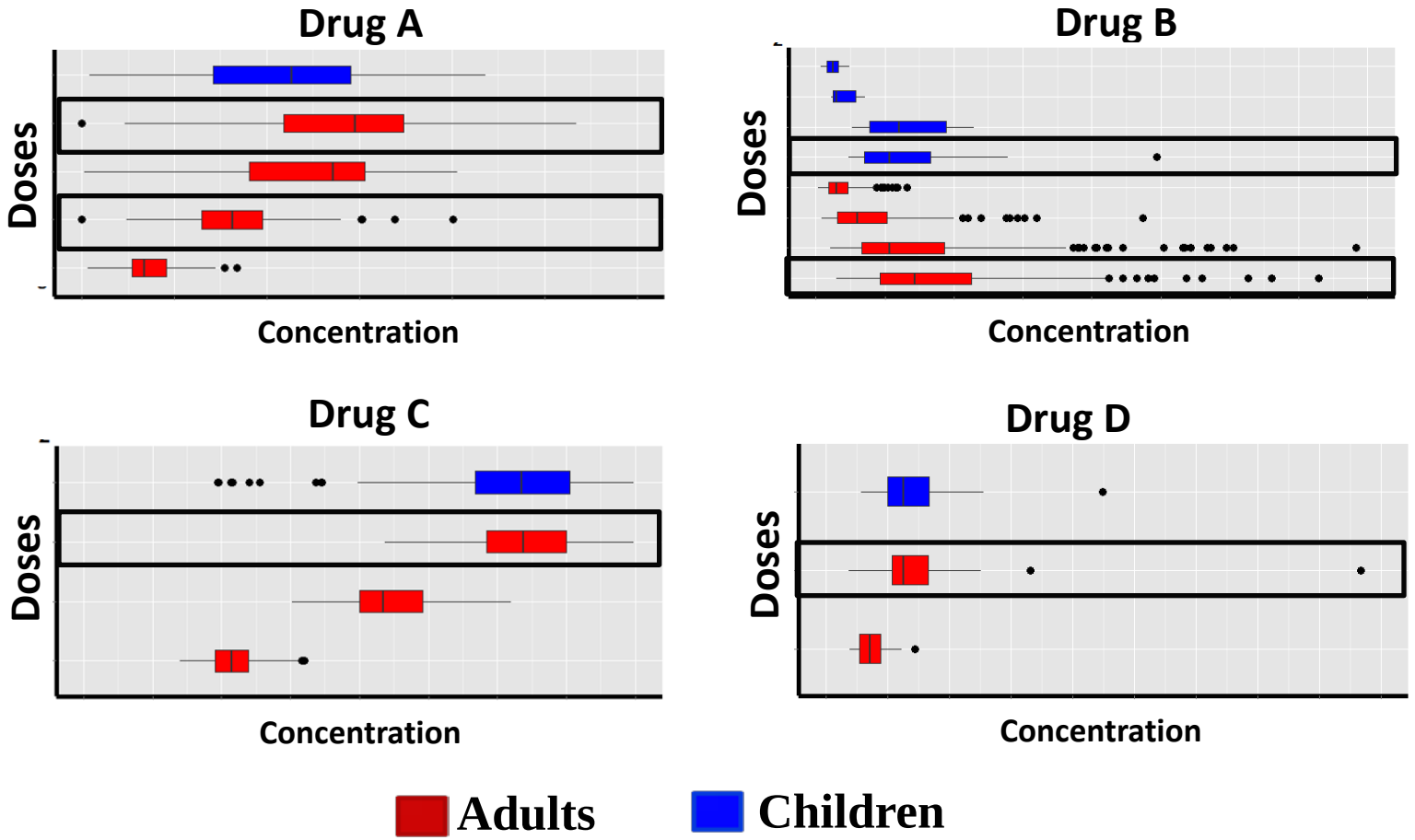


Concentration Metric Utilized for Comparing Exposures in Adults and Children

- Cmin: trough concentration at steady state
- Cavg: average concentration at steady state
- Same metric utilized between adults and children for a given drug

Concentrations at Approved Doses in Adults & Children



*Doses in the boxes denote highest recommended maintenance doses

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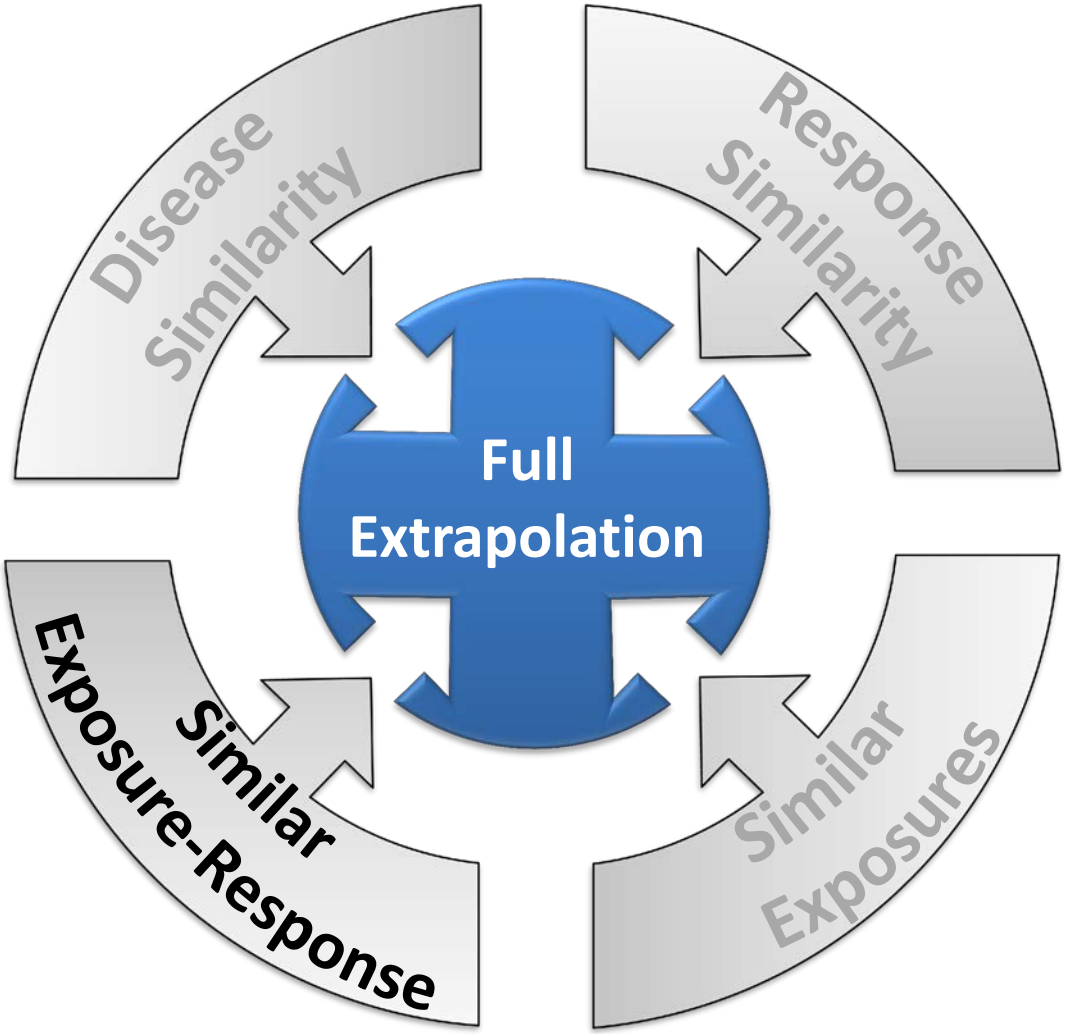
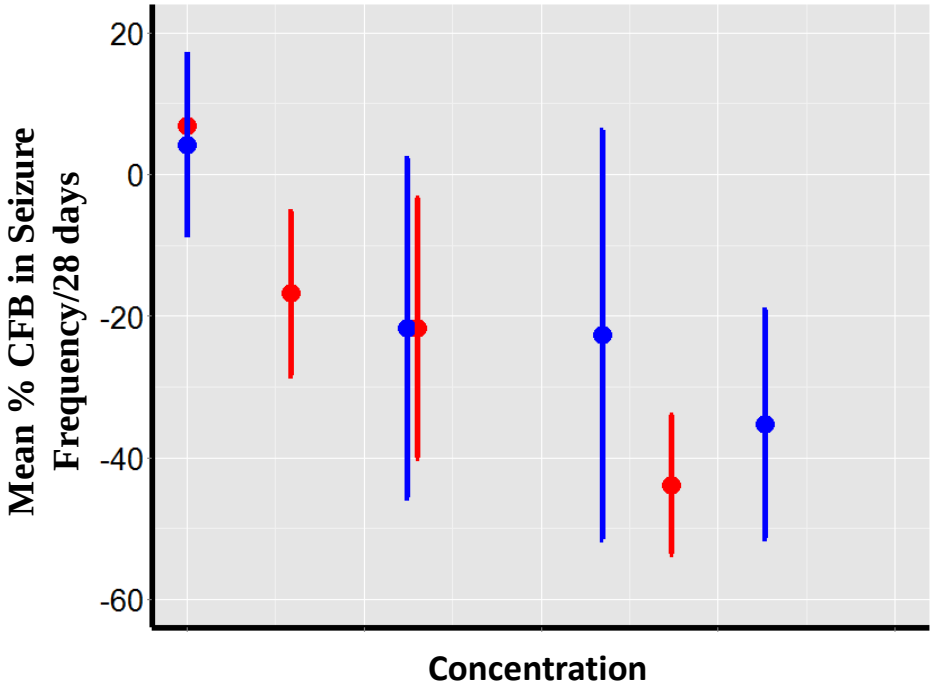


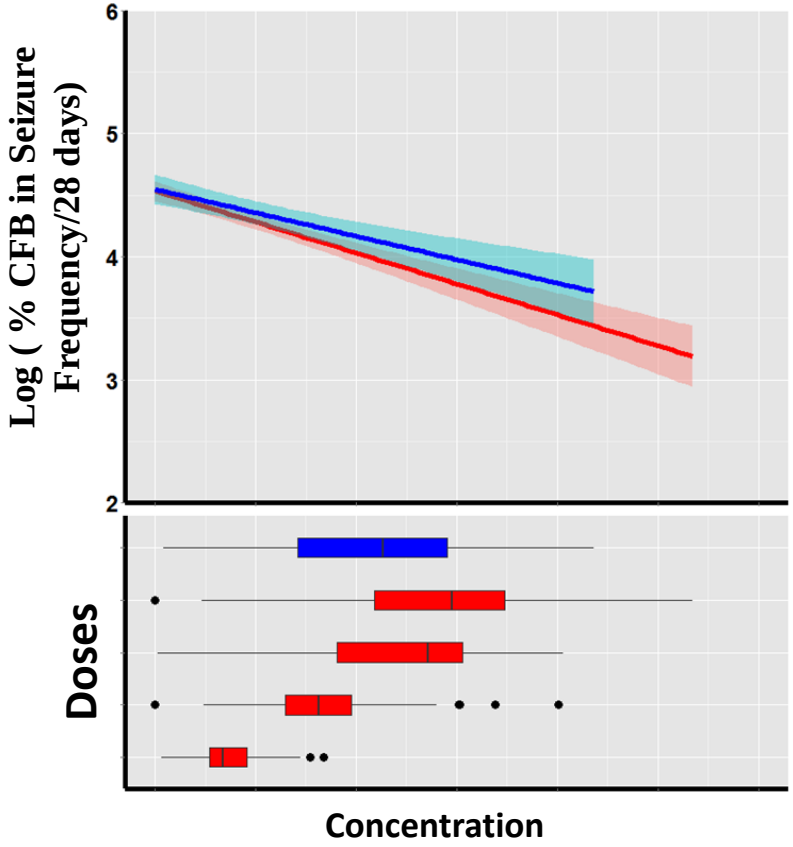
Methodology

a) Graphical Analysis

b) Model Based Analysis

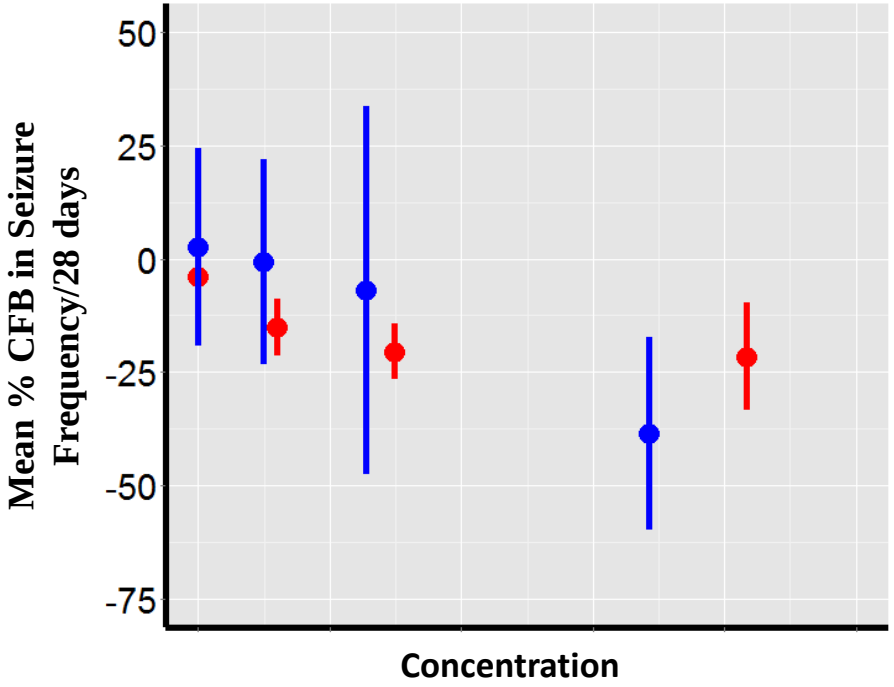
Drug A
Exposure-Response in Adults & Children

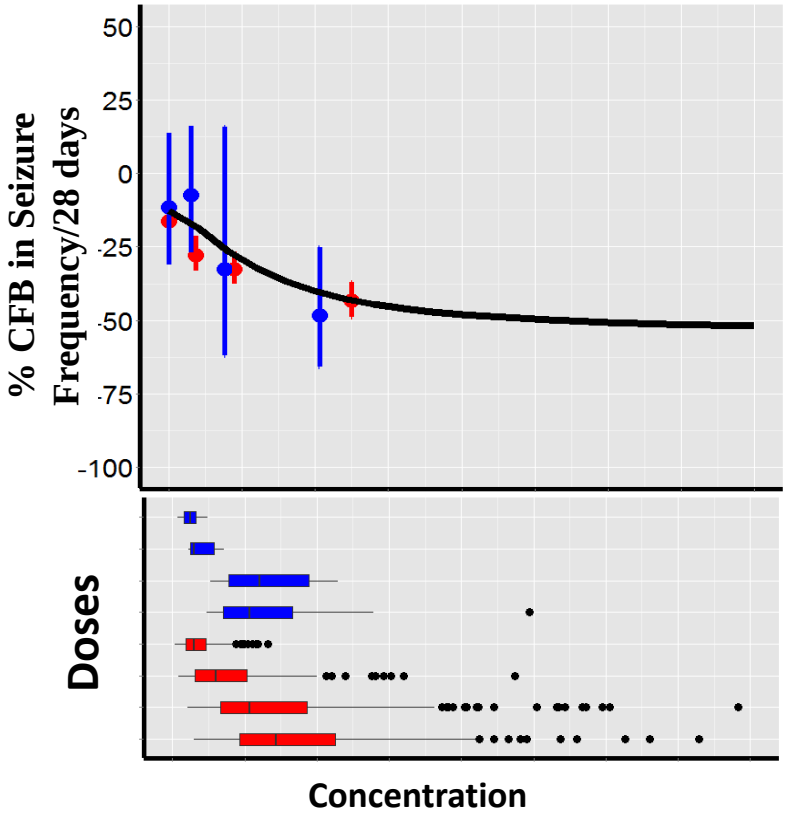




Adults Children

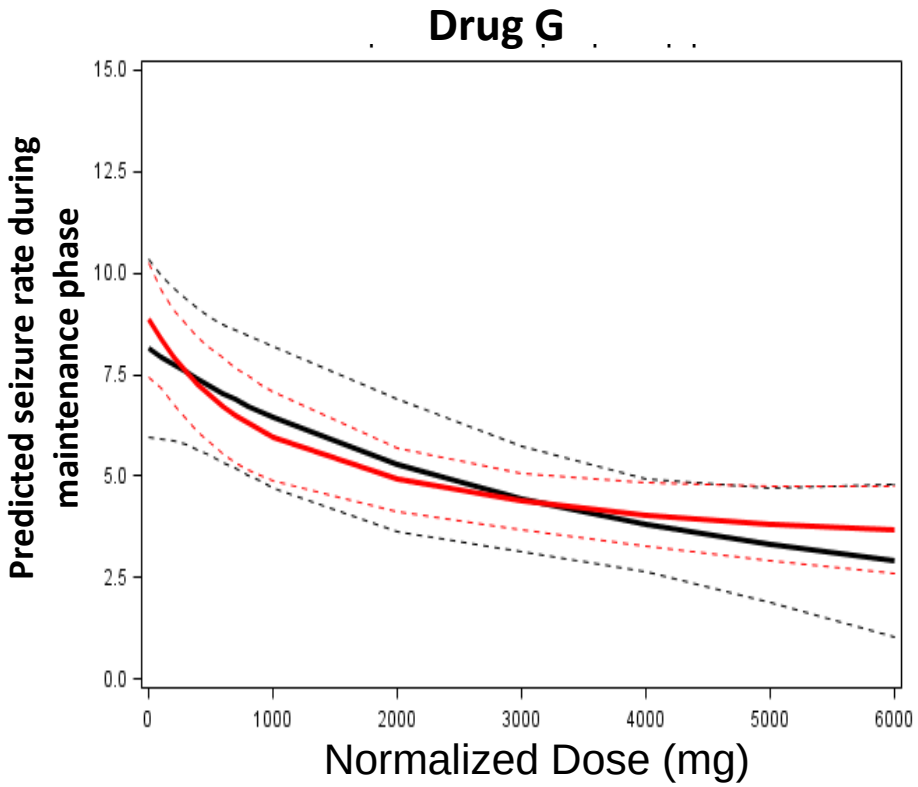
Drug B
Exposure-Response in Adults & Children





Adults Children

Drug G
Exposure-Response in Adults & Children

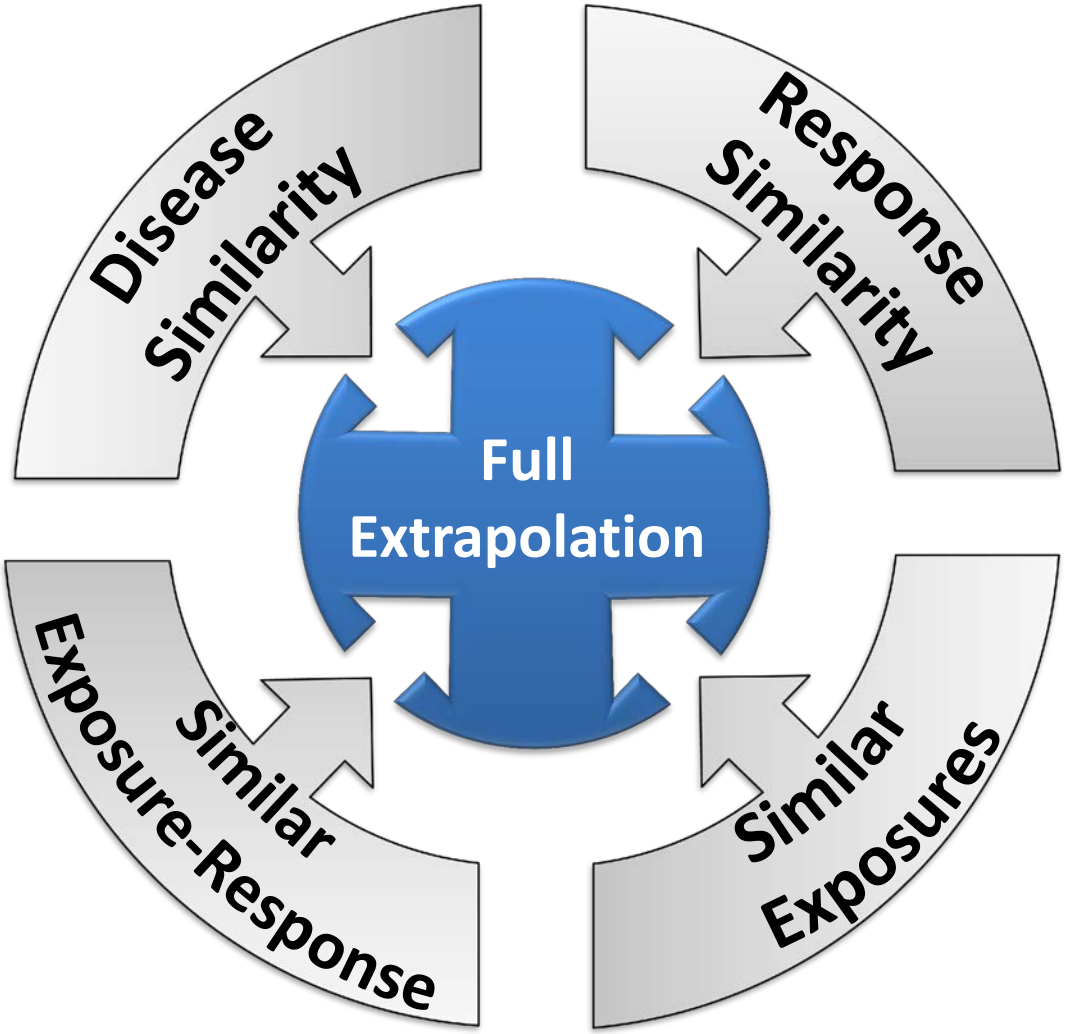


Evidence Gathered from AEDs Approved Between 1960-1980

Carbamazepine	• Generally acceptable therapeutic range of total carbamazepine in plasma (i.e. 4-12 µg/mL) is the same in adult and children
Phenytoin	• Dose in pediatrics was selected such that it produces plasma concentration within the generally accepted therapeutic target of 10-20 µg/mL, which is same for adults
Valproic acid	• Approved in ≥ 10 years age, same dose and the same target therapeutic plasma concentration range (50 -100 µg/mL) are recommended.

Source: Labels for carbamazepine, phenytoin and valproic acid

Quantitative Assessment of Response, Exposures and Exposure-Response Supports "Full Extrapolation" of Efficacy



Required information to Support an Indication for the Treatment of POS in Patients ≥ 4 years

- Approved indication for the treatment of POS in adults.

- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and children (4 years of age and older) populations.

- Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.

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