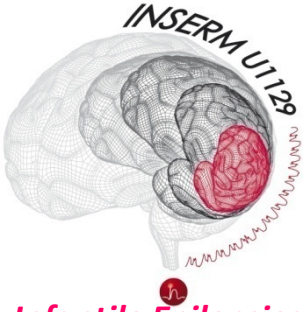

Infantile Epilepsies & Brain Plasticity

POS (Partial onset seizures)
Extrapolation from adults to children
Clinical setting

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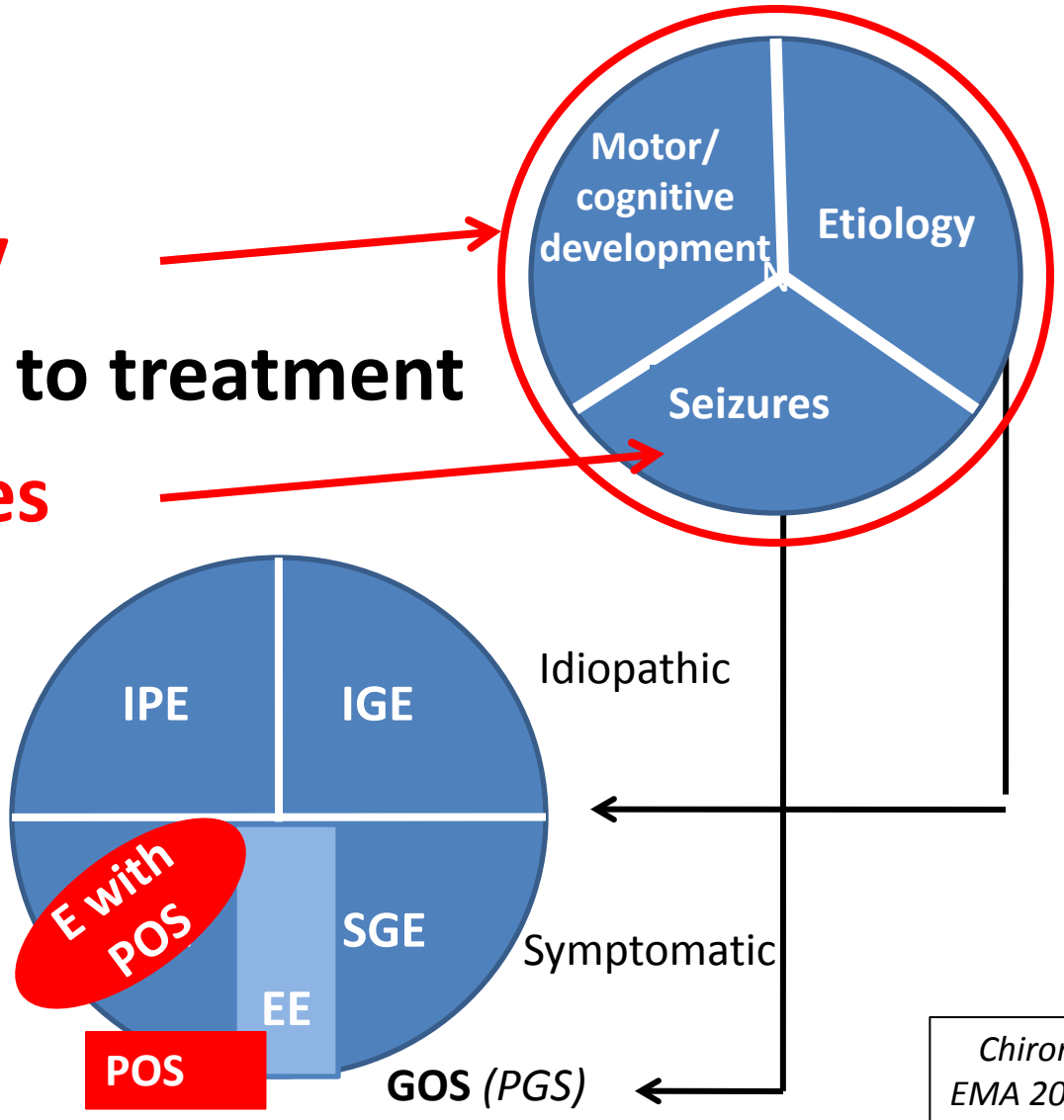
Extrapolation framework (focussed on **efficacy**)

- Pharmacology
- **Disease: Epilepsy**
- **Clinical response to treatment**
  - **Efficacy: Seizures**
  - Safety



E with both POS & GOS = Epileptic Encephalopathies

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Rationale for Extrapolation in POS in children (focussed on efficacy)

- **Similarities of disease children/adults:**
  - age of onset
  - aetiology
  - pathophysiology

- **Similarities of clinical response to treatment**
  - clinical endpoint
  - no biomarker available
  - related compounds: response rate in children similar to adults

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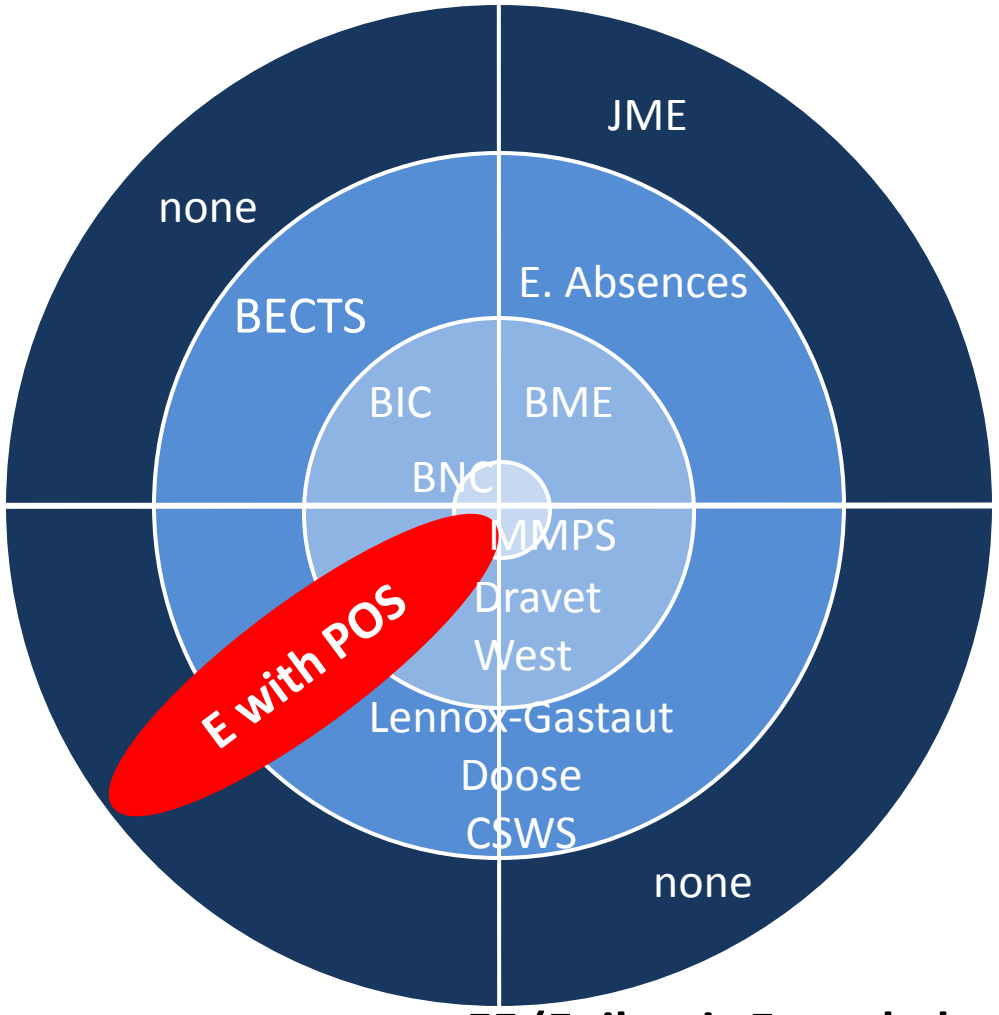
I. Disease: E. with POS

1. Age of onset



IPE
(Idiopathic Partial Epilepsies)

IGE
(Idiopathic Generalised Epilepsies)

SPE
(Symptomatic Partial Epilepsies)

SGE
(Symptomatic Generalised Epilepsies)

EE (Epileptic Encephalopathies)

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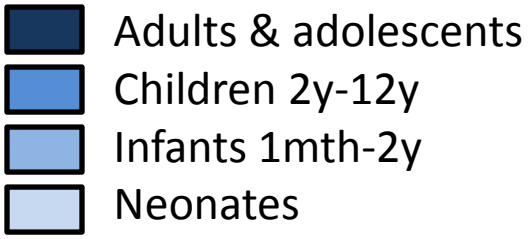
I. Disease: E. with POS

2. Etiology



- **Same as adults**
  - Children 2y-18y with POS
- **Different from adults**
  - Children with BECTS (Benign Epilepsy with Centro Temporal Spikes)

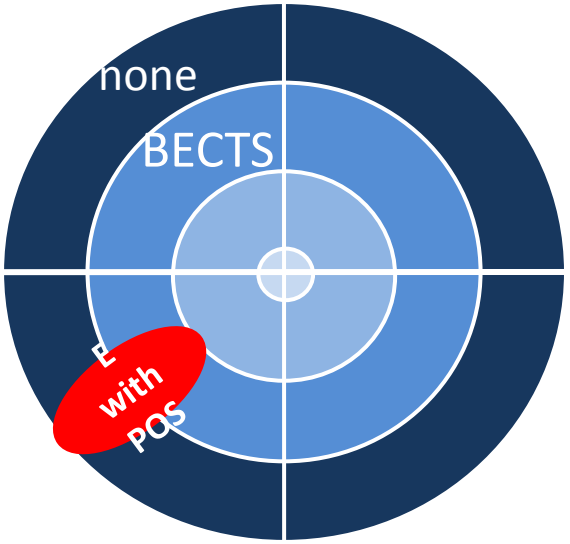
    no lesion, no pharmacoresistance
  - Infants with E with POS

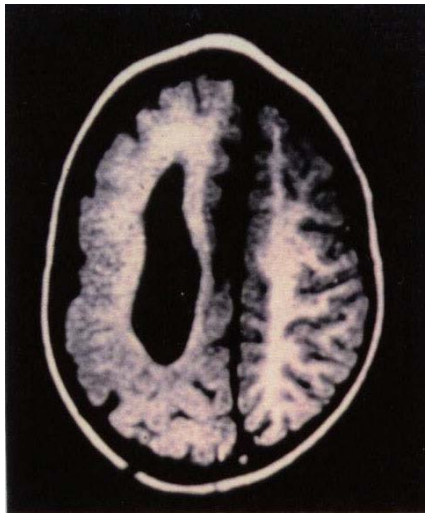
    more extended lesions (unilateral)

    malformations ++
  - Neonates with POS

    more diffuse lesions (bilateral)

    anoxo-ischemic ++





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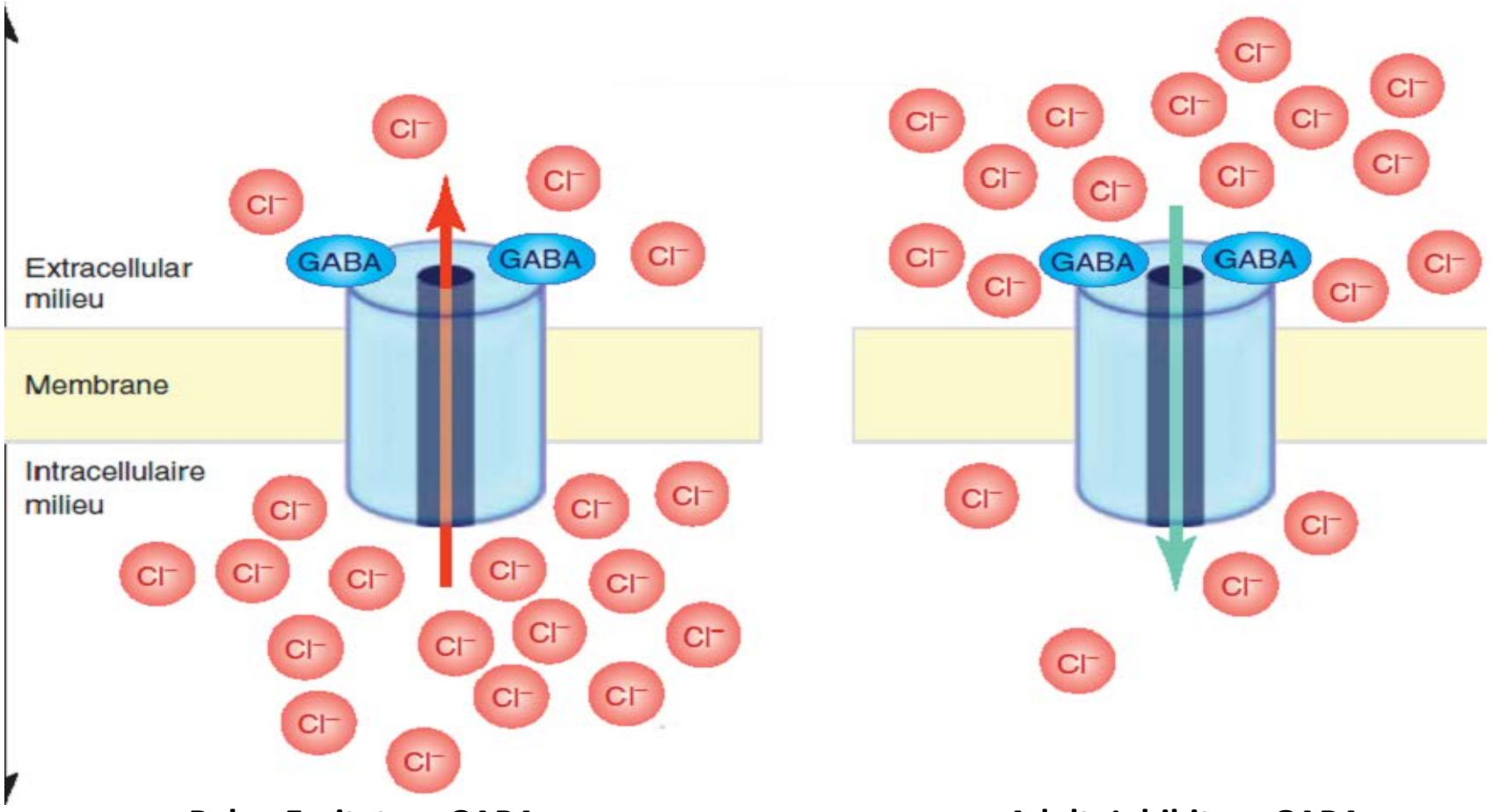
I. Disease: E.with POS/POS

3. Pathophysiology (i)

- **Same as in adults** : POS in **mature** brain
  - Children 2y-18y (rat models >P21)
- **Different from adults**: POS in **immature** brain
  - Immature brain is **more epileptogenic** that mature brain, under 2y (rat models <P21)
    - Epilepsy more frequent, seizures more numerous *(Wasterlain, BenAri, reviews 2013)*
    - Seizures induce neuroplasticity, « seizures beget seizures », more pharmacoresistance *(Berg 2001)*
  - In neonates, GABA is ***excitatory*** instead of inhibitory

I. Disease: E.with POS/POS

3. Pathophysiology (ii)



Baby: Excitatory GABA

Adult: Inhibitory GABA

II. Clinical response: Seizures (POS)

1. The efficacy endpoint

- Endpoint used in adults and children, at any age
- Quantified end-point (seizure frequency)
  - Efficacy = more than 50% decrease in POS frequency
- Objective endpoint (electro-clinical event) subjectively reported (could eventually be improved using video recording)
- Electrical component record (EEG discharge) is the same as in adults and children, at any age

II. Clinical response/efficacy: POS

2. Clinical symptoms

There are **age-related differences**

- In children 2y-18y

  same clinical seizures as in adults

- In infants 1mth-2y

  clinical seizures often **more subtle** than over 2y

- In neonates

  seizures often non-motor (« minor seizures »)

  seizures often **infraclinical** (only EEG discharge)

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II. Clinical response: Efficacy POS

3. Treatment data

- The controlled data available are RCT with new AEDs as **adjunctive therapy** *versus* placebo
- There are **age-related differences**
  - In children 2y-18y: **same** results as in adults
  - In infants 1mth-2y: **some differences** with adults and children >2y
  - In neonates: no RCT *versus* placebo available

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Comparing efficacy between adults and children in Epilepsy with POS

	RCT as adjunctive therapy *versus* placebo	Nb of trials	Nb patients (major trial) & ages	Decreased seiz. frequency (Placebo)
TPM	**Adults** *(Faught 1996)*	**7**	**749 (181)**	**30% (13%)* p<.05**
	Children *(Elterman 1999)*	**1**	**86 / 2-16y**	**33% (11%) p=.03**
LTG	**Adults** *(Matsuo 1993)*	**11**	**571 (191)**	**36% (8%) p=.008**
	Children *(Duchowny 99)*	**1**	**199 / 2-16y**	**36% (7%) p=.007**
OXC	**Adults** *(Barcs 2000)*	**1**	**694**	**40% (8%)** p=.0001**
	Children *(Glauser 2000)*	**1**	**267 / 3-17y**	**35% (9%) p=.0001**
GBP	**Adults** *(US study 1993)*	**3**	**416 (306)**	**18% (8%)° p<.05**
	Children *(Appleton 1999)*	**1**	**247 / 3-12y**	**17% (7%) p<.05**
LVT	**Adults** *(Cereghino 2000)*	**1**	**268**	**40% (11%) p<.001**
	Children *(Glauser 2006)*	**1**	**198 / 4-16y**	**43% (16%) p<.001**

* 200mg, ** 1200mg, ° 1200mg, °° 3000mg

Chiron et al, Drugs 2008

Comparing efficacy between adults, children & **infants** in Epilepsy with POS

	RCT as adjunctive therapy *versus* placebo	Nb of trials	Nb patients (major trial)	Decrease seiz. number (Placebo)	
TPM	**Adults** *(Faught et al 1996)*	7	749 (181)	30% (13%) p<0.05	
	Children *(Elterman et al 1999)*	1	86 / 2-16y	33% (11%) p=0.03	
	Infants *(Novotny et al 2010)*	1	149 / **1m-2y**	**10% (16%)° NS**	
LTG	**Adults** *(Matsuo et al 1993)*	11	571 (191)	36% (8%) p=0.007	
	Children *(Duchowny et al 99)*	1	199 / 2-16y	36% (7%) p=0.008	enrichment
	Infants *(Pina-Garza et al 2008)*	1	38 / **1m-2y**	**escape 58% (94%) NS**	withdrawal
OXC	**Adults** *(Barcs et al 2000)*	1	694	40% (8%) p=0.0001	
	Children *(Glauser et al 2000)*	1	267 / 3-17y	35% (9%) p=0.0001	pseudo-
	Infants *(Pina-Garza et al 2005)*	1	128 / **1m-4y**	**83% (46%) p<0.05**	placebo
LVT	**Adults** *(Cereghino et al 00)*	1	268	40% (11%) p<0.001	
	Children *(Glauser et al 06)*	1	198 / 4-16y	43% (16%) p<0.001	
	Infants *(Pina-Garza et al 2009)*	1	116 / **1m-4y**	**44% (7%) p<0.001**	

° 25mg/kg/d

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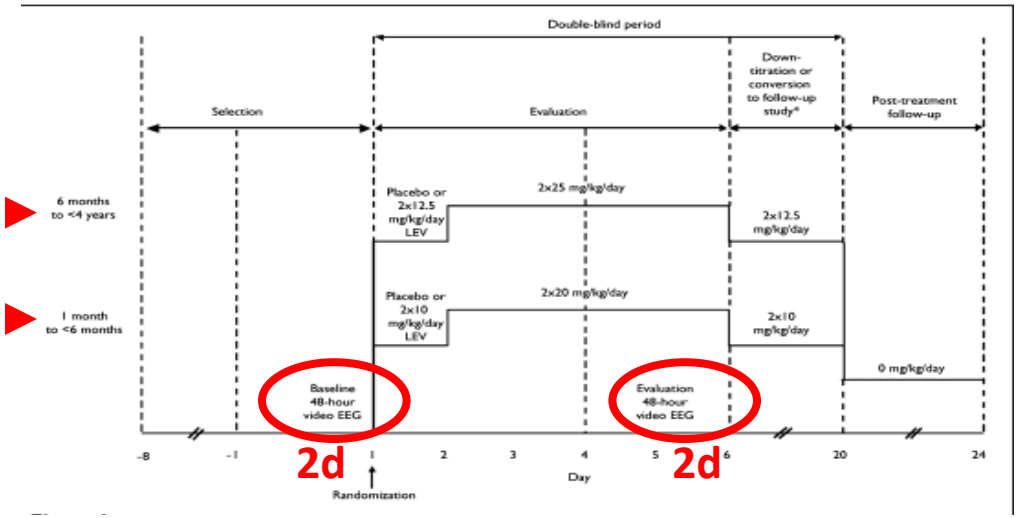
III. Extrapolation: benefits for paediatric patients with epilepsy (1)

- Extrapolating from adult with POS (source population) would **avoid unnecessary trials** in the target population:
  - **Epilepsy with POS** (non idiopathic)
  - Children aged **2y-18y**
  - For **efficacy** as adjunctive therapy
- The concept is already **20 year-old**:
  - Sheridan et al, *Epilepsy Res* 1996 (NIH working group)
  - Chiron & Pons, *Drugs* 2008 (Eilat VII conference 2004)
  - EMA 2009 Paediatric epilepsy experts group meeting (Guidelines EMA/153272/2010)
  - Pellock et al, *Neurology* 2012
  - EMA 2012-2016 Extrapolation WG, concept/reflection papers

III. Extrapolation: benefits for paediatric patients with epilepsy (2)

- Efficacy RCT in POS could therefore be performed **in infants only (1mth-2y)** (Neonates to be looked at separately)
- **Adapted designs** are needed



Adjunctive levetiracetam for POS in children aged 1mth-4y *Pina-Garza et al 2009*

- **Recruitment difficulties**
  - Not because of too few patients (networks, associations)
  - Not because of placebo (adapted designs)
  - But **because of designs unsuited** to infants (too long duration, too many visits, unnecessary biology samples, ..)

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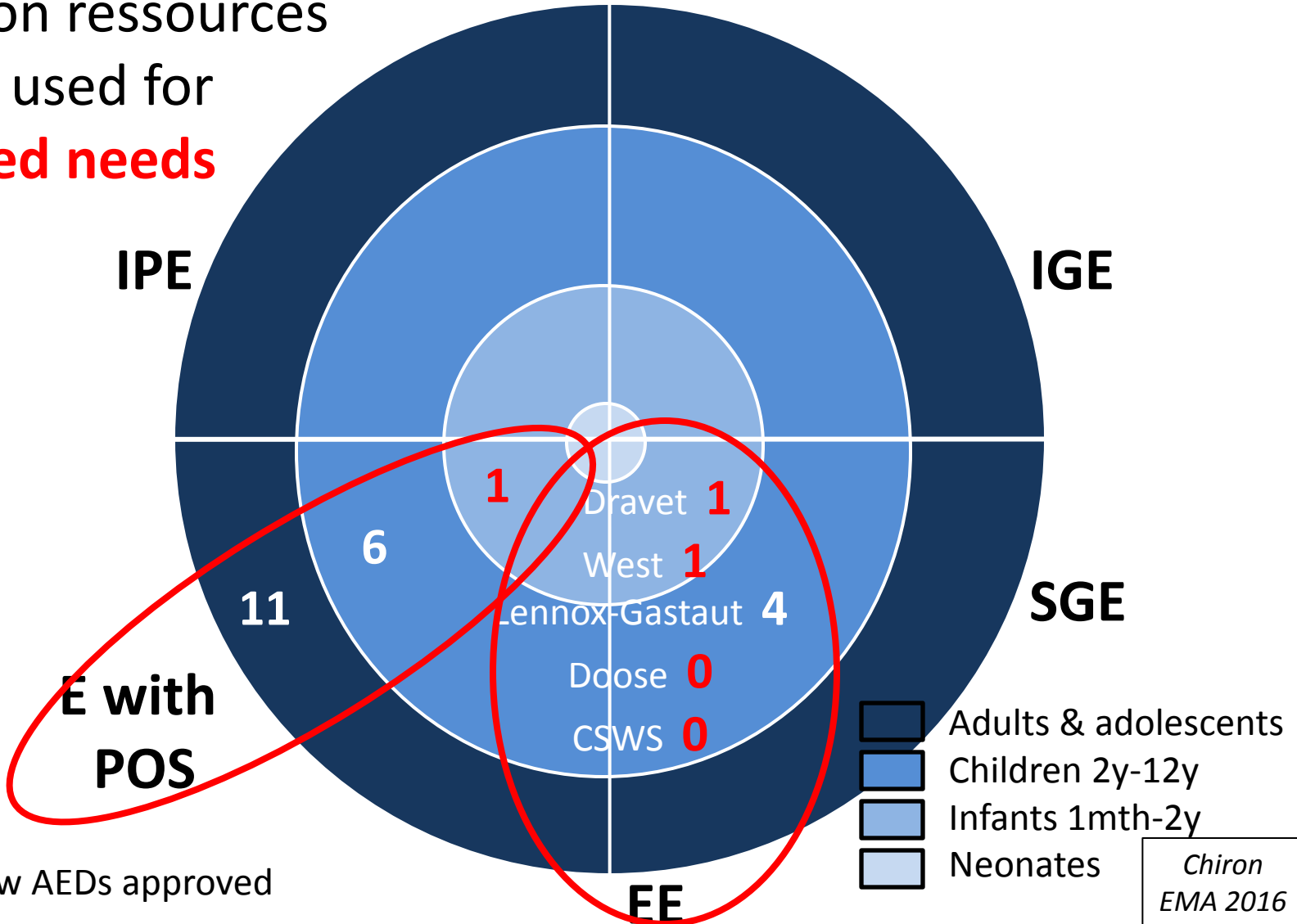
III. Extrapolation: benefits for paediatric patients with epilepsy (3)

In addition ressources could be used for **uncovered needs**



Conclusion: the current strategy is the contrary

AED		*Approval*
• Vigabatrin (Sabril°)	any age	IS (orphan)
• **Levetiracetam (Keppra°)**	**> 1mth**	**POS**
• Stiripentol (Diacomit°)	> 1y	Dravet (orphan)
• **Lamotrigine (Lamictal°)**	**> 2y**	**POS** + LGS + IGE
• **Topiramate (Epitomax°)**	**> 2y**	**POS** + LGS
• Felbamate (Taloxa°)	> 4y	LGS
• Rufinamide (Inovelon°)	> 4y	LGS (orphan)
• **Gabapentin (Neurontin°)**	**> 6y**	**POS**
• **Oxcarbazepine (Trileptal°)**	**> 6y**	**POS**
• **Perampanel (Fycompa°)**	**> 12y**	**POS**

		RCT performed
• Pregabalin (Lyrica°)	adult POS	POS 2y-18y
• Zonisamide (Zonigran°)	adult POS	POS 2y-18y
• Eslicarbazepine (Zebinix°)	adult POS	POS 2y-18y
• Lacosamide (Vimpat°)	adult POS	POS 2y-18y
• Retigabine (Trobalt°)	adult POS	POS 2y-18y

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Key Messages (Epilepsy)

1- Developmental physiology may modify the effect of drugs in children : GABA may be excitatory instead of inhibitory in neonates

2- Most pediatric epilepsy syndromes do not exist in adults precluding extrapolation

3- POS is an exception with similarities in the disease profile and therapeutic responses

4- There are other examples that may enlarge the field of extrapolation in epilepsy syndromes: Lennox-Gastaut syndrome, idiopathic generalised epilepsies

5- There is no biomarker available yet to be used in for epilepsy in pharmacometrics

6- Pharmacometrics cannot yet cover most of the epilepsy syndromes as there are no pharmacodynamic models to describe each of them

7- This is presently a limitation for extrapolation showing the way for future research. More research is needed on pathophysiology and modeling of pharmacodynamics.