Treatment of neonatal seizures

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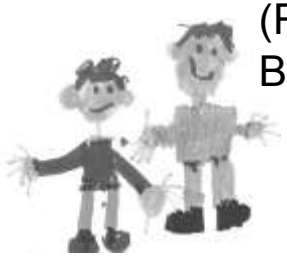
The child first and always

Are relatively common
(1-3.5 per thousand births)



(Ronnen et al 1999;
Berg et al 2012)

Clinical seizures are tip of the ice berg

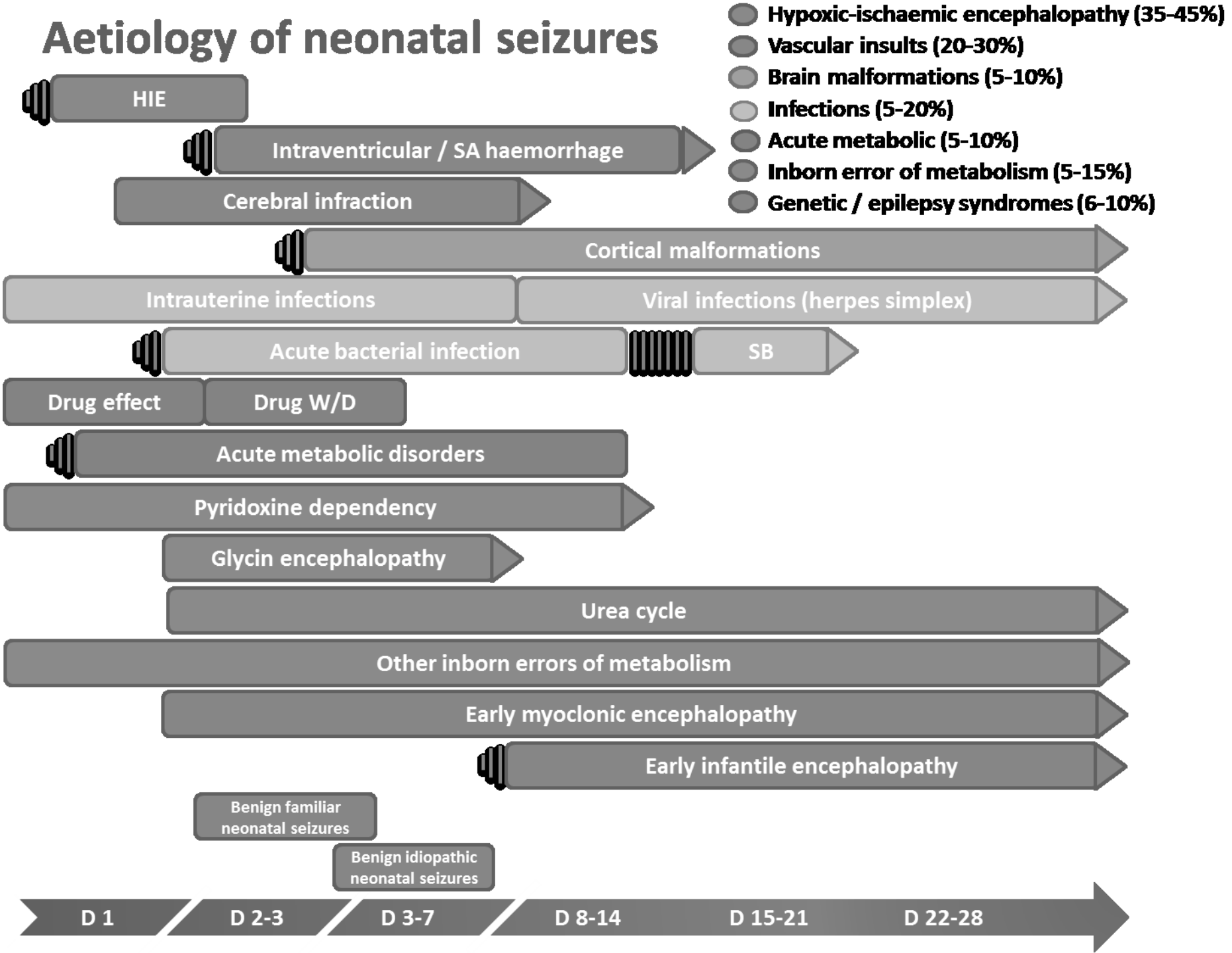
(Mizrahi and Kellaway1989
Lawrence et al 2009)

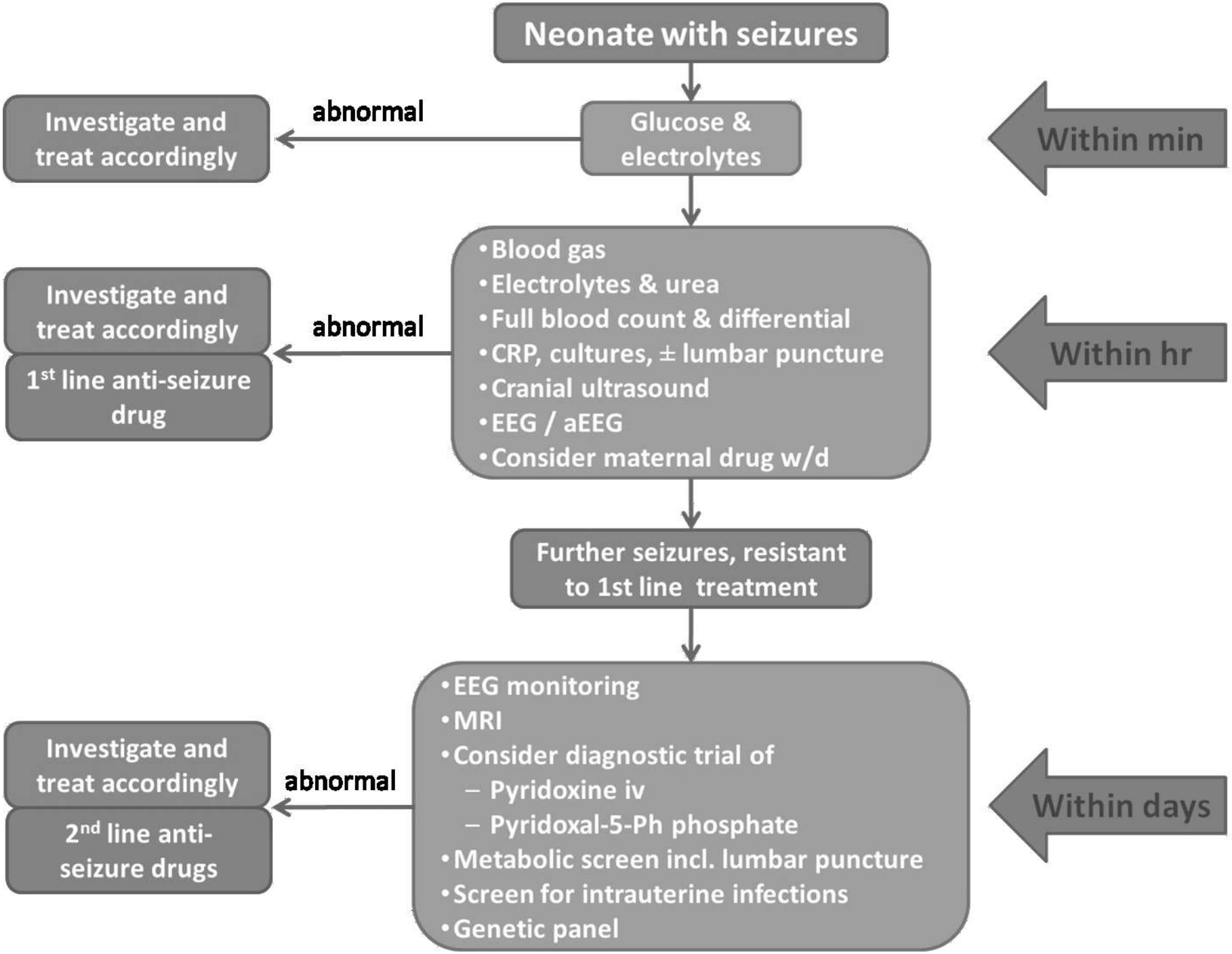
Treatment is challenging

(Painter et al 1999; Boylan et al 2003;
Pressler & Mangum 2013)

Multidisciplinary approach needed

Aetiology of neonatal seizures




Neonate with seizures
Glucose & electrolytes
abnormal
Investigate and treat accordingly
Within min
•Blood gas
•Electrolytes & urea
•Full blood count & differential
•CRP, cultures, ± lumbar puncture
•Cranial ultrasound
•EEG / aEEG
•Consider maternal drug w/d
abnormal
Investigate and treat accordingly
1st line anti-seizure drug
Within hr
Further seizures, resistant to 1st line treatment
•EEG monitoring
•MRI
•Consider diagnostic trial of
– Pyridoxine iv
– Pyridoxal-5-Ph phosphate
•Metabolic screen incl. lumbar puncture
•Screen for intrauterine infections
•Genetic panel
abnormal
Investigate and treat accordingly
2nd line anti-seizure drugs
Within days

Current clinical practice

1st Author	Year	Area	Population			1st line AED
			babies	hospital	doctors	
Carmo	2005	Au/Nz			87	95% PB*
Bartha	2007	US		7		82% PB
Bassan	2008	Israel			102	86% PB
Blume	2008	US	6099	31		76% PB
Vento	2010	EU		13		100% PB
Wickstrom	2012	Sw			170	185-100% PB

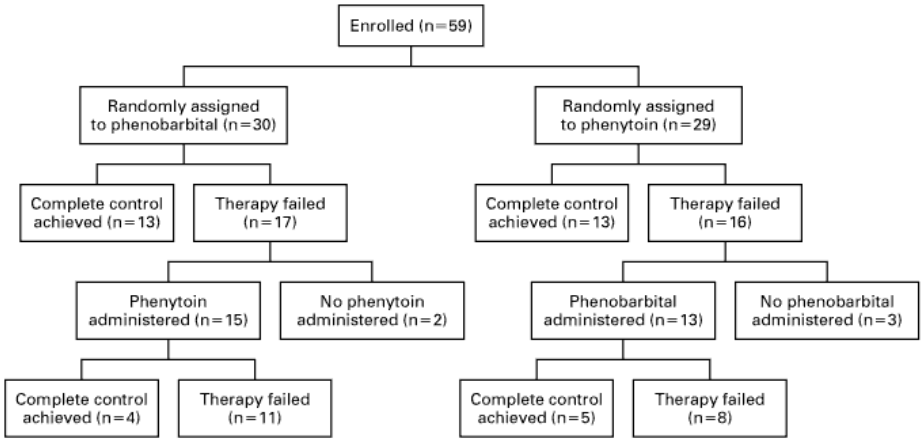
Choice of 2nd line AED variable between and within continents

*** PB: Phenobarbital**

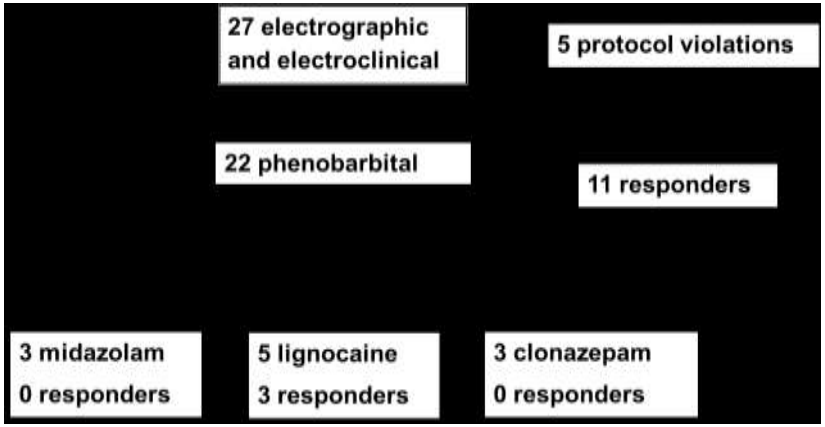
Evidence based treatment

- **Cochrane Report (Booth and Evans 2004)**
  - Reduction of seizure frequency
  - Reduced mortality / long-term disability
  - **Only 2 RCT with adequate outcome measures (EEG)**

Painter et al NEJM 1999



Boylan et al Neurology 2004:

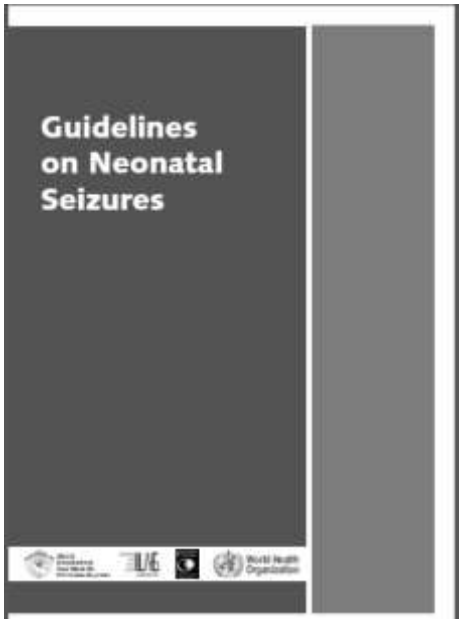


Evidence based treatment

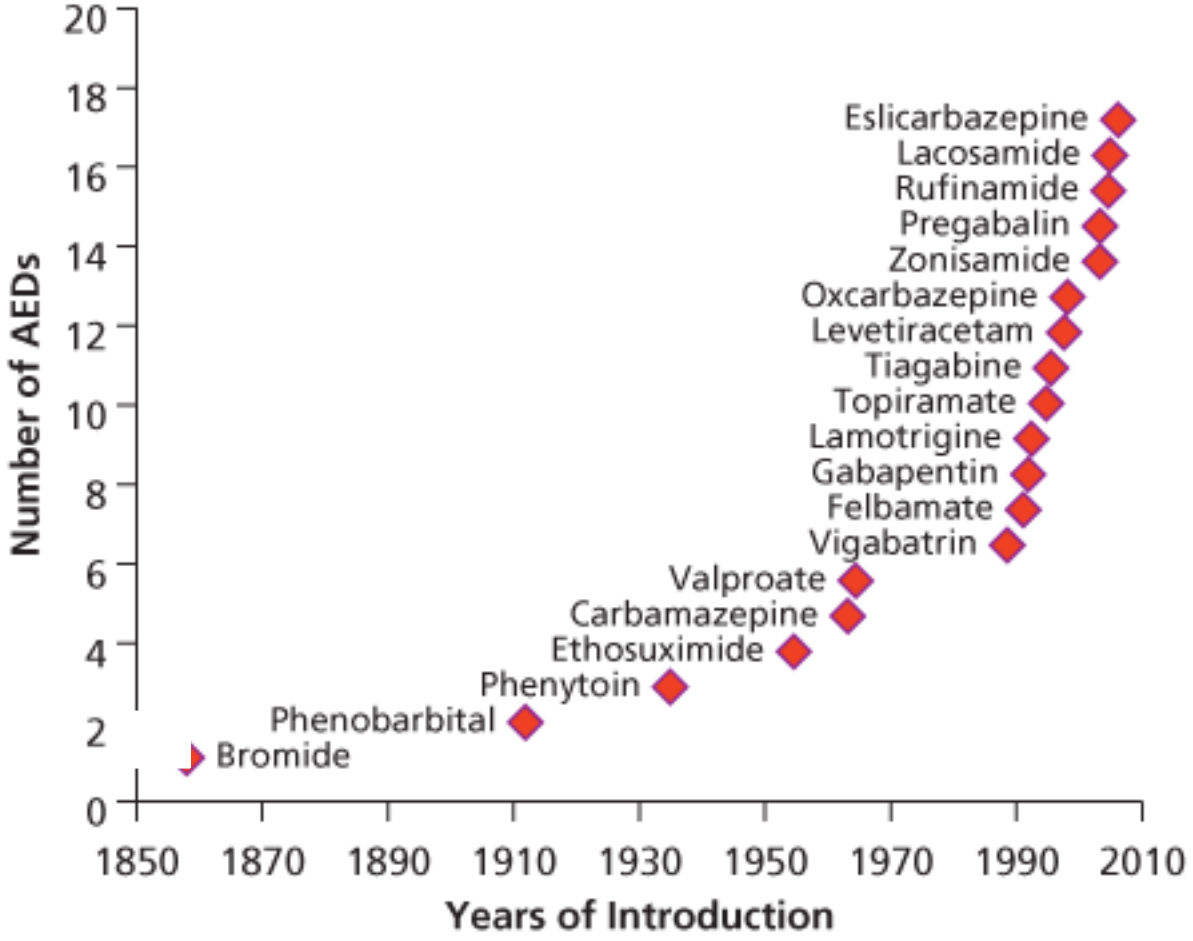
- **Cochrane Report (Booth and Evans 2004)**
  - Reduction of seizure frequency
  - Reduced mortality / long-term disability
  - **Only 2 RCT with adequate outcome measures (EEG)**
    - **Painter et al NEJM 1999**:
      PB vs PHT, 50% seizure free in both arms, 60% for PB + PHT
    - **Boylan et al Neurology 2004**:
      50% seizure free on PB, too small for evaluation of 2nd line treatment
  - **Conclusion:**
    Little evidence to support use of any AED

WHO Guidelines (2011)

- Evidence based guidelines for management of neonatal seizures by WHO, ILAE & IBE
- Recommendations for developing countries to tertiary care centres
- 11 recommendations based on literature review
- 4 recommendations on treatment, plus one on prophylaxis

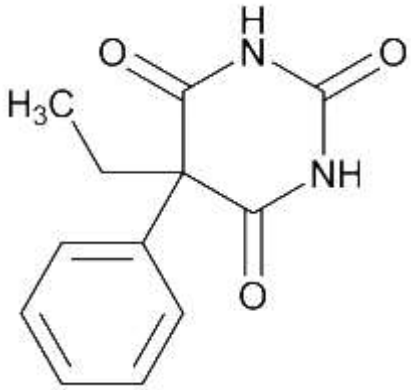


New AED in adults vs neonates

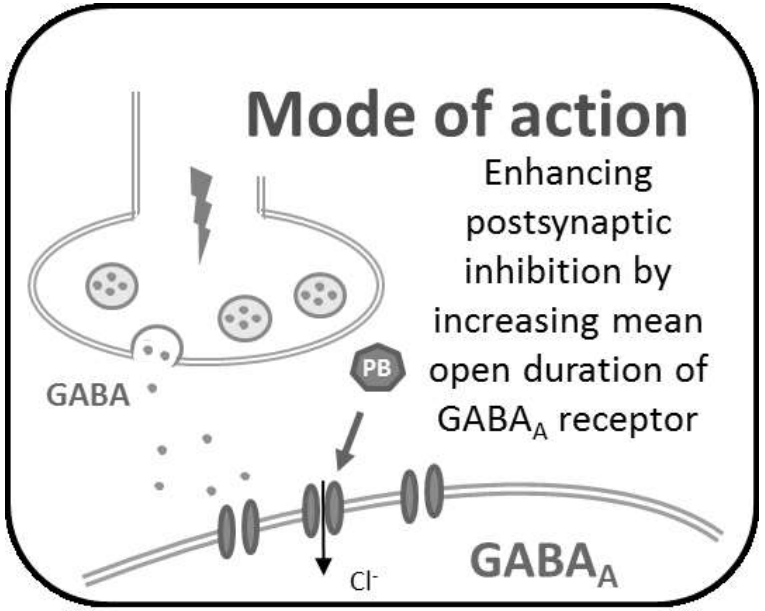


AED: antiepileptic drug.

Phenobarbital



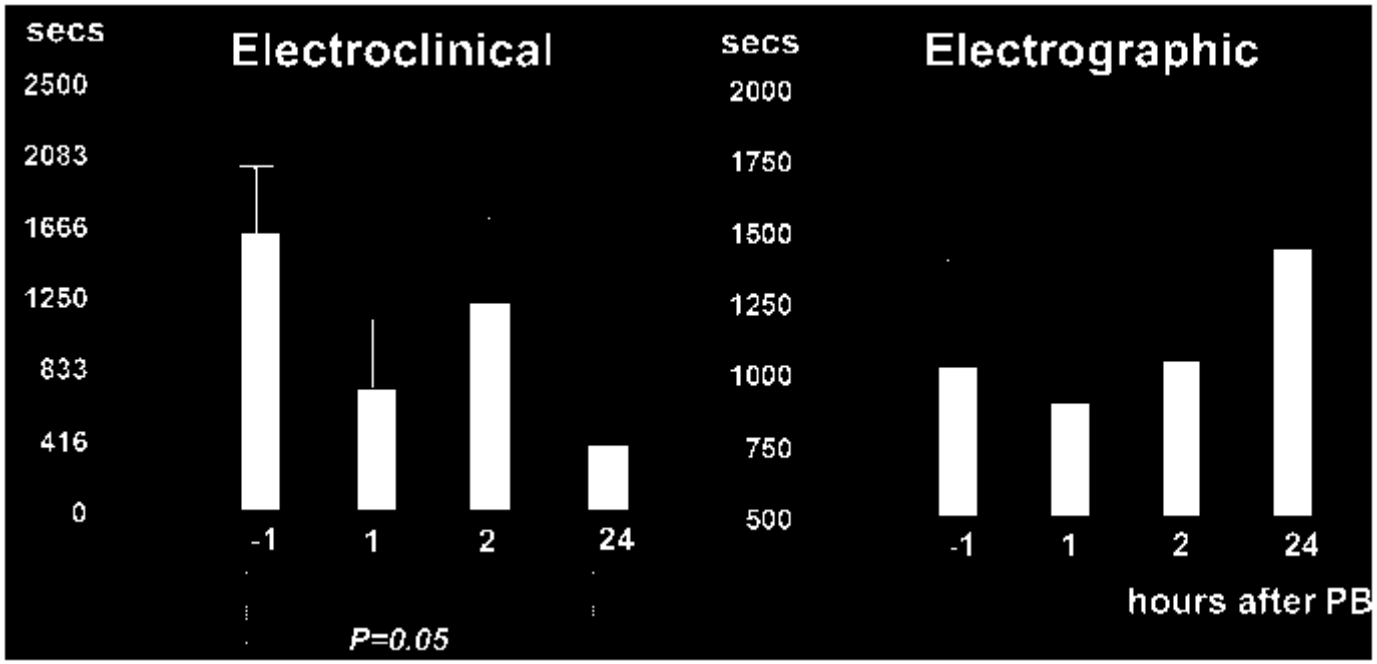
- PK data
  - Metabolism: hepatic
  - $T_{1/2}$ 80-160 hrs
  - Drug interactions +
- Efficacy in neonates
  - First line choice
  - 2 RCTs: seizure freedom in 43-50%
  - Electro-clinical dissociation↑
- Dose in neonates
  - LD: 20 mg/kg, repeat if required
  - MD: 5 mg/kg/day
- Adverse events
  - CNS sedation
  - Respiratory depression
  - Possible adverse neuro-developmental outcome



Painter 1999, Boylan 2004; Slaughter 2013, Donovan 2016

Electroclinical dissociation

- Induced by treatment of seizures
- Described with PB and phenytoin

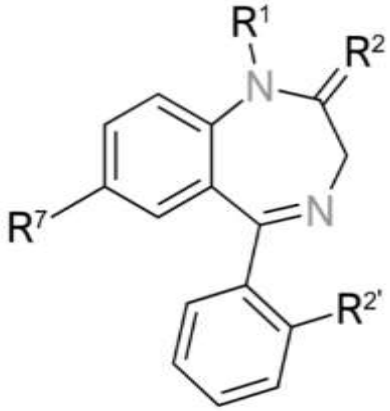


Clinical seizures are he tip of the iceberg

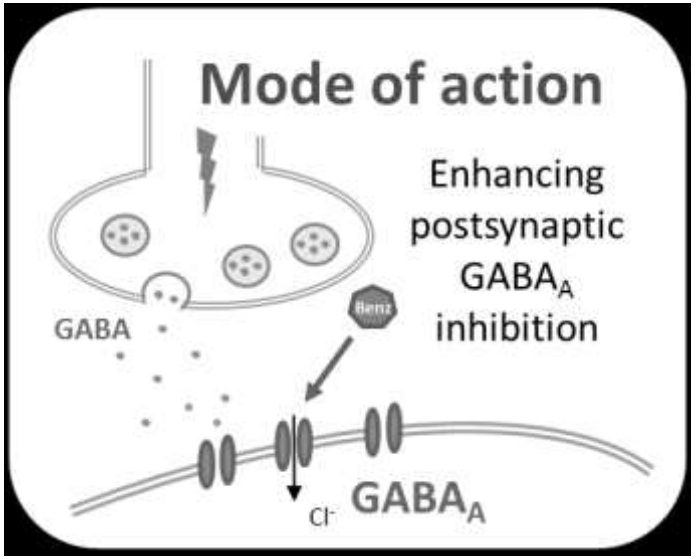
EEG monitoring of treatment

Boylan et al, 2003

Midazolam

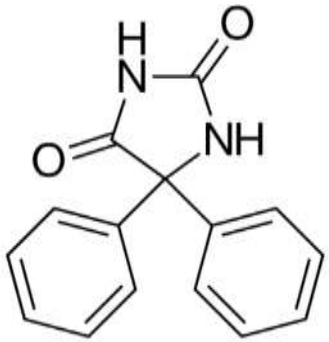


- PK data
  - Rapid onset
  - Pharmacologically active metabolites
  - $T_{1/2}$ 6-14 hrs
- Efficacy in neonates
  - Second line choice
  - Some evidence
- Dose in neonates
  - LD: 0.05 mg/kg over 10 min
  - MD: 0.15–0.5 mg/kg/h
- Adverse events
  - CNS sedation
  - Respiratory depression
  - Hypotension

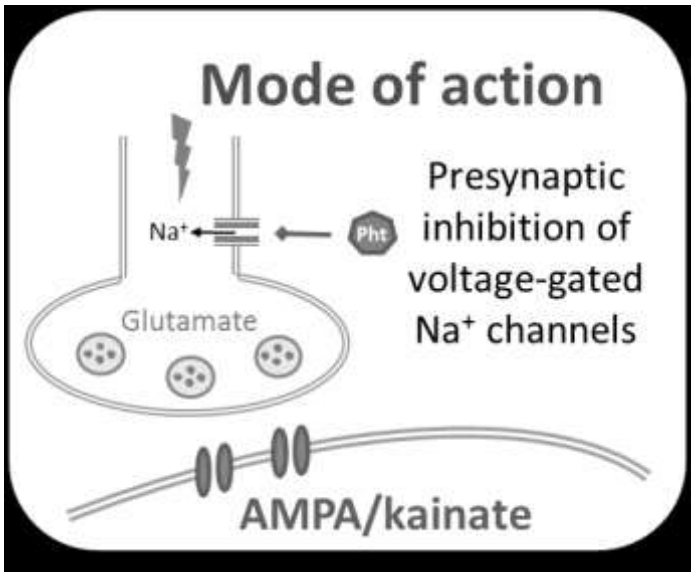


Castro Conde 2005; Shany 2007; Slaughter 2013, Donovan 2016

Phenytoin

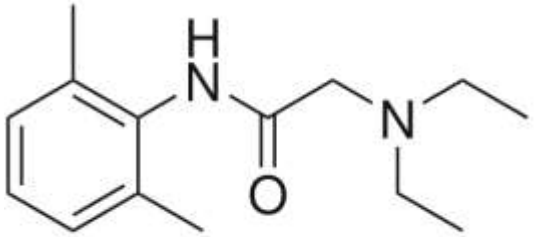


- PK data
  - T1/2: 20 hrs in 1st week, 5-10 hr in week 2-4
  - Nonlinear PK
- Efficacy in neonates
  - Second line choice
  - Some evidence from 1 RCT
- Dose in neonates
  - LD: 15-20 mg/kg iv over 20 min
  - MD: 4-8 mg/kg/day
- Adverse events
  - irritation at injection site
  - CNS depression, hypotension
  - cardiac (arrhythmias, impaired conduction)
  - Increase of electro-clinical dissociation

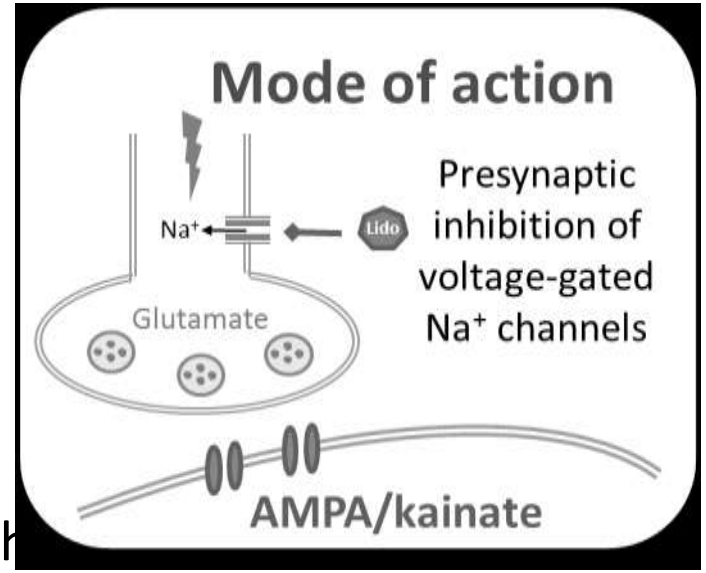


Slaughter 2013, Donovan 2016

Lidocaine

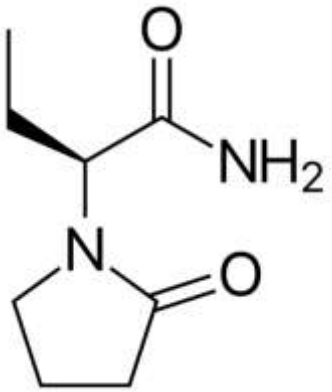


- PK data
  - T1/2: 20 hrs in 1st week, 5-10 hr in week 2-4
  - Nonlinear PK
- Efficacy in neonates
  - Second line choice
  - Uncontrolled studies suggest efficacy in 60-78% as 2nd or 3rd line
- Dose in neonates
  - LD: 2 mg/kg
  - MD: 5-7 mg/kg/h for 4 h, reduce over 24 h
  - Adapt dose for cooling (van den Broek 2013)
- Adverse events
  - Cardio-toxic, particularly arrhythmias
  - Sedation

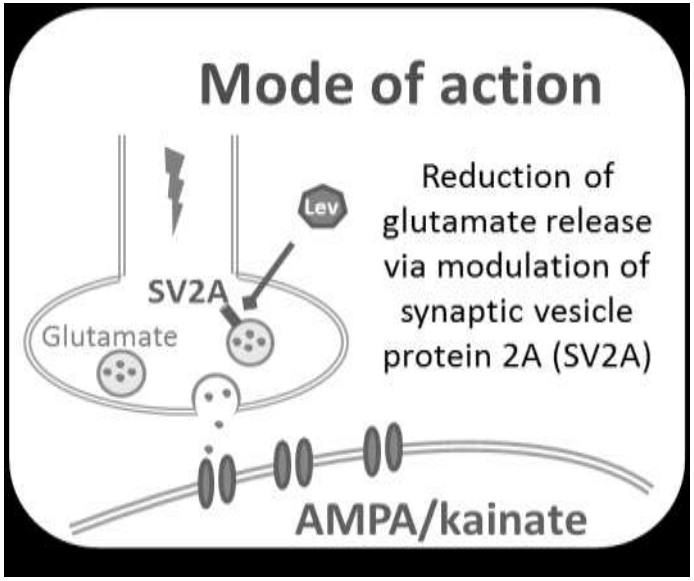


Hellstrom- Westas 1988 Boylan 2004, Malingre 2006, Shany 2007, Lundqvist 2013, van den Broek 2013, Weeke 2016

Levetiracetam



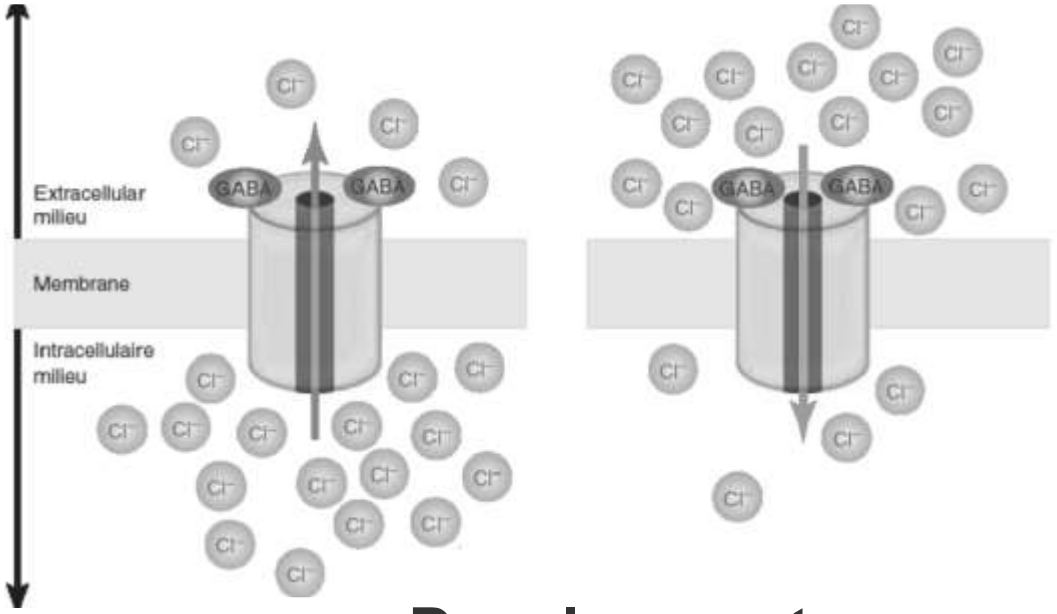
- PK data
  - Metabolism: renal
  - T ½ 9-18 hrs
  - No drug interactions
- Efficacy in neonates
  - Second line choice, also 1st line (no RCT)
  - Uncontrolled studies suggest good efficacy (30-86%), most no EEG
- Dose in neonates
  - LD: 10 -50 mg/kg
  - MD: 40-50 mg/kg/day
- Adverse events
  - Mild sedation
  - Possibly bradycardia



Ramantani 2011; Fürwentsches 2010; Abend et al 2011; Venkatesan 2017

GABA

excitatory **inhibitory**



Development

Baby
High NKCC1, low KCC2

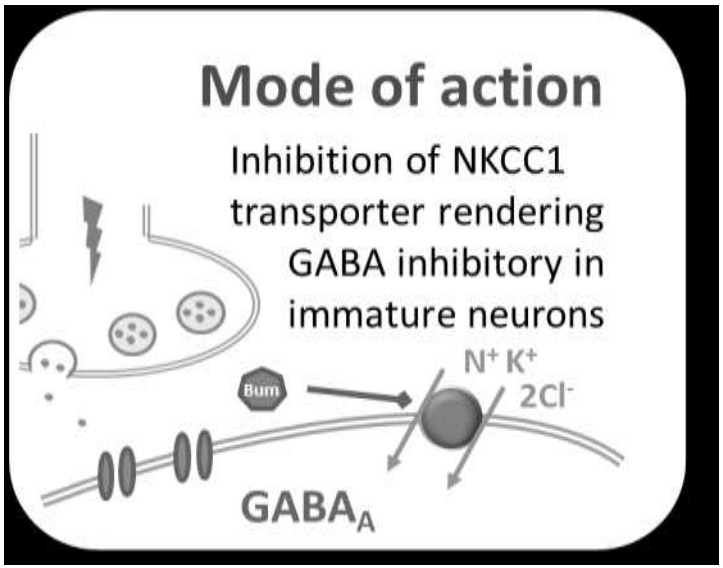
Adult
Low NKCC1, high KCC2

Co-transporter

Ben-Ari 2002

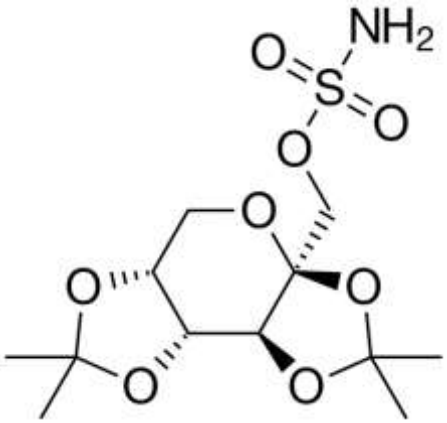
Bumetanide

- PK data
  - Metabolism: renal
  - T ½ 8-9 hrs
- Efficacy in neonates
  - No proven efficacy
- Dose in neonates
  - 0.01-0.05 mg/kg as diuretic
  - Antiseizure dose unknown
- Adverse events
  - Dehydration with hypotension
  - Hypernatremia
  - Hearing loss

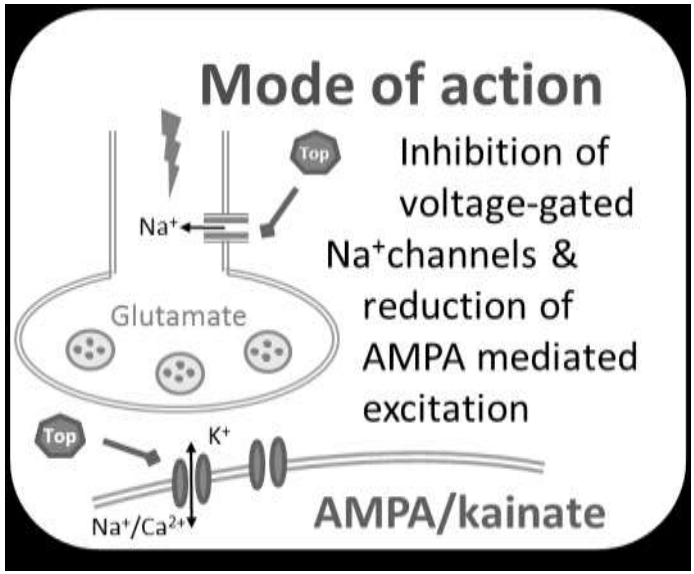


Kahle et al 2009; Pressler and Mangum 2013; Pressler et al 2015

Topiramate



- PK data
  - Metabolism: renal
  - T ½ 36 hrs
- Efficacy in neonates
  - Animal data:neuroprotective properties
  - Case study suggests some efficacy, no EEG
- Dose in neonates
  - No iv preperation
  - No dose availabe (5mg/kg/day)
- Adverse events
  - Lethargy, irritability, cognitive dulling anorexia, and metabolic acidosis in infants
  - Unknown in neonates



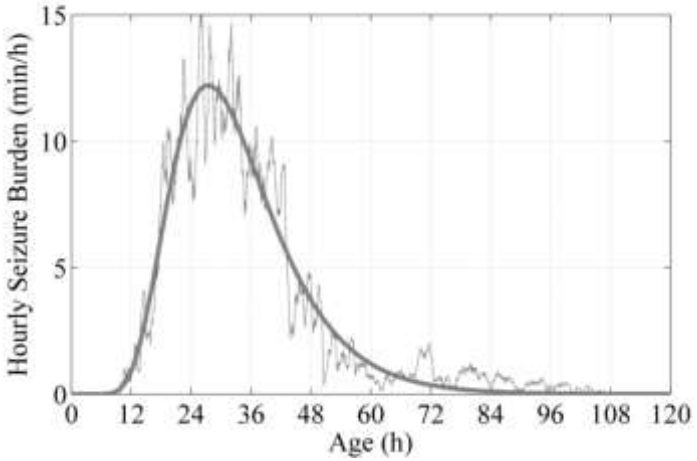
Soul 2009; Filippi et al 2010; Pressler and Mangum 2013;

	Retrospective, studies with >10 cases	Prospective, uncontrolled or RCT, insufficient powered	RCT
Phenobarbital	Boylan 2002* Connell 1989	Bye & Flanagan 1995*	Painter 1999*
Phenytoin	Connell 1989	Bye & Flanagan 1995*	Painter 1999*
Midazolam	van Leuven 2004 Castro Conde 2005* Shany 2007 Yamamoto 2007	Boylan et al 2004*	None
Levetiracetam	Khan 2011* Ramantani 2011 Abend 2011* Venkatesan 2017	None	None
Diazepam	Connell 1989	None	None
Lorazepam	None	Maytal et al, 1991 Deshmukh et al, 1986	None
Clonazepam	Andre 1986	Bye & Flanagan 1995*	None
Lidocaine	Shany 2007 Yamamoto 2007 Lundqvist 2013 van den Broek 2013	Hellstrom- Westas 1988 Boylan 2004* Malingre 2006	None
Bumetanide	Kahle 2009	Pressler 2015*	None
Topiramate	Filippi et al 2010	None	None

*** with EEG**

Challenges of clinical trials and drug development in neonatal seizure

- Age dependent mechanisms of neurotransmitter
- Ethical predicament
  - Vulnerable age group
  - Acute symptomatic seizures critically ill, co-morbidity
- Logistical difficulties
  - Diagnosis and monitoring
  - Recruitment
  - Regulatory requirements (EMA/FDA)
- Expensive, but low return



Chiron et al 2008; Lawrence et al , 2009, Lynch et al 2012

Open questions

- Should we treat subclinical seizures or only clinical?
  - Subclinical seizures associated with poor outcome (McBride 2002)
  - Treatment may improve outcome (van Rooij 2007; Glass 2009)
- Will treatment of neonatal seizures improve outcome?
  - Higher seizure burden associated with poor outcome (Kharoshankaya 2016)
- How long should we treat neonatal seizures?
  - No evidence that treatment beyond the neonatal period improves outcome (Guillet & Kwon 2007; Abend in press)

Conclusion

- Treatment of neonatal seizures has no evidence
- Phenobarbital accepted as standard of care
- No recommendations re 2nd line treament
- Off-lable use of drugs to be avoided
- More controlled trials nessesary

Acknowledgements

Neonatal Task force

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UCL HOSPITALS

The child first and always

wellcome trust

MRC Medical Research Council

SEVENTH FRAMEWORK PROGRAMME

Funded by the European Union

NEMO