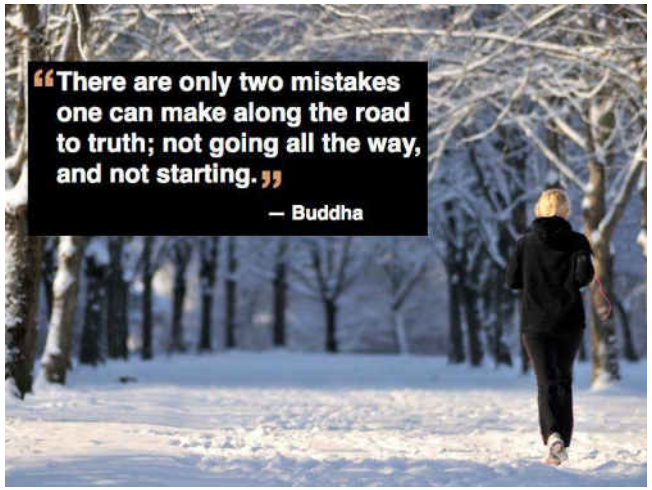


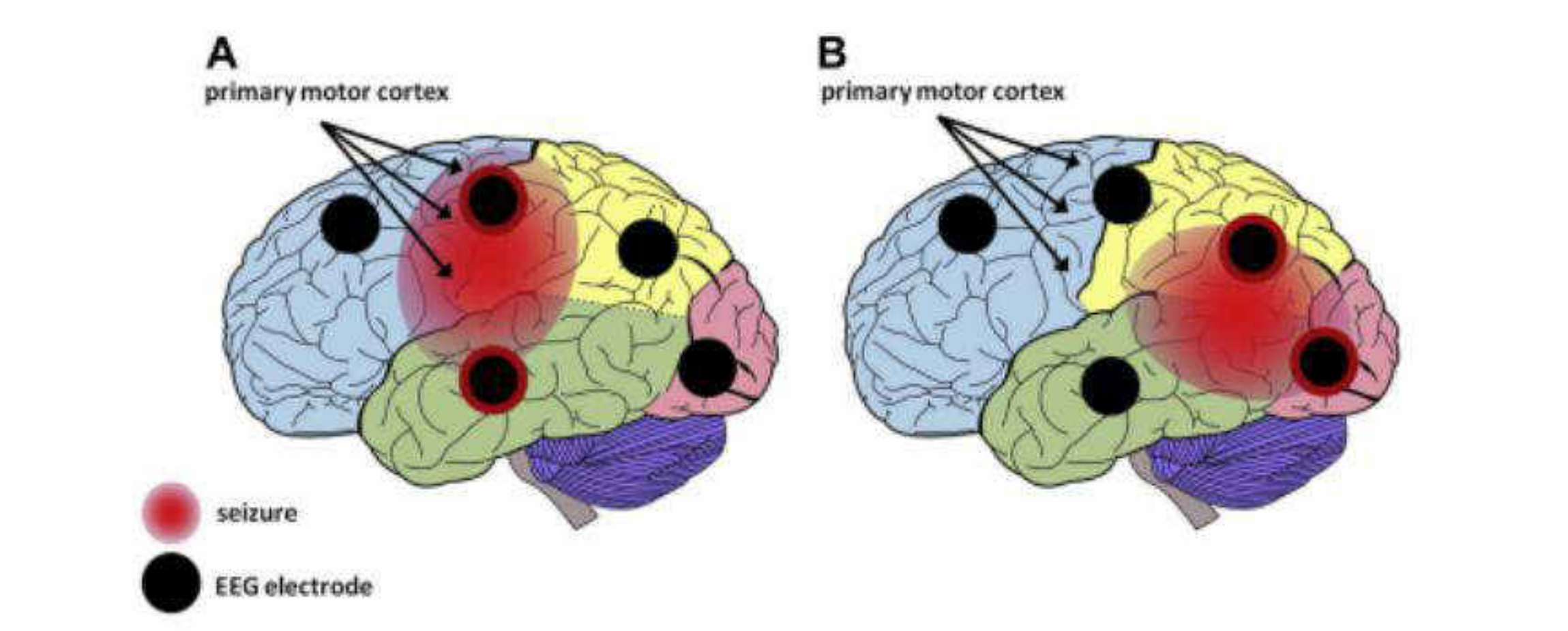
Neonatal seizures - update

Sanjay Wazir

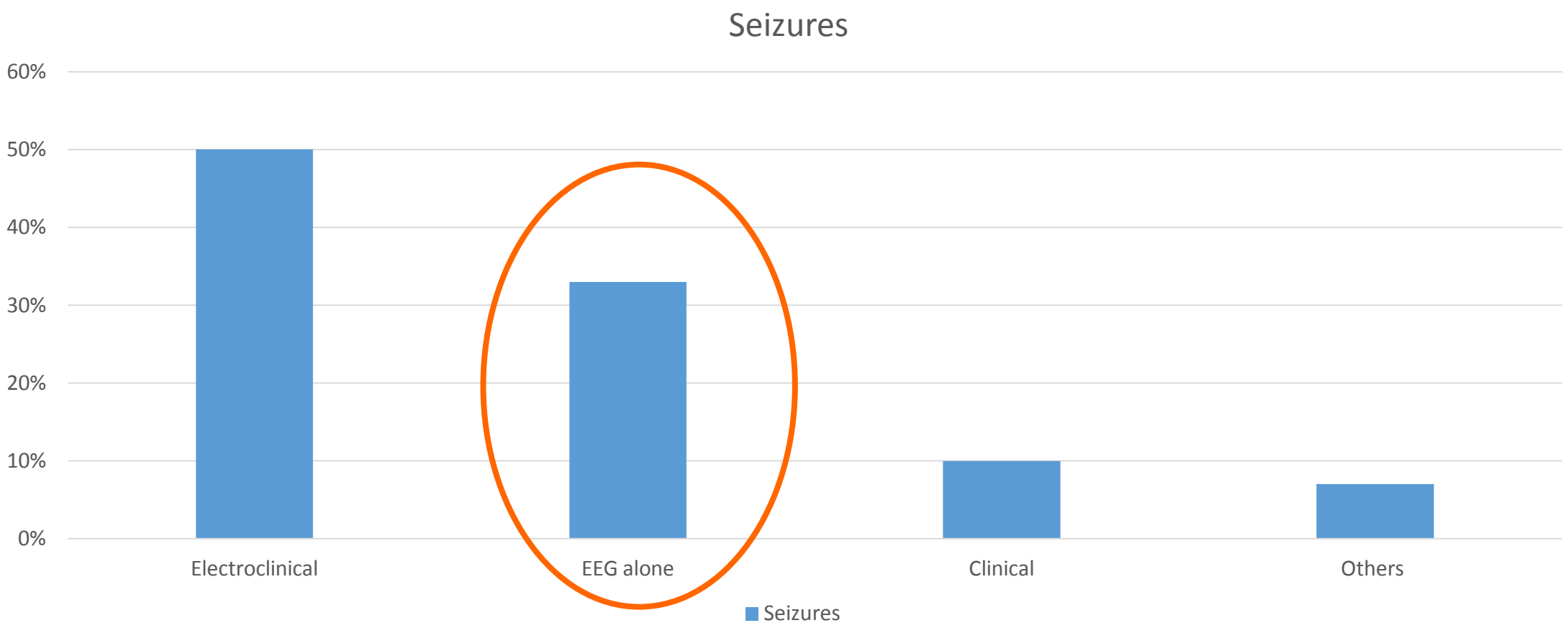
Consultant NICU

Cloudnine hospital Gurgaon

Difference between clinical and subclinical seizures



Neonatal seizures are often subclinical

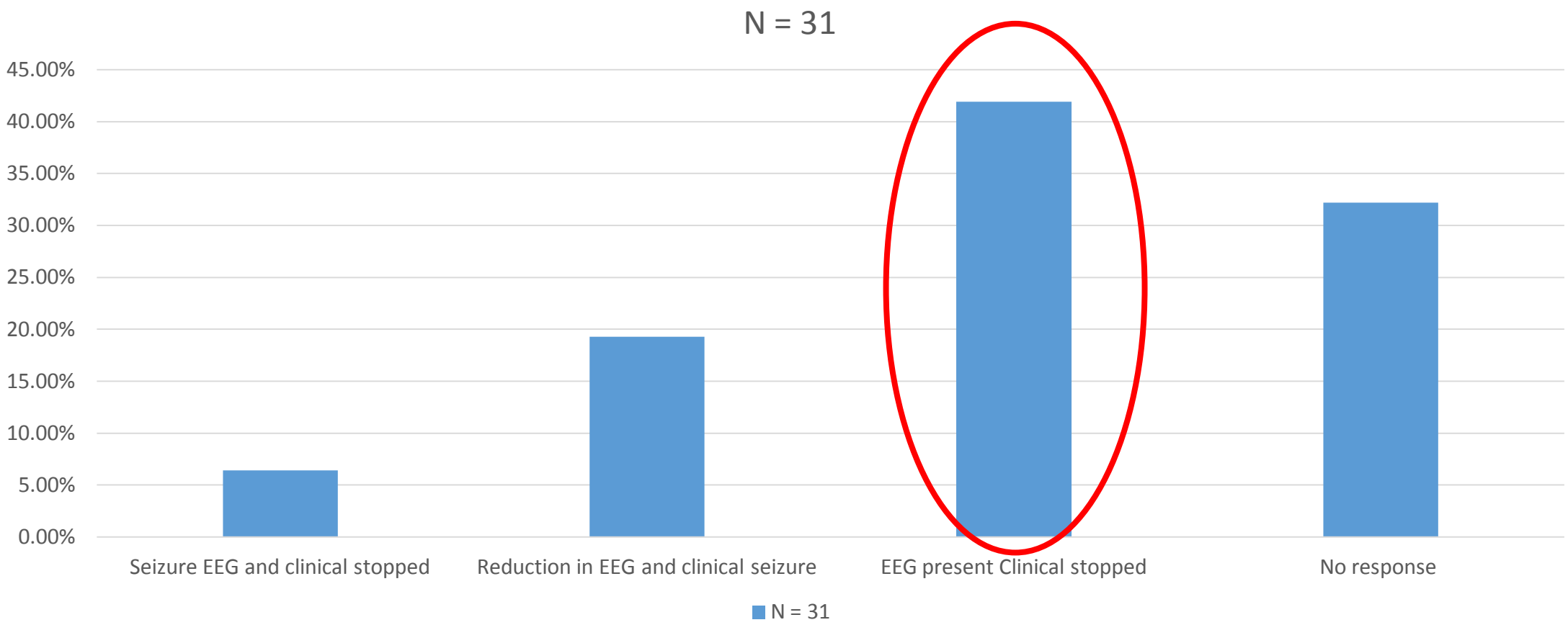


Confusion....

- 51 infants with encephalopathy and/or risk HIE
  - All infants were given prophylactic phenobarbitone
  - Total no of seizures 526
  - 9% had clinically diagnosed seizures
  - 19% on video monitoring
- 3 infants aggressively treated for 31 clinical events with no EEG PROBLEMS
- 2 infants were not given treatment – one had 38 seizures and other had 56 EEG seizures
- 42% (5/12) received inappropriate treatment

Murray DM Archives Dis Childhood 2007

Uncoupling phenomenon



J Connell Arch Dis Child. 1989 Apr; 64(4 Spec No): 459–464

Is this time for us to move from clinical to electrographic monitoring of seizures/at risk babies

Monitoring of neonantal seizures

- Conventional EEG (Video EEG)
  - Gold standard for seizure detection
  - Difficult to implement
- aEEG
  - Lower sensitivity but more practical
  - Lowest sensitivity for seizures that are brief, focal and distal form recording electrodes
  - Artifact prone
- Combination of EEG and aEEG
- SDA (Seizure detection algorithms)

Seizures - do they damage brain

Impact of clinical alone seizures in HIE

- Secondary analysis of NICHD trial
- Presence of clinical seizures
- Bayles MDI at 18 months

Table 5

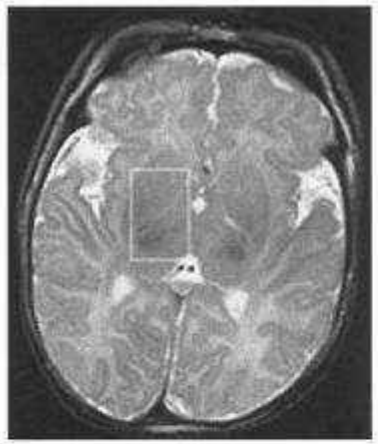
Linear Regression Model for MDI

Covariates	Estimate	*P* value
Seizures	−3.26	.37
Hypothermia treatment	4.61	.18
Severe HIE	−8.89	.03

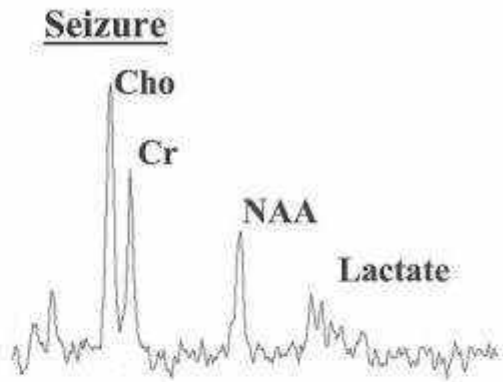
Abbreviations: HIE, hypoxic-ischemic encephalopathy; MDI, Bayley Mental Development Index.

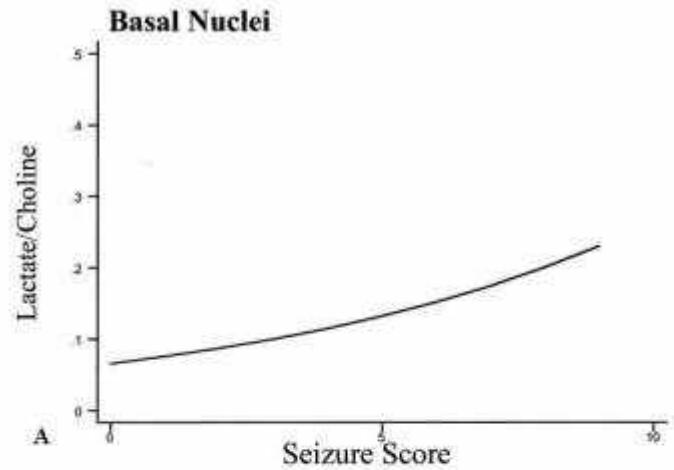
Kwon JM J Child Neurol. 2011 Mar;26(3):322-8

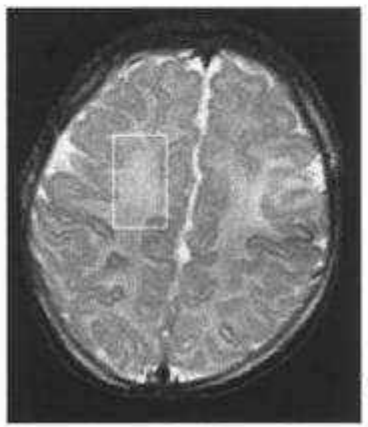
Impact of seizures on brain – *Miller 2002 Neurology*



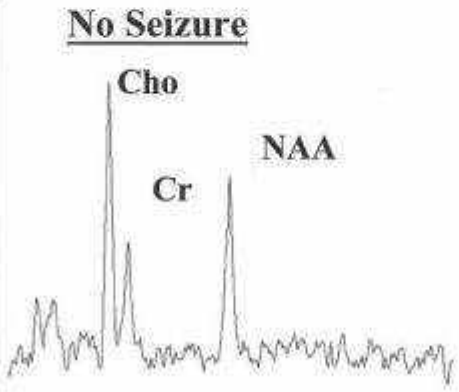
Basal Nuclei

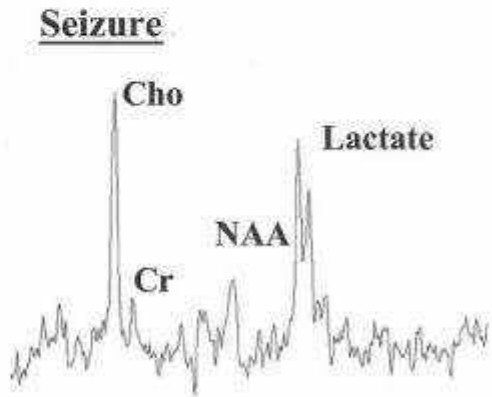


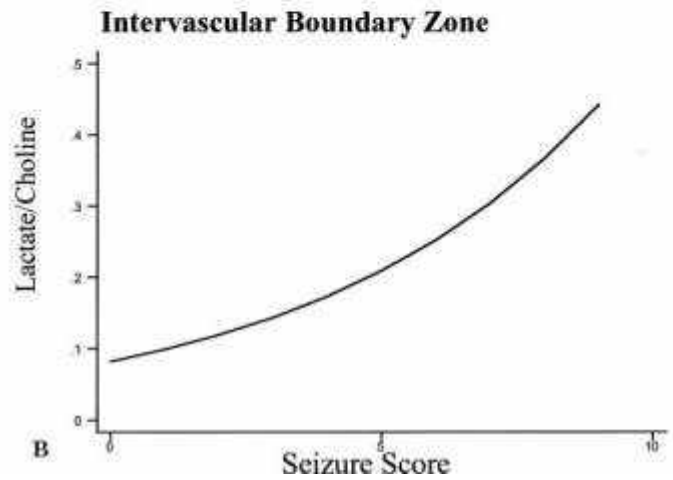




Intervascular Boundary Zone







ESz associated with brain injury in newborns with therapeutic hypothermia

- 52% had Esz on EEG
- Most common on first day and during and after rewarming
- in multivariate logistic regression, high seizure burden was independently associated with greater injury on MRI

Shah DK Arch Dis Child Fetal Neonatal Ed. 2014 May;99(3):F219-24

EEG seizures and neurodevelopment

- 68 infants at risk of seizure – continuous EEG monitoring (40 vs 28)
- 43% of them had electrical seizure status
- Death 25% vs 3.5% Esz group vs non Esz group
- The occurrence of ESz was correlated with microcephaly (p = 0.04), severe CP and failure to thrive
- Greater the number of Esz, more likely to have these severe outcomes

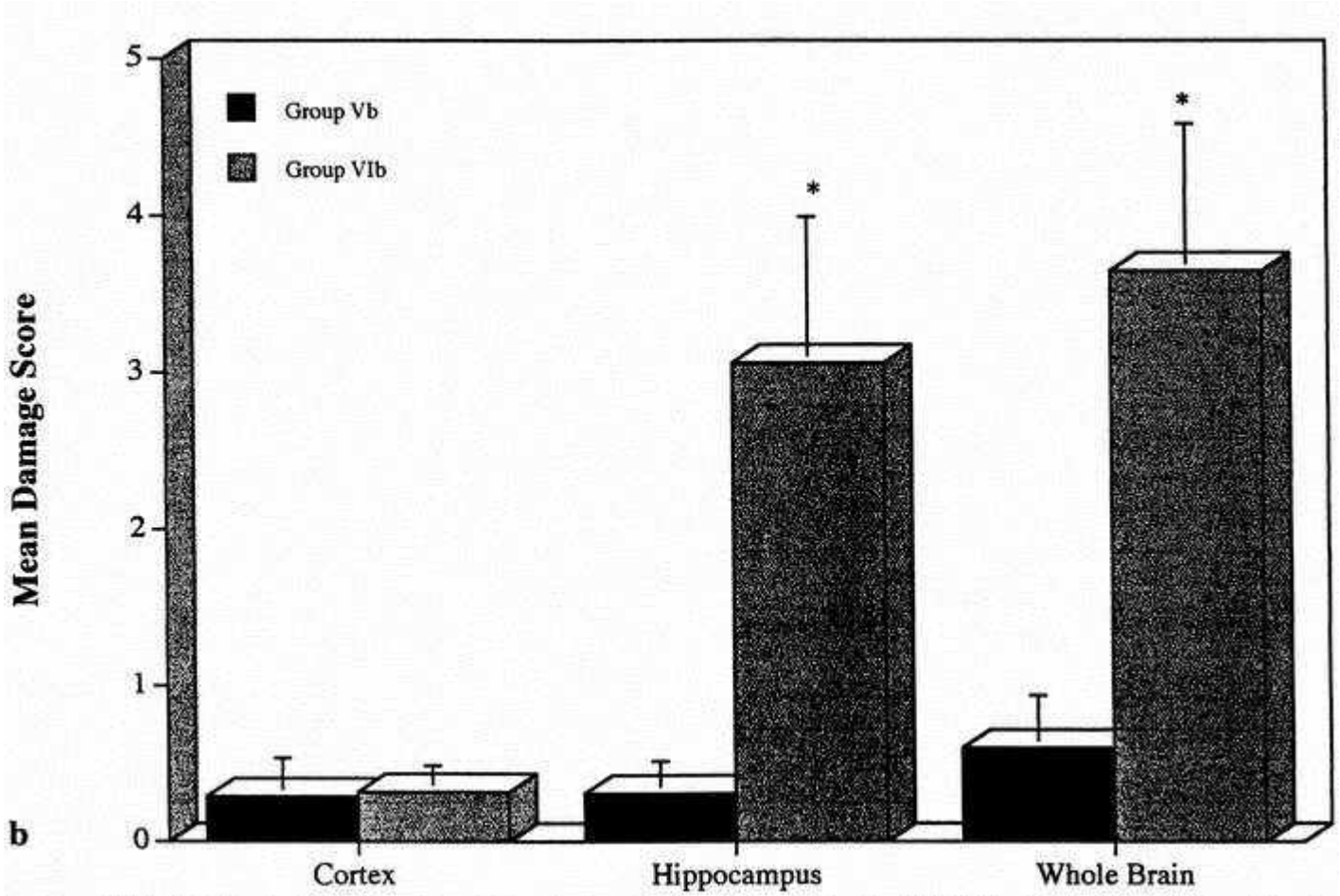
McBride MC Neurology [2000, 55(4):506-513]

Neurodevelopment at 1 year and subclinical seizures

- Objective – Neurodevelopment of EEG vs EEG plus clinical seizures at 1 year
- Small study of 30 infants
- Mixed population (680-4100 gm and all etiologies)
- Neonatal seizures but not electrical seizures associated with neurodevelopmental issues

Kurul SH J Maternal Fetal Neonatal Medicine 2013

Animal study of seizure on HIE



Wirrell E *Pediatric Research* (2001)

Does treatment of electrographic seizures make the baby better

Subclinical Neonatal seizures

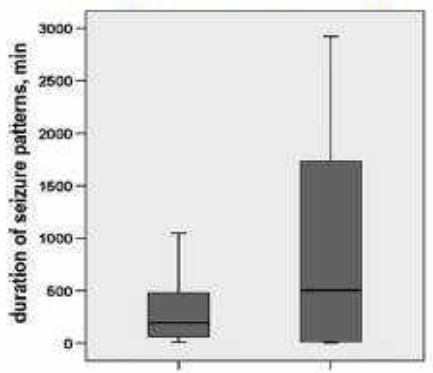
Effect of Treatment of Subclinical Neonatal Seizures Detected With aEEG: Randomized, Controlled Trial

WHAT'S KNOWN ON THIS SUBJECT: Seizures are common in full-term infants with HIE. A substantial portion of neonatal se

AUTHORS: Linda G. M. van Rooij, MD,[a] Mona C. Toet, MD, PhD,[a] Alexander C. van Huffelen, MD, PhD,[b] Floris Groenendaal, MD, PhD,[a] Wijnand Laan, PhD,[c] Alexandra Zecic, MD,[d] Timo de Haan, MD, PhD,[e] Irma L. M. van Straaten, MD, PhD,[f] Sabine Vrancken, MD,[g] Gerda van Wezel, MD, PhD,[h] Jaqueline van der Sluijs, MD,[i] Henk ter Horst, MD,[j] Danilo Gavilanes, MD, PhD,[k] Sabrina Laroche, MD,[l] Gunnar Naulaers, MD, PhD,[m] and Linda S. de Vries, MD, PhD[a]

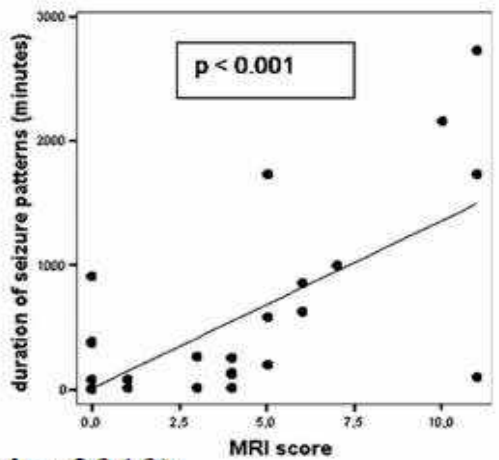
Neo HIE randomized to clinical seizure management versus aEEG based management

Seizure duration



aEEG No aEEG

MRI injury



(Pediatrics 2010)

Treating EEG Seizures in Hypoxic Ischemic Encephalopathy: A Randomized Controlled Trial
Pediatrics, October ‘15

- Neonates ≥36 weeks with moderate or severe HIE were randomly assigned to either treatment of electrographic seizures alone (ESG) or treatment of clinical seizures (CSG).

- Conventional EEG video was monitored in both groups for up to 96 hours.

- Cumulative electrographic seizure burden (SB) was calculated in seconds and converted to log units for analysis

Treating EEG Seizures in Hypoxic Ischemic Encephalopathy: A Randomized Controlled Trial, Pediatrics, October ‘15

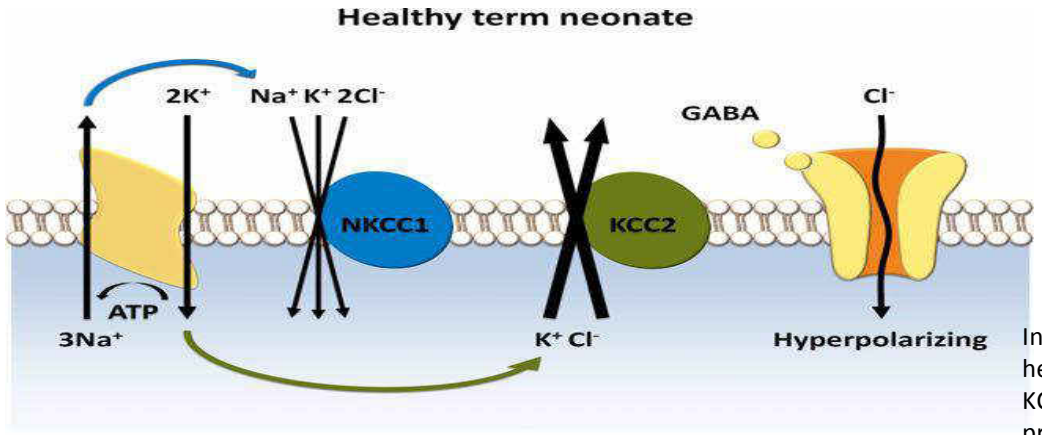
Median SB (interquartile range) in seconds in ESG was lower than in CSG, P = .02

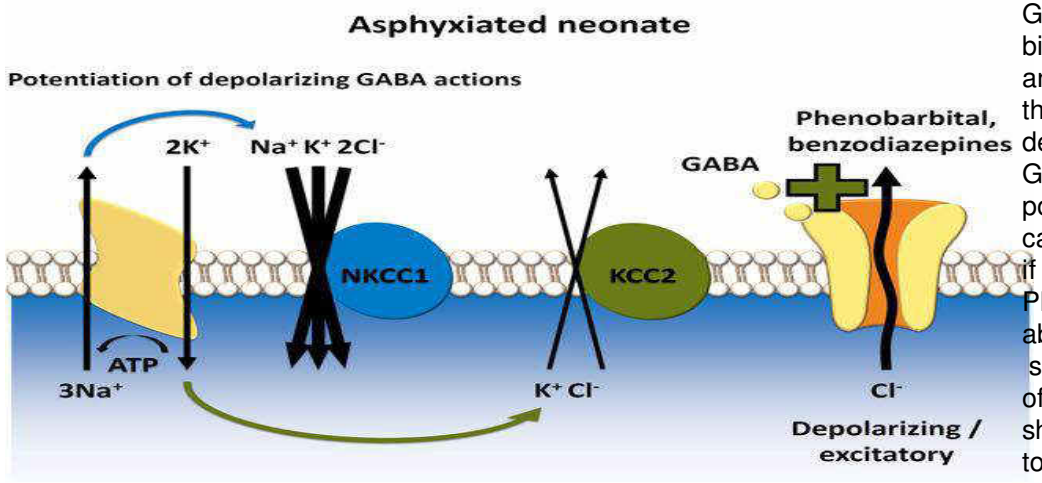
In neonates with HIE, EEG monitoring and treatment of electrographic seizures results in significant reduction in SB.

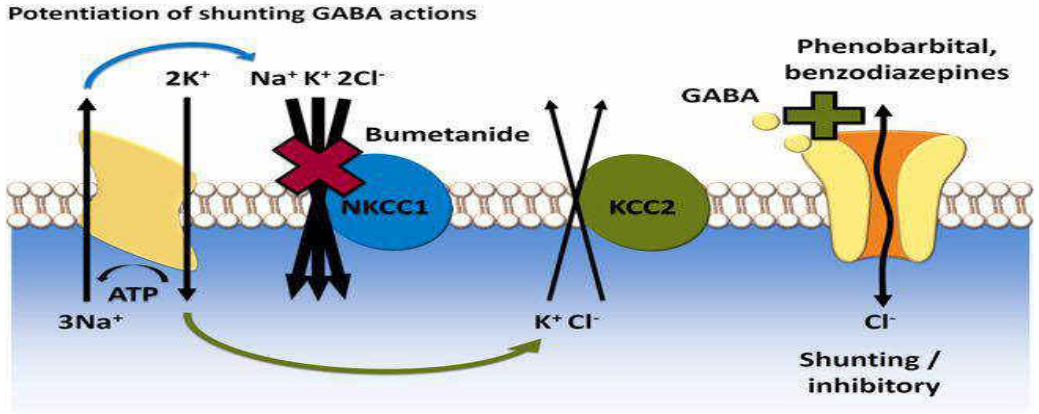
80% follow up at 18-24 months

SB is associated with more severe brain injury and significantly lower performance scores across all domains on BSID III.

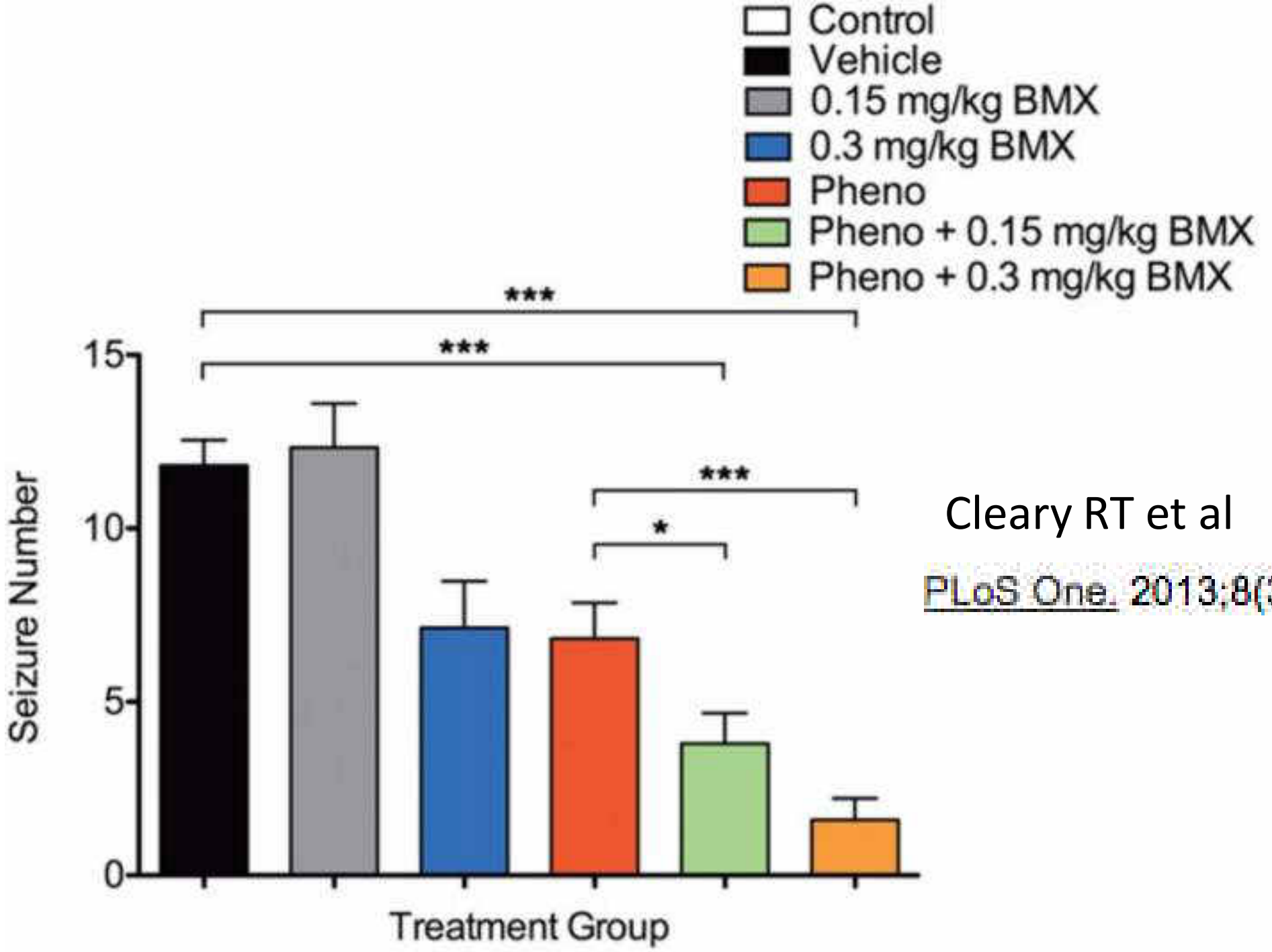
What to treat with







In healthy cortical neurons of human neonates, Cl extrusion via KCC2 is likely to be more efficient than uptake via NKCC1, which promotes a postsynaptic hyperpolarizing current triggered by GABAergic signaling. (Middle) After neuronal trauma caused by birth asphyxia, functional up-regulation of NKCC1 takes place, and the direction of the Cl current is reversed which leads to depolarizing GABA responses. Under these conditions, application of positive modulators of GABAARs (phenobarbital, benzodiazepines) can lead to aggravation of seizures promoted by the depolarizing if not directly excitatory Cl current. Pharmacologic block of NKCC1 by bumetanide attenuates or abolishes the depolarizing GABA response, and subsequent application of positive modulators of GABAARs will lead to effective shunting inhibition, which clamps the membrane potential close to its resting level, thereby preventing action-potential generation in the postsynaptic neuron. (



Cleary RT et al

PLoS One. 2013;8(3):e57148.

Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy

(NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015 May (dose allocation: 0·05 mg/kg, n=4; 0·1 mg/kg, n=3; 0·2 mg/kg, n=6; 0·3 mg/kg, N – 10)

Results suggested that bumetanide as an add-on to phenobarbital does not improve seizure control in newborn infants who have HIE and might increase the risk of hearing loss.

Conclusions

- Clinical diagnosis of seizures is often inaccurate
- Electographic seizures are common and often missed in absence of monitoring in our country
- High seizure burden is associated with more adverse long term effects
- Search of the most effective treatment for seizures is still on