

# Neonatal Seizures

Treatment Controversies and Options  
A clinical perspective

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# Neonatal Seizures

Most common for a consult in the newborn ICU

It can be dramatic and anxiety provoking

Incidence varies: 1- 3.5/1000 live births in term infants

Higher reported in premies

Families concerned about consequences and later epilepsy

# Neonatal Seizures

## 1970- 2017

### Milestones

- HIE was the most common etiology and Phenobarbital was the first line drug used
- Physiology: GABA is inhibitory(1970's)  
GABA is excitatory( 2000's)
- Brain injury- most studies are still based on animal models
- Extent of brain injury in human neonates is now defined by MRI/MRS
- Standard snap shot EEG is replaced by use LTM-EEG technology in tertiary centers
- Emphasis on aggressive treatment of electrographic seizures
- Etiology of seizures better identified by 4 major tools:
  - MRI/MRS
  - Neurometabolic studies
  - Epilepsy genetic panels
  - Placental Pathology

# Neonatal Seizures

## 1970- 2017

### Major Milestones

2017

HIE ( perinatal encephalopathy)still remains the most common etiology

\*Phenobarbital slightly declined in use still remains the first line drug (96%)

\*Use of phenytoin has significantly declined

\*Use of Levetiracetam ( Keppra ) has increased ten-fold

\*Ahmad K J Perinatol 2016; El-Dib Mohamed Semin Fet & Neonat Med 2017

# Neonatal Seizures

What about controversies .....

# Neonatal Seizures

## Controversies

**Controversies concerning Neonatal Seizures. Scher,MS and Painter MJ/ Pediatr Clinics of North America 1989; 36 : 281**

**Controversies in the diagnosis and management of Neonatal Seizures . Low PS.J Singapore Paediatr Soc 1991; 33: 6-10**

**Controversies in treatment of Neonatal Seizures. Hahn JS. Pediatr Neurol 1993; 9: 330-1**

**Controversies in treatment of Neonatal Seizures Young RSK Pediatr Neurol 1993; 9: 331-2**

**Neonatal seizures : Diagnostic and Therapeutic Controversies Legido A. Rev Neurol 1996; 24: 694-700**

# Neonatal Seizures

## Controversies

Neonatal seizures : Diagnostic and Therapeutic Controversies  
Legido A. Rev Neurol **1996**; 24: 694-700

Current controversies in diagnosis and management of neonatal seizures. Laroia Laroia N. Indian Pediatr. **2000** 37: 367-72

Controversies in neonatal seizure management. Glass HC, Wirrell E.  
J Child Neurol. **2009** May;24(5):591-9.

Seizures: controversies and challenges in translating new therapies from the lab to the isolette. Chapman KE, Raol YH, Brooks-Kayal A.  
Eur J Neurosci. **2012** Jun;35(12):1857-65.

# Neonatal Seizures

## Areas of controversy

What is the best way to detect and monitor neonatal seizures ?

Are clinical only or electrographic only events truly seizures ?

Do neonatal seizures cause brain injury ?

How aggressively should neonatal seizures be treated ?

Role older drugs versus newer drugs in the treatment of neonatal sz ?

How long do you treat infants with neonatal seizures ?

Glass H JCN 2009

# Neonatal Seizures

## Treatment

### Why Controversies

- Most studies on brain injury are from studies on animal models
- No evidence based guide lines to treat NS
- No clear policy to treat acute clinical sz ( eg: 1<sup>st</sup> choice; 2<sup>nd</sup> choice etc)
- No uniform protocols to treat electrographic seizures
- No randomized controlled studies comparing different drugs
- Concerns about the long term side effects of old drugs (phenobarb)
- Limited pharmacokinetic data about newer drugs

# Neonatal Seizures

## Controversies in Treatment

### Objectives

Why treat neonatal seizures ?

Why not to treat neonatal seizures ?

How aggressively to treat ?

What to treat with ?

Old drugs

Newer drugs

How long to treat ?

# Neonatal Seizures

## Why Treat

### Concerns about Brain Injury

There is compelling evidence predominantly from animal studies ( [Sankar 1998](#) )

There is a 55-70 fold increase risk for CP; 5 fold increase for ID and 18 fold increase risk for later epilepsy ( [Holden 1982](#) )

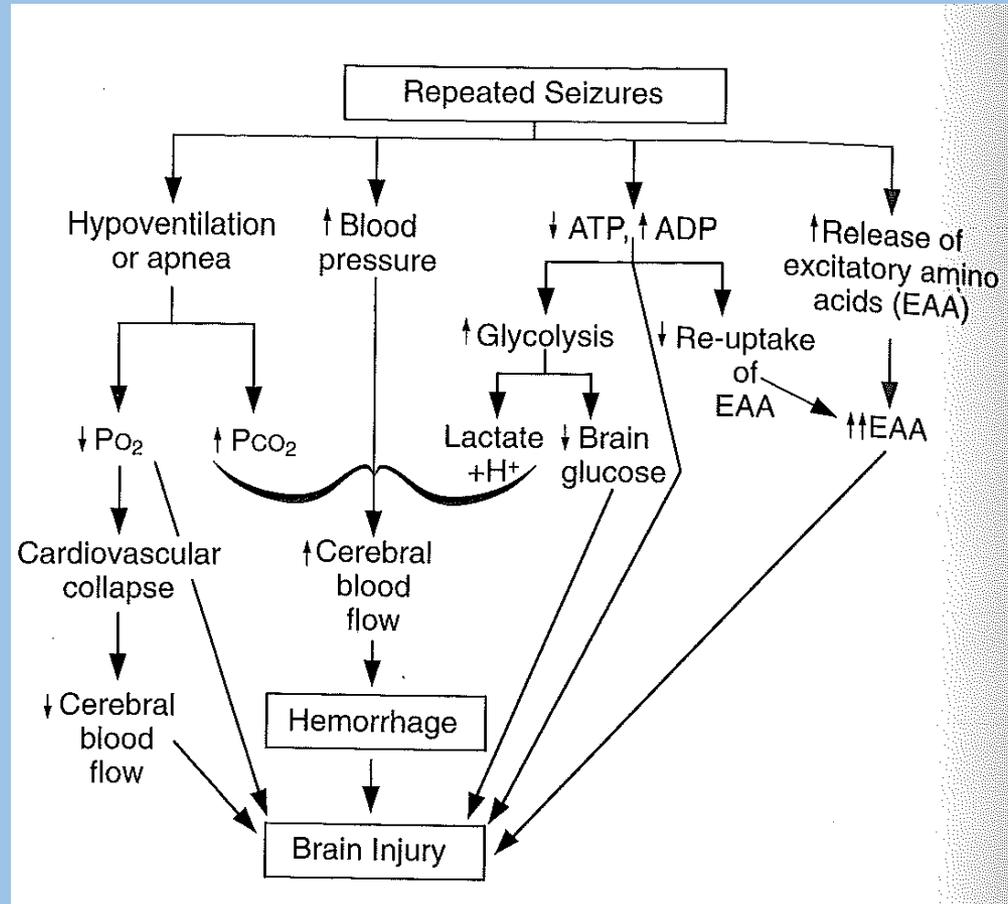
Both clinical and EEG seizures cause severe neurological sequelae in humans neonates ( [Legido A; Pediatrics 2001](#) )

HIE with seizures was associated with worse outcome than without seizures ( [Glass HJ of Pediatrics 2009](#) )

Seizures may exacerbate underlying brain injury in the setting of hypoxic ischemic encephalopathy ( [Dzhala V 2000](#) ; [Wirrel 2001](#) )

# Neonatal Seizures

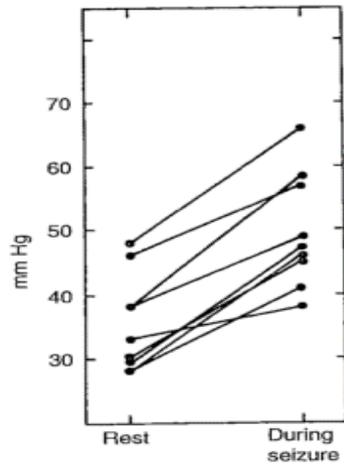
## Why Treat



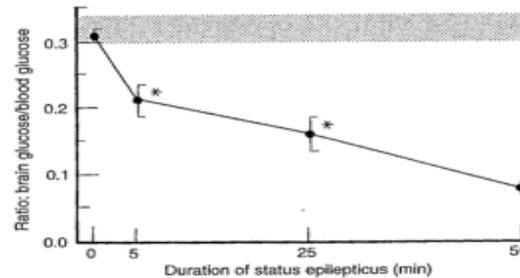
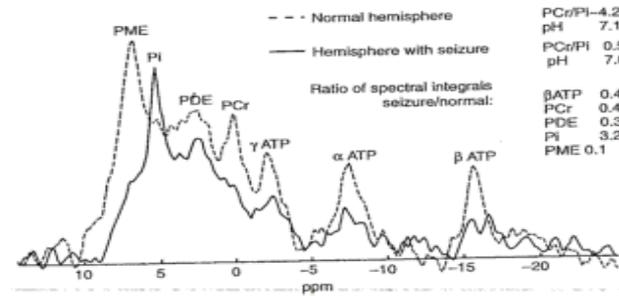
# Neonatal Seizures

Why treat

## Brain Injury



Changes in mean systemic blood pressure with seizures



Volpe JJ 2012

# Neonatal Seizures

## Why Treat

### Risk of Post Neonatal Epilepsy

- Risk of post neonatal epilepsy varies from 15- 35 % ( Scher 1993 )
- Treatment of early seizures may prevent later epilepsy.
  - \* In 2 observational studies treating subclinical sz (EEG ) were associated with lower incidence of postnatal epilepsy 8.3- 9.4 %  
(\* (HellstromWestas 1995; \*Toet 2005)
- Early MRI patterns may predict later epilepsy ( Jung DE 2015)

# Neonatal Seizures

## Objectives

Why treat neonatal seizures ?

Why not to treat neonatal seizures ?

What to treat ?

How aggressively to treat ?

What to treat with ?

Old drugs

New drugs

How long to treat ?

# Neonatal Seizures

## Why not to treat

- Most seizures are related to acute reversible transient causes
- Most seizures may resolve in a matter of few days
- Early treatment may not prevent later epilepsy
- Risk of post neonatal epilepsy is mostly based on etiology of neonatal seizures
- Data of acute and long term consequences are mostly from animal models ( seizures in animal models are induced by chemicals; neuronal loss shown in these experimental models may not be relevant in human infant)
- Adverse effects of the anticonvulsants used are of concern
- No clear human data to support the notion that aggressive therapy of neonatal seizures improves long term outcome.( epileptogenesis and later epilepsy)

\*Guillet et al found that recurrence was independent of phenobarb prophylaxis in 146 children: 30% with Rx vs 23% without Rx

# Neonatal Seizures

## Objectives

Why treat neonatal seizures ?

Why not treat neonatal seizures ?

**How aggressively to treat ?**

What to treat with ?

Old drugs

Newer drugs

How long to treat ?

# Neonatal Seizures

How aggressively to treat?

Electro clinical dissociation

## Overestimation

Clinically evident seizure like behavior may not have EEG correlation

## Underestimation

Electrographic seizures may not have clinical or behavior correlation

\*Mizrahi E 1987; Clancy R 1995

# Neonatal Seizures

## How Aggressively to Treat

### Clinical events without EEG changes

- Many neonatal behaviors may resemble seizures eg: jitteriness
- Neonatal behaviours may be brainstem “release” phenomenon
- Neonatal seizures may originate in subcortical/brain stem regions  
eg: inferior colliculi in rats may generate paddling or treading movts

# Neonatal Seizures

How aggressively to treat

EEG changes without clinical events

Often seen in neonates with very frequent electrographic seizures

\*Clancy et al\* reported that only 21% of EEG seizures had clinical correlation

\* Epilepsia 1988

\*\*Wietstock et al reported 24 % with EEG seizures had no clinical correlates

\*\*J Child Neurol 2016

\*\*\*Buraniqi E et al reported 23% of premies (Mean GA 32.8 wks) with electrographic seizures had no clinical correlates

\*\*\* J Child Neurol 2017

Lack of clinical correlates most commonly seen after loading doses of anticonvulsants

# Neonatal Seizures

## How Aggressively to treat ?

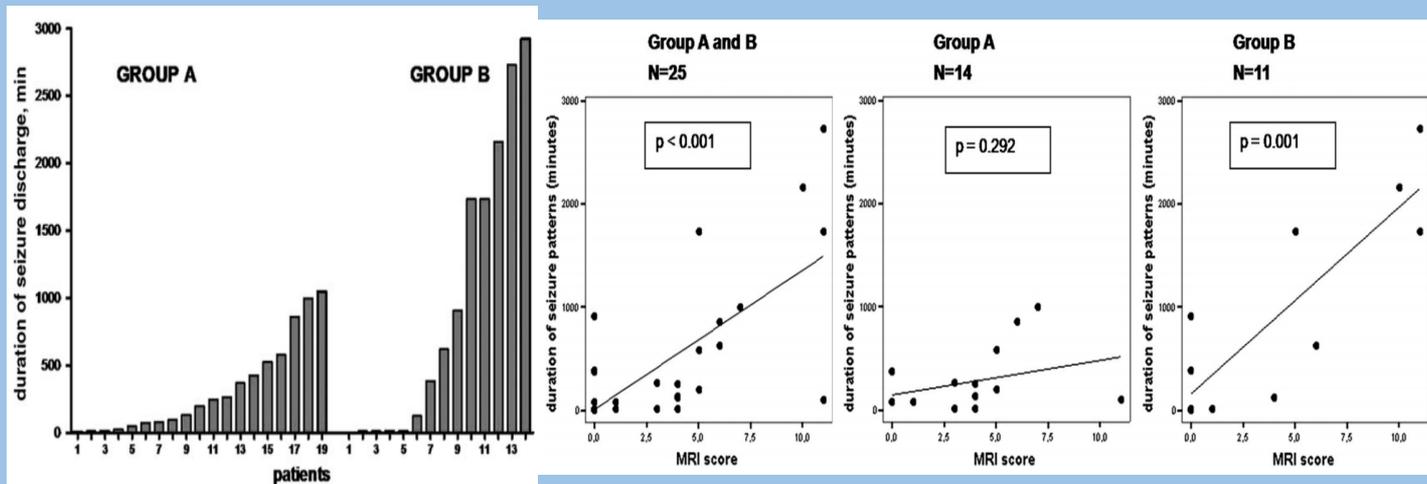
### Electroclinical Dissociation

**Clinical only:** there is some debate if clinical only events (no EEG correlates) should be aggressively treated or not. Some clinical events may have seizure focus which may not be recorded by scalp EEG. Due to potential side effects of the AED many may not pursue with treating these events and careful monitoring is reasonable. Isolated clinical events may not be detrimental but recurrent events may need a careful re-look to consider treatment.

**Electrographic seizures:** Most clinicians will opt to treat electrographic seizures.

# Do seizures predict outcome?

- 11-center randomized trial; N=42 term babies with HIE + sz (aEEG)
- Group A (treat all clinical and electrographic seizures, N = 23)
- Group B (treat only clinical seizures, N = 19)
- Evaluated subsequent severity of injury on MRI



Van Rooji Pediatrics 2010

- Treatment correlated with reduced seizure duration
- Only clinical only arm showed seizure duration  $\propto$  MRI abnormality
- Were the seizures but not the MRI affected by treatment?

# Neonatal Seizures Survey

\*Are electrographic neonatal seizures harmful ?

	Yes	Don't know
Pediatric Neurologists	38%	47%
Neonatologists	34 %	43%

\* Would you treat electrographic seizures ?

	Yes	No	Don't know
Pediatric Neurologists	40%	30%	remaining
Neonatologists	38%	35%	remaining

\*Basan H Ped Neurol 2008

# Neonatal Seizures

How aggressively should NS be treated?

Goal is to eliminate both clinical and electrographic seizures

To treat only clinical events without electrographic correlates is debatable

# Neonatal Seizures

## aEEG ( Amplitude Integrated EEG)

aEEG is widely used in Europe and in many US tertiary centers

aEEG : ease application; interpretation at bedside by trained nurses/MD's

\*aEEG is considered low accuracy for seizure detection

\*aEEG actual sensitivity for individual seizure detection 12- 38%

Conventional LTM EEG with concurrent video is still gold standard

\*\* ACNS advocates use of continuous LTM in the diagnosis of NS

\*Snelhass RA Clin Neurophysiol 2007; \*\* 2011

# Neonatal Seizures

Beware: The misuse of technology and the law of unintended consequences:

\*Freeman JM: J Am Society of Exp Neuro Therapeutics 2007

“Whether seizures or subclinical seizures themselves cause harm to the developing brain is unclear. The effectiveness of medications for treatment of seizures in the newborn has not been well established . Therefore the consequences of automated EEG for the detection of sub clinical neonatal seizures are likely to be similar to the introduction of electronic fetal monitoring : creation of another pseudo disease followed by unwarranted intervention and increased legal liability”

\*Late Prof John Freeman from Johns Hopkins

# Neonatal Seizures

## Objectives

Why treat neonatal seizures ?

What to treat ?

How aggressively to treat ?

**What to treat with ?**

Old drugs

New drugs

How long to treat ?

# Neonatal Seizures

## What to Treat With

- First line and second line drugs have remained the same over decades
- No evidence based clinical guidelines are still available
- Very little evidence to support the use of one drug over the other
- Increasing recognition of neuronal apoptosis related to older AED's such as phenobarbital; phenytoin; VPA and diazepam
- Poor efficacy of phenobarb and diazepam may be related to  
excitatory nature of GABA receptors in the newborn (animals)
- Lack of randomized placebo controlled trials makes it difficult to  
know the absolute efficacy of various old and new anticonvulsants
- Many published studies are **not** based on LTM EEG's.
- Limited pharmacokinetic studies and safety data on newer drugs

# Neonatal Seizures

## Anti Convulsant Drug Therapy

“there is little evidence to support the use of any of the anticonvulsants currently used in the neonatal period”

Booth D. Cochrane Database 2004

# Neonatal Seizures

## Anti Convulant Drug Therapy

There is concern and concensus that currently used AEDs are often ineffective for treatment of neonatal seizures.

Sankar R , Painter MJ .Neurology 2005

# Neonatal Seizures

## Anti Convulant Drug Therapy

\*WHO evidence guidelines on neonatal seizures emphasize the lack of evidence for the management of neonatal seizures.

\*WHO Guidelines on neonatal seizures, Geneva 2011

# Neonatal Seizures

## Anticonvulsant Drug Therapy

We are not alone !

There are other types of seizure disorders and epilepsy that have no well studied randomized control drug trials:

Lennox-Gastaut syndrome

Infantile spasms

ESES ( electrical status epilepticus in sleep)

Early Infantile and Early Myoclonic Encephalopathy (EIEE/EMEE)

# Neonatal Seizures

## Anticonvulsant Drug therapy

### Old Drugs

Phenobarbital

Phenytoin ( fosphenytoin)

# Neonatal Seizures

## Anticonvulsant Drug Therapy

### Why use Phenobarbital ?

Use as first line drug for decades for neonatal seizures

Availability worldwide

Cheap

Pharmacokinetics well studied and predictable

Long half-life especially in HIE babies (> 120 hrs).

Crosses the BBB in less than 30 minutes

Less protein binding (33%)

Use as maintenance orally is feasible

# Neonatal Seizures

## Anticonvulsant Drug Therapy

**Painter and Scher NEJM 1999**

( Phenobarbital vs Phenytoin)

A double blind placebo controlled study

Seizures were monitored on continuous LTM EEG

<b>Drug IV route</b>	<b>Response</b>
Phenobarb	43 %
+ Phenytoin	57%
Phenytoin	45%
+ Phenobarb	62%

**Conclusion:** Overall response with either drug < 50% No significant differences between these 2 drugs in controlling electrographic seizures

# Neonatal Seizures Treatment

J Child Neurol 2009; 24 ; 148

Original Article

## Neonatal Seizures: Treatment and Treatment Variability in 31 United States Pediatric Hospitals

Heidi K. Blume, MD, MPH, Michelle M. Garrison, PhD, and Dimitri A. Christakis, MD, MPH

Neonatal seizures are one of the most common neurological disorders in infants. However, the optimal treatment strategy for neonatal seizures remains controversial and there is little data regarding current treatment of neonatal seizures. In this study we describe the current treatment of neonatal seizures and variation in practice among 31 pediatric hospitals in the United States. We retrospectively identified 6099 infants hospitalized in the first month of life in one of 31 pediatric hospitals participating in the Pediatric Health Information System, with a discharge diagnosis of seizure. As expected, most treated infants received phenobarbital.

However, there was significant interhospital variability for all treatments studied including any antiepileptic drug treatment, phenytoin treatment, antiepileptic drug treatment through discharge, number of antiepileptic drugs used, and treatment with pyridoxine ( $P < .001$ ). These findings highlight the need for rigorous controlled outcome studies to determine optimal therapy for neonatal seizures and devise treatment standards.

**Keywords:** neonatal seizure; antiepileptic drugs; seizure treatment; phenobarbital

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hosted at  
<http://online.sagepub.com>

# Neonatal Seizures

Hellstrom-Westas L . Acta Paedrica 2015

**Table 2** Surveys investigating preferred, or actually administered, anti-epileptic drug treatment of neonatal seizures

Study	Subjects	Country	1st AED	2nd AED	3rd AED	Prophylactic AED
Wheless et al. 2005 (25). 33 questions, 645 treatment options, scenarios	Paediatric neurologists (epileptologists), 39/41 (95%)	USA	Benzodiazepine/ Phenobarbital	Lorazepam	Fosphenytoin	Infant with NE, mean (SD) 8.2 (5.5) weeks
Batha et al. 2007 (26). Administered AED, database	Infants with seizure diagnosis, all gestational ages (n = 480)	USA (5 NICUs)	Phenobarbital 82%	Lorazepam 9%	Phenytoin 2%	75%
Silverstein & Fenters 2008 (27). Off-label use of AED, survey	Paediatric neurologists at 2007 Annual Child Neurology Society meeting, 55 replies	71% USA, 20% Canada, 9% other		Levetiracetam 47%, topiramate 55%	Levetiracetam and/or topiramate 73%	
Blume et al. 2009 (28). Administered AED, database	Infants with seizure diagnosis (ICD-9 779.0, 345.1-9), all gestational ages (n = 6099)	USA (31 states)	Phenobarbital 76%	Phenytoin 16%	Benzodiazepines	67% (day prior to discharge)
Vento et al. 2010 (22). Questionnaire with 3 parts (diagnosis, treatment)	Neonatologists at European university hospitals, 13/20 (65%)	10 European countries, see table 1	Phenobarbital 100%	85% midazolam, 7.5% clonazepam, 7.5% phenytoin	85% lidocaine, 7.5% lidocaine/phenyl, 7.5% midazolam/diaz	
Koppelstätter et al. 2011 (29). Levetiracetam use, survey	German University Hospitals, 35/36 (97.2%)	Germany		45.7% used levetiracetam; 20% used levetiracetam in preterms		
Glass et al. 2012 (24). Web survey, 23 multiple choice	Neonatologists (24.9%), Paediatric neurologists (55.9%), Neonatal neurologist/neurocritical care (19.2%), 193/400-500 (-45%)	USA (75%), UK, Europe, Canada	Preterm: Phenobarbital 72.2%, Lorazepam 21.9%	Preterm: Phenytoin 40.6%, Phenobarbital 26.2%	Preterm: Phenytoin 35.2%, Levetiracetam 21%	
			Term: Phenobarbital 70.9%, Lorazepam 23.1%	Term: Phenytoin 42.8%, Phenobarbital 27.2%	Term: Phenytoin 34.9%, Levetiracetam 18.9%	

AED = Anti-epileptic drug; ICD-9 = International Classification of Diseases, version 9; NE = Neonatal encephalopathy; NICU = Neonatal intensive care unit

# Neonatal Seizures

## Concerns about Phenobarbital

Experimental data emerged 3 decades ago about phenobarbital exposure had adverse effects on survival and morphology of cultured neurons of fetal mouse tissue and raised concerns about its use in the treatment of neonatal seizure

(Bergey GK 1991 Serrano EE 1988)

Recent evidence that even brief treatment with conventional anticonvulsants such as phenobarbital, diazepam, phenytoin and valproate all increase apoptotic neuronal death in normal immature rodent models in cortex thalamus basal ganglia

Bittigau P. Proc Natl Acad Sci 2002

Neuronal apoptosis in rat neurons at serum concentration level 25-35 mc/ml

Bittigau P. Ann NY Acad Sci 2003

# Neonatal Seizures

## Anticonvulsant Drug Therapy

### Why use Phenytoin/ Fosphenytoin ?

Another old with well studied pharmacokinetics and uses

Well established as highly effective drug for status epilepticus

Less cardio vascular side effects

Crosses BBB in < 20 minutes

Converted to phenytoin by phosphatases in < 8 minutes IV

Effective in neonatal seizures abolishing clinical and EEG seizures

Combined with phenobarbital is effective in 65 %

# Neonatal Seizures

## Anticonvulsant Drug Therapy

### Concerns about Phenytoin

\*In rat neurons triggers neuronal apoptosis at a dose of 20 mg/kg  
(ie: Plasma concentration of 10- 15 mc/ml )

Reduced protein binding and likely to increase free phenytoin levels

May displace free bilirubin and increases risk for kernicterus

Lastly phenytoin is not ideally used orally as a maintenance drug for neonatal seizures

\* Bittigau P. Ann NY Acad Sc 2003

# Neonatal Seizures

## Old Drugs

Despite problems and less efficacy both phenobarbital and fosphenytoin still remain main stay in the initial drug therapy for neonatal seizures

# Neonatal Seizures

## Objectives

Why treat neonatal seizures ?

What to treat ?

How aggressively to treat ?

What to treat with ?

Old drugs

Newer drugs

How long to treat ?

# Neonatal Seizures

## Newer Antiepileptic Drugs (AED)

Levetiracetam

Topiramate

Bumetanide

Flupirtine ( potassium channel opener tested in rats )

# Neonatal Seizures

## Newer AED's

Most newer AED's are currently off label reported as case series

Clinical use and data are insufficient to recommend them as first line.

Levetiracetam and topiramate have favorable pharmacokinetic profiles.

Topiramate and levetiracetam **do not cause neuronal apoptosis or disrupt synaptic development** in animal models ( Kim JJ 2007)

Topiramate and Lev may have neuroprotective properties. (Kim, J. 2007 )

Experience with newer drugs is reported only as case series.

# Neonatal Seizures

## Levetiracetam

### Animal Data

No neurotoxic effects in 7 day old rats at doses up to 100 mg/kg ( [Manthley D Exp Neurol 2005](#) )

- LEV given prophylactically to HIE induced rats reduced clinical and electrical seizures
- ( [Talós DM Pediatr Res 2013](#) )

- LEV appeared to exert a disease modifying effect on HIE induced seizures)
- ( [Giler C Exp Neurol 2004](#) )

LEV significantly reduced the number of apoptotic cells in the hippocampus ,  
cerebral cortex and thalami ( [Kilicdag H Early Hum Dev 2013](#) )

- LEV suppressed acute seizures induced by perinatal hypoxia and
- diminished later life seizure susceptibility and seizure induced neuronal
- injury in rodent neonatal seizure model. ( [Jensen FE Pediatr Res 2011](#) )
- 
- LEV and Topiramate have no effects on apoptosis in the developing brain.
- ( [Talós DM Pediatr Res 2013](#) )

# Neonatal Seizures

## Levetiracetam

Clinical Data ( Total 144 cases) All case series

- \*Abend NS ; J Child Neurol 2011
- \*Ramantani G; Eur J Pediatr Neurol 2011
- \*Khan O ; Pedi Neurol 2011
- \*Khan O ; Pedi Neurol 2013
- \*Rakshabhuvankar A ; J Clin Neurosci 2013
- \*Neininiger MP : Neuropediatrics 2015
- \*Lo-Yee Yau M ; World J Clin Pediatr 2015

(Dose range 10- 55 MG/KG Response rate 35- 100 % ( overall 90 %)

Surveys have indicated levetiracetam being used as second line ( Silverstein F 2008)

A double blind randomized controlled trial of IV Levetiracetam is currently in progress in Children's Hospital, San Diego, Ca.

An observational study comparing Lev and Phenobarbital as first line is currently in progress at Univ of Cincinnati

# Neonatal Seizures

## Levetiracetam

### Clinical Study

Ramantani G et al Eur J Ped Neurol 2011

A prospective study using LEV as first line drug

N 38 preterm and term infants

Dose range 10 mg/kg load to max 60 mg/kg

Some needed phenobarbital IV for persistent seizures

30/38 infants became seizure free in one week

EEG markedly improved in 24 infants in 4 weeks.

# Neonatal Seizures

## Levetiracetam

### Clinical Study

Falsaperla R J Pediatr Neurosci 2017

A prospective study using LEV as first line drug

N= 16 neonates ( 12 term and 4 pre term)

LEV initial dose 10 mg/kg BID

Maintenance Dose up to 40 mg/kg BID

All responded to LEV monotherapy

Response within 24- hours to 15 days ( mean 96 hrs)

# Neonatal Seizures

## Levetiracetam

LEV is currently often used as second or third line treatment for neonatal seizures

Availability of IV preparation has enabled its use off label

Mechanism is action in unknown but suggestive of interaction with SVP 2A( synaptic vesicle protein)

It is not linked to plasma proteins-so no risk of displacement of other protein bound substances

Minimal hepatic metabolism involved

It is not metabolized by cytochrome P450 system

Mean half life in neonates range from 9 to 18 hours Q 8hourly dose may be preferable

Several animal studies have suggested LEV's safety in the newborn infants ( does not cause apoptotic degeneration)

A Phase 2 randomized study as first line drug being conducted at Univ of Ca at San Diego

# Neonatal Seizures

## Levetiracetam

### Human Studies in Neonatal Seizures

Studies about its use published are small retrospective series

Most of them received LEV as second or third line drug treatment

Methodological issues make them difficult to interpret the results

Many of the neonates have already received other drugs

Unclear if seizure cessation is LEV efficacy or natural resolution

Current evidence suggests that LEV works best in 30% of neonates

El-Dib M. and Soul J. *Sem Fetal & Neonatal Med* 2017

# Neonatal Seizures

Levetiracetam

## Current Use

As first line drug for neonatal seizures is still not prevalent

Studies are underway of LEV as first line drug for neonatal seizures

As second line is widely catching up.

Almost everyone uses LEV as third line for neonatal seizures

# Neonatal Seizures

Anticonvulsant Drug Therapy

Newer Drugs Topiramate ( AMPA Modulator)

TPM has multiple mechanisms of action ( Koh & Jensen Ann Neurol 2001 )

In animals models with cerebral ischemia TPM reduced severity of brain injury alone or with hypothermia. ( Scubert S. 2005; Brain Res )

In animals models not shown to have any harmful effects on developing brain

Neuroprotective effects have been described in rats related to AMPA mediated effects and kainate receptor inhibition (Koh & Jensen Ann Neurol 2001 )

No clear data on human neonates/no IV formulation limits use.

Susceptible to drug interactions and effects of hypothermia ( CP450) ( Ped Neurol 2011; 2012)

Low risk for apoptosis ( Sem Fetal & Neonatal Med 2017)

Trial as adjuvant with hypothermia in HIE currently in progress in USA and Italy

# Neonatal Seizures

## Anticonvulsant Drug Therapy

### Newer Drugs

#### \* Bumetanide ( NKCC1 transporter inhibitor)

- A loop diuretic widely used for decades in neonates as a diuretic
- Inhibits NKCC1 ( Cl<sup>-</sup>-cotransporter) that is highly expressed in immature neurons
- Blockade of NKCC1 decreases neuronal Cl<sup>-</sup> levels and restores GABA inhibition
- Combining with phenobarbital augments GABA inhibition and may control seizures not controlled by phenobarbital alone
- \*\*Augments neuroprotective effects of phenobarbital in HIE models with hypothermia
- A large double blind multicenter RCT study completed at Harvard ( [Soul J , Staley KJ et al](#)).

\*Dzhazla V, Staley K Ann Neurol \*\* Liu Y Ped Res 2012

# Neonatal Seizures

## Bumetanide Enhances Phenobarbital Efficacy in a Neonatal Seizure Model

Volodymyr I. Dzhalala, PhD,<sup>1,2</sup> Audrey C. Brumback, PhD,<sup>2</sup> and Kevin J. Staley, MD<sup>1,2</sup>

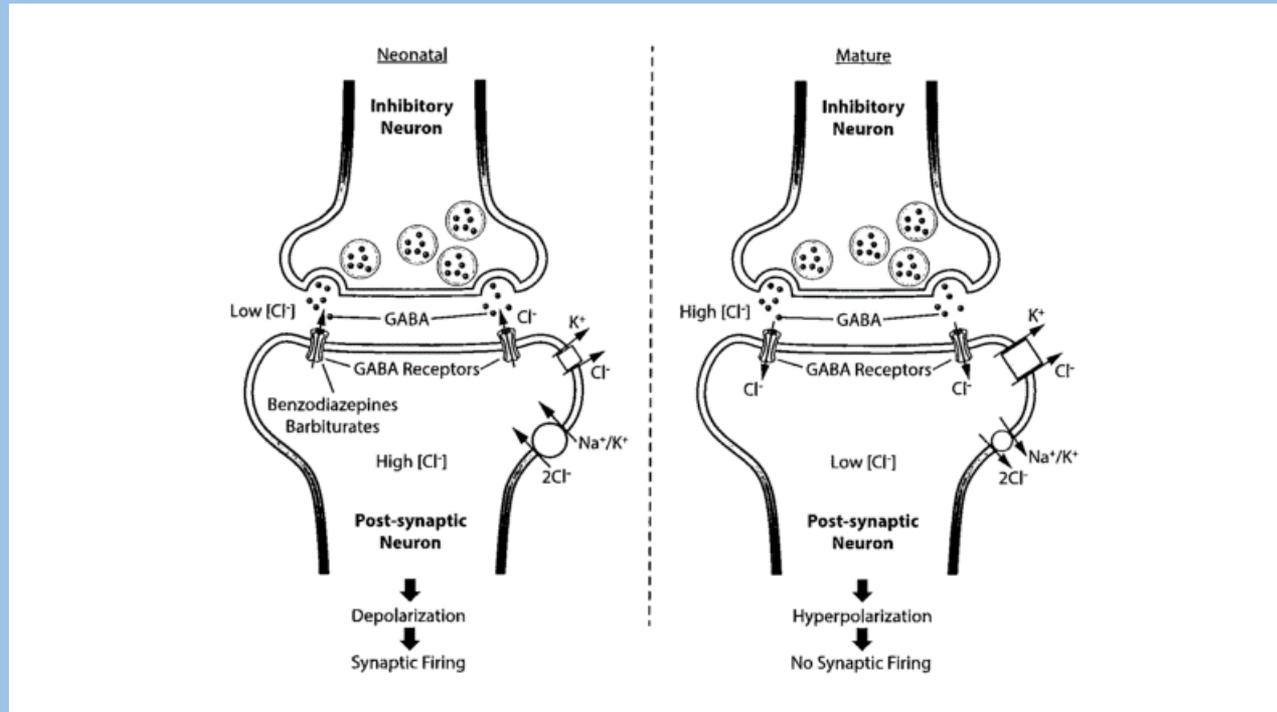
**Objectives:** High levels of expression of the  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  (NKCC1) cotransporter in immature neurons cause the accumulation of intracellular chloride and, therefore, a depolarized  $\text{Cl}^-$  equilibrium potential ( $E_{\text{Cl}}$ ). This results in the outward flux of  $\text{Cl}^-$  through  $\text{GABA}_A$  channels, the opposite direction compared with mature neurons, in which  $\text{GABA}_A$  receptor activation is inhibitory because  $\text{Cl}^-$  flows into the cell. This outward flow of  $\text{Cl}^-$  in neonatal neurons is excitatory and contributes to a greater seizure propensity and poor electroencephalographic response to GABAergic anticonvulsants such as phenobarbital and benzodiazepines. Blocking the NKCC1 transporter with bumetanide prevents outward  $\text{Cl}^-$  flux and causes a more negative GABA equilibrium potential ( $E_{\text{GABA}}$ ) in immature neurons. We therefore tested whether bumetanide enhances the anticonvulsant action of phenobarbital in the neonatal brain.

**Methods:** Recurrent seizures were induced in the intact hippocampal preparation in vitro by continuous 5-hour exposure to low- $\text{Mg}^{2+}$  solution. The anticonvulsant efficacy of phenobarbital, bumetanide, and the combination of these drugs was studied.

**Results:** Phenobarbital failed to abolish or depress recurrent seizures in 70% of hippocampi. In contrast, phenobarbital in combination with bumetanide abolished seizures in 70% of hippocampi and significantly reduced the frequency, duration, and power of seizures in the remaining 30%.

**Interpretation:** Thus, alteration of  $\text{Cl}^-$  transport by bumetanide enables the anticonvulsant action of phenobarbital in immature brain. This is a mechanistic demonstration of rational anticonvulsant polypharmacy. The combination of these agents may comprise an effective therapy for early-life seizures.

# Neonatal Seizures



GABA acts excitatory in immature neurons due to over expression of NKCC1 and under expression of KCC2 resulting in increased intraneuronal Cl ions and depolarization (excitation)

Mature neurons have over expression of KCC2 and low intraneuronal Cl ions concentration resulting in GABA induced hyperpolarization (inhibition)

# Neonatal Seizures

Anticonvulsant Drug Therapy

Newer Drugs

Flupirtine ( Potassium channel openers)

\*A recent study in rats has shown excellent efficacy

In 5 minutes completely abolished electrographic and clinical sz

Potential use in humans in KCNQ2 and KCNQ3 epilepsies

Raol YH et al Ann Neurol 2009

# Neonatal Seizures

## Anticonvulsant Drug Therapy

\*AED's administered for Neonatal Seziures

( N- 420) ( from 8 tertiary care centers)

Drug	N	%
Phenobarbital	387	(92%)
Levetiracetam	130	( 31%)
Fosphenytoin	116	(27%)
Benzodiazepine	81	(19 %)
Midazolam infusion	34	(8%)
Vitamins ( B6 etc)	32	(8 %)

\* Glass H et al Journal of Child Neurology 2016

# Neonatal Seizures

## Anti Convulsant Drug Therapy

\*Informal personal poll of neonatal neurologists from 4 major tertiary centers :

1. Every one uses phenobarbital as the first choice
2. Second choice is still Fosphenytoin in 2/4 centers
3. Second choice is Levetiracetam in 2/4 centers
4. Second choice of IV Midazolam in 1/4 if EEG shows status
5. All agree that practices vary according to the Attendings
6. Use of Topomax is still not common because no IV form.
7. No one uses Pentobarbital coma in the neonates

# Neonatal Seizures

## Preterm Babies

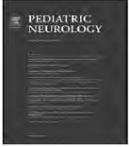
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Original Article

**Seizures in Preterm Neonates: A Multicenter Observational Cohort Study**

 CrossMark

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92 preterm infants ( < 28 weeks to 37 weeks)

Phenobarbital was initial drug used in majority of infants

HIE and ICH most common causes.

More subclinical seizure detected in preterm ( 24% ) than term(14% )

Mortality was twice ( 35% ) in preterm than term ( 15% )

Recommending routine LTM EEG monitoring in preterm infants

# Neonatal Seizures

## Hypothermia

Therapeutic hypothermia is standard of care in neonatal HIE

\*Hypothermia is likely to reduce seizure burden

\*\* Hypothermia might affect biotransformation of drugs via hepatic cytochrome enzymes P450 ( CYP450)

\*\*Effect of hypothermia is exaggerated in HIE hindering drug metabolism and elimination

Both phenobarb and phenytoin metabolism but levetiracetam is not depressed by hypothermia

\* J Pediatr \*\*Crit Care Med 200 \*\*Expert opin Drug Metab Toxicol 2011

# Neonatal Seizures

## AED Therapy

### Persistent Electrographic Sz

- Most electrographic sz respond to optimal doses phenobarb/fosphenytoin
- Usually response seen in 24 – 72 hours
- May try IV lorazepam 0.05 MG/kg bolus x 1-2 doses
- IV Levetiracetam is gaining a role as an excellent option
- IV Midazolam continuous infusion is used in selected cases
- IV Pentobarb infusion is only very rarely used in the neonates
- IV Lidocaine is used in Europe commonly but not in USA
- Trial of Pyridoxine ( B6) is warranted in all intractable cases

# Neonatal Seizures

## Midazolam

Anti convulsant effect at GABA receptors

Apoptosis has not been well studied

Concerns are sedation, mortality and lengthy hospital stay etc

Efficacy as 2<sup>nd</sup> or 3<sup>rd</sup> line for refractory NS has been published as case series

Small sample size and methodological issues hamper interpretation

Use of midazolam may be considered for refractory NS

# Neonatal Seizures

## Drug Therapy

### Vitamin Therapy

Use in selected intractable cases

Pyridoxine (Vit B6 ) 100- 200 mg IV with concurrent EEG

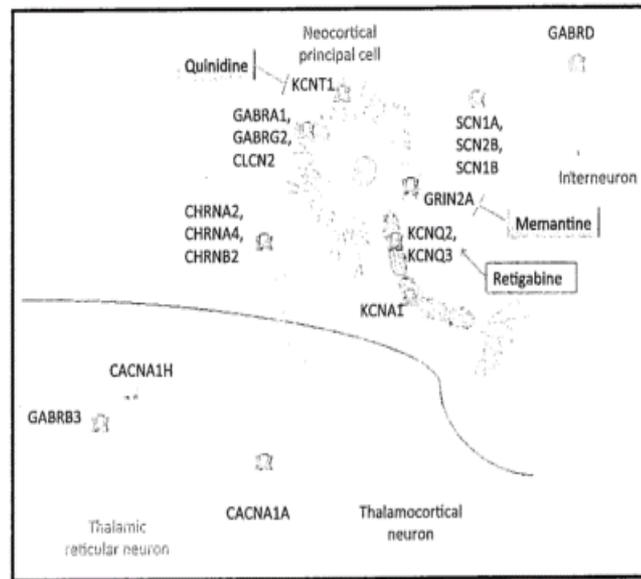
Biotin 5-15 mg tid ( PO)

Folinic acid 4 mg/kg/IV/PO/ tid

Pyridoxal 4 Phosphate 30 mg/kg/day PO divided TID

# Neonatal Seizures

## Future Drug Therapy



**Figure** Epileptic channelopathies. The tentative roles of some ion channels in genetic epilepsy are indicated schematically, with gain-of-function mutations shown in red and loss-of-function mutations in blue. Memantine and quinidine are being investigated as potential therapies for GRIN2A and KCNT-1-related epilepsies, respectively, that may ameliorate the gain of function in the respective channels as discussed in the text. Retigabine, which opens potassium channels, is being investigated as a potential therapy for loss-of-function mutations related KCNQ2 and KCNQ3 epilepsies (Adapted from Hani et al.<sup>6</sup>). (Color version of figure is available online.)

# Neonatal Seizures

## Acute Drug Therapy

### Usual Strategy

Load with Phenobarb 20 mg/kg-may go up  
with 5mg/kg increments to 30 mg/kg-40mg/Kg  
Be prepared to intubate in those with 40 mg/Kg

If no response

Add IV Fosphenyoin 20 mg /kg If no response  
May try another dose 5 mg/kg IV

If no response

Give IV Levetiracetam 20 mg/Kg  
May try doses up to 40- 50 MG/KG IV

If no response

Consider IV Midazolam infusion

# Neonatal Seizures

## Acute Drug Therapy

### Modified Strategy

Load with Phenobarb 20 mg/kg-may go up  
with 5mg/kg increments to 30 mg/kg-40mg/Kg  
be prepared to intubate in those with 40 mg/Kg

If no response

Load IV Levetiracetam 40-60 mg/kg ( high dose)

If no response

Load IV Fosphenytoin 20 mg /kg

If no response

Try Pyridoxine 100-200 mg IV

If no response

Consider IV Midazolam infusion

# Neonatal Seizures

## Objectives

Why treat neonatal seizures ?

What to treat ?

How aggressively to treat ?

What to treat with ?

Old drugs

New drugs

How long to treat ?

# Neonatal Seizures

## How Long to Treat

There is little agreement on this issue /no clear policy /guidelines exist

There are no randomized controlled studies comparing the effects of AED treatment vs no treatment on short and long term outcome.

\*Surveys have indicated duration of Rx days to years –no uniformity

\*\* Neonatologists tend advocate shorter duration than neurologists

\*Massingale TW J Perinatol 1993; Bartha AI Pedi Neurol 2007; Basan H 2008

\*\* Basan H 2008; Wickerstrom R Pedi Neurol 2013

In general, infants with severe HIE brain injury; cortical malformations, large bleeds and genetic epilepsies may need longer duration of treatment.

# Neonatal Seizures Drug Therapy

## Criteria to stop AED therapy

- 80%-85% of neonates will need only short term maintenance therapy ( weeks)
  - \*May consider to discontinue if following criteria are met:
    - No seizure recurrence
    - Normal followup EEG
    - Normal Neurological Examination
- \*Volpe JJ Pediatrics 1989
- Those who need long term AED therapy (15-20 % ) have consequences of severe HIE/malformations/metabolic/genetic/meningoencephalitis

# Neonatal Seizures

## Conclusions of Controversies

### Current state of treatment for neonatal seizures

There is no evidence based studies to support current AED use

Current management is largely based on old tradition ; case series and clinical experience

Clinical trials in neonates have logistical and ethical problems

AED's based on age specific mechanisms might hold promise use of newer drugs

Trials of levetiracetam, topiramate and bumetanide are being conducted methodically and may alter future drug treatment of neonatal seizures

There is a strong need for more evidence based studies and data for the management of neonatal seizures.

# Controversies in Neonatal Seizures

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# Controversies in Neonatal Seizures

Thank you for your kind attention