LEVETIRACETAM IN NEONATES

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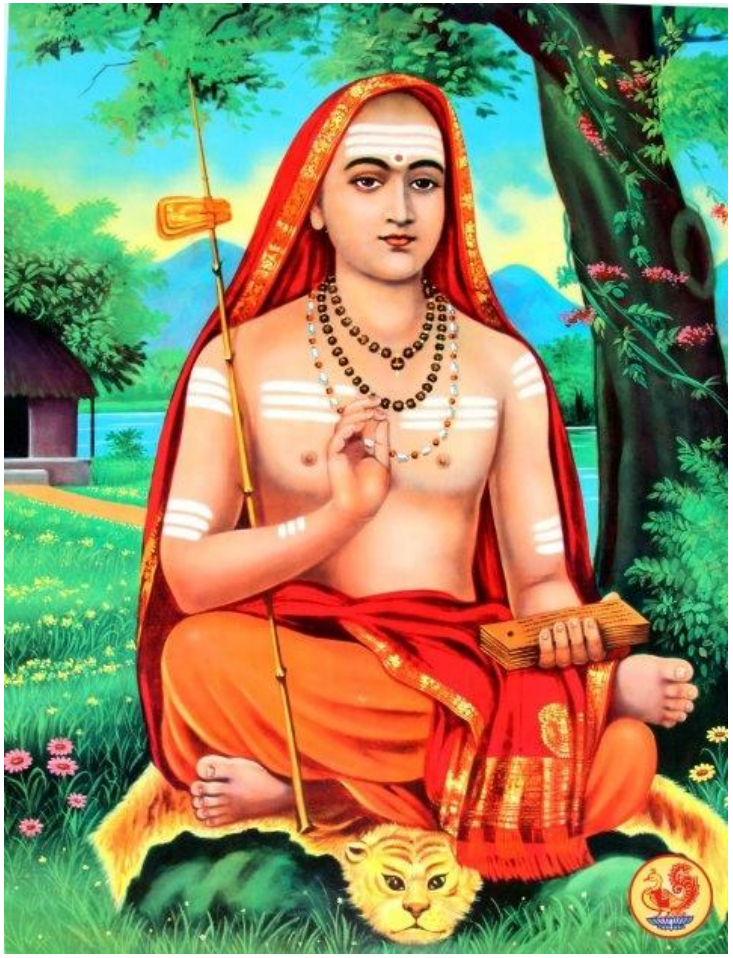
WHETHER TO USE LEVETIRACETAM IN NEONATAL CONVULSIONS

- When to use?
- Which type of seizures?
- How much(dose of drug) to use?
- How long to use?

MANDAN MISHRA



SANKARACHARYA

Indian Evidence Based Medicine

1)Eye witness

2)Logic

3)Guidelines by authority in subject

Eye Witness

Study (Design)	Study Population	Levetiracetam Dose	Study Definitions	Results
Maitre et al[46] (retrospective cohort study)	280 patients had at least 1 seizure and received either LEV or PB or both; GA: 38 weeks (IQR: 35–39); 106 received PB only; 33 received LEV only; 141 patients received both PB and LEV; HIE cause: 39 of 280 patients (39%)	Dose was determined by prescriber. Median cumulative dose: 360 mg/kg (IQR:152–675)	Motor, cognitive, and communication skills or language development were assessed using the DAYC at 12 mo and BSID at 24 mo; Cumulative dose was calculated using the sum of total daily dose/kg for each day until hospital discharge	Of the surviving patients, 62% had DAYC scores available at 12 mo that were within the average range in all 3 categories for LEV and PB; 32% had BSID scores available at 24 mo following LEV therapy, showing 2.6-point decrease ($p = 0.001$) in motor scores and a 2.2-point decrease in cognitive scores ($p = 0.001$) for every 300 mg/kg; patients taking PB showed an 8-point decrease ($p = 0.01$) in motor scores and a 9-point decrease ($p = 0.023$) in cognitive scores for every 100 mg/kg of exposure. 159 patients (75%) were evaluated for CP at 2 years of age. No association was found with LEV therapy. PB therapy was associated with a 2.3-fold increased risk of developing CP for every 100 mg/kg. Mortality rate at 2 years of age was 24% (68 patients)
Abend et al[44] (retrospective cohort study)	23 neonates with EEG-confirmed seizures; GA: 38 ± 1.7 weeks; PNA at administration: 14 ± 13 days; HIE cause: 8 of 23 patients (34.8%)	LD: 10–20 mg/kg MD: 10–80 mg/kg/day divided in 2 doses; First line: 17% Second line: 61% Third or later: 22%	Seizure improvement was defined as a reduction greater than 50% in electrographic seizures	Seizure improvement: within 24 hr for 8 of 23 patients (35%), within 24–72 hr in 7 of 23 patients (17%). 8 of 23 patients (35%) had no seizure reduction; 3 of 23 patients (13%) received LEV after seizures terminated. 17 patients (81%) were discharged home with LEV therapy; There were no cardiopulmonary AEs and no discontinuation of LEV therapy due to serious or intolerable AEs.

AE, adverse event; AED, antiepileptic drug; BSID, Bayley Scale of Infant Development; CP, cerebral palsy; DAYC, Development Assessment of Young Children; EEG, electroencephalography; GA, gestational age; HIE, hypoxic ischemic encephalopathy; IQR, interquartile range; IV, intravenous; LD, loading dose; LEV, levetiracetam; MD, maintenance dose; PB, phenobarbital; PNA, postnatal age

Eye Witness

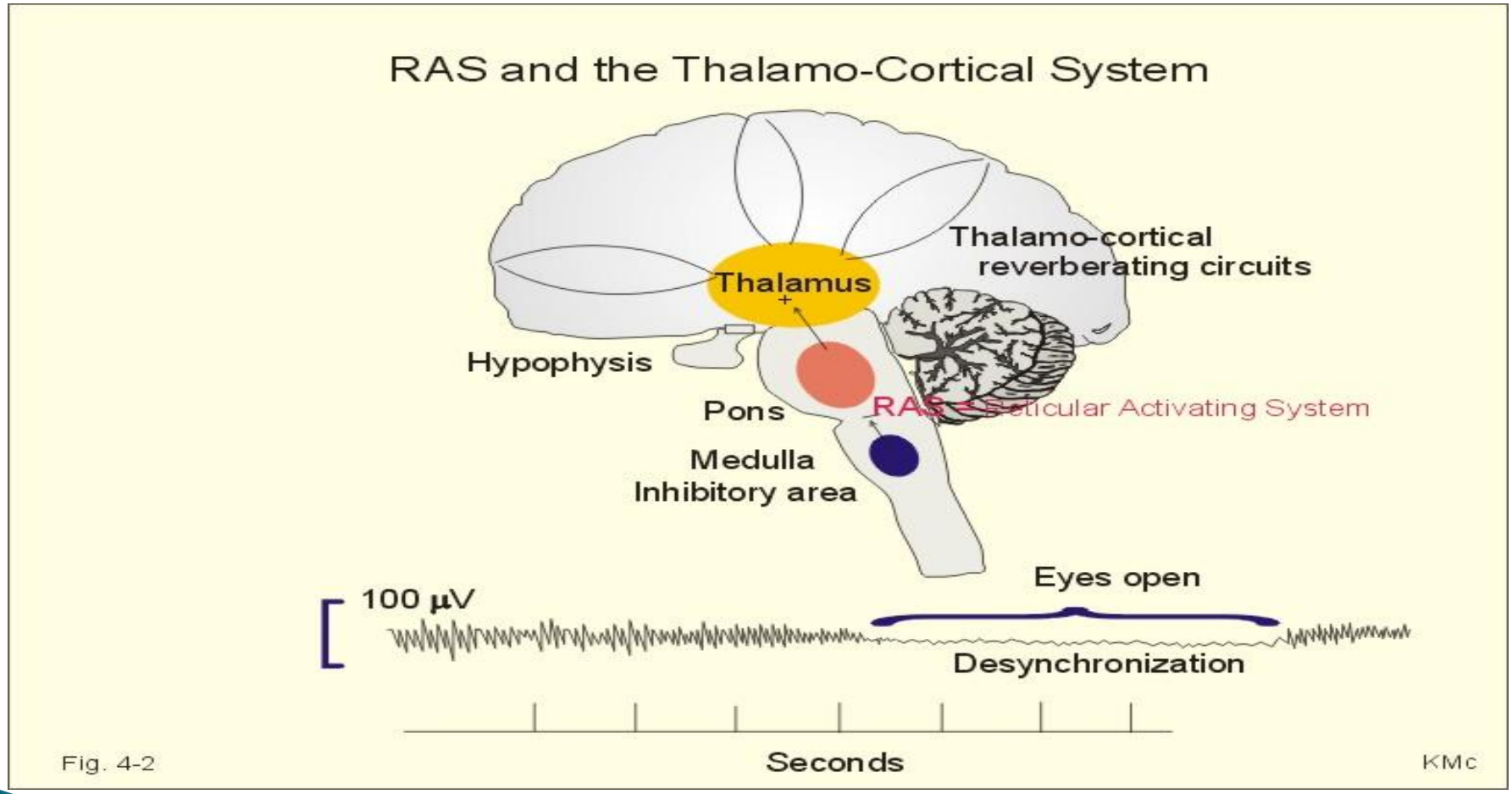
Study	Gestational Age	Sex	Hospital Course	Levetiracetam Dose*	Outcome
Hmaimess, et al[41]	–	Male	Seizures were uncontrolled at 10 days of life with phenytoin and clonazepam. Diagnosis was malignant migrating partial seizures refractory to many AEDs (186 vEEG confirmed seizures per day).	10 mg/kg/day; increased to 30 mg/kg/day	LEV decreased seizure activity to 66/day by the 8th day of treatment. After 14 mo on LEV, patient had 1 seizure per day.
Shoemaker et al[42]	41.86 weeks	Female	Refractory seizures at birth while receiving therapeutic doses of phenobarbital and fosphenytoin.	Loading dose = 60 mg/kg; maintenance dose = 30 mg/kg/day	Seizure activity was controlled within 17 min of bolus administration. At 18 mo follow-up, the patient was free of seizures on LEV monotherapy. No developmental delay.
	25.86 weeks	Male	Seizure activity on days of life 1 and 3. The patient was maintained on phenytoin. At 2 months of age, the patient developed seizures and was switched to LEV.	30 mg/kg/day	At 4 mo of age, the patient was seizure free on LEV monotherapy. Developmental delay was present.
	26 weeks	Male	Developed partial seizures 3 days after diagnosis of group B streptococcus meningitis. Fosphenytoin therapy was initiated then was switched to oxcarbazepine a few days later but discontinued due to hypophosphatemia. Oral LEV was initiated.	30 mg/kg/day	At 1 yr of life, the patient was seizure free on LEV monotherapy. Moderate developmental delay.

Eye witness

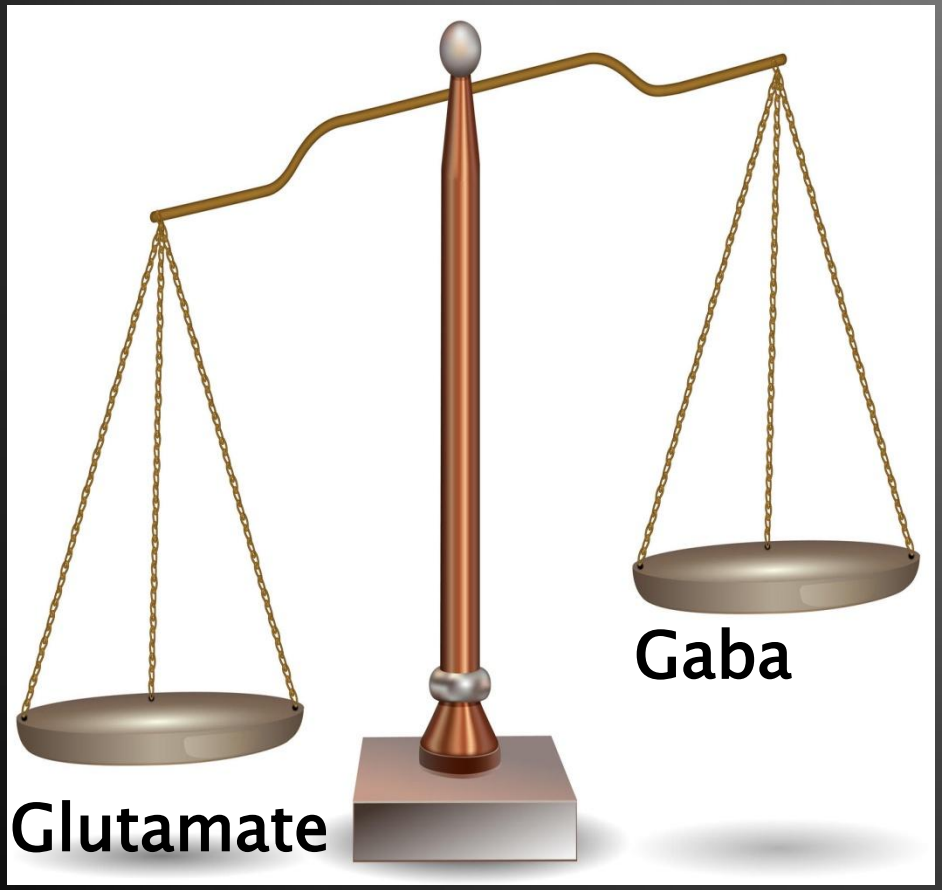
LOGIC

- Normal Neonatal Brain
- Neonatal convulsions
- Drug Action
- Conclusions

Normal neonatal brain

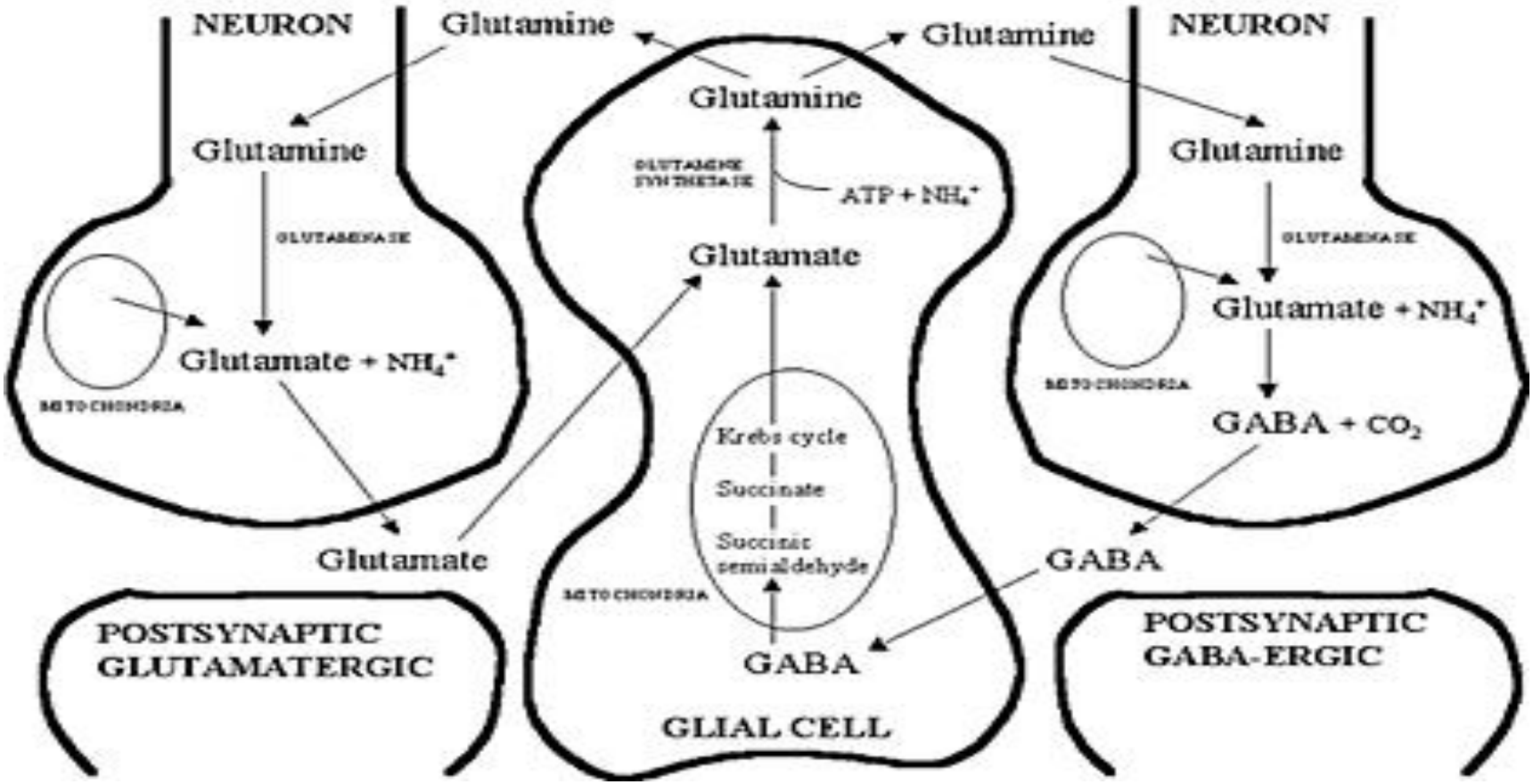


Neonatal Convulsions

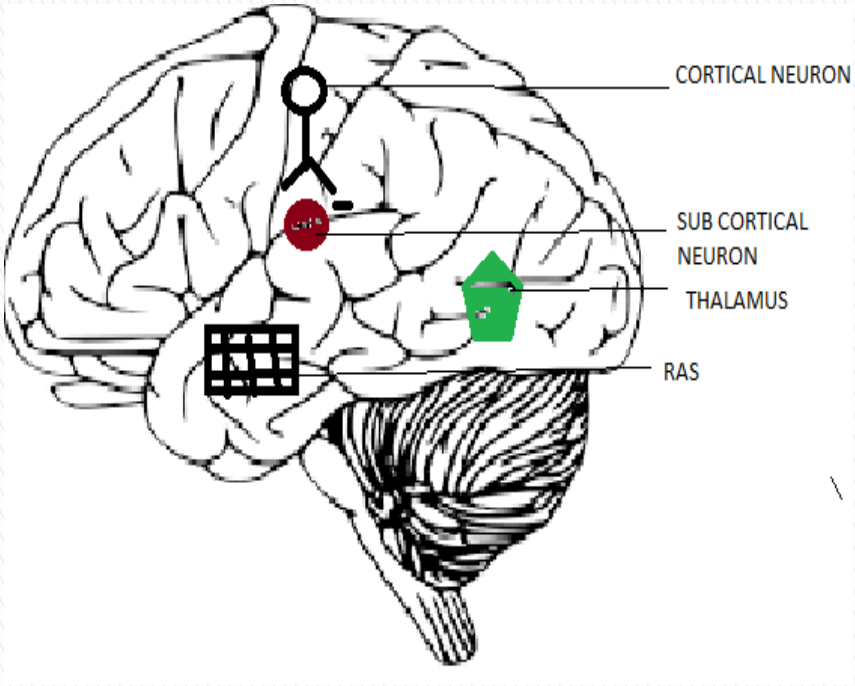


- Disturbed balance between excitatory and inhibitory neurotransmitters
- Excitatory:Glutamate
- Inhibitory:Gaba

Neonatal convulsions



Types of Neonatal seizures



- Subtle seizures
- Multi focal clonic
- Generalized tonic
- Myoclonic

Mechanism of Action

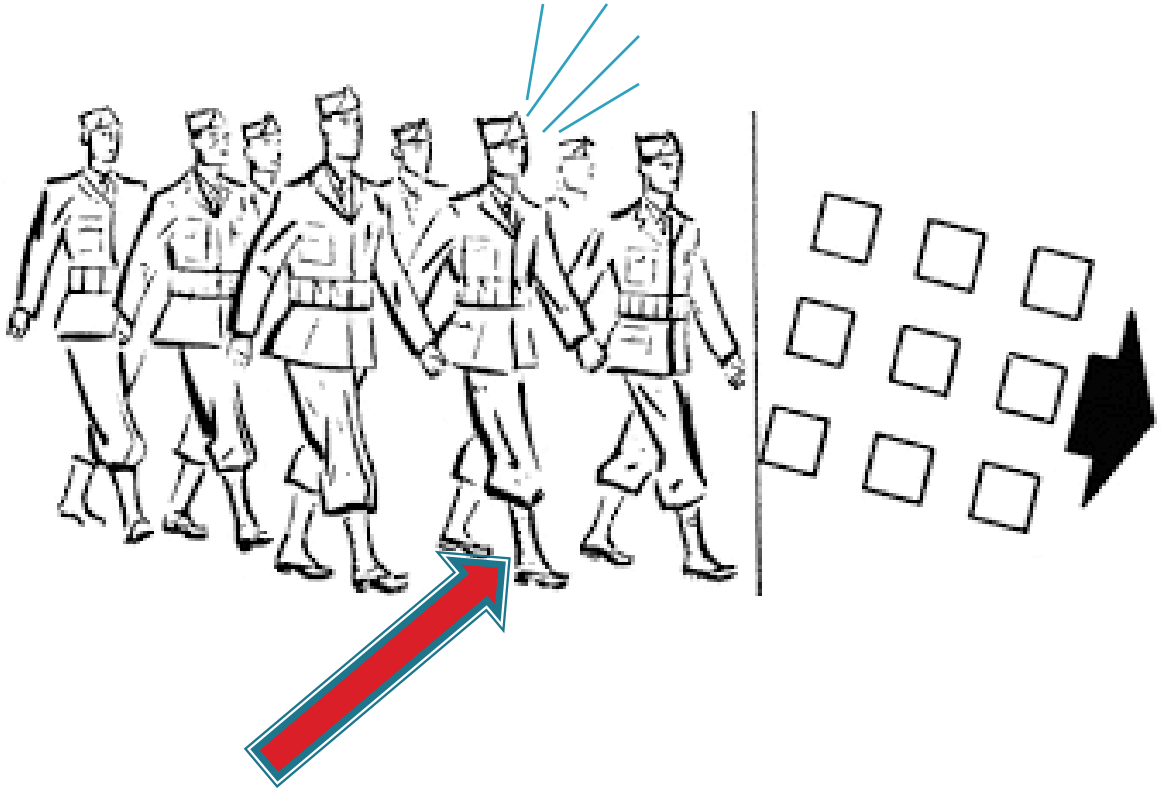
- **Signal to noise ratio**

- Depends upon levels of cytosolic calcium levels.
- When cytosolic calcium levels are high, signal to noise ratio is altered resulting in seizures.
- Levetiracetam inhibits the release and influx of calcium into cytosol thereby reducing the signal to noise ratio

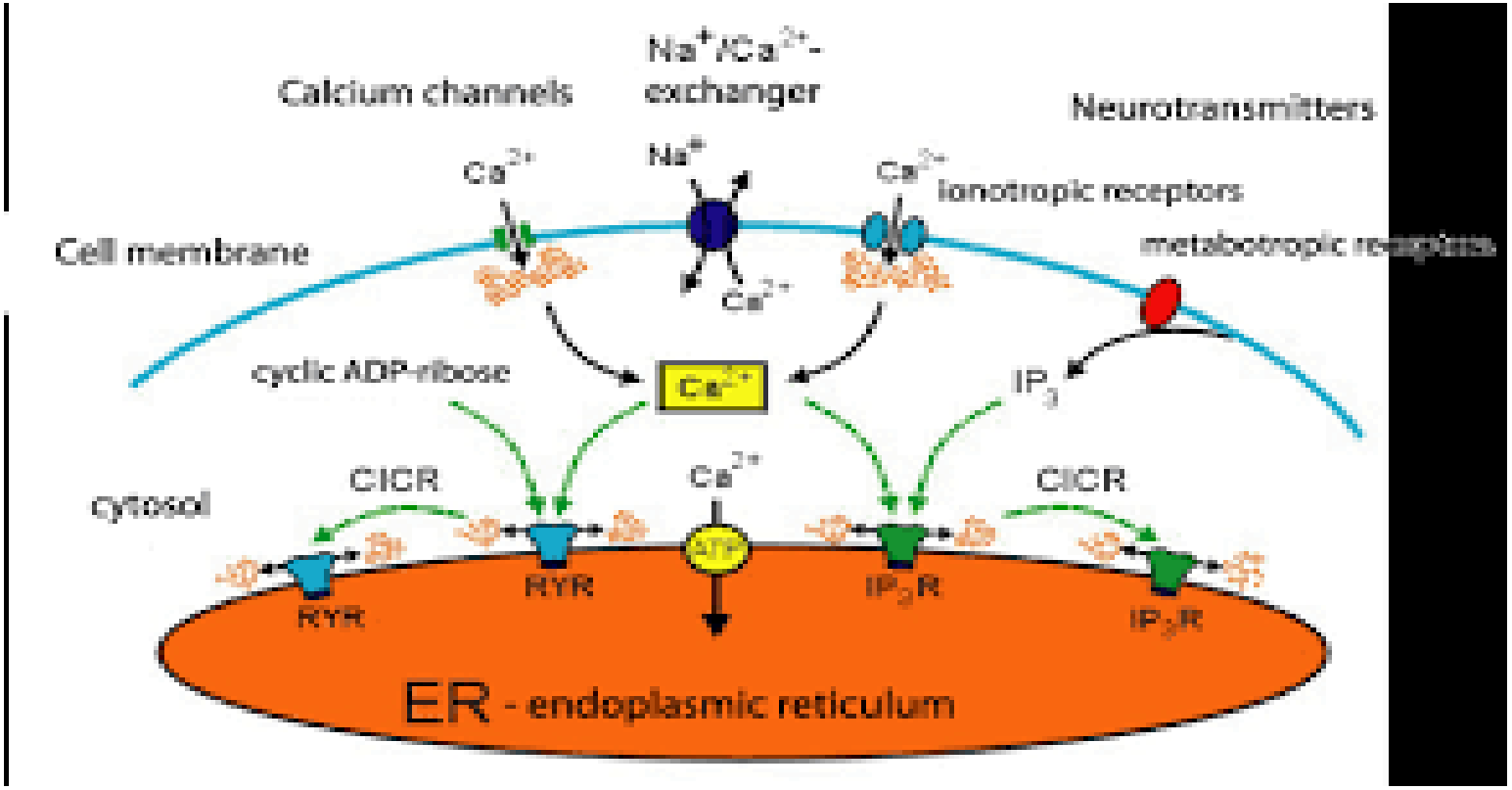
- **SV2A agonist**

- Synaptotagmin is a calcium sensor for exocytosis in pre synaptic vesicle leading to excitatory NT release into synaptic junction.
- SV2A regulates the activity of synaptotagmin leading to inhibition of calcium mediated exocytosis.
- Levetiracetam acts as an agonist of synaptic vesicle protein 2A

SIGNAL TO NOISE RATIO



MOA(Signal to noise ratio)



Conclusions

- Can be used in neonates
- Do not use in subtle and generalized tonic seizures
- **“Use in Myoclonic seizures, especially stimulus sensitive thalamocortical myoclonus”**

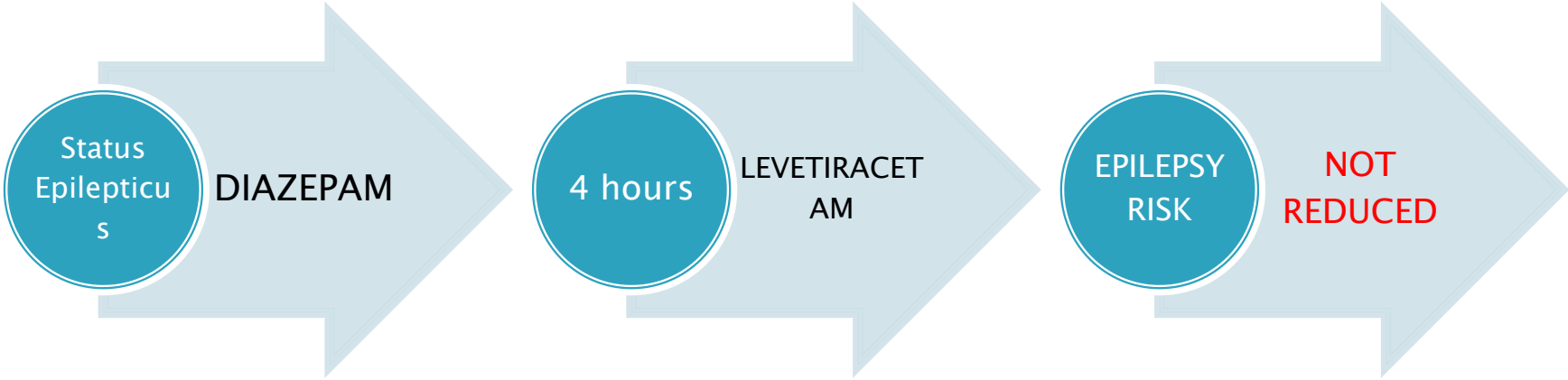
Guidelines by Authority

“DOES NOT EXIST”

Practical Considerations

- When to use?
- Which type of seizure to use?
- How much to use?
- How long to use?

BrandtC & Elien M



Comparision

LEVETIRACETAM

- Respiratory depressant action absent
- Myocardial depressant action absent
- Metabolic demand:?
- Multifocal clonic seizure:use unknown
- **Myoclonic:more useful**
- **Drug interactions absent**

PHENOBARBITONE

- Respiratory depressant action present
- Myocardial depressant action present
- Metabolic demand:Decreased
- Multifocal clonic seizure:useful
- **Myoclonic: less useful**
- **Drug interactions present**

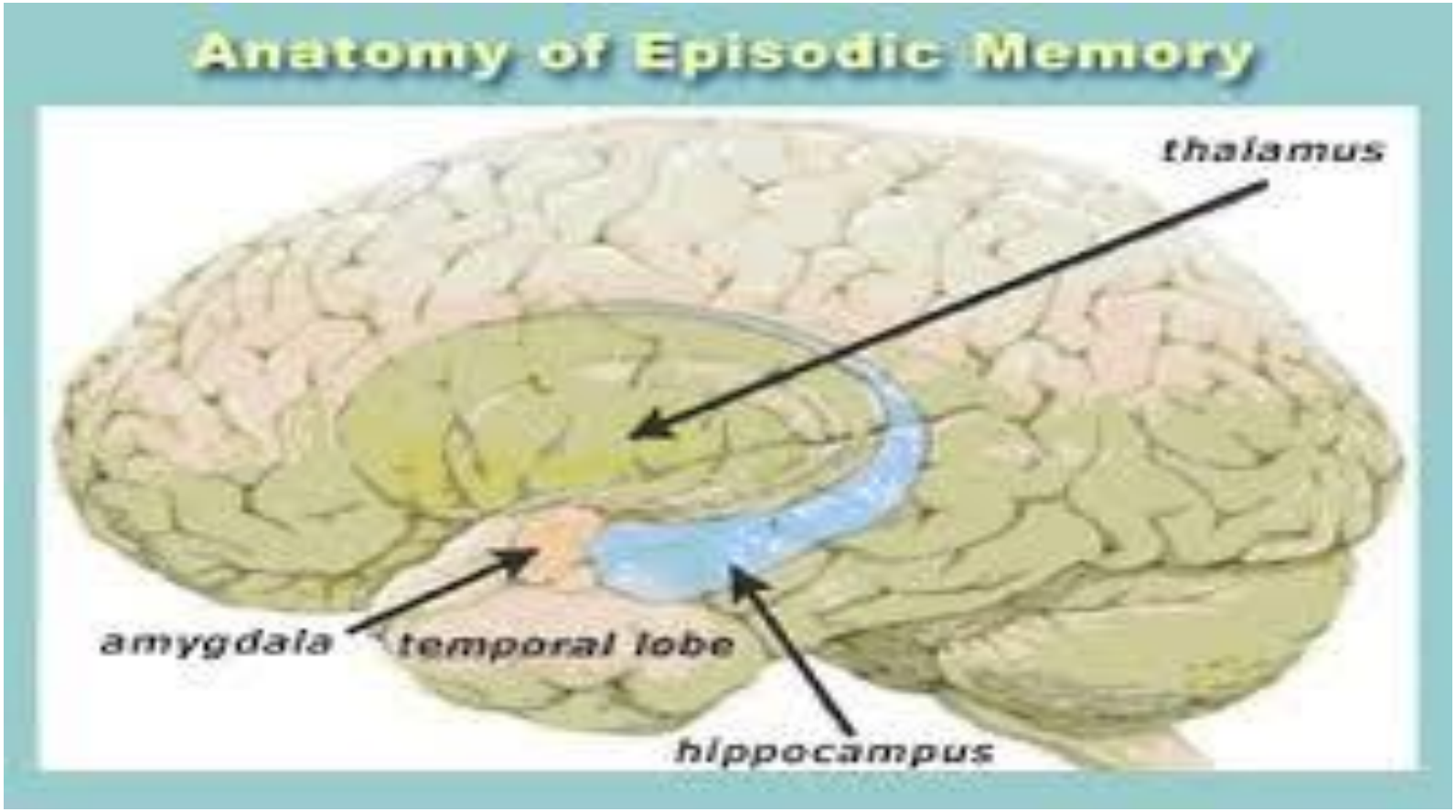
Comparision

LEVETIRACETAM	VALPROATE
Liver dysfunction absent	Liver dysfunction present
In instances where there is increased levels of ammonia,it is safe	In instances where there is increased levels of ammonia,it is unsafe
Pharmacoresistance not seen(MDR protein)	Pharmacoresistance seen

Neonatal dosing(how much)

- Loading dose :40mg/kg(some units start with 20mg/kg)
- 1cc=100mg…
- "Accidental overdose reported but non fatal!"
- Maintainance dose
  - < 7 days-10mg/kg q8h
  - > 7 days-20mg/kg q12h
- Can use higher doses in exceptional circumstances

How long


Anatomy of Episodic Memory
thalamus
amygdala
temporal lobe
hippocampus

How Long

- Dentate gyrus is a part of Hippocampus
- Involved in episodic memory formation and exploration of new environment
- LEV ,on prolonged use has potential side effects due to effect on dentate gyrus
- Manifestations include Hyperactivity,psychosis ,tremors

Carry Home Message

- Routinely don't use
- Can be used in stimulus sensitive myoclonic convulsions
- Higher doses tolerated better
- Stop as soon as primary etiology is better