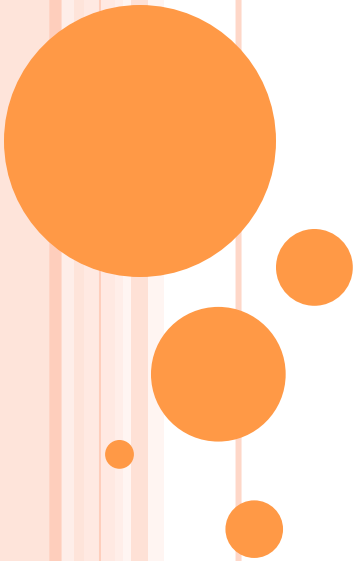
Antiepileptic Drugs



History

- Hippocrates(400 B C)- ***On the sacred disease***
- Bromides(1957)
- Phenobarbital(1912)
- Ketogenic Diet(1920)
- Phenytoin (1938)- H Houston Meritt and Tracy Putnam
- Carbamazepine(Trigeminal Neuralgia-1962, Seizure-1965)
- Valproate(1967)
- Levetiracetam (1998)

Definitions

- **Antiepileptic drug :** decreases the frequency and/or severity of seizures in people with epilepsy
- **Antiepileptic drug :** Treats the symptom of seizures, not the underlying epileptic condition
- **Goal of therapy** : maximize quality of life by minimizing seizures and adverse drug effects

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Definitions

- **Seizure**: the clinical manifestation of anŒ Seizure: the clinical manifestation of an abnormal synchronization and excessive excitation of a population of cortical neurons

- **Epilepsy**: a tendency toward recurrent seizures unprovoked by acute systemic or neurologic insults.

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Definitions

Status Epilepticus

- **Convulsive Status Epilepticus :** continuous convulsive seizures lasting > 5 min, or two or more seizures- and patient's does not return to baseline consciousness
- **Non-Convulsive Status Epilepticus :** change in mental status from baseline >30 min, with evidence of ictal discharges on EEG
- **Refractory Status Epilepticus :** seizure activity continues after 1st line and 2nd line AEDs management failed (>60 min)

Guidelines for management of Epilepsy in India- GEMIND, IES

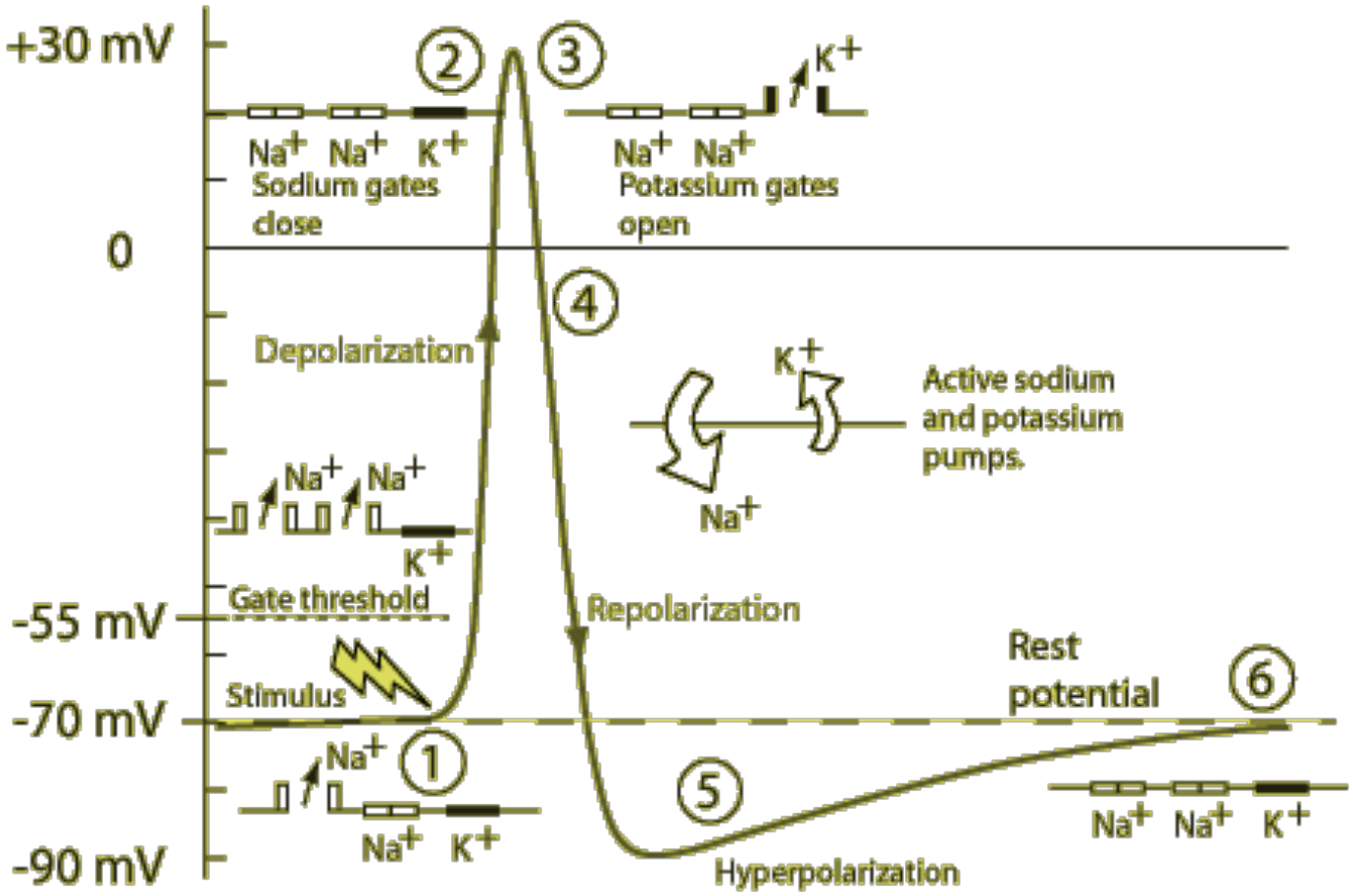
Definitions

- **Medically Intractable Epilepsy:** 2 AEDs used in optimal dosage, or continued epilepsy after > 2 yrs of appropriate treatment(adults),

- Or – Children with epileptic encephalopathy, infantile spasm, seizure >1/month, catastrophic onset epilepsy, disabling epilepsy

Guidelines for management of Epilepsy in India- GEMIND, IES

Neuronal Action potential



Mechanism of Seizure generation

Deregulation of balance

Excitation (too much)Œ

- Ionic-inward Na+, Ca++ currents (EPSPs)
- Neurotransmitters : glutamate, aspartate

Inhibition (too little)

- Ionic-inward CI-, outward K+ currents(IPSPs)
- Neurotransmitter: GABA

Neurotransmitters

GLUTAMATE

- Brain's major excitatory neurotransmitter™

Two groups of receptors

- Inotropic -fast synaptic transmission
  - NMDA, AMPA, kainate
  - Gated Ca++ and gated Na+ channels

- Metabotropic -slow synaptic transmission
  - Regulation of second messengers (cAMP and Inositol)
  - Modulation of synaptic activity

Neurotransmitters

GABA

- Major inhibitory neurotransmitter in the CNS

Œ

Two types of receptors

- GABA-A

• Post-synaptic
• Specific recognition sites
• Linked to CI- channel

- GABA-B

• Pre-synaptic reduction in calcium influx
• Mediated by K+ currents

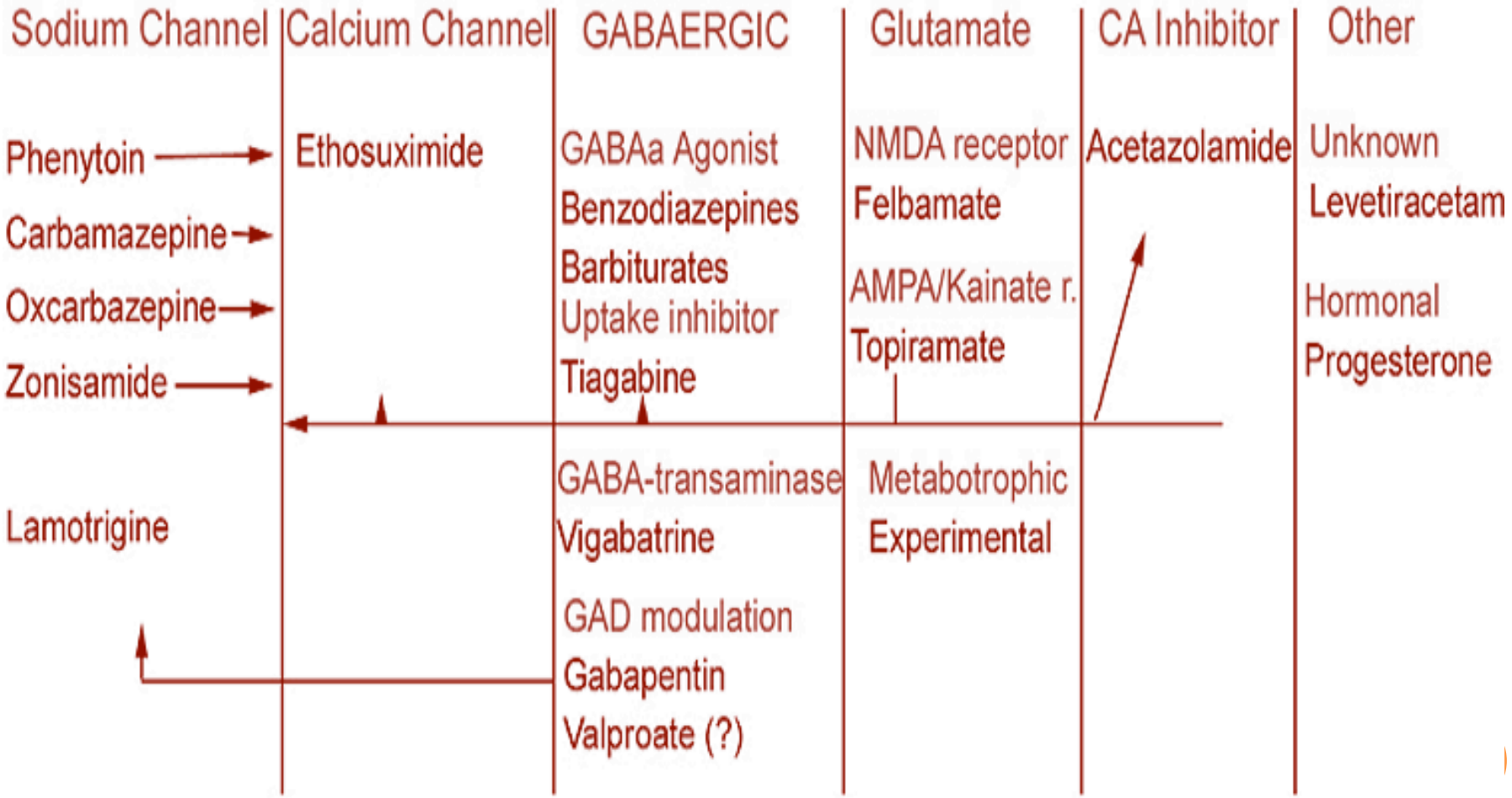
CLASSIFICATION *(DECKERS' ET AL)*

- **Group 1**- Blockade of voltage-dependent Na+ or Ca channels (generalised and partial seizures)
- **Group 2 -** enhance inhibitory events mediated by GABA (absence, generalised, partial seizures)
- **Group 3 -** blocks T-type calcium channels (absence seizures).
- **Group X**- reduce events mediated by excitatory amino acids-glutamate

Some drugs like leviracetam, Hormonal agents, MgSO4 unaccounted.

Most of the AEDs act by more than 1 mechanism

CLASSIFICATION



Pharmacokinetics

Absorption

- Essentially complete for all AEDs (except gabapentin- dose dependent,)
- Timing varies widely by drug, formulation, patient characteristics
- Generally slowed by food in stomach (CBZ may be exception, lamotrigine not slowed by food)
- Therapeutic levels- Usually takes several hours (importance for interpreting blood levels)

Pharmacokinetics

Elimination

- Metabolism/biotransformation — generally hepatic (usually rate-limiting step)
- Excretion — mostly renal
- Active and inactive metabolites
- Changes in metabolism over time (Auto-induction with carbamazepine, with polytherapy enzyme induction or inhibition)
- Differences in metabolism by age, systemic disease

DRUG	Protein binding	Clearance	T1/2 (hrs)	Therapeutic level Mcg/ml	PK Interaction	Withdrawl over
PHT	90	100% H	12-60 Dose dependent	10 - 20	YES	4 wks
CBZ	75-85	100% H	SD 20-55 Chr Rx 10-30	6 - 12	YES	4wks
VPA	75-95	100% H	6-18	50 - 100	YES	4wks
LEV	<10%	66% renal	4-8	20 -60	No	

AED INTERACTION

Metabolism inducer

- Carbamazepine
- Phenytoin
- Phenobarbital
- Primidone

Metabolism Inhibitor

- Valproate
- Felbamate
- Topiramate

Neither inducer/inhibitor

- Gabapentin
- Lamotrigine
- Pregabalin
- Tiagabine
- Levetiracetam
- Zonisamide

Protein Bound

- Valproate
- Phenytoin
- Tiagabine
- Carbamazepine
- Oxcarbazepine
- Topiramate

AED Interactions- Comorbidities

Effects	Older AED	Newer AED
Metabolic disorder may increase risk of hepatotoxicity	VPA	-
Increased risk of hyponatremia	CBZ	OXC
Measurable increase in free fraction with hypoalbuminemia	PHT, VPA	-
Metabolism affected by renal disease	PB	GBP, LEV, TPM
Metabolism affected by liver disease	CBZ, PHT, VPA	LTG, ZNS, OXC, TGB

Adverse effects

Acute (dose related - reversible)

Adverse effects	AED
Dizziness, Fatigue, Ataxia, Diplopia	*all AEDs*
Irritability/behaviour change	*Levetiracetam, Gabapentin*
Weight loss/anorexia	*Topiramate, zonisamide, felbamate*
Weight gain	*Valproate (associated with PCOS in women), Carbamazepine, Gabapentin, Pregabalin*
Tics and Insomnia	*Lamotrigine*
Metabolic acidosis	*Topiramate*
Language dysfunction	*Topiramate*
Photosensitivity	*Zonisamide*

Adverse effects

Idiosyncratic (uncommon, serious)

Adverse effects	Drugs
Renal stones	*Topiramate, zonisamide*
Anhydrosis, heat stroke	*Topiramate, zonisamide*
Acute closed-angle glaucoma	*Topiramate*
Hyponatremia	*Carbamazepine, oxcarbazepine* (used in DI)
Aplastic anemia	*Valproate, Carbamazepine, Felbamate, Zonisamide,*
Hepatic Failure	*Valproate, Felbamate, Lamotrigine, Phenobarbital*
Peripheral vision loss	*Vigabatrin*
Stupor- spike wave	*Zonisamide*

Adverse effects

Idiosyncratic (uncommon, serious)

- Rash - Phenytoin, Lamotrigine, Zonisamide, Carbamazepine

- *Risk of "dangerous or even fatal skin reactions" such as Steven-Johnson Syndrome and Toxic epidermal necrolysis is increased in patients with HLA-B*1502 allele*

- *Estimated absolute risk for those with the allele: 5%*

Adverse effects

Long term (vary in severity and reversibility)

Endocrine/Metabolic	AEDs
Osteomalacia, osteoporosis	Carbamazepine, Phenobarbital, Phenytoin, Oxcarbazepine (**ADOPT trial**- RCT on bisphosphonates v/s Ca/Vitamin D supplementation- ongoing)
Folate deficiency (anaemia, teratogenesis)	Phenobarbital, Phenytoin, Carbamazepine, Valproate
Altered connective tissue metabolism or growth (facial coarsening, gum hyperplasia, hirsutism)	Phenytoin, Phenobarbital

- Neuropathy, Cerebellar Syndrome : Phenytoin

AED SERUM LEVEL

- Optimizing AED therapy
- ŒAssessing compliance
- ŒTo monitor pharmacodynamic and pharmacokinetic interactions.
- Most often individual patients define their own “ therapeutic range” for AEDs.
- New AEDs there is no clearly defined “therapeutic range”.

AEDs- before starting

Discuss:

- Adverse effects- dose dependent and serious
- Likelihood of success
- Recording/reporting- seizures, adverse effects, potential precipitants

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AEDs- choice

- Limited Placebo controlled trials available- especially newer AEDs
- Several drugs are commonly used for indications other than those for which they are officially approved/ recommended
- Partial epilepsy- choice depends on drug side-effect profile & patient's preference/concerns
- Generalized epilepsy- choice depends on predominant seizure type(s) , drug side-effect & patient's preference/ concerns

ILAE Summary Guidelines and Summary of AAN evidence-based guidelines

AEDs- choice

Seizure type	GTCS	Partial	Absence	Myoclonic
BEST EVIDENCE	Valproate Topiramate	Carbamazepine Oxcarbazepine Phenytoin Topiramate	Ethosuximide Valproate	Valproate Levetiracetam Clonazepam
Alternatives	Phenytoin Carbamazepine Levetiracetam Lamotrigine	Lamotrigine Gabapentine Gabapentine Levetiracetam Valproate Phenobarbitol Pregabilin Zonisamide	Lamotrigine Levetiracetam Levetiracetam Clonazepam Topiramate Felbamate	Zonisamide Topiramate

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AED- How to start

- Monotherapy preferred- simplifies Rx, fewer adverse effects and drug interactions
- ~70-80% seizures are controlled on monotherapy alone
- Monotherapy with different drug should be tried together before starting polytherapy
- Conversion to single drug from multiple drugs
- Eliminate sedative drugs first (barbiturate/ benzodiazepine)
- Withdraw AEDs slowly over several months

AEDs- WHEN TO STOP

- Seizure freedom for ≥2 years implies overall >60% chance of success

- Favourable factors
- Control achieved easily on one drug at low dose
- No previous unsuccessful attempts at withdrawal
- Normal neurologic exam and EEG
- Primary generalized seizures except JME

- Consider relative risks/benefits (e.g., driving, pregnancy)

Practice parameter. Neurology. 1996;47:600–602.

Neurosurgery and AEDs

- Perioperative seizures are relatively rare, and all available drugs do not have 100% efficacy in preventing them.
- Great degree of heterogeneity among neurosurgical patients
- Incidence of epilepsy differs between patients with trauma, intracerebral hemorrhage and tumors – and even tumor type and localization
- AEDs interfere with adjuvant treatments for brain tumors: severe skin reaction ns (Stevens–Johnson syndrome) in patients under-going radiotherapy while taking phenytoin, phenobarbital or carbamazepine are reported.
- AEDs decrease efficacy of chemotherapy due to liver enzyme induction by carbamazepine , phenobarbital and phenytoin

Neurosurgery and AEDs (traumatic brain injury)

- Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS- ***level II recommendation***
- AEDs are indicated to decrease the incidence of early PTS (within 7 days of injury)- ***level II recommendation***
- Risk factors for late PTS-

(1) Glasgow Coma Scale (G CS) Score less than 10 .

(2) Cortical contusion.

(3) Depressed skull fracture.

(4) Subdural /epidural/ intracerebral hematoma .

(5) Penetrating head wound.

Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XIII: Antiseizure prophylaxis. J Neurotrauma 2007; 24 (Suppl 1):S83 –S86.

Neurosurgery and AEDs (subarachnoid hemmorhage)

Rosengart AJ, Huo D, Tolentino J. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. J Neurosurg 2007; 107:253 – 260. - META ANALYSIS

- Significantly increased risk of neurologic complications in patients after subarachnoid hemorrhage, who were treated with AEDs.
- Patients at risk of seizures not yet defined
- Incidence of seizures is also uncertain (??<10%)

Neurosurgery and AEDs (Prophylaxis in brain tumors)

Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev 2008:CD004424.

- No difference between the intervention and control groups in preventing a first seizure in patients with brain tumors
- Patients treated with antiepileptic agents had a higher risk of adverse effect than those untreated

Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors – report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology 2000; 54:1886 –1893.

- Discourages the prophylactic use of AEDs
- Duration of prophylactic therapy in patients without preoperative seizures should be restricted to the first postoperative week

Neurosurgery and AEDs (Therapeutic use in brain tumors)

- In patients with preoperative seizures- AEDs should be given
- Factors for post operative seizures-

1. the amount of resection,
2. parietal tumor localization
3. seizure complexity
4. pre-operative seizure duration

Van Breemen MSM, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms and management. Lancet Neurol 2007; 6:421–430.

Neurosurgery and AEDs (epileptogenesis)

- Latent period of epileptogenesis following acute brain insult
- Newer therapies directed at cellular level under investigation-
- Tetrodotoxin and BDNF(brain derived neurotrophic factor)- promising in vitro results

Prince DA, Parada I, Scalise K, et al. Epilepsy following cortical injury: cellular and molecular mechanisms as targets for potential prophylaxis. Epilepsia 2009; 50 (Suppl 2):S30 –S40.

Prophylaxis - phenytoin v/s Levetiracetam

Lim DA, Tarapore P, Chang E, et al. Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: a randomized phase II pilot study. J Neurooncol 2009; 93:349 –354.

- No difference in efficacy could be detected
- Levetiracetam showed fewer adverse effects.
- Good tolerability with Levetiracetam

AEDs & Pregnancy

- EPTOIN : Fetal Hydantoin Syndrome
- VALPROATE : Neural tube defects
- OTHER CONGENITAL MALFORMATIONS
  - Cardiac defects
  - Genitourinary defects
  - supplementation in all
  - Oral clefts
  - Risk with AED monotherapy 4.5% (OR 2.6)
  - Risk with Polytherapy 8.6% (OR 5.1)

Holmes et al. N Engl J Med. 2001;344:1132–1138. [PubMed]

Consensus

- **Monotherapy with lowest dose CBZ**
- **Periconceptional Folate Supplementation 5 mg**
- **Vit K at 34th and 36th wk (GEMIND)**
- **MSAFP at 16 wk, and USG at 18 wk (GEMIND)**

AEDs and Lactation

- Breastfeeding should be encouraged unless clear risk posed

- Probably safe:
  - Carbamazepine
  - Phenytoin
  - Valproate
  - Lamotrigine

- "Use with caution" in lactating women:
  - Primidone
  - Phenobarbital
  - Ethosuximide

Pennell et al. Epilepsy and Behavior. 2007. 11: 263-9

Status epilepticus

- **Out of Hospital Setting (first 5 min):** Diazepam (rectal) 0.5 mg/kg oral OR Midazolam (buccal) 0.2-0.3 mg/kg OR Lorazepam 2 mg/Diazepam 5-10 mg iv

- **First Stage(5-20 min)**

  Lorazepam 0.1 mg/kg(max 4 mg) iv OR

  Diazepam 0.5 mg/kg (max 10 mg) iv

Wait for 5 min and repeat if no response (give pyridoxine 100 mg iv <2 yrs old)

- **Second stage(20-60 min)- Established GCSE**

  Phenytoin 15-20 mg/kg loading iv (@ 50mg/min max)

  Fosphenytoin 20-25 mg/kg loading (@150 mg/min max)

  ↓ (seizure persists 10 min after loading)

  Consider

  Phenytoin 5-10 mg/kg iv Or Fosphenytoin 5mg/kg iv

  Alternatives

  Valproate 25-35 mg/kg iv loading(max @ 6mg/kg/min)

  Phenobarbitone 20 mg/kg iv loading(max @ 60mg/min)- needs ventilator backup

- Investigate: ABG- glucose, LFT, RFT, BUN, electrolytes, Ca, LP(if suspected), CT head

- **Refractory Status Epilepticus(>60 min)**

  Mechanical Ventilation-

Drug	Loading/Bolus(iv)	Maintenance (infusion)
Midazolam	0.1mg/kg(max 10 mg)	0.2-0.4 mg/kg/h
Propofol	2-5 mg/kg	5-10 mg/kg/h
Thiopentone	10-20 mg/kg	0.5-1 mg/kg/h

  Weaning Off: Seizure free 12 hrs(EEG burst suppression) reduce infusion every 3 hrs, if seizure recur, reinstitute coma with same drug

- **NCSE-** consider using Propofol/midazolam

AED	Dose/ dosing frequency	Remarks	Theraupt ic level (Mcg/mL)	Adverse effects
Phenytoin	300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); od-bid Loading dose: 20 mg/ kg @ <50 mg/min infusion	Cardiac monitoring check BP	10 -20	Gum hyperplasia, Lymphadenopathy, Hirsutism, Osteomalacia; Hyperglycemia Dizziness, Diplopia, Ataxia Incoordination
Valproate	750–2000 mg/d (20–60 mg/kg); bid-qid	Start 15 mg/kg/day Increment wkly 5-10mg/kg/day	50 – 100	Hepatotoxicity Thrombocytopenia Hyperammonemia Pancreatitis
Carbamazepi ne	600–1800 mg/d (15–35 mg/kg, child); bid qid	Start low and increase slowly Oral form only	6-12	Leukopenia, Aplastic anemia, Hyponatremia,
Leveracetam	1000–3000 mg/d; bid			Sedation Fatigue Incoordination Psychosis

AED	Dose/ dosing frequency	Remarks	Therauptic level (Micrmol/L)	Adverse effects
Gabapentin	Start 300 mg OD, increase - 900 to 1,800 mg divided TDS/QID		70 - 120	Weight gain, peripheral edema behavioral changes
Lamotrigine	Start 50 mg OD(25 mg with VPA), increase to 300-500 mg – divided BD (max 150 mg OD withVPA)	Risk of rash/ SJS/TEN increased with concomitant valproate use, reduced with slow titration	10 - 60	Rash(Steven johnson syndrome), arthritis, tics, insomnia
Felbamate	Start 1200 mg daily divided TDS/ QID or 15 -45 mg/kg/day divided 6 to 8 hours		125 - 250	Anorexia, vomiting, insomnia, somnolence, aplastic anemia, hepatotoxicity
Topiramate	Begin with 50 mg daily; increase to 50 - 400 mg daily divided 12 hrly		15 - 60	Dizziness, somnolence, ataxia, confusion, fatigue, paresthesias, speech difficulities, diplopia, impaired concentration and nausea

AED	Dose/ dosing frequency	Remarks	Theraup tic level (Micrmol /L)	Adverse effects
Oxcarbazepin	150 mg BD increase 150 mg each week , Max dose 600 mg BD	CBZ can be directly switched to Oxcarbazepine	50 - 140	Hyponatremia (more common in elderly), rash
Tiagabine	Start 4mg OD, BD next week, then TDS,in 4th week 4 mg QID, Max- dose – 56 mg/day		50 – 250 (nmol/L)	Stupor or spike wave stupor, Weakness
Zonisamide	Start 25 mg OD, add 25 mg every week , max – 300 mg BD		45 - 180	Rash, renal calculi, hypohidrosis, Irritability, photosensitivity, weight loss
Vigabatrin	Start 500 mg BD, increase to 1500 mg BD over 1 month	Regular vision testing required,	6-78	30% patients permanently loss of peripheral vision,
Clobazam	10 mg HS, max 30 mg OD	rebound seizures upon abrupt or over-rapid discontinuation of therapy(BZD withdrawal syndrome)	-	Somnolence, Ataxia, Dysarthria, Diplopia, Gelastic seizures, urticaria, rashes

- THANK YOU