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.

*American Epilepsy Society 2010*
Definitions

- **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.

*American Epilepsy Society 2010*
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)
- Ionic-inward Na+, Ca++ currents (EPSPs)
- Neurotransmitters: glutamate, aspartate

Inhibition (too little)
- Ionic-inward Cl-, 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
- Two types of receptors
  - GABA-A
    - Post-synaptic
    - Specific recognition sites
    - Linked to Cl- 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*
<table>
<thead>
<tr>
<th>Sodium Channel</th>
<th>Calcium Channel</th>
<th>GABAergic</th>
<th>Glutamate</th>
<th>CA Inhibitor</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Ethosuximide</td>
<td>GABAa Agonist</td>
<td>NMDA receptor</td>
<td>Acetazolamide</td>
<td>Unknown</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Benzodiazepines</td>
<td>Felbamate</td>
<td></td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
<td>Barbiturates</td>
<td>AMPA/Kainate r.</td>
<td></td>
<td>Hormonal</td>
</tr>
<tr>
<td>Zonisamide</td>
<td></td>
<td>Uptake inhibitor</td>
<td>Topiramate</td>
<td></td>
<td>Progesterone</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td>Tiagabine</td>
<td>Metabotropic</td>
<td></td>
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<td>GABA-transaminase</td>
<td>Experimental</td>
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<td></td>
<td>Vigabatrin</td>
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<tr>
<td></td>
<td></td>
<td>GAD modulation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Gabapentin</td>
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<tr>
<td></td>
<td></td>
<td>Valproate (?)</td>
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</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>DRUG</th>
<th>Protein binding</th>
<th>Clearance</th>
<th>T1/2 (hrs)</th>
<th>Therapeutic level Mcg/ml</th>
<th>PK Interaction</th>
<th>Withdrawal over</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>90</td>
<td>100% H</td>
<td>12-60 Dose dependent</td>
<td>10 - 20</td>
<td>YES</td>
<td>4 wks</td>
</tr>
<tr>
<td>CBZ</td>
<td>75-85</td>
<td>100% H</td>
<td>SD 20-55 Chr Rx 10-30</td>
<td>6 - 12</td>
<td>YES</td>
<td>4wks</td>
</tr>
<tr>
<td>VPA</td>
<td>75-95</td>
<td>100% H</td>
<td>6-18</td>
<td>50 - 100</td>
<td>YES</td>
<td>4wks</td>
</tr>
<tr>
<td>LEV</td>
<td>&lt;10%</td>
<td>66% renal</td>
<td>4-8</td>
<td>20 -60</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Effects</th>
<th>Older AED</th>
<th>Newer AED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic disorder may increase risk of hepatotoxicity</td>
<td>VPA</td>
<td>-</td>
</tr>
<tr>
<td>Increased risk of hyponatremia</td>
<td>CBZ</td>
<td>OXC</td>
</tr>
<tr>
<td>Measurable increase in free fraction with hypoalbuminemia</td>
<td>PHT, VPA</td>
<td>-</td>
</tr>
<tr>
<td>Metabolism affected by renal disease</td>
<td>PB</td>
<td>GBP, LEV, TPM</td>
</tr>
<tr>
<td>Metabolism affected by liver disease</td>
<td>CBZ, PHT, VPA</td>
<td>LTG, ZNS, OXC, TGB</td>
</tr>
</tbody>
</table>
# Adverse Effects

## Acute (dose related - reversible)

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>AED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness, Fatigue, Ataxia, Diplopia</td>
<td>all AEDs</td>
</tr>
<tr>
<td>Irritability/behaviour change</td>
<td>Levetiracetam, Gabapentin</td>
</tr>
<tr>
<td>Weight loss/anorexia</td>
<td>Topiramate, zonisamide, felbamate</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Valproate (associated with PCOS in women), Carbamazepine, Gabapentin, Pregabalin</td>
</tr>
<tr>
<td>Tics and Insomnia</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Language dysfunction</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>
# Adverse Effects

**Idiosyncratic (uncommon, serious)**

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

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

- Neuropathy, Cerebellar Syndrome: Phenytoin
**AED SERUM LEVEL**

- Optimizing AED therapy
- Assessing compliance
- To 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
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

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>GTCS</th>
<th>Partial</th>
<th>Absence</th>
<th>Myoclonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST EVIDENCE</td>
<td>Valproate</td>
<td>Carbamazepine</td>
<td>Ethosuximide</td>
<td>Valproate Clonazepam</td>
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<td></td>
<td>Topiramate</td>
<td>Oxcarbazepine</td>
<td>Valproate</td>
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<td>Phenytoin</td>
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<td></td>
<td></td>
<td>Topiramate</td>
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<tr>
<td>Alternatives</td>
<td>Phenytoin</td>
<td>Lamotrigine</td>
<td>Lamotrigine</td>
<td>Zonisamide</td>
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<td></td>
<td>Carbamazepine</td>
<td>Gabapentine</td>
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<td>Lamotrigine</td>
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<td>Lamotrigine</td>
<td>Levetiracetam</td>
<td>Levetiracetam</td>
<td>Topiramate</td>
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<td>Lamotrigine</td>
<td>Valproate</td>
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<td>Lamotrigine</td>
<td>Phenobarbital</td>
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<td>Lamotrigine</td>
<td>Pregabalin</td>
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<td>Lamotrigine</td>
<td>Clonazepam</td>
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<td>Topiramate</td>
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<td>Phenytoin</td>
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<td>Carbamazepine</td>
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<td>Levetiracetam</td>
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<td></td>
<td>Levetiracetam</td>
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<tr>
<td></td>
<td>Valproate</td>
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<tr>
<td></td>
<td>Topiramate</td>
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</tbody>
</table>

*American Epilepsy Society 2010*
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)

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.

NEUROSURGERY AND AEDS
(SUBARACHNOID HEMMORHAGE)


- 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)


- 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


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

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

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

- EPITOIN: 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)

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 -

  *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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading/Bolus(iv)</th>
<th>Maintenance (infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.1mg/kg (max 10 mg)</td>
<td>0.2-0.4 mg/kg/h</td>
</tr>
<tr>
<td>Propofol</td>
<td>2-5 mg/kg</td>
<td>5-10 mg/kg/h</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>10-20 mg/kg</td>
<td>0.5-1 mg/kg/h</td>
</tr>
<tr>
<td>AED</td>
<td>Dose/ dosing frequency</td>
<td>Remarks</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); od-bid</td>
<td>Loading dose: 20 mg/kg @ &lt;50 mg/min infusion</td>
</tr>
<tr>
<td>Valproate</td>
<td>750–2000 mg/d (20–60 mg/kg); bid-qid</td>
<td>Start 15 mg/kg/day Increment wkly 5-10mg/kg/day</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>600–1800 mg/d (15–35 mg/kg, child); bid qid</td>
<td>Start low and increase slowly Oral form only</td>
</tr>
<tr>
<td>Leveracetam</td>
<td>1000–3000 mg/d; bid</td>
<td></td>
</tr>
<tr>
<td>AED</td>
<td>Dose/ dosing frequency</td>
<td>Remarks</td>
</tr>
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<td>------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Start 300 mg OD, increase - 900 to 1,800 mg divided TDS/QID</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Start 50 mg OD(25 mg with VPA), increase to 300-500 mg – divided BD (max 150 mg OD with VPA)</td>
<td>Risk of rash/ SJS/TEN increased with concomitant valproate use, reduced with slow titration</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Start 1200 mg daily divided TDS/ QID or 15 -45 mg/kg/day divided 6 to 8 hours</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Begin with 50 mg daily; increase to 50 - 400 mg daily divided 12 hrly</td>
<td></td>
</tr>
<tr>
<td>AED</td>
<td>Dose/ dosing frequency</td>
<td>Remarks</td>
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<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Oxcarbazepin</td>
<td>150 mg BD increase 150 mg each week, Max dose 600 mg BD</td>
<td>CBZ can be directly switched to Oxcarbazepine</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Start 4mg OD, BD next week, then TDS, in 4th week 4 mg QID, Max- dose – 56 mg/day</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Start 25 mg OD, add 25 mg every week, max – 300 mg BD</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Start 500 mg BD, increase to 1500 mg BD over 1 month</td>
<td>Regular vision testing required,</td>
</tr>
<tr>
<td>Clobazam</td>
<td>10 mg HS, max 30 mg OD</td>
<td>rebound seizures upon abrupt or over-rapid discontinuation of therapy(BZD withdrawal syndrome)</td>
</tr>
</tbody>
</table>
THANK YOU